Enantioselective zinc-mediated conjugate alkynylation of saccharin-derived 1-*aza*-butadienes

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Supporting Information

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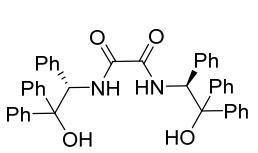
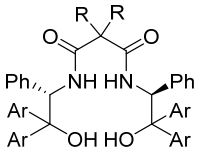
Preliminary experiments with chalcone *N*-tosyl imine (1j).

Preliminary studies for the conjugate alkynylation of α,β-unsaturated imines were carried out using the addition of phenylacetylene (**2a**) to the *N*-tosylimine of chalcone (**1j**). The conditions previously developed in our group for the zinc-mediated conjugate alkynylation of unsaturated carbonyl compounds were applied.[1] The reactive system was prepared by heating a solution of ligand (20 mol %), alkyne **2a** (7.5 equiv.) and diethylzinc (2 equiv.) in toluene to 70 °C for 1 hour followed by addition of the imine **1j** after cooling at room temperature. The reaction gave two compounds that could be separated and characterized as enamine (*Z*)-**3ja** and imine **3ja'**. Imine **3ja'** most probably results from quick isomerization of the (*E*)-enamine, initially formed, to avoid repulsion of the phenyl and phenylethynyl groups. The Z-enamine was stable for several days in the NMR tube while imine **3ja'** hydrolyzed almost completely after 24 hours in the NMR tube. Table S-1 shows the most representative results obtained with imine **1j.**

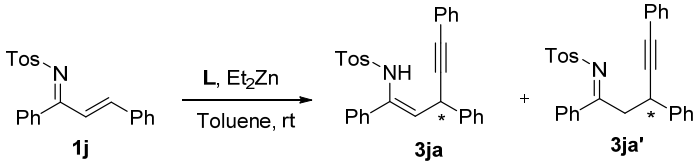
Table S1. Enantioselective reaction of phenylacetylene (**2a**) and the *N*-tosylimine of chalcone (**1j**). Short screening of catalysts.[a]



L4



L5 R = Me, Ar = Ph
L6 R = Et, Ar = Ph
L7 R = Et, Ar = 4-ClC_6H_4



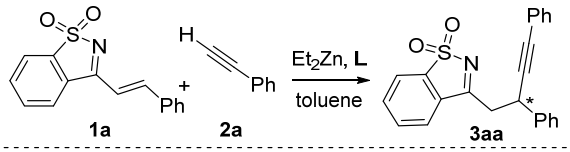
1j **3ja** **3ja'**

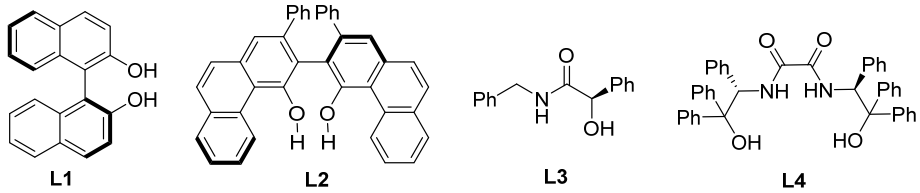
Entry	Ligand	yield (%)	**3ja:3ja'**[b]	ee_{3ja} (%)[c]	$ee_{3ja'}$ (%)[c]
1	**L4**	31	40:60	24	33
2	**L5**	74	80:20	22	22
3	**L6**	52	76:24	43	34
4	**L7**	45	72:28	73	75

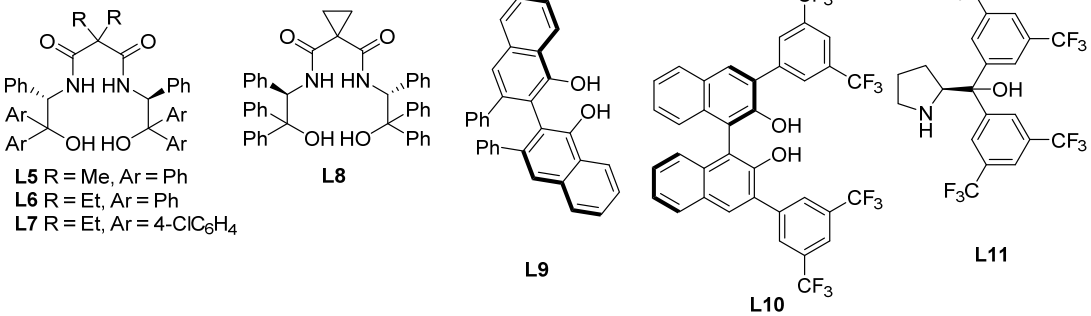
[a] **1** (0.125 mmol), **2a** (0.938 mmol), 1.5 M Et_2Zn in toluene (0.250 mmol), **L** (0.0250 mmol), toluene (1.5 mL), rt., 3 hours. [b] Determined by NMR. [c] Determined by HPLC with chiral stationary phases.

Additional Optimization Experiments with Imine 1a

Table S2. Enantioselective reaction between phenylacetylene (**2a**) and imine **1a**. Chiral ligand study.[a]



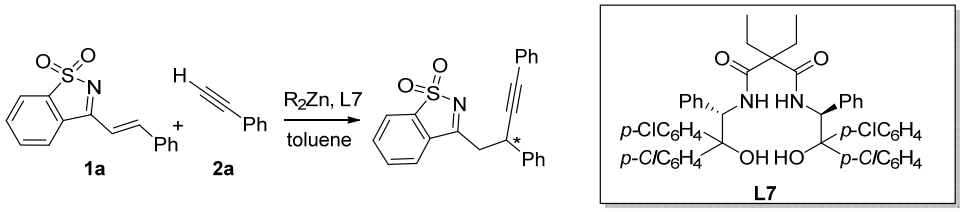




entry	L	yield (%)	*ee* (%)[b]
1	**L1**	22	0
2	**L2**	48	-22
3	**L3**	65	26
4	**L4**	49	10
5	**L5**	48	-65
6	**L6**	50	-71
7	**L7**	53	-72
8	**L8**	54	30
9	**L9**	38	45
10	**L10**	22	0
11	**L11**	29	0

[a] **1a** (0.125 mmol), **2a** (0.938 mmol), 1.5 M Et_2Zn in toluene (0.50 mmol), **L7** (0.025 mmol), toluene (1.5 mL), rt, 3 hours. [b] Determined by HPLC with chiral stationary phases. Different sign indicates opposite enantiomers.

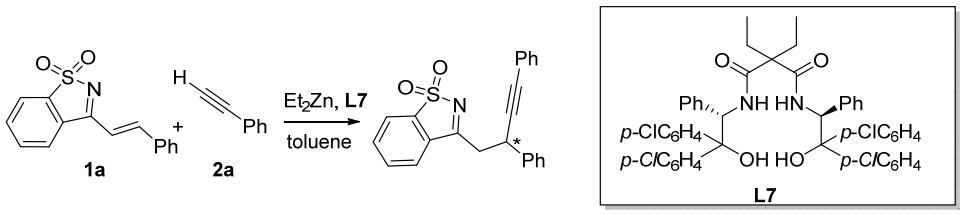
Table S3. Enantioselective reaction between phenylacetylene (**2a**) and imine **1a**. Effect of the number of equivalents of dialkylzinc reagent.[a]



entry	Et_2Zn (equiv.)	yield (%)	*ee* (%)[b]
1	1.3	52	63
2	2	41	67
3	3	50	64
4	4	53	80
5	5	43	64
6[c]	4	50	58

[a] **1a** (0.125 mmol), **2a** (0.938 mmol), **L7** (0.0125 mmol), toluene (1.5 mL), rt, 3 hours. [b] Determined by HPLC with chiral stationary phases. [c] Me_2Zn was used instead of Et_2Zn.

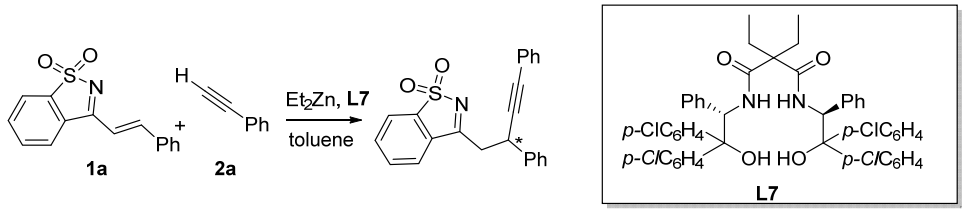
Table S4. Enantioselective reaction between phenylacetylene (**2a**) and imine **1a**. Effect of the number of equivalents of alkyne.[a]



entry	**2a** (equiv.)	yield (%)	*ee* (%)[b]
1	4	38	57
2	5	47	85
3	7.5	53	80

[a] **1a** (0.125 mmol), **2a**, 1.5 M Et_2Zn in toluene (0.50 mmol), **L7** (0.0125 mmol), toluene (1,5 mL), rt, 3 hours. [b] Determined by HPLC with chiral stationary phases.

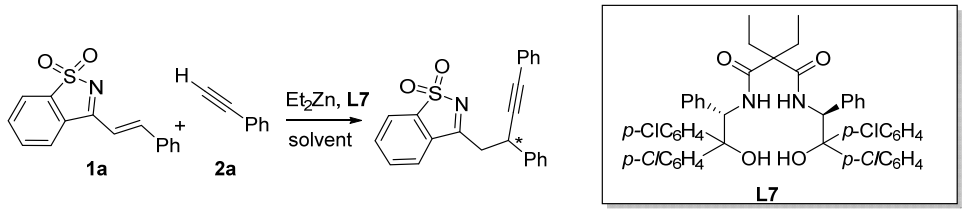
Table S5. Enantioselective reaction between phenylacetylene (**2a**) and imine **1a**. Effect of the concentration.[a]



Entry	[**1a**] (M)	yield (%)	*ee* (%)[b]
1	0.063	59	59
2	0.090	47	85
3	0.126	38	63

[a] **1a** (0.125 mmol), **2a** (0.625 mmol), 1.5 M Et_2Zn in toluene (0.50 mmol), **L7** (0.0125 mmol), toluene, rt, 3 hours. [b] Determined by HPLC with chiral stationary phases.

Table S6. Enantioselective reaction between phenylacetylene (**2a**) and imine **1a**. Effect of the solvent.[a]



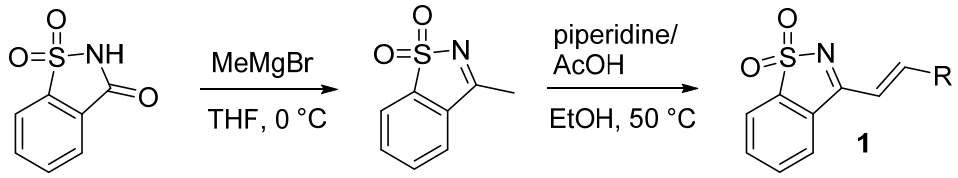
entry	solvent	yield (%)	*ee* (%)[b]
1	toluene	47	85
2	1,2-dichloroethane	46	41
3[c]	CH_2Cl_2	40	40
4[c]	THF	20	0

[a] **1a** (0.125 mmol), **2a** (0.625 mmol), 1.5 M Et_2Zn in toluene (0.50 mmol), **L7** (0.0125 mmol), solvent (1.5 mL), rt, 3 hours. [b] Determined by HPLC with chiral stationary phases. c **2a** (0.625 mmol), 1.5 M Et_2Zn in toluene (0.50 mmol) and **L7** (0.0125 mmol) in toluene (0.5 mL) at 70 ºC for 2 h and then **1a** (0.125 mmol) in solvent (1.o mL), rt, 3 hours.

Materials and methods

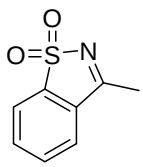
All reagents were purchased from commercial suppliers and used without further purification. All solvents employed in the reactions were distilled from appropriate drying agents prior to use. Toluene for the enantioselective reactions was freshly distilled from CaH_2 prior to use. Reactions were monitored by TLC analysis using Merck Silica Gel 60 F-254 thin layer plates. Flash column chromatography was performed on Merck silica gel 60, 0.040-0.063 mm. Melting points were determined in capillary tubes. NMR spectra were run at 300 MHz for ^1H and at 75 MHz for ^{13}C NMR using residual nondeuterated solvent as internal standard (δ 7.26 ppm for ^1H and 77.0 ppm for ^{13}C in $CDCl_3$, and δ 2.50 ppm for ^1H and 39.52 ppm for ^{13}C in DMSO-d_6, respectively). Chemical shifts are given in ppm. The carbon type was determined by DEPT experiments. High resolution mass spectra (ESI) were recorded on an AB SCIEX Triple TOF spectrometer equipped with an electrospray source with a capillary voltage of 4.5 kV. Specific optical rotations were measured using sodium light (D line 589 nm). Chiral HPLC analyses were performed in a chromatograph equipped with a UV diode-array detector using chiral stationary phase columns from Daicel or Phenomenex.

General procedure for the synthesis of saccharin-derived-1-*aza*-butadienes 1



Compounds **1** were prepared following a modified literature procedure.[2,3] The synthesis of compound **1a** is illustrated.

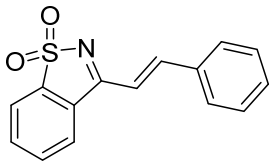
3-Methylbenzo[d]isothiazole 1,1-dioxide[2]



A 3 M solution of MeMgBr in diethyl ether (21 mL, 62.8 mmol) was added dropwise to a solution of saccharin (5 g, 27.3 mmol) in dry THF (40 mL) a 0 °C under nitrogen. The reaction mixture was stirred overnight at room temperature and quenched with aqueous saturated NH_4Cl (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic layers washed with brine (2 × 25 mL). After drying with $MgSO_4$ and evaporation of the solvent under reduced pressure, column chromatography eluting with hexane:EtOAc gave 3.96 g (80% yield) of the title compound. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.96–7.86 (m, 1H),

7.81–7.65 (m, 3H), 2.67 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 173.4 (C), 139.7 (C), 134.1 (CH), 133.7 (CH), 131.7 (C), 124.3 (CH), 122.5 (CH), 17.7 (CH_3).

(*E*)-3-Styrylbenzo[d]isothiazole 1,1-dioxide (1a)[3a]

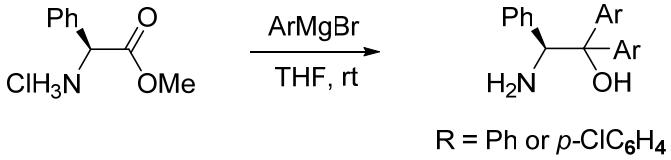


Benzaldehyde (0.98 mL, 9.6 mmol), piperidine (5 drops), and acetic acid (5 drops) were added in this order to a pre-heated solution of 3-methylbenzo[*d*]isothiazole 1,1-dioxide (0.78 g, 4.3 mmol) in absolute ethanol (15 mL) at 80 ºC. The mixture was stirred overnight and, then, cooled to 0 ºC and filtered. The solid was washed with cold ethanol (5 × 10 mL) and Et_2O (5 × 5 mL) to give 1.1 g (93% yield) of **1a**. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.32 (d, *J* = 15.6 Hz, 1H), 8.00–7.94 (m, 1H), 7.93–7.86 (m, 1H), 7.82–7.65 (m, 4H), 7.53–7.44 (m, 3H), 7.30 (d, *J* = 15.6 Hz, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.2 (C), 148.0 (CH), 140.8 (C), 134.4 (C), 133.8 (CH), 133.7 (CH), 132.0 (CH), 131.7 (C), 129.4 (CH), 129.2 (CH), 123.9 (CH), 123.0 (CH), 113.7 (CH).

In some cases, compounds **1** were obtained contaminated with a by-product of unknown structure, which was not soluble in chloroform. In these cases, compounds **1** could be obtained pure by suspending the mixture in hot chloroform (100 mL), filtering and concentrating the filtrate.

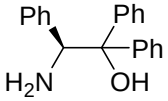
Synthesis of ligands L6 and L7

General procedure for the synthesis of 1,1,2-triaryl-2-aminoethanols



R = Ph or *p*-ClC_6H_4

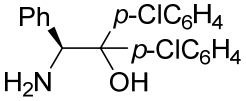
(*S*)-2-Amino-1,1,2-triphenylethan-1-ol



A commercially available 3 M solution of PhMgBr in dry diethyl ether (20 mL, 60 mmol) was introduced via syringe in a round bottom flask under nitrogen followed by diethyl ether (40 mL) and introduced in an ice bath. (*S*)-methyl phenylglycinate hydrochloride (1.65 g, 10 mmol) was added in two portions and the mixture stirred at room temperature for 6 hours. After this time, the mixture was poured into ice (ca. 35 g) and acidified with 6 M HCl (15 mL). The mixture was filtered and the solid washed with cold Et_2O (3 × 5 mL). The solid was treated with 2 M NaOH in MeOH (60 mL) and concentrated under reduced pressure. The resulting crude was

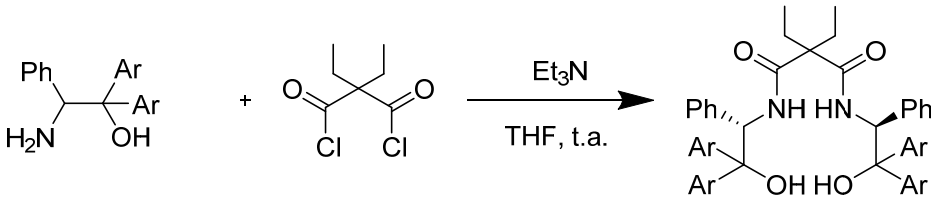
stirred in a 1:1 mixture of water and dichloromethane (100 mL) for 10 min. The layers were separated and the organic layer was washed with water (3 × 25 mL), dried and concentrated under reduced pressure to give 1.85 g (65% yield) of the title compound. White solid, mp 140-142, $[\alpha]_D^{25}$ –195.8 (*c* 1.3, MeOH); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.78 (m, 2H), 7.44–7.39 (m, 2H), 7.31–7.26 (m, 1H), 7.15–7.11 (m, 7H), 7.08–7.02 (m,3H), 5.02 (s, 1H), 1.71 (br s, NH_2); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 146.5 (C), 143.9 (C), 140.0 (C), 128.6 (CH), 128.5 (2CH), 127.4 (CH), 127.3 (CH), 127.2 (CH), 127.0 (CH), 126.5 (CH), 126.2 (CH), 126.0 (CH), 79.5 (C), 61.8 (CH).

(*S*)-2-Amino-1,1-bis(4-chlorophenyl)-2-phenylethan-1-ol



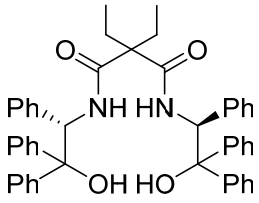
2.21 g (62%) were obtained. White solid; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.70–7.67 (m, 2H), 7.42–7.39 (m, 2H), 7.19–7.13 (m, 5H), 7.04 (s, 4H), 4.95(s, 1H), 1.63 (br s, NH_2); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 144.7 (C), 142.1 (C), 139.4 (C), 133.2 (C), 132.3 (C), 128.7 (CH), 128.5 (CH), 127.9 (2CH), 127.7 (CH), 127.6 (CH), 127.5 (CH), 78.9 (C), 61.6 (CH).

General procedure for the synthesis of bis-hydroxiamides[1]



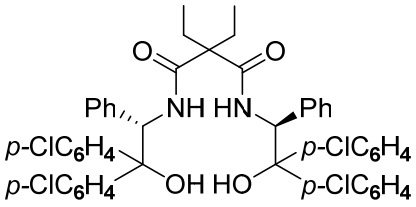
L6, Ar = Ph
L7, Ar = *p*-ClC_6H_4

***N,N'*-Bis[(1*S*)-1,2,2-triphenyl-2-hydroxyethyl]-2,2-diethylpropanodiamide (L6)**



Diethylmalonyl dichloride (141 µL, 0.82 mmol) was added dropwise to a solution of (*S*)-2-amino-1,1,2-triphenylethan-1-ol (472 mg, 1.63 mmol) and triethylamine (229 µL, 1.64 mmol) in THF (11 mL) at 0 ºC. The mixture was stirred at room temperature for 2 horas, filtered and the filtrate concentrated under reduced pressure to give 340 mg (58% yield) of ligand **L6**. White solid; mp 254-255 ºC; $[\alpha]_D^{25}$ –168 (*c* 0.06, MeOH); **^{1}H NMR** (300 MHz, DMSO-d_6) δ 9.02 (d, *J* = 8.4 Hz. 1H), 7.55 (d, *J* = 7.1 Hz, 2H), 7.29–7.21 (m, 5H), 7.11–7.00 (m, 8H), 6.17 (s, 1H), 5.86 (d, *J* = 8.4 Hz, 1H), 1.55–1.40 (m, 2H), –0.04 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR** (75 MHz, DMSO-d_6) δ 171.8 (C), 146.1 (C), 145.0 (C), 139.4 (C), 129.2 (2CH), 127.7 (2CH), 127.2 (2CH), 126.6 (2CH), 126.4 (CH), 126.2 (3CH), 126.1 (3CH), 79.7 (C), 59.2 (CH), 57.0 (C), 30.7 (CH_2), 8.6 (CH_3).

***N,N'*-Bis[(*S*)-2,2-bis(4-chlorophenyl)-2-hydroxy-1-phenylethyl)-2,2-diethylmalonamide (L7)**



The same procedure as for the synthesis of **L6** was followed. After the reaction was completed, the mixture was concentrated, suspended in EtOAc and filtered. The solid was dissolved in dichloromethane and washed with brine, dried over $MgSO_4$ and concentrated to give **L7** in 71% yield. White solid; mp 243-246 °C; $[\alpha]_D^{25}$ –175 (*c* 0.05, MeOH); **^{1}H NMR** (300 MHz, DMSO-d_6) δ 9.05 (d, *J* = 8.7 Hz, 2H), 7.59 (d, *J* = 8.7 Hz, 4H), 7.37 (d, *J* = 8.7 Hz, 4H), 7.28 (d, *J* = 8.7 Hz, 4H), 7.16 (d, *J* = 8.7 Hz, 4H), 7.04 (s, 10H), 6.37 (s, 2H), 5.84 (d, *J* = 8.7 Hz, 2H), 1.49 (tt, *J* = 15.3, 7.0 Hz, 4H), –0.10 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (75 MHz, DMSO-d_6) δ 171.9 (C), 144.8 (C), 143.5 (C), 139.0 (C), 131.5 (C), 131.1 (C), 129.2 (CH), 128.2 (CH), 128.1 (CH), 127.8 (CH), 127.4 (CH), 126.9 (CH), 126.6 (CH), 79.4 (C), 59.2 (CH), 57.1 (C), 30.8 (CH_2), 8.5 (CH_3).

Enantioselective conjugate alkynylation of imines 1 and characterization data for compounds 3

Enantioselective addition of terminal arylacetylenes 2 (R^2 = Aryl) to imines 1

A 1.5 M solution of Et_2Zn in toluene (0.34 mL, 0.5 mmol) was added dropwise to a solution of ligand **L7** (10.5 mg, 0.0125 mmol) and alkyne **2a-d** (0.625 mmol) in dry toluene (0.5 mL) at room temperature under nitrogen. The mixture was stirred at 70 ºC for 2 h. After cooling to room temperature, a solution of imine **1** (0.125 mmol) in toluene (1 mL) was added via syringe and the solution was stirred until the reaction was complete (TLC). The reaction was quenched with 20% aqueous NH_4Cl (1.0 mL), extracted with CH_2Cl_2 (3 × 15 mL), washed with brine (15 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with hexane:Et_2O mixtures afforded compound **3**.

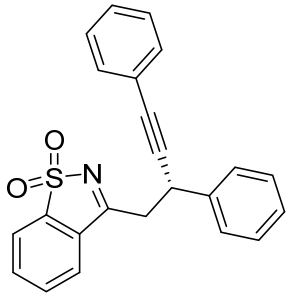
Racemic products **3** (R^2 = Aryl) were prepared following the same procedure but using *N*-benzil-2-hydroxy-2-phenylacetamide instead of **L7**.

Enantioselective addition of terminal alkylacetylenes 2 (R^2 = Alkyl) to imines 1

A 1.5 M solution of Et_2Zn in toluene (0.17 mL, 0.25 mmol) was added dropwise to a solution of ligand **L6** (9 mg, 0.0125 mmol) and alkyne **2e-h** (0.625 mmol) in dry toluene (0.5 mL) at room temperature under nitrogen. The mixture was introduced in a bath at 70 ºC for 2 hours and allowed to reach room temperature. Imine **1** (0.125 mmol) in dry toluene (1 mL) was added via syringe and the reaction mixture stirred until the reaction was complete (TLC). After this time, the reaction was quenched with 20% aqueous NH_4Cl (1.0 mL), diluted in CH_2Cl_2 (50 mL), washed with brine (10 mL), dried over $MgSO_4$. After filtration and concentration under reduced pressure, column chromatography eluting with hexane:Et_2O mixtures afforded compound **3**. In some cases we oserved the formation of the conjugate ethylation product **6**, which was not collected, except in some representative examples.

Near racemic compounds **3** (R^2 = Alkyl) were prepared by mixing enantiomeric compounds **3** obtained in separated reactions with **L6** or *ent*-**L6**

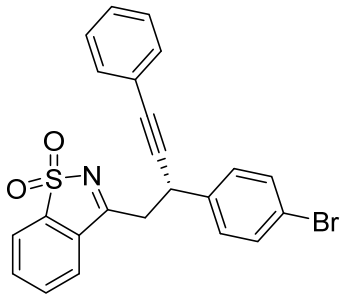
(*S*)-3-(2,4-diphenylbut-3-yn-1-yl)benzo[*d*]isothiazole 1,1-dioxide (3aa)



Obtained 21.8 mg (47%); ethylation product **6** (9.3 mg, 25%) was also isolated. The enantiomeric excess (85%) was determined by HPLC (Chiralcel OD-H), hexane:*i*PrOH 80:20 1 mL/min, major enantiomer: t_r = 29.1 min, minor enantiomer: t_r = 25.8 min.

Oil; $[\alpha]_D^{25}$ –2.5 (*c* 0.8, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.96–7.86 (m, 1H), 7.76–7.58 (m, 2H), 7.57–7.49 (m, 2H), 7.43–7.26 (m, 8H), 4.65 (dd, *J* = 8.4, 6.3 Hz, 1H), 3.55 (dd, *J* = 15.3, 8.4 Hz, 1H), 3.41 (dd, *J* = 15.4, 6.3 Hz, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 173.7 (C=N), 156.0 (C), 153.5 (C), 140.0 (C), 133.9 (CH), 133.7 (CH), 131.8 (CH), 131.4 (C), 129.1 (CH), 128.4 (CH), 127.9 (CH), 127.7 (CH), 124.3 (CH), 122.9 (CH), 122.7 (CH), 89.0 (C), 85.2 (C), 39.9 (CH_2), 36.1 (CH); HRMS (ESI) *m/z*: 372.4620 $[M+H]^+$, $C_{23}H_{18}NO_2S^+$ requires 372.4615.

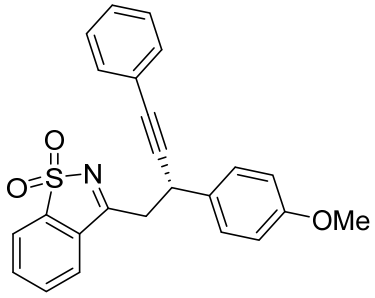
(*S*)-3-(2-(4-Bromophenyl)-4-phenylbut-3-yn-1-yl)benzo[*d*]isothiazole 1,1-dioxide (3ba)



Obtained 33.2 mg (59%). The enantiomeric excess (69%) was determined by HPLC (Chiralcel OD-H), hexane:*i*PrOH 80:20 1.5 mL/min, major enantiomer: t_r = 21.7 min, minor enantiomer: t_r = 35.1 min.

Yellow solid; mp 174-176 °C; $[\alpha]_D^{25}$ +1.3 (c 0.8, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.87–7.81 (m, 1H), 7.71–7.53 (m, 3H), 7.46–7.39 (m, 2H), 7.39–7.33 (m, 2H), 7.31–7.24 (m, 2H), 7.25–7.18 (m, 3H), 4.57 (dd, *J* = 7.9, 6.5 Hz, 1H), 3.47 (dd, *J* = 15.8, 8.0 Hz, 1H), 3.32 (dd, *J* = 15.8, 6.5 Hz, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 173.3 (C), 139.9 (C), 139.0 (C), 133.9 (CH), 133.8 (CH), 132.2 (CH), 131.8 (CH), 131.2 (C), 129.5 (CH), 128.5 (CH), 128.4 (CH), 124.2 (CH), 122.7 (CH), 122.6 (C), 121.8 (C), 88.5 (C), 85.3 (C), 39.6 (CH_2), 35.3 (CH); HRMS (ESI) m/z: 450.0160 $[M+H]^+$, $C_{23}H_{17}BrNO_2S^+$ requires 450.0158.

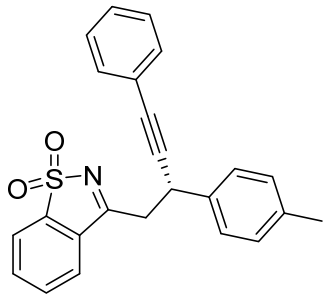
(*S*)-3-(2-(4-Methoxyphenyl)-4-phenylbut-3-yn-1-yl)benzo[*d*]isothiazole (3ca)



Obtained 20.1 mg (40%). The enantiomeric excess (33%) was determined by HPLC (Chiralcel OD-H), hexane:*i*PrOH 80:20 1.5 mL/min, major enantiomer: t_r = 25.5 min, minor enantiomer: t_r = 18.7 min.

Oil; $[\alpha]_D^{25}$ –27.5 (*c* 0.9, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.97–7.86 (m, 1H), 7.75–7.57 (m, 3H), 7.49–7.40 (m, 2H), 7.35–7.30 (m, 2H), 7.30–7.23 (m, 3H), 6.94–6.85 (m, 2H), 4.60 (dd, *J* = 8.1, 6.4 Hz, 1H), 3.79 (s, 3H), 3.52 (dd, *J* = 15.3, 8.2 Hz, 1H), 3.38 (dd, *J* = 15.3, 6.5 Hz, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 173.7 (C), 159.1 (C), 139.8 (C), 133.8 (CH), 133.5 (CH), 131.9 (C), 131.7 (CH), 131.3 (C), 128.6 (CH), 128.2 (CH), 124.3 (CH), 122.8 (C), 122.5 (CH), 114.3 (CH), 89.3 (C), 84.8 (C), 55.4 (CH_3), 39.9 (CH_2), 35.2 (CH); HRMS (ESI) m/z: 402.1158 $[M+H]^+$, $C_{24}H_{20}NO_3S$ requires 402.1158.

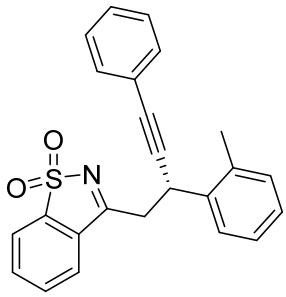
(*S*)-3-(2-(4-Methylphenyl)-4-phenylbut-3-yn-1-yl)benzo[*d*]isothiazole (3da)



Obtained 16.0 mg (33%). The enantiomeric excess (58%) was determined by HPLC (Chiralcel OD-H), hexane:*i*PrOH 80:20 1.5 mL/min, major enantiomer: t_r = 17.0 min, minor enantiomer: t_r = 13.4 min.

Yellow solid; mp 143-145 °C; $[\alpha]_D^{25}$ –5.3 (*c* 0.6, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.96–7.84 (m, 1H), 7.77–7.59 (m, 3H), 7.47–7.38 (m, 2H), 7.37–7.22 (m, 5H), 7.21–7.11 (m, 2H), 4.61 (dd, *J* = 8.4, 6.2 Hz, 1H), 3.52 (dd, *J* = 15.3, 8.4 Hz, 1H), 3.39 (dd, *J* = 15.3, 6.3 Hz, 1H), 2.34 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 173.7 (C), 139.9 (C), 137.5 (C), 137.0 (C), 133.8 (CH), 133.6 (CH), 131.7 (CH), 131.4 (C), 129.7 (CH), 128.3 (CH), 128.3 (CH), 127.5 (CH), 124.4 (CH), 123.0 (C), 122.6 (CH), 89.3 (C), 84.9 (C), 39.9 (CH_2), 35.7 (CH), 21.2 (CH_3); HRMS (ESI) m/z: 386.1208 $[M+H]^+$, $C_{24}H_{20}NO_2S^+$ requires 386.1209.

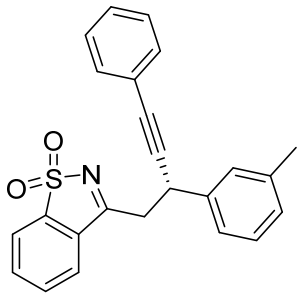
(*S*)-3-(2-(2-Methylphenyl)-4-phenylbut-3-yn-1-yl)benzo[*d*]isothiazole (3ea)



Obtained 17.3 mg (36%). The enantiomeric excess (53%) was determined by HPLC (Chiralpak AD-H), hexane:*i*PrOH 80:20 1 mL/min, major enantiomer: t_r = 11.9 min, minor enantiomer: t_r = 15.2 min.

Oil; $[\alpha]_D^{25}$ –11.6 (*c* 0.9, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.96–7.87 (m, 1H), 7.80–7.59 (m, 4H), 7.32–7.26 (m, 3H), 7.26–7.18 (m, 5H), 4.80 (dd, *J* = 9.2, 5.3 Hz, 1H), 3.51 (dd, *J* = 15.2, 9.2 Hz, 1H), 3.34 (dd, *J* = 15.2, 5.3 Hz, 1H), 2.49 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 173.9 (C), 139.9 (C), 138.2 (C), 135.3 (C), 133.9 (CH), 133.7 (CH), 131.7 (CH), 131.5 (C), 131.1 (CH), 128.3 (CH), 128.3 (CH), 127.8 (CH), 127.6 (CH), 126.9 (CH), 124.5 (CH), 122.9 (C), 122.7 (CH), 89.4 (C), 84.7 (C), 38.3 (CH_2), 32.9 (CH), 19.5 (CH_3); HRMS (ESI) m/z: 386.1213 $[M+H]^+$, $C_{24}H_{20}NO_2S^+$ requires 386.1209.

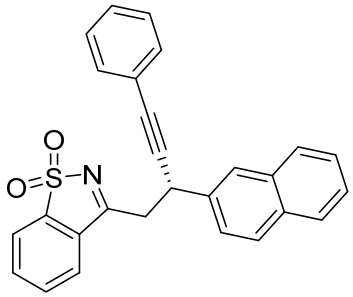
(*S*)-3-(2-(3-Methylphenyl)-4-phenylbut-3-yn-1-yl)benzo[*d*]isothiazole (3fa)



Obtained 16.8 mg (35%). The enantiomeric excess (71%) was determined by HPLC (Chiralcel OD-H), hexane:*i*PrOH 80:20 1 mL/min, major enantiomer: t_r = 20.9 min, minor enantiomer: t_r = 18.0 min.

Oil; $[\alpha]_D^{25}$ –5.1 (*c* 0.5, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.91 (dt, *J* = 7.5, 0.9 Hz, 1H), 7.76–7.58 (m, 3H), 7.36–7.30 (m, 4H), 7.29–7.22 (m, 4H), 7.09 (d, *J* = 7.6 Hz, 1H), 4.60 (dd, *J* = 8.5, 6.2 Hz, 1H), 3.53 (dd, *J* = 15.2, 8.6 Hz, 1H), 3.39 (dd, *J* = 15.2, 6.2 Hz, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 173.7 (C), 140.0 (C), 139.9 (C), 138.9 (C), 133.8 (CH), 133.6 (CH), 131.8 (CH), 131.5 (C), 129.0 (CH), 128.6 (CH), 128.4 (CH), 128.3 (CH), 124.6 (CH), 124.4 (CH), 123.0 (C), 122.7 (CH), 89.1 (C), 85.1 (C), 39.9 (CH_2), 36.1 (CH), 21.6 (CH_3); HRMS (ESI) m/z: 386.1214 $[M+H]^+$, $C_{24}H_{20}NO_2S^+$ requires 386.1209.

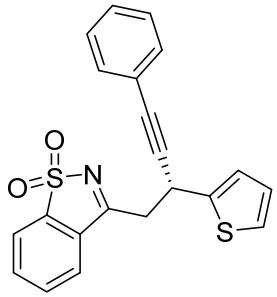
(*S*)-3-(2-(Naphthalen-2-yl)-4-phenylbut-3-yn-1-yl)benzo[*d*]isothiazole 1,1-dioxide (3ga)



Obtained 18.5 mg (35%). The enantiomeric excess (83%) was determined by HPLC (Chiralcel AS-H), hexane:*i*PrOH 80:20 1 mL/min, major enantiomer: t_r = 53.7 min, minor enantiomer: t_r = 60.9 min.

Oil; $[\alpha]_D^{25}$ +1.8 (c 0.5, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.01–7.96 (m, 1H), 7.93–7.78 (m, 4H), 7.74–7.58 (m, 4H), 7.52–7.45 (m, 2H), 7.40–7.33 (m, 2H), 7.28 (q, *J* = 3.1 Hz, 3H), 4.83 (dd, *J* = 8.4, 6.2 Hz, 1H), 3.63 (dd, *J* = 15.5, 8.4 Hz, 1H), 3.49 (dd, *J* = 15.4, 6.2 Hz, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 173.7 (C), 140.0 (C), 137.3 (C), 133.8 (CH), 133.7 (CH), 133.6 (C), 132.9 (CH), 131.8 (CH), 131.4 (C), 129.0 (CH), 128.4 (CH), 128.4 (CH), 128.1 (CH), 127.8 (CH), 126.6 (CH), 126.3 (CH), 125.5 (CH), 124.3 (CH), 122.9 (C), 122.8 (C), 122.7 (CH), 89.0 (C), 85.4 (C), 39.8 (CH_2), 36.2 (CH); HRMS (ESI) m/z: 422.1209 $[M+H]^+$, $C_{27}H_{20}NO_2S^+$ requires 422.1209.

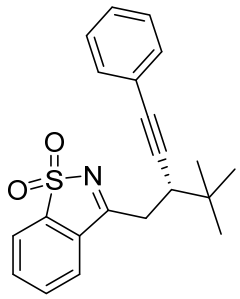
(*R*)-3-(4-Phenyl-2-(thiophen-2-yl)but-3-yn-1-yl)benzo[*d*]isothiazole 1,1-dioxide (3ha)



Obtained 23.1 mg (49%). The enantiomeric excess (70%) was determined by HPLC (Chiralcel OD-H), hexane:*i*PrOH 80:20 1 mL/min, major enantiomer: t_r = 31.9 min, minor enantiomer: t_r = 27.7 min.

Oil; $[\alpha]_D^{25}$ +3.5 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.95–7.89 (m, 1H), 7.80–7.60 (m, 3H), 7.41–7.32 (m, 2H), 7.32–7.25 (m, 3H), 7.25–7.19 (m, 1H), 7.17–7.09 (m, 1H), 6.98–6.90 (m, 1H), 4.97 (dd, *J* = 7.5, 6.5 Hz, 1H), 3.62 (dd, *J* = 15.8, 7.7 Hz, 1H), 3.52 (dd, *J* = 15.8, 6.7 Hz, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 173.2 (C), 143.2 (C), 139.9 (C), 134.0 (CH), 133.8 (CH), 131.8 (CH), 131.3 (C), 128.6 (CH), 128.4 (CH), 127.2 (CH), 125.7 (CH), 125.0 (CH), 124.3 (CH), 122.7 (CH), 122.6 (C), 88.5 (C), 84.6 (C), 40.1 (CH_2), 31.1 (CH); HRMS (ESI) m/z: 395.0880 $[M+NH_4]^+$, $C_{24}H_{19}N_2O_2S_2^+$ requires 395.0882.

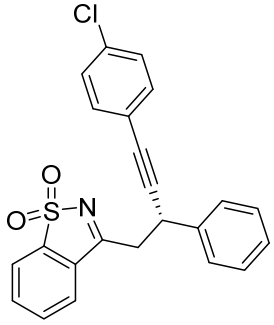
(*S*)-3-(2-(*tert*-Butyl)-4-phenylbut-3-yn-1-yl)benzo[*d*]isothiazole 1,1-dioxide (3ia)



Obtained 37.0 mg (84%). The enantiomeric excess (35%) was determined by HPLC (Chiralcel OD-H), hexane:*i*PrOH 80:20 1 mL/min, major enantiomer: t_r = 14.0 min, minor enantiomer: t_r = 9.0 min.

White solid; mp 90-93 °C; $[\alpha]_D^{25}$ –40.5 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.95–7.88 (m, 1H), 7.81–7.59 (m, 3H), 7.24–7.14 (m, 5H), 3.24–3.06 (m, 3H), 1.18 (s, 9H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 175.8 (C), 140.0 (C), 133.8 (CH), 133.5 (CH), 131.7 (C), 131.6 (CH), 128.2 (CH), 128.0 (CH), 124.6 (CH), 123.2 (C), 122.6 (CH), 89.6 (C), 85.3 (C), 42.2 (CH), 34.4 (C), 32.1 (CH_2), 27.5 (CH_3); HRMS (ESI) m/z: 352.1370 $[M+H]^+$, $C_{21}H_{22}NO_2S^+$ requires 352.1366.

(*S*)-3-(4-(4-Chlorophenyl)-2-phenylbut-3-yn-1-yl)benzo[*d*]isothiazole 1,1-dioxide (3ab)

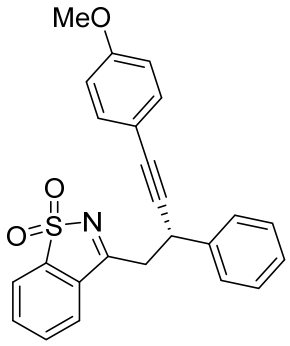


Obtained 21.8 mg (43%). The enantiomeric excess (83%) was determined by HPLC (Chiralcel OD-H), hexane:*i*PrOH 80:20 1 mL/min, major enantiomer: t_r = 26.9 min, minor enantiomer: t_r = 32.7 min.

Brown solid; mp 113-116 °C; $[\alpha]_D^{25}$ –1.9 (*c* 0.8, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.96–7.84 (m, 2H), 7.76–7.56 (m, 5H),

7.54–7.48 (m, 3H), 7.43–7.33 (m, 3H), 7.33–7.20 (m, 5H), 4.64 (dd, *J* = 8.5, 6.1 Hz, 1H), 3.53 (dd, *J* = 15.6, 8.5 Hz, 1H), 3.40 (dd, *J* = 15.5, 6.1 Hz, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 173.5 (C), 139.9 (C), 139.8 (C), 134.4 (C), 133.9 (CH), 133.7 (CH), 133.0 (CH), 131.3 (C), 129.2 (CH), 128.7 (CH), 127.9 (CH), 127.6 (CH), 124.2 (CH), 122.7 (CH), 121.4 (C), 90.0 (C), 84.0 (CH), 39.7 (CH_2), 36.0 (CH); HRMS (ESI) m/z: 406.0662 $[M+H]^+$, $C_{23}H_{17}ClNO_2S^+$ requires 406.0663.

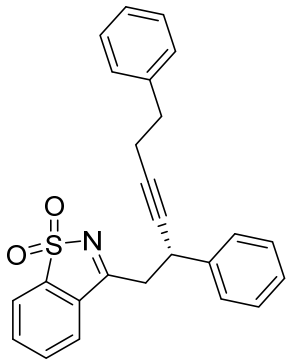
(*S*)-3-(4-(4-Methoxyphenyl)-2-phenylbut-3-yn-1-yl)benzo[*d*]isothiazole 1,1-dioxide (3ac)



Obtained 23.1 mg (46%). The enantiomeric excess (54%) was determined by HPLC (Chiralpak AD-H), hexane:*i*PrOH 80:20 1 mL/min, major enantiomer: t_r = 44.8 min, minor enantiomer: t_r = 28.8 min.

Oil; $[\alpha]_D^{25}$ –3.5 (*c* 0.9, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.94–7.86 (m, 1H), 7.74–7.65 (m, 1H), 7.65–7.58 (m, 2H), 7.56–7.50 (m, 2H), 7.42–7.32 (m, 3H), 7.27 (d, *J* = 9.0 Hz, 2H), 6.78 (d, *J* = 8.9 Hz, 2H), 4.62 (dd, *J* = 8.4, 6.2 Hz, 1H), 3.78 (s, 3H), 3.53 (dd, *J* = 15.2, 8.4 Hz, 1H), 3.39 (dd, *J* = 15.2, 6.2 Hz, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 173.7 (C), 159.6 (C), 140.1 (C), 139.8 (C), 133.7 (CH), 133.5 (CH), 133.1 (CH), 131.3 (C), 129.0 (CH), 127.7 (CH), 127.5 (CH), 124.3 (CH), 122.5 (CH), 114.9 (C), 113.9 (CH), 87.4 (C), 85.0 (C), 55.3 (CH), 39.9 (CH_2), 36.1 (CH_3); HRMS (ESI) m/z: 419.1424 $[M+NH_4]^+$, $C_{24}H_{23}N_2O_3S^+$ requires 419.1424.

(*S*)-3-(2,6-Diphenylhex-3-yn-1-yl)benzo[*d*]isothiazole 1,1-dioxide (3ad)

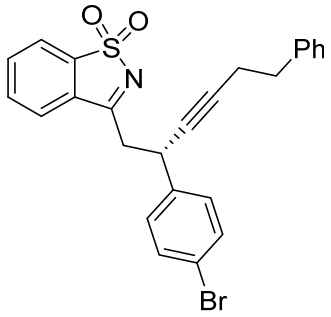


Obtained 34.0 mg (68%). The enantiomeric excess (95%) was determined by HPLC (Chiralcel OD-H), hexane:*i*PrOH 80:20, 1mL/min. Major enantiomer t_r = 29.5 min, minor enantiomer t_r = 24.7 min.

Oil; $[\alpha]_D^{25}$ +6.2 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (300 MHz,$CDCl_3$) δ 7.91–7.87 (m, 1H), 7.74–7.61 (m, 2H), 7.51–7.49 (m, 1H), 7.40–7.04 (m, 10H), 4.36 (ddt, *J* = 8.4, 6.2, 2.3 Hz, 1H), 3.40 (dd, *J* = 15.0, 8.6 Hz, 1H), 3.27 (dd, *J* = 15.0, 8.6 Hz, 1H), 2.74 (t, *J* = 7.4 Hz, 2H), 2.55–2.35 (m, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 173.9 (C), 140.5 (C), 139.9 (C), 133.7 (CH), 133.6 (CH), 131.5 (C), 128.9 (CH), 128.7 (CH), 128.4 (CH), 127.6 (CH), 127.6 (CH), 126.3 (CH), 124.3 (CH), 122.6 (CH), 84.7 (C), 80.5 (C), 40.1 (CH_2), 35.6 (CH),

35.0 (CH_2), 21.0 (CH_2); HRMS (ESI) *m/z*: 400.1363, $[M+H]^+$, $C_{25}H_{22}NO_2S^+$ requires 400.1366.

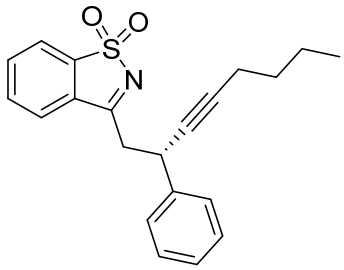
(*S*)-3-(2-(4-Bromophenyl)-6-phenylhex-3-yn-1-yl)benzo[*d*]isothiazole 1,1-dioxide (3bd)



Obtained 21.0 mg (35%). The enantiomeric excess (96%) was determined by HPLC (Chiralcel AD-H), hexane:*i*PrOH 80:20, 1mL/min. Major enantiomer t_r = 18.6 min, minor enantiomer t_r = 21.8 min.

Oil; $[\alpha]_D^{25}$ +4.3 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (300 MHz,$CDCl_3$) δ 7.92–7.90 (m, 1H), 7.73 (td, *J* = 7.4, 1.2 Hz, 1H), 7.66 (td, *J* = 7.5, 1.2 Hz, 1H), 7.53–7.50 (m, 1H), 7.44–7.40 (m, 2H), 7.28–7.15 (m, 7H), 4.34 (ddt, *J* = 8.4, 6.4, 2.2 Hz, 1H), 3.32 (dd, *J* = 15.7, 8.1 Hz, 1H), 3.20 (dd, *J* = 15.7, 8.1 Hz, 1H), 2.74 (t, *J* = 7.4 Hz, 2H), 2.48–2.42 (m, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 173.3 (C), 140.5 (C), 139.7 (C), 139,4 (C), 133.6 (CH), 133.6 (CH), 131.8 (CH), 131.8 (C), 129.2 (CH), 128.5 (CH), 128.3 (CH), 126.2 (CH), 124.0 (CH), 122.6 (CH), 121.3 (C), 84.8 (C), 80.0 (C), 39.7 (CH_2), 34.8 (CH_2), 34.6 (CH), 20.7 (CH_2). HRMS (ESI) *m/z*: 478.0473, $[M+H]^+$, $C_{25}H_{21}BrNO_2S^+$ requires 478.0471.

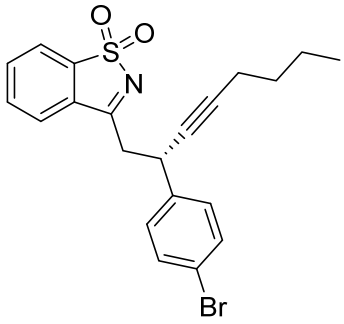
(*S*)-3-(2-Phenyloct-3-yn-1-yl)benzo[*d*]isothiazole 1,1-dioxide (3ae)



Obtained 19.3 mg (44%). The enantiomeric excess (88%) was determined by HPLC (Chiralpak IC), hexane:*i*PrOH 80:20, 1mL/min. Major enantiomer t_r = 26.18 min, minor enantiomer t_r = 22.72 min.

Yellow solid; mp 91-93 ºC; $[\alpha]_D^{25}$ +4.7 (*c* 0.95, $CHCl_3$); **^{1}H NMR** (300 MHz,$CDCl_3$) δ 7.91–7.89 (m, 1H), 7.69 (dtd, *J* = 16.8, 7.3, 1.2 Hz, 2H), 7.60–7.57 (m, 1H), 7.47–7.43 (m, 2H), 7.36–7.30 (m, 2H), 7.27–7.22 (m, 1H), 4.39 (ddt, *J* = 8.5, 6.2, 2.3 Hz, 1H), 3.40 (dd, *J* = 15.0, 8.6 Hz, 1H), 3.27 (dd, *J* = 15.0, 6.2 Hz, 1H), 2.13 (td, *J* = 6.9, 2.2 Hz, 2H), 1.46–1.21 (m, 4H), 0.83 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 173.8 (C), 140.6 (C), 139.8 (C), 133.6 (CH), 133.4 (CH), 131.5 (C), 128.8 (CH), 127.4 (CH), 127.4 (CH), 124.2 (CH), 122.5 (CH), 85.5 (C), 79.4 (C), 40.0 (CH_2), 35.6 (CH), 30.7 (CH_2), 21.9 (CH_2), 18.4 (CH_2), 13.5 (CH_3); HRMS (ESI) *m/z*: 352.1363, $[M+H]^+$, $C_{21}H_{22}NO_2S^+$ requires 352.1366.

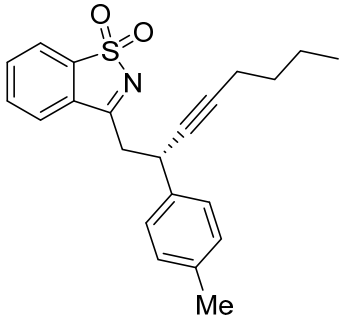
(*S*)-3-(2-(4-Bromophenyl)oct-3-yn-1-yl)benzo[*d*]isothiazole (3be)



Obtained 20.4 mg (38%). The enantiomeric excess (97%) was determined by HPLC (Chiralpak IC), hexane:*i*PrOH 80:20, 1mL/min. Major enantiomer t_r = 26.56 min, minor enantiomer t_r = 24.13 min.

Yellow solid; mp 152-155 ºC; $[\alpha]_D^{25}$ +7.23 (*c* 0.98, $CHCl_3$); **^{1}H NMR** (300 MHz,$CDCl_3$) δ 7.92–7.89 (m, 1H), 7.71 (dtd, *J* = 16.1, 7.4, 1.3 Hz, 2H), 7.60–7.58 (m, 1H), 7.48–7.43 (m, 2H), 7.36–7.31 (m, 2H), 4.37 (ddt, *J* = 8.6, 6.4, 2.3 Hz, 1H), 3.38 (dd, *J* = 15.4, 8.1 Hz, 1H), 3.24 (dd, *J* = 15.4, 6.5 Hz, 1H), 2.13 (td, *J* = 6.9, 2.3 Hz, 2H), 1.43–1.23 (m, 4H), 0.84 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 173.6 (C), 139.9 (C), 139.8 (C), 133.8 (CH), 133.7 (CH), 132.0 (CH), 131.4 (C), 129.4 (C), 124.3 (CH), 122.7 (CH), 121.5 (C), 85.9 (C), 79.1 (C), 39.9 (CH_2), 35.0 (CH), 30.8 (CH_2), 22.0 (CH_2), 18.5 (CH_2), 13.7 (CH_3). HRMS (ESI) *m/z*: 430.0473, $[M+H]^+$, $C_{21}H_{21}BrNO_2S^+$ requires 430.0471.

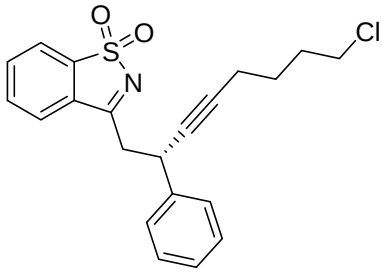
(*S*)-3-(2-(*p*-Tolyl)oct-3-yn-1-yl)benzo[*d*]isothiazole 1,1-dioxide (3de)



Obtained 19.2 mg (42%). The enantiomeric excess (92%) was determined by HPLC (Chiralcel OD-H), hexane:*i*PrOH 80:20, 0.7mL/min. Major enantiomer t_r = 18.32 min, minor enantiomer t_r = 16.35 min.

Yellow solid; mp 131-135 ºC; $[\alpha]_D^{25}$ +1.61 (*c* 0.99, $CHCl_3$); **^{1}H NMR** (300 MHz,$CDCl_3$) δ 7.91–7.88 (m, 1H), 7.69 (dtd, *J* = 16.0, 7.3, 1.3 Hz, 2H), 7.61–7.58 (m, 1H), 7.35–7.32 (m, 2H), 7.15–7.13 (m, 2H), 4.35 (ddt, *J* = 8.5, 6.1, 2.3 Hz, 1H), 3.38 (dd, *J* = 15.0, 8.6 Hz, 1H), 3.25 (dd, *J* = 15.0, 6.2 Hz, 1H), 2.32 (s, 3H), 2.11 (td, *J* = 6.9, 2.2 Hz, 2H), 1.42–1.23 (m, 4H), 0.83 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 174.1 (C), 140.0 (C), 137.8 (C), 137.3 (C), 133.7 (CH), 133.5 (CH), 131.6 (C), 129.6 (CH), 127.4 (CH), 124.4 (CH), 122.6 (CH), 85.4 (C), 79.7 (C), 40.2 (CH_2), 35.4 (CH), 30.8 (CH_2), 22.0 (CH_2), 21.2 (CH_3), 18.5 (CH_2), 13.7 (CH_3). HRMS (ESI) *m/z*: 366.1523, $[M+H]^+$, $C_{22}H_{24}NO_2S^+$ requires 366.1522.

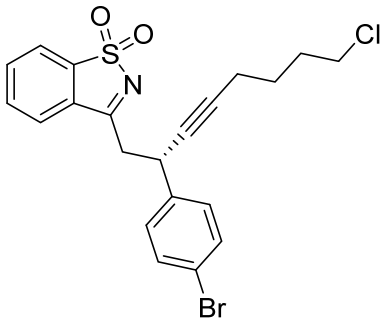
(*S*)-3-(8-Chloro-2-phenyloct-3-yn-1-yl)benzo[*d*]isothiazole 1,1-dioxide (3af)



Obtained 22.3 mg (48%). The enantiomeric excess (96%) was determined by HPLC (Chiralpak IC), hexane:*i*PrOH 80:20, 1mL/min. Major enantiomer t_r = 34.72 min, minor enantiomer t_r = 32.14 min.

Oil; $[\alpha]_D^{25}$ –2.44 (*c* 0.98, $CHCl_3$); **^{1}H NMR** (300 MHz,$CDCl_3$) δ 7.92–7.90 (m, 1H), 7.70 (dtd, *J* = 16.8, 7.4, 1.3 Hz, 2H), 7.60–7.56 (m, 1H), 7.47–7.43 (m, 2H), 7.37–7.31 (m, 2H), 7.29–7.23 (m, 1H) 4.40 (ddt, *J* = 8.4, 5.3, 2.3 Hz, 1H), 3.50 (td, *J* = 6.5, 2.1 Hz, 2H) 3.40 (dd, *J* = 15.3, 8.9 Hz, 1H), 3.27 (dd, *J* = 15.3, 5.9 Hz, 1H), 2.19 (td, *J* = 6.8, 2.2 Hz, 2H), 1.83–1.74 (m, 2H), 1.61–1.51 (m, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 173.8 (C), 140.5 (C), 140.0 (C), 133.8 (CH), 133.7 (CH), 131.5 (C), 129.0 (CH), 127.7 (CH), 127.5 (CH), 124.3 (CH), 122.7 (CH), 84.7 (C), 80.3 (C), 44.8 (CH_2), 40.1 (CH_2), 35.6 (CH), 31.5 (CH_2), 25.8 (CH_2), 18.2 (CH_2); HRMS (ESI), *m/z*: 386.0976, $[M+H]^+$, $C_{21}H_{21}ClNO_2S^+$ requires 386.0976.

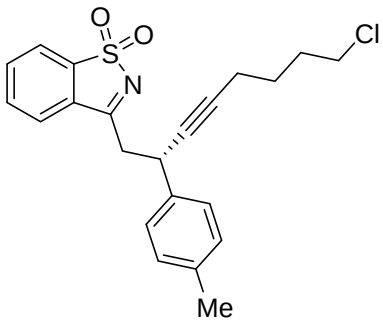
(*S*)-3-(2-(4-Bromophenyl)-8-chlorooct-3-yn-1-yl)benzo[*d*]isothiazole 1,1-dioxide (3bf)



Obtained 20.3 mg (36%). The enantiomeric excess (93%) was determined by HPLC (Chiralpak AD-H), hexane:*i*PrOH 80:20, 1mL/min. Major enantiomer t_r = 21.33 min, minor enantiomer t_r = 17.69 min.

Yellow solid; mp 116-119 ºC; $[\alpha]_D^{25}$ +4.65 (*c* 1.0, CH_3Cl); **^{1}H NMR** (300 MHz,$CDCl_3$) δ 7.93–7.90 (m, 1H), 7.72 (dtd, *J* = 15.9, 7.4, 1.3 Hz, 2H), 7.61–7.57 (m, 1H), 7.49–7.44 (m, 2H), 7.36–7.31 (m, 2H), 4.38 (ddt, *J* = 8.4, 6.0, 2.3 Hz, 1H), 3.49 (td, *J* = 6.5, 1.8 Hz, 2H) 3.39 (dd, *J* = 15.7, 8.5 Hz, 1H), 3.25 (dd, *J* = 15.7, 6.2 Hz, 1H), 2.19 (td, *J* = 6.8, 2.2 Hz, 2H), 1.83–1.73 (m, 2H), 1.61–1.51 (m, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 173.5 (C), 139.9 (C), 139.6 (C), 133.9 (CH), 133.8 (CH), 132.1 (CH), 131.3 (C), 129.3 (CH), 124.2 (CH), 122.8 (CH), 121.6 (C), 84.9 (C), 79.9 (C), 44.7 (CH_2), 39.8 (CH_2), 34.9 (CH), 31.5 (CH_2), 385.8 (CH_2), 18.1 (CH_2); HRMS (ESI), *m/z*: 464.0079, $[M+H]^+$, $C_{21}H_{20}BrClNO_2S^+$ requires 464.0081.

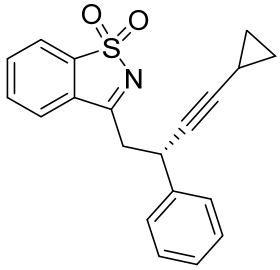
(*S*)-3-(8-Chloro-2-(p-tolyl)oct-3-yn-1-yl)benzo[*d*]isothiazole 1,1-dioxide (3df)



Obtained 28.0 mg (58%). The enantiomeric excess (91%) was determined by HPLC (Chiralpak AS-H), hexane:*i*PrOH 80:20, 1mL/min. Major enantiomer t_r = 32.5 min, minor enantiomer t_r = 29.7 min.

Yellow solid; mp 85-89 ºC; $[\alpha]_D^{25}$ –3.50 (*c* 0.95, CH_3Cl); **^{1}H NMR** (300 MHz,$CDCl_3$) δ 7.92–7.89 (m, 1H), 7.70 (dtd, *J* = 16.0, 7.4, 1.3 Hz, 2H), 7.61–7.58 (m, 1H), 7.35–7.31 (m, 2H), 7.17–7.13 (m, 2H), 4.36 (ddt, *J* = 8.5, 5.5, 2.4 Hz, 1H), 3.49 (td, *J* = 6.5, 2.2 Hz, 2H), 3.38 (dd, *J* = 15.3, 8.9 Hz, 1H), 3.25 (dd, *J* = 15.2, 5.9 Hz, 1H), 2.33 (s, 3H), 2.18 (td, *J* = 6.7, 1.9 Hz, 2H), 1.83–1.73 (m, 2H), 1.60–1.50 (m, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 173.9 (C), 139.9 (C), 137.6 (C), 137.4 (C), 133.8 (CH), 133.6 (CH), 131.5 (C), 129.7 (CH), 127.4 (CH), 124.3 (CH), 122.7 (CH), 84.4 (C), 80.5 (C), 44.8 (CH_2), 40.1 (CH_2), 35.2 (CH), 31.5 (CH_2), 25.8 (CH_2), 21.2 (CH_3), 18.2 (CH_2); HRMS (ESI), *m/z*: 400.1132, $[M+H]^+$, $C_{22}H_{23}ClNO_2S^+$ requires 400.1133.

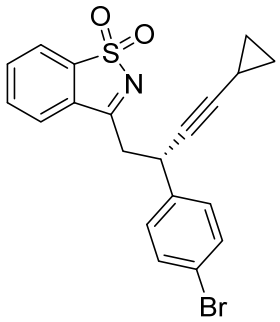
(*S*)-3-(4-Cyclopropyl-2-phenylbut-3-yn-1-yl)benzo[*d*]isothiazole 1,1-dioxide (3ag)



Obtained 25.6 mg (61%). The enantiomeric excess (93%) was determined by HPLC (Chiralpak AS-H), hexane:*i*PrOH 80:20, 1mL/min. Major enantiomer t_r = 28.7 min, minor enantiomer t_r = 34.3 min.

Oil; $[\alpha]_D^{25}$ +6.56 (*c* 0.98, CH_3Cl); **^{1}H NMR** (300 MHz,$CDCl_3$) δ 7.91–7.88 (m, 1H), 7.69 (dtd, *J* = 16.9, 7.4, 1.2 Hz, 2H), 7.59–7.56 (m, 1H), 7.45–7.41 (m, 2H), 7.36–7.29 (m, 2H), 7.27–7.22 (m, 1H), 4.34 (ddd, *J* = 8.3, 6.2, 1.8 Hz, 1H), 3.38 (dd, *J* = 14.9, 8.5 Hz, 1H), 3.26 (dd, *J* = 14.9, 6.3 Hz, 1H), 1.17 (ttd, *J* = 8.2, 5.0, 1.8, 1H), 0.70–0.61 (m, 2H), 0.60–0.47 (m, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 173.9 (C), 140.6 (C), 139.9 (C), 133.7 (CH), 133.6 (CH), 131.5 (C), 128.9 (CH), 127.6 (CH), 127.5 (CH), 124.4 (CH), 122.6 (CH), 88.7 (C), 74.7 (C), 40.1 (CH_2), 35.7 (C), 8.2 (CH_2), 8.2 (CH_2), -0.4 (CH); HRMS (ESI), *m/z*: 336.1055, $[M+H]^+$, $C_{20}H_{18}NO_2S^+$ requires 336.1053.

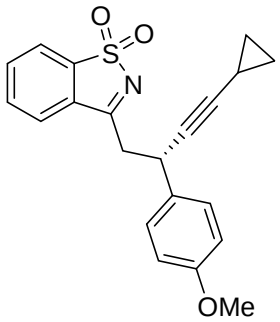
(*S*)-3-(2-(4-bromophenyl)-4-cyclopropylbut-3-yn-1-yl)benzo[*d*]isothiazole 1,1-dioxide (3bg)



Obtained 23.3 mg (45%). The enantiomeric excess (96%) was determined by HPLC (Chiralpak AD-H), hexane:*i*PrOH 80:20, 1mL/min. Major enantiomer t_r = 20.01 min, minor enantiomer t_r = 16.73 min.

Yellow solid; mp 119-121 ºC; $[\alpha]_D^{25}$ +6.28 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (300 MHz,$CDCl_3$) δ 7.92–7.89 (m, 1H), 7.71 (dtd, *J* = 16.1, 7.4, 1.2 Hz, 2H), 7.60–7.57 (m, 1H), 7.47–7.43 (m, 2H), 7.34–7.29 (m, 2H), 4.33 (ddd, *J* = 8.2, 6.5, 1.8 Hz, 1H), 3.36 (dd, *J* = 15.3, 8.2 Hz, 1H), 3.24 (dd, *J* = 15.3, 6.5 Hz, 1H), 1.17 (ttd, *J* = 8.2, 5.0, 1.8, 1H), 0.71–0.67 (m, 2H), 0.59–0.48 (m, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 173.5 (C), 139.9 (C), 139.6 (C), 133.8 (CH), 133.7 (CH), 132.0 (CH), 131.4 (C), 129.4 (CH), 124.3 (CH), 122.7 (CH), 121.5 (C), 89.0 (C), 74.3 (C), 39.8 (CH_2), 35.0 (CH), 8.3 (CH_2), 8.2 (CH_2), –0.4 (CH); HRMS (ESI), *m/z*: 414.0154, $[M+H]^+$, $C_{20}H_{17}BrNO_2S^+$ requires 414.0158.

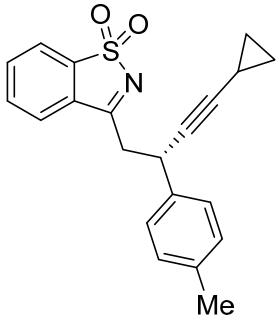
(*S*)-3-(4-Cyclopropyl-2-(4-methoxyphenyl)but-3-yn-1-yl)benzo[*d*]isothiazole 1,1-dioxide (3cg)



Obtained 31.5 mg (69%). The enantiomeric excess (92%) was determined by HPLC (Chiralpak AD-H), hexane:*i*PrOH 80:20, 1mL/min. Major enantiomer t_r = 21.98 min, minor enantiomer t_r = 19.32 min.

Yellow solid; mp 112-115 ºC; $[\alpha]_D^{25}$ +7.46 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (300 MHz,$CDCl_3$) δ 7.91–7.88 (m, 1H), 7.69 (dtd, *J* = 16.0, 7.4, 1.3 Hz, 2H), 7.59–7.56 (m, 1H), 7.37–7.32 (m, 2H), 6.87–6.82 (m, 2H), 4.30 (ddd, *J* = 8.2, 6.4, 1.8 Hz, 1H), 3.78 (s, 3H), 3.35 (dd, *J* = 14.9, 8.3 Hz, 1H), 3.24 (dd, *J* = 14.9, 6.5 Hz, 1H), 1.16 (ttd, *J* = 8.2, 5.0, 1.8, 1H), 0.69–0.62 (m, 2H), 0.59–0.46 (m, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 174.0 (C), 159.1 (C), 139.9 (C), 133.7 (CH), 133.5 (CH), 132.7 (C), 131.6 (C), 128.6 (CH), 124.5 (CH), 122.6 (CH), 114.3 (CH), 88.5 (C), 75.1 (C), 55.5 (CH_3), 40.3 (CH_2), 35.0 (CH), 8.2 (CH_2), 8.2 (CH_2), -0.4 (CH); HRMS (ESI), *m/z*: 366.1159, $[M+H]^+$, $C_{21}H_{20}NO_3S^+$ requires 366.1158.

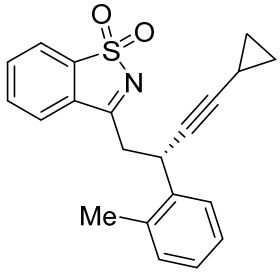
(*S*)-3-(4-Cyclopropyl-2-(p-tolyl)but-3-yn-1-yl)benzo[*d*]isothiazole 1,1-dioxide (3dg)



Obtained 31.0 mg (69%). The enantiomeric excess (93%) was determined by HPLC (Chiralcel OD-H), hexane:*i*PrOH 80:20, 1mL/min. Major enantiomer t_r = 16.5 min, minor enantiomer t_r = 14.4 min.

Yellow solid; mp 104-107 ºC; $[\alpha]_D^{25}$ +1.32 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (300 MHz,$CDCl_3$) δ 7.92–7.89 (m, 1H), 7.69 (dtd, *J* = 16.2, 7.3, 1.3 Hz, 2H), 7.60–7.57 (m, 1H), 7.34–7.30 (m, 2H), 7.15–7.12 (m, 2H), 4.30 (ddd, *J* = 8.3, 6.2, 1.7 Hz, 1H), 3.35 (dd, *J* = 14.9, 8.5 Hz, 1H), 3.24 (dd, *J* = 14.9, 6.3 Hz, 1H), 2.32 (s, 3H), 1.17 (ttd, *J* = 8.2, 5.0, 1.8, 1H), 0.70–0.61 (m, 2H), 0.58–0.45 (m, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 174.0 (C), 139.9 (C), 137.6 (C), 137.3 (C), 133.7 (CH), 133.5 (CH), 131.6 (C), 129.6 (CH), 127.4 (CH), 124.5 (CH), 122.6 (CH), 88.5 (C), 74.9 (C), 40.2 (CH_2), 35.4 (CH), 21.2 (CH_3), 8.2 (CH_2), 8.2 (CH_2), -0.4 (CH); HRMS (ESI), *m/z*: 350.1212, $[M+H]^+$, $C_{21}H_{20}NO_2S^+$ requires 350.1209.

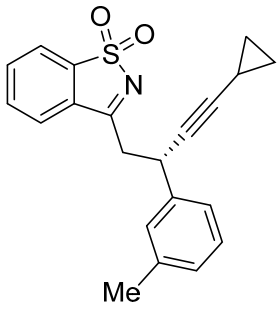
(*S*)-3-(4-Cyclopropyl-2-(*o*-tolyl)but-3-yn-1-yl)benzo[–]isothiazole 1,1-dioxide (3eg)



Obtained 24.0 mg (55%). The enantiomeric excess (85%) was determined by HPLC (Chiralpak AD-H), hexane:*i*PrOH 80:20, 1mL/min. Major enantiomer t_r = 10.50 min, minor enantiomer t_r = 9.93 min.

Yellow solid; mp 143-146 ºC; $[\alpha]_D^{25}$ –17.8 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (300 MHz,$CDCl_3$) δ 7.93–7.90 (m, 1H), 7.71 (dtd, *J* = 14.2, 7.3, 1.4 Hz, 2H), 7.65–7.61 (m, 1H), 7.59–7.56 (m, 1H), 7.25–7.14 (m, 3H), 4.50 (ddd, *J* = 9.3, 5.3, 1.8 Hz, 1H), 3.34 (dd, *J* = 14.7, 9.3 Hz, 1H), 3.19 (dd, *J* = 14.7, 5.3 Hz, 1H), 2.42 (s, 3H), 1.13 (ttd, *J* = 8.2, 5.0, 1.8, 1H), 0.67–0.58 (m, 2H), 0.56–0.42 (m, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 174.1 (C), 140.0 (C), 138.8 (C), 135.1 (C), 133.7 (CH), 133.6 (CH), 131.6 (C), 131.0 (CH), 127.6 (CH), 127.5 (CH), 126.8 (CH), 124.6 (CH), 122.6 (CH), 88.2 (C), 75.0 (C), 38.6 (CH_2), 32.5 (CH), 19.4 (CH_3), 8.2 (CH_2), 8.1(CH_2), -0.4 (CH); HRMS (ESI), *m/z*: 350.1212, $[M+H]^+$, $C_{21}H_{20}NO_2S^+$ requires 350.1209.

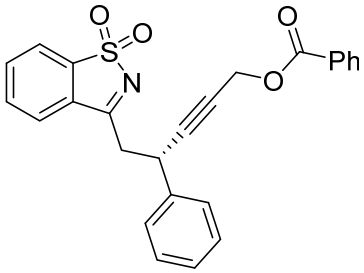
(*S*)-3-(4-Cyclopropyl-2-(*m*-tolyl)but-3-yn-1-yl)benzo[*d*]isothiazole 1,1-dioxide (3fg)



Obtained 28.0 mg (64%). The enantiomeric excess (82%) was determined by HPLC (Chiralpak AY-H), hexane:*i*PrOH 80:20, 1mL/min. Major enantiomer t_r = 46.0 min, minor enantiomer t_r = 43.8 min.

Oil; $[\alpha]_D^{25}$ +11.2 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (300 MHz,$CDCl_3$) δ 7.91–7.89 (m, 1H), 7.69 (dtd, *J* = 21.7, 7.4, 1.1 Hz, 2H), 7.60–7.57 (m, 1H), 7.23–7.21 (m, 3H), 7.07–7.04 (m, 1H), 4.29 (ddd, *J* = 8.5, 6.2, 1.8 Hz, 1H), 3.36 (dd, *J* = 14.8, 8.8 Hz, 1H), 3.25 (dd, *J* = 14.8, 6.1 Hz, 1H), 2.32 (s, 3H), 1.17 (ttd, *J* = 8.3, 5.0, 1.8, 1H), 0.69–0.64 (m, 2H), 0.58–0.47 (m, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 174.0 (C), 140.5 (C), 139.9 (C), 138.7 (C), 133.7 (CH), 133.5 (CH), 131.6 (C), 128.9 (CH), 128.4 (CH), 128.3 (CH), 124.5 (CH), 124.4 (CH), 122.6 (CH), 88.7 (C), 74.8 (C), 40.1 (CH_2), 35.8 (CH), 21.5 (CH_3), 8.2 (CH_2), 8.2 (CH_2), -0.4 (CH); HRMS (ESI), *m/z*: 350.1211, $[M+H]^+$, $C_{21}H_{20}NO_2S^+$ requires 350.1209.

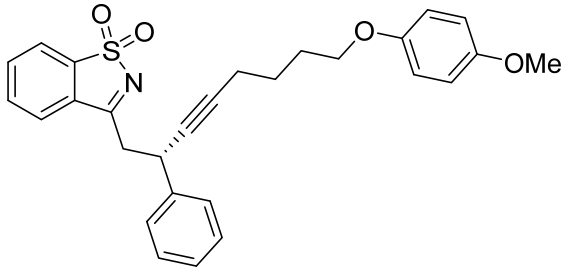
(*S*)-5-(1,1-Dioxidobenzo[d]isothiazol-3-yl)-4-phenylpent-2-yn-1-yl benzoate (3ah)



Obtained 34.0 mg (63%). The enantiomeric excess (93%) was determined by HPLC (Chiralpak IC), hexane:*i*PrOH 70:30, 1mL/min. Major enantiomer t_r = 56.5 min, minor enantiomer t_r = 46.8 min.

Oil; $[\alpha]_D^{25}$ +15.6 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (300 MHz,$CDCl_3$) δ 8.04–8.02 (m, 2H), 7.86–7.83 (m, 1H), 7.66–7.55 (m, 4H), 7.47–7.41 (m, 4H), 7.36–7.23 (m, 3H), 4.90 (dd, *J* = 2.1, 1.5 Hz, 2H), 4.53–4.47 (m, 1H), 3.49 (dd, *J* = 15.7, 8.2 Hz, 1H), 3.33 (dd, *J* = 15.7, 6.4 Hz, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 173.5 (C), 166.0 (C), 139.8 (C), 139.4 (C), 133.9 (CH), 133.7 (CH), 133.4 (CH), 131.3 (C), 130.0 (CH), 129.7 (C), 129.1 (CH), 128.5 (CH), 127.9 (CH), 127.6 (CH), 124.2 (CH), 122.6 (CH), 86.8 (C), 78.8 (C), 53.0 (CH_2), 39.5 (CH_2), 35.3 (CH); HRMS (ESI), *m/z*: 430.1104, $[M+H]^+$, $C_{25}H_{20}NO_4S^+$ requires 4301108.

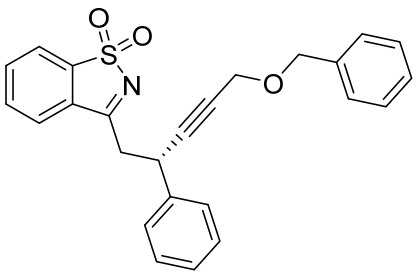
(*S*)-3-(8-(4-Methoxyphenoxy)-2-phenyloct-3-yn-1-yl)benzo[*d*]isothiazole 1,1-dioxide (3ai)



Obtained 39.3 mg (66%); the conjugate ethylation product **6** (12.3 mg, 33%). The enantiomeric excess (99%) was determined by HPLC (Chiralpak OD-H), hexane:*i*PrOH 80:20, 1mL/min. Major enantiomer t_r = 38.7 min, minor enantiomer t_r = 48.1 min.

Oil; $[\alpha]_D^{25}$ +10.3 (*c* 0.96, $CHCl_3$); **^{1}H NMR** (300 MHz,$CDCl_3$) δ 7.89–7.86 (m, 1H), 7.68–7.64 (m, 2H), 7.58–7.56 (m, 1H), 7.47–7.44 (m, 2H), 7.36–7.31 (m, 2H), 7.28–7.22 (m, 1H), 6.81 (s, 4H), 4.40–4.37 (m, 1H) 3.86 (td, *J* = 6.3, 2.2 Hz, 2H), 3.76 (s, 3H), 3.39 (dd, *J* = 15.1, 8.7 Hz, 1H), 3.27 (dd, *J* = 15.1, 6.1 Hz, 1H), 2.21 (td, *J* = 7.1, 2.3 Hz, 2H), 1.79–1.71 (m, 2H), 1.63–1.55 (m, 4H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 173.1 (C), 153.8 (C), 153.3 (C), 140.6 (C), 139.9 (C), 133.8 (CH), 133.6 (CH), 131.5 (C), 129.9 (CH), 127.7 (CH), 127.5 (CH), 124.4 (CH), 122.6 (CH), 115.5 (CH), 114.8 (CH), 85.1 (C), 80.0 (C), 68.0 (CH_2), 55.9 (CH_3), 40.1 (CH_2), 35.7 (CH), 28.5 (CH_2), 25.3 (CH_2), 18.6 (CH_2); HRMS (ESI), *m/z*: 474.1732, $[M+H]^+$, $C_{28}H_{28}NO_4S^+$ requires 474.1734.

(*S*)-3-(5-(Benzyloxy)-2-phenylpent-3-yn-1-yl)benzo[d]isothiazole 1,1-dioxide (3aj)

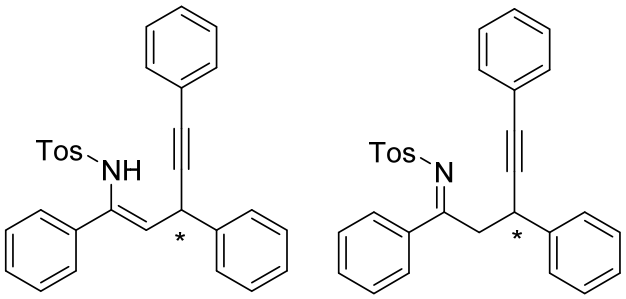


Obtained 30.7 mg (59%); the conjugate ethylation product **6** (5.3 mg, 14%). The enantiomeric excess (80%) was determined by HPLC (Chiralpak AD-H), hexane:*i*PrOH 80:20, 1mL/min. Major enantiomer t_r = 45.4 min, minor enantiomer t_r = 26.9 min.

Oil; $[\alpha]_D^{25}$ +3.8 (*c* 0.65, $CHCl_3$); **^{1}H NMR** (300 MHz,$CDCl_3$) δ 7.89–7.86 (m, 1H), 7.72–7.61 (m, 2H), 7.58–7.55 (m, 1H), 7.49–7.45 (m, 2H), 7.37–7.27 (m, 8H), 4.52 (d, *J* = 1.9 Hz, 2H), 4.17 (d, *J* = 2.0 Hz, 2H), 3.48 (dd, *J* = 15.9, 8.5 Hz, 1H), 3.32 (dd, *J* = 15.8, 6.1 Hz, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 173.5 (C), 139.9 (C), 139.8 (C), 137.6 (C), 133.9 (CH), 133.7 (CH), 131.3 (C), 129.1 (CH), 128.5 (CH), 128.2 (CH), 127.90 (CH), 127.85 (CH), 127.6 (CH), 124.2 (CH), 122.7 (CH), 86.3 (C), 80.7 (C), 71.6 (CH_2),

57.6 (CH_3), 39.7 (CH_2), 35.3 (CH); HRMS (ESI), *m/z*: 416.1312, $[M+H]^+$, $C_{25}H_{22}NO_3S^+$ requires 416.1315.

4-Methyl-*N*-(1,3,5-triphenylpent-1-en-4-yn-1-yl)benzenesulfonamide (3ja) and 4-Methyl-*N*-(1,3,5-triphenylpent-4-yn-1-ylidene)benzenesulfonamide (3ja')



3ja **3ja'**

Obtained 24.5 mg (43%) as a mixture enamine **3ja**/imine **3ja'** (72/28).

Enamine **3ja**: The enantiomeric excess of enamine **3ja** (73%) was determined by HPLC (Chiralpak AD-H), hexane:*i*PrOH 90:10 1 mL/min, major enantiomer: t_r = 14.2 min, minor enantiomer: t_r = 17.5 min.

Brown solid; mp 45-50 °C; $[\alpha]_D^{25}$ +7.6 (*c* 1.0, $CHCl_3$, 73% *ee*); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.3 Hz, 2H), 7.43–7.37 (m, 2H), 7.37–7.31 (m, 3H), 7.25–7.07 (m, 5H), 6.80 (s, 1H), 5.51 (dd, *J* = 8.1, 0.8 Hz, 1H), 4.35 (d, *J* = 8.1 Hz, 1H), 2.30 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 143.93 (C), 139.57 (C), 136.89 (C), 136.76 (C), 135.73 (C), 131.82 (CH), 129.66 (CH), 128.80 (CH), 128.42 (CH), 128.38 (CH), 128.08 (CH), 127.55 (CH), 127.47 (CH), 127.45 (CH), 127.36 (CH), 127.32 (CH), 124.19 (CH), 122.8 (C), 87.55 (C), 84.83 (C), 35.67 (CH), 21.56 (CH_3).

Imine **3ja':** The enantiomeric excess of imine **3ja'** (75%) was determined by HPLC (Chiralpak AD-H), hexane:*i*PrOH 90:10 1 mL/min, major enantiomer: t_r = 28.3 min, minor enantiomer: t_r = 22.9 min.

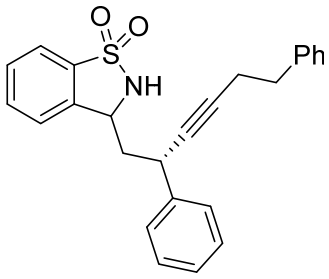
Oil; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.1 Hz, 4H), 7.61 (bd, *J* = 7.4 Hz, 2H), 7.55–7.47 (m, 1H), 7.43–7.29 (m, 7H), 7.23–7.16 (m, 3H), 7.08 (bd, *J* = 6.5 Hz, 2H), 4.75 (s, 1H), 3.96 (s, 1H), 3.82 (s, 1H), 2.44 (s, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 180.53 (C), 143.65 (C), 140.50 (C), 138.49 (C), 137.70 (C), 132.88 (CH), 131.54 (CH), 129.53 (CH), 129.14 (CH), 128.82 (CH), 128.51 (CH), 128.02 (CH), 127.96 (CH), 127.60 (CH), 127.44 (CH), 127.29 (CH), 123.04 (C), 89.15 (C), 85.86 (C), 41.38 (CH2), 37.32 (CH), 21.64 (CH_3).

Synthesis of compound 3ad at 1 mmol scale

Ligand **L6** (90 mg, 0.126 mmol) was introduced in a round bottom flask and purged with nitrogen. Dry toluene (5 mL), alkyne **2e** (6.3 mmol) and a 1.5 M solution of diethyzinc in toluene (1.7 mL, 2.52 mmol) were added in this order. The mixture was introduced in a bath at 70 ºC for 2 hours and allowed to reach room temperature. Imine **1a** (1.26 mmol) in dry toluene (10 mL) was injected ant the reaction mixture stirred until completion (TLC). After this time, the reaction was quenched with 20% aqueous NH_4Cl (5 mL), diluted in CH_2Cl_2 (100 mL), washed with brine (100 mL), dried over $MgSO_4$. After filtration and concentration under reduced pressure, column chromatography eluting with toluene:Et_2O (9:1) afforded compound **3ad** (280 mg, 56%, 88% *ee*).

Synthetic transformations of compound 3ad

3-((*S*)-2,6-Diphenylhex-3-yn-1-yl)-2,3-dihydrobenzo[d]isothiazole 1,1-dioxide (**4**)



$NaBH_4$ (8 mg, 0.2 mmol) was added to a solution of compound **3ad** (20 mg, 0.05 mmol) in THF (1 mL) at room temperature under nitrogen atmosphere. After 1 h, the reaction was quenched with 1M HCl and extracted with CH_2Cl_2, the organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography gave amine **4** (16 mg, 80%) as a 69:31 diastereomer mixture.

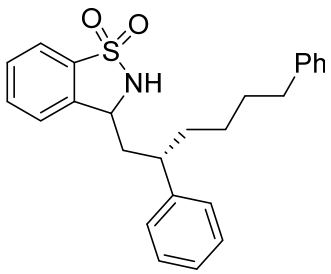
Major diastereomer: The enantiomeric excess (95%) was determined by HPLC (Lux Cellulose 4), hexane:iPrOH 80:20, 1 mL/min. Major enantiomer t_r = 36.5 min, minor enantiomer t_r = 24.1 min.

Oil; $[\alpha]_D^{25}$ +11.1 (*c* 0.7, $CHCl_3$); **^{1}H NMR** (300 MHz,$CDCl_3$) δ 7.78–7.75 (m, 1H), 7.59 (td, *J* = 7.5, 1.3 Hz, 1H), 7.52 (td, *J* = 7.4, 1.2 Hz, 1H), 7.35–7.19 (m, 11H), 4.80 (d, *J* = 4.6 Hz, 1H), 4.55 (dt, *J* = 9.4, 4.6 Hz, 1H), 3.90–3.85 (m, 1H), 2.86 (t, *J* = 7.3 Hz, 2H), 2.59 (td, *J* = 7.3, 2.2 Hz, 2H), 2.26–2.18 (m, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 140.69 (C), 140.68 (C), 140.2 (C), 135.6 (C), 133.1 (CH), 129.5 (CH), 129.1 (2CH), 128.7 (2CH), 128.6 (2CH), 127.5 (2CH), 126.4 (CH), 124.6 (CH), 121.6 (CH), 84.9 (C), 81.5 (C), 56.3 (CH), 44.8 (CH_2), 35.8 (CH), 35.1 (CH_2), 20.9 (CH_2); HRMS (ESI), *m/z*: 402.1530, $[M+H]^+$, $C_{25}H_{24}NO_2S^+$ requires 402.1522.

Minor diastereomer: The enantiomeric excess (92%) was determined by HPLC (Chiralcel OD-H), hexane:iPrOH 80:20, 1mL/min. Major enantiomer t_r = 13.1 min, minor enantiomer t_r = 27.6 min

Oil; $[\alpha]_D^{25}$ −11.7 (*c* 0.3, $CHCl_3$); **^{1}H NMR** (300 MHz,$CDCl_3$) δ 7.78–7.75 (m, 1H), 7.58 (td, *J* = 7.5, 1.3 Hz, 1H), 7.53–7.48 (m, 1H), 7.32–7.15 (m, 11H), 4.77 (d, *J* = 6.0 Hz, 1H), 4.69–4.64 (m, 1H), 3.95–3.90 (m, 1H), 2.89 (t, *J* = 6.9 Hz, 2H), 2.66 (td, *J* = 7.0, 2.1 Hz, 2H), 2.03–1.97 (m, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 141.0 (C), 140.8 (C), 140.6 (C), 136.7 (C), 133.1 (CH), 129.4 (CH), 128.8 (2CH), 128.7 (2CH), 128.6 (2CH), 127.4 (2CH), 127.2 (CH), 126.6 (CH), 124.3 (CH), 121.5 (CH), 85.3 (C), 80.8 (C), 56.5 (CH), 45.0 (CH_2), 35.6 (CH), 35.0 (CH_2), 20.7 (CH_2); HRMS (ESI), *m/z*: 402.1530, $[M+H]^+$, $C_{25}H_{24}NO_2S^+$ requires 402.1522.

3-((*S*)-2,6-Diphenylhexyl)-2,3-dihydrobenzo[d]isothiazole 1,1-dioxide (**5**)



A solution of **3ad** (20 mg, 0.05 mmol) in MeOH (1 mL) was stirred under hydrogen atmosphere in the presence of 10% Pd/C for 30 min. Then, the reaction mixture was filtered through celite® eluting with EtOAc and the solvent was removed under reduced pressure. Purification by flash chromatography gave compound **5** (15.3 mg, 75%) as a 74:26 diastereomeric mixture.

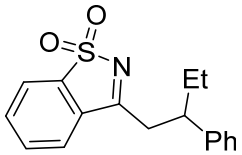
Major diastereomer: The enantiomeric excess (94%) was determined by HPLC (Lux Cellulose 4), hexane:iPrOH 80:20, 1mL/min. Major enantiomer t_r = 21.4 min, minor enantiomer t_r = 25.7 min

Oil; $[\alpha]_D^{25}$ −26.7 (*c* 0.8, $CHCl_3$); **^{1}H NMR** (300 MHz,$CDCl_3$) δ 7.74–7.71 (m, 1H), 7.54 (td, *J* = 7.5, 1.4 Hz, 1H), 7.47 (t, *J* = 7.1 Hz, 1H), 7.33–7.10 (m, 11H), 4.67–4.61 (m, 1H), 4.23 (d, *J* = 4.2 Hz, 1H), 2.88–2.78 (m, 1H), 2.56–2.50 (m, 2H), 2.29 (ddd, *J* = 14.4, 5.7, 4.2 Hz, 1H), 2.10 (dt, *J* = 14.6, 9.0 Hz, 1H), 1.74–1.54 (m, 4H), 1.29–1.18 (m, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 144.0 (C), 142.6 (C), 140.4 (C), 135.4 (C), 133.0 (CH), 129.4 (CH), 129.1 (2CH), 128.5 (2CH), 128.4 (2CH), 127.8 (2CH), 127.1 (CH), 125.8 (CH), 124.4 (CH), 121.5 (CH), 57.1 (CH), 44.0 (CH), 43.6 (CH_2), 36.6 (CH_2), 35.9 (CH_2), 31.5 (CH_2), 27.0 (CH_2); HRMS (ESI), *m/z*: 406.1841, $[M+H]^+$, $C_{25}H_{28}NO_2S^+$ requires 406.1835.

Minor diastereomer: The enantiomeric excess (84%) was determined by HPLC (Lux Cellulose 4), hexane:iPrOH 80:20, 1mL/min. Major enantiomer t_r = 17.8 min, minor enantiomer t_r = 14.7 min.

Oil; $[\alpha]_D^{25}$ +41.3 (*c* 0.3, $CHCl_3$); **^{1}H NMR** (300 MHz,$CDCl_3$) δ 7.75–7.72 (m, 1H), 7.57 (td, *J* = 7.5, 1.3 Hz, 1H), 7.51–7.46 (m, 1H), 7.40–7.34 (m, 2H), 7.29–7.22 (m, 6H), 7.18–7.09 (m, 3H), 4.55 (d, *J* = 6.0 Hz, 1H), 4.22 (ddd, *J* = 11.1, 5.9, 3.0 Hz, 1H), 2.94–2.84 (m, 1H), 2.55–2.49 (m, 2H), 2.15–2.02 (m, 2H), 1.69–1.53 (m, 4H), 1.28–1.23 (m, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 143.5 (C), 142.7 (C), 141.3 (C), 135.7 (C), 133.2 (CH), 129.3 (CH), 129.2 (2CH), 128.5 (2CH), 128.4 (2CH), 127.8 (2CH), 127.1 (CH), 125.8 (CH), 124.2 (CH), 121.5 (CH), 56.1 (CH), 43.6 (CH), 43.5 (CH_2), 37.3 (CH_2), 35.9 (CH_2), 31.5 (CH_2), 27.3 (CH_2); HRMS (ESI), *m/z*: 406.1841, $[M+H]^+$, $C_{25}H_{28}NO_2S^+$ requires 406.1835.

3-(2-Phenylbutyl)benzo[d]isothiazole 1,1-dioxide (6)



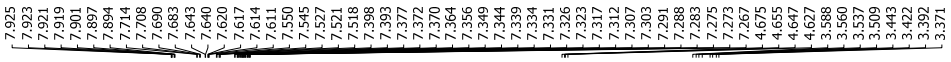
^{1}H NMR (300 MHz,$CDCl_3$) δ 7.88–7.84 (m, 1H), 7.68 (td, *J* = 7.4, 1.2 Hz, 1H), 7.61 (td, *J* = 7.5, 1.3 Hz, 1H), 7.49–7.46 (m, 1H), 7.31–7.25 (m, 2H), 7.23–7.15 (m, 3H), 3.27–3.16 (m, 3H), 1.98–1.91 (m,1H), 1.82–1.72 (m, 1H), 0.84 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 175.4 (C), 143.3 (C), 139.8 (C), 133.8 (CH), 133.5 (CH), 131.6 (C), 128.8 (CH), 127.7 (CH), 127.0 (CH), 124.1 (CH), 122.5 (CH), 45.1 (CH_2), 38.5 (CH), 28.8 (CH_3), 12.2 (CH_2); HRMS (ESI), *m/z*: 300.1050, $[M+H]^+$, $C_{17}H_{18}NO_2S^+$ requires 300.1053.

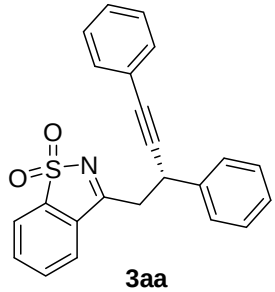
References

1. G. Blay, M. C. Muñoz, J. R. Pedro and A. Sanz-Marco, *Adv. Synth. Catal.,* 2013, **355**, 1071.

2. M. Rommel, T. Fukuzumi and J. Bode, *J. Am. Chem. Soc*., 2008, **130**, 17266.

3. (*a*) C. M. Young, D. G. Stark, T. H. West, J. E. Taylor and A. D. Smith, *Angew. Chem. Int. Ed.,* 2016, **55**, 14394; (*b*) X. Feng, Z. Zhou, C. Ma, X. Yin, R. Li, L. Dong and Y.-C. Chen, *Angew. Chem. Int. Ed.,* 2013, **52**, 14173; (*c*) E. Li, H. Jin, P. Jia, X. Dong and Y. Huang, *Angew. Chem. Int. Ed.,* 2016, **55**, 11591; (*d*) Q. An, J. Shen, N. Butt, D. Liu, Y. Liu and W. Zhang, *Adv. Synth. Catal.,* 2015, **357**, 3627.

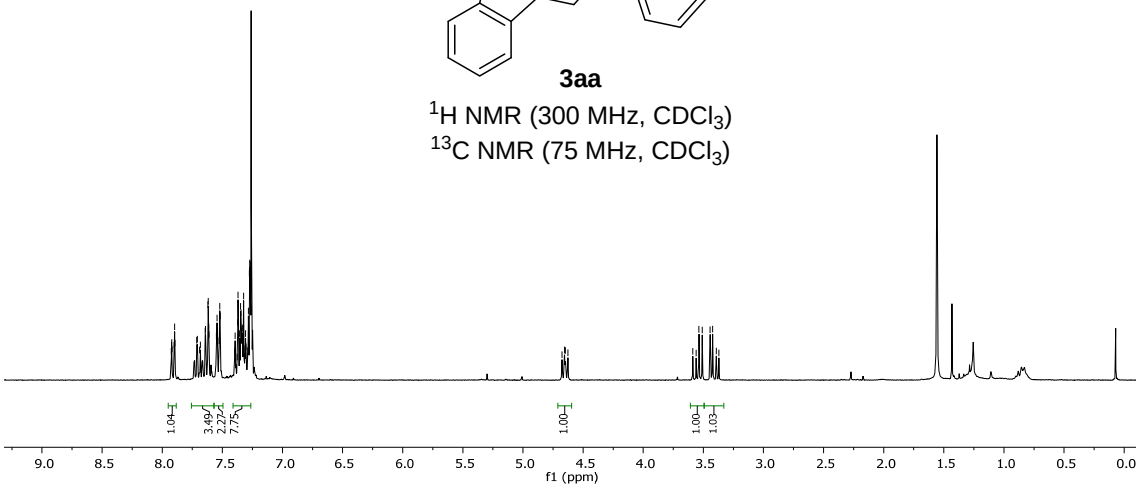


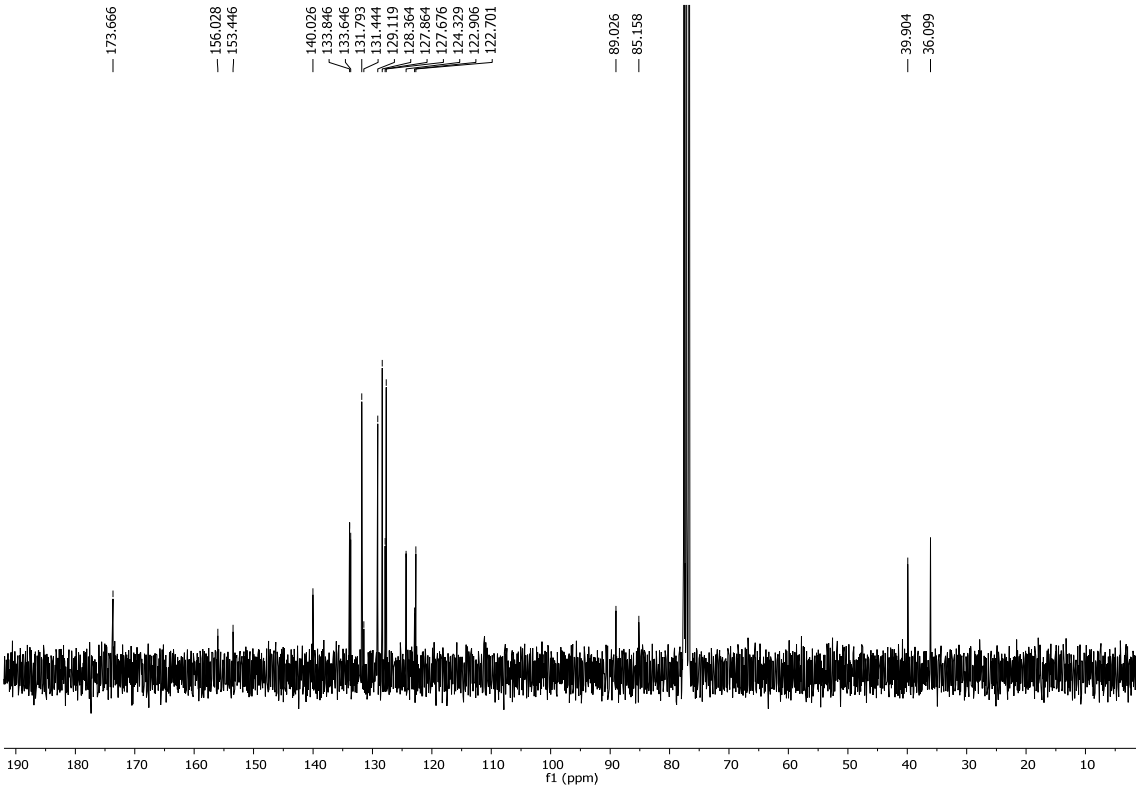


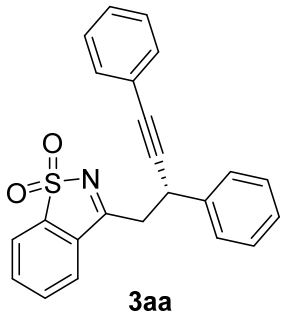
3aa

^{1}H NMR (300 MHz, $CDCl_3$)

^{13}C NMR (75 MHz, $CDCl_3$)

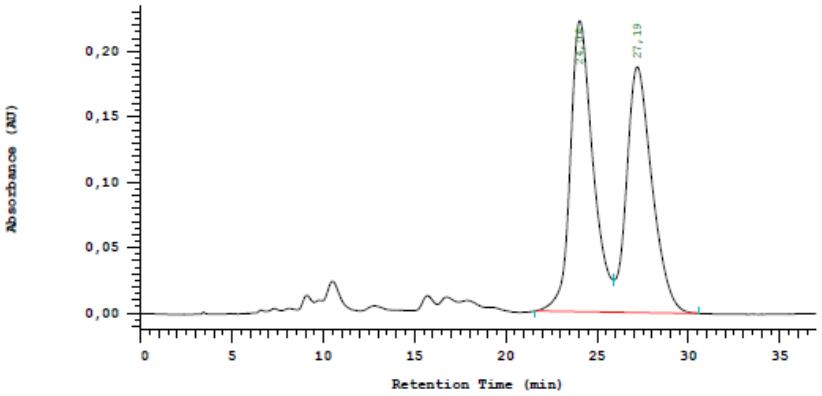






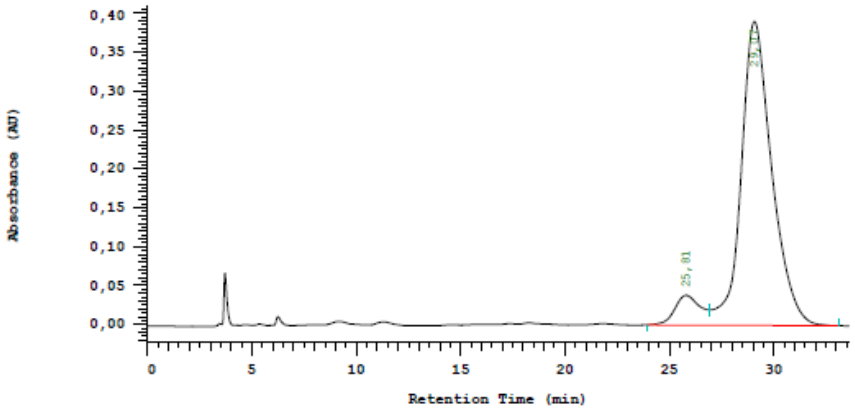
3aa

Racemic or near racemic mixture:

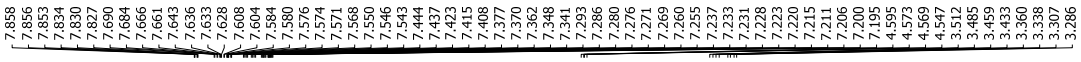


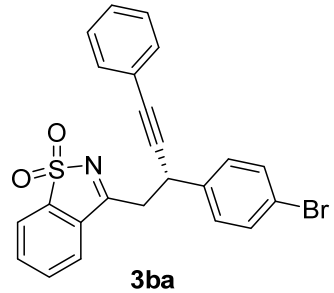
No.	RT	Area	Area %	Name
1	24,04	9629085	51,439	
2	27,19	9090504	48,561	
		18719589	100,000	

Enantioselective reaction:



No.	RT	Area	Area %	Name
1	25,81	1643736	7,628	
2	29,07	19905358	92,372	
		21549094	100,000	

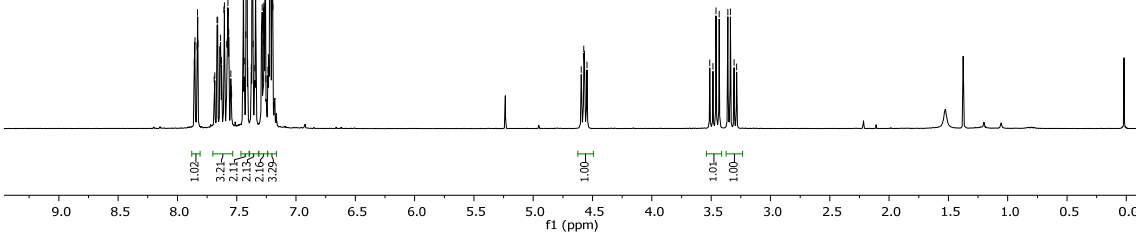


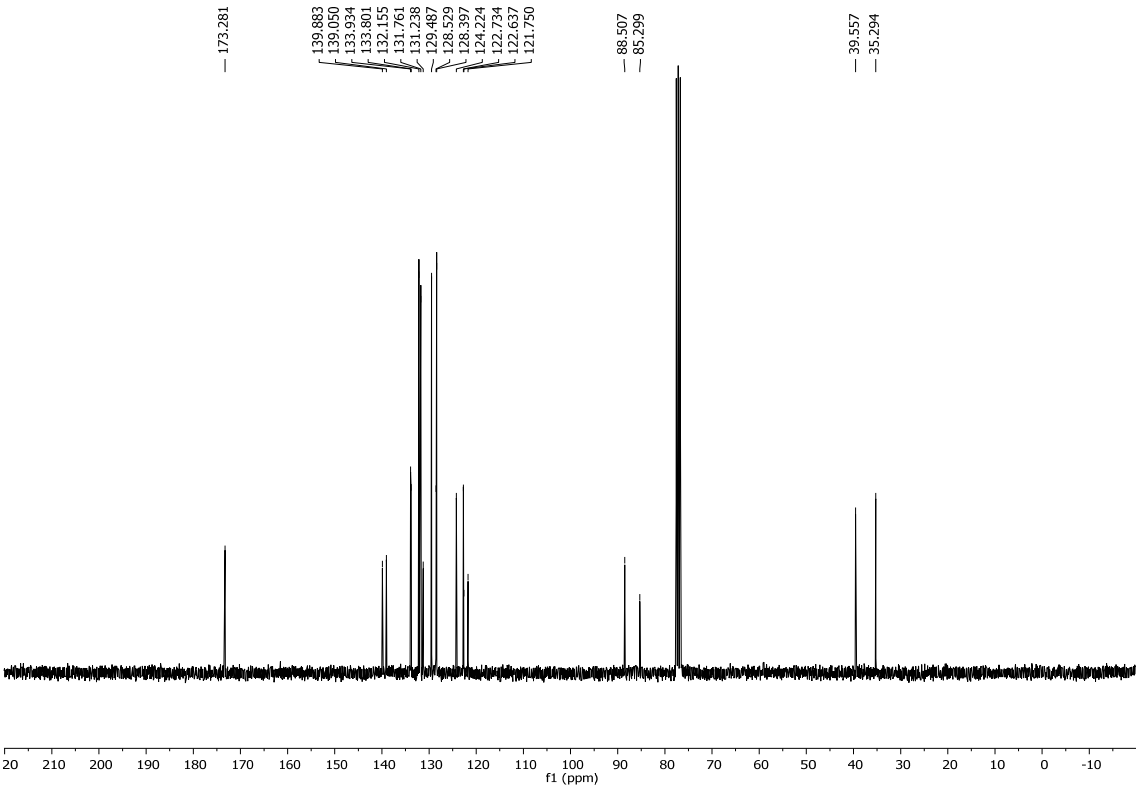


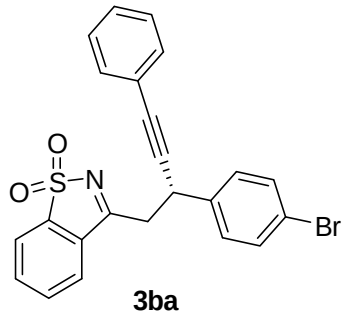
3ba

^{1}H NMR (300 MHz, $CDCl_3$)

^{13}C NMR (75 MHz, $CDCl_3$)

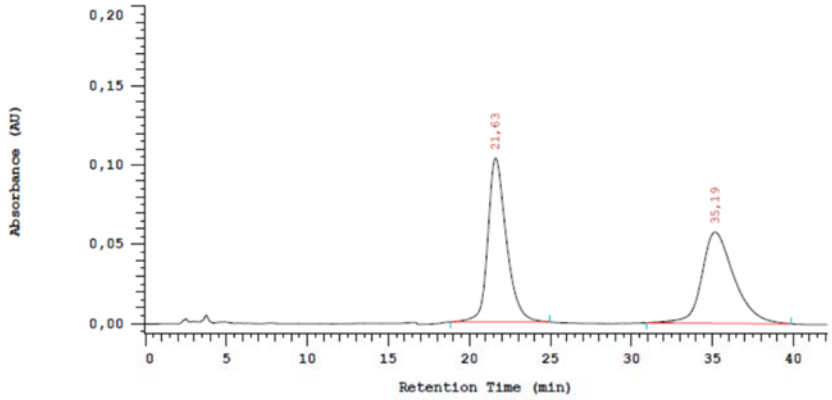






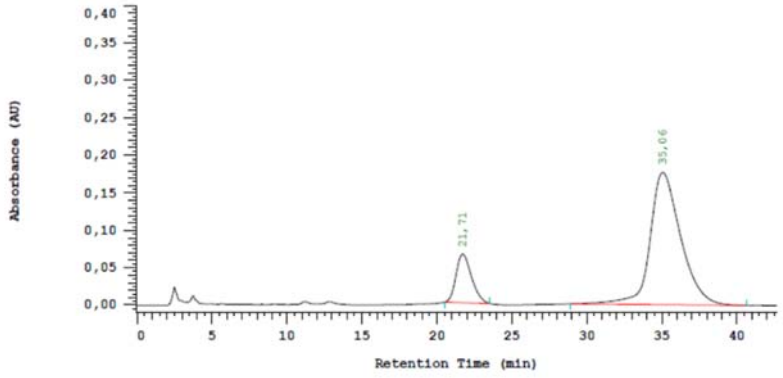
3ba

Racemic or near racemic mixture:

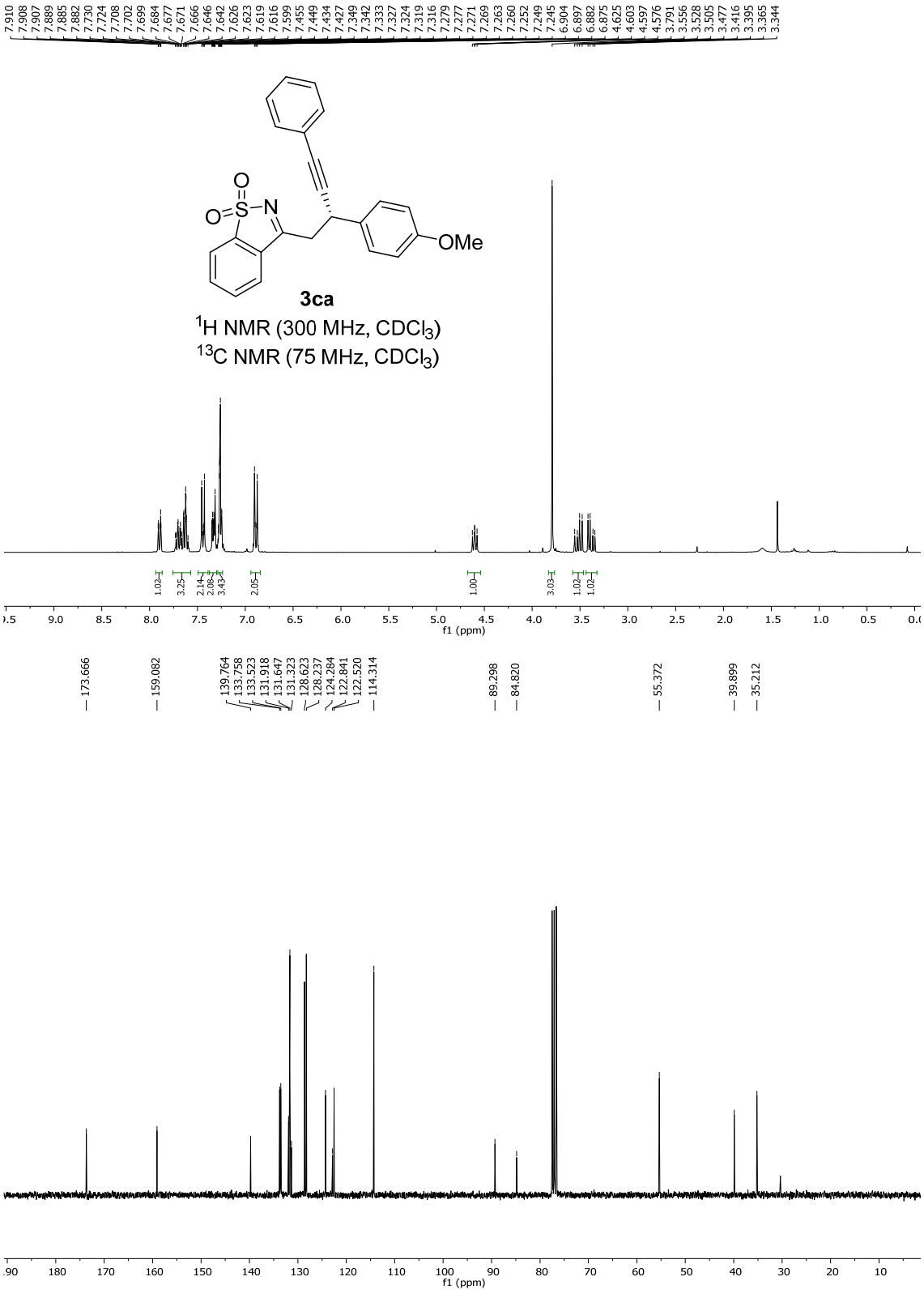


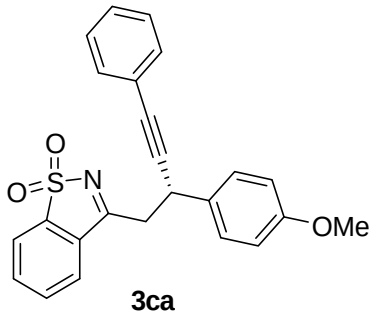
No.	RT	Area	Area %	Name
1	21,63	4093595	50,700	
2	35,19	3980515	49,300	
		8074110	100,000	

Enantioselective reaction:



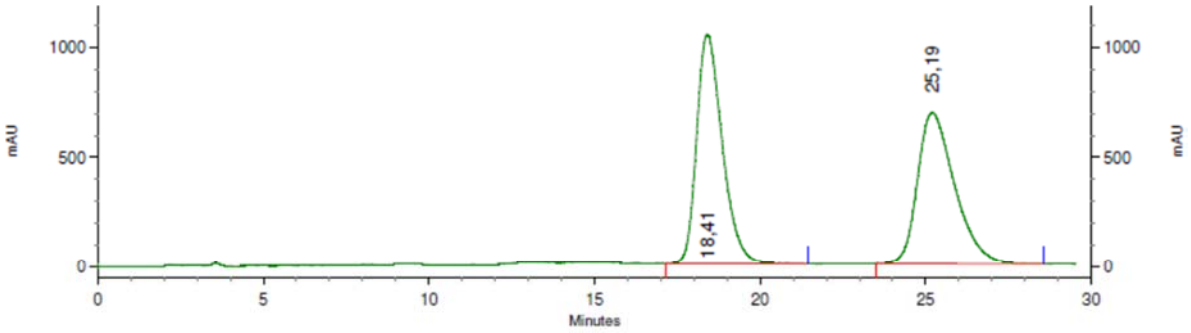
No.	RT	Area	Area %	Name
1	21,71	2334560	15,647	
2	35,06	12586035	84,353	
		14920595	100,000	


7.910
7.908
7.907
7.889
7.885
7.882
7.730
7.724
7.708
7.702
7.699
7.684
7.677
7.671
7.666
7.646
7.642
7.626
7.623
7.619
7.616
7.599
7.455
7.449
7.434
7.427
7.349
7.342
7.333
7.327
7.324
7.319
7.316
7.279
7.277
7.271
7.269
7.263
7.260
7.252
7.249
7.245
6.904
6.897
6.882
6.875
4.625
4.603
4.597
4.576
3.791
3.556
3.528
3.505
3.477
3.416
3.395
3.365
3.344
O
O=S–N
OMe
3ca
1H NMR (300 MHz, CDCl3)
13C NMR (75 MHz, CDCl3)
1.02
3.25
2.14
2.08
3.43
2.05
1.00
3.03
1.02
1.02
f1 (ppm)
173.666
159.082
139.764
133.758
133.523
131.918
131.647
131.323
128.623
128.237
124.284
122.841
122.520
114.314
89.298
84.820
55.372
39.899
35.212
f1 (ppm)



3ca

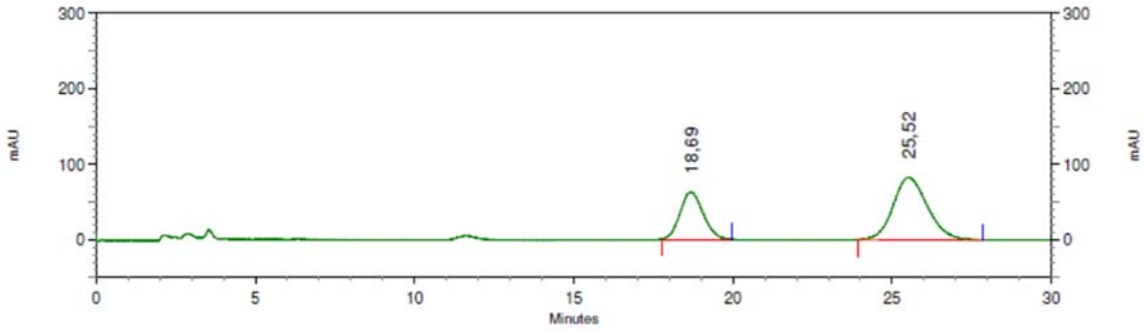
Racemic or near racemic mixture:



9: 245 nm, 4 nm Results

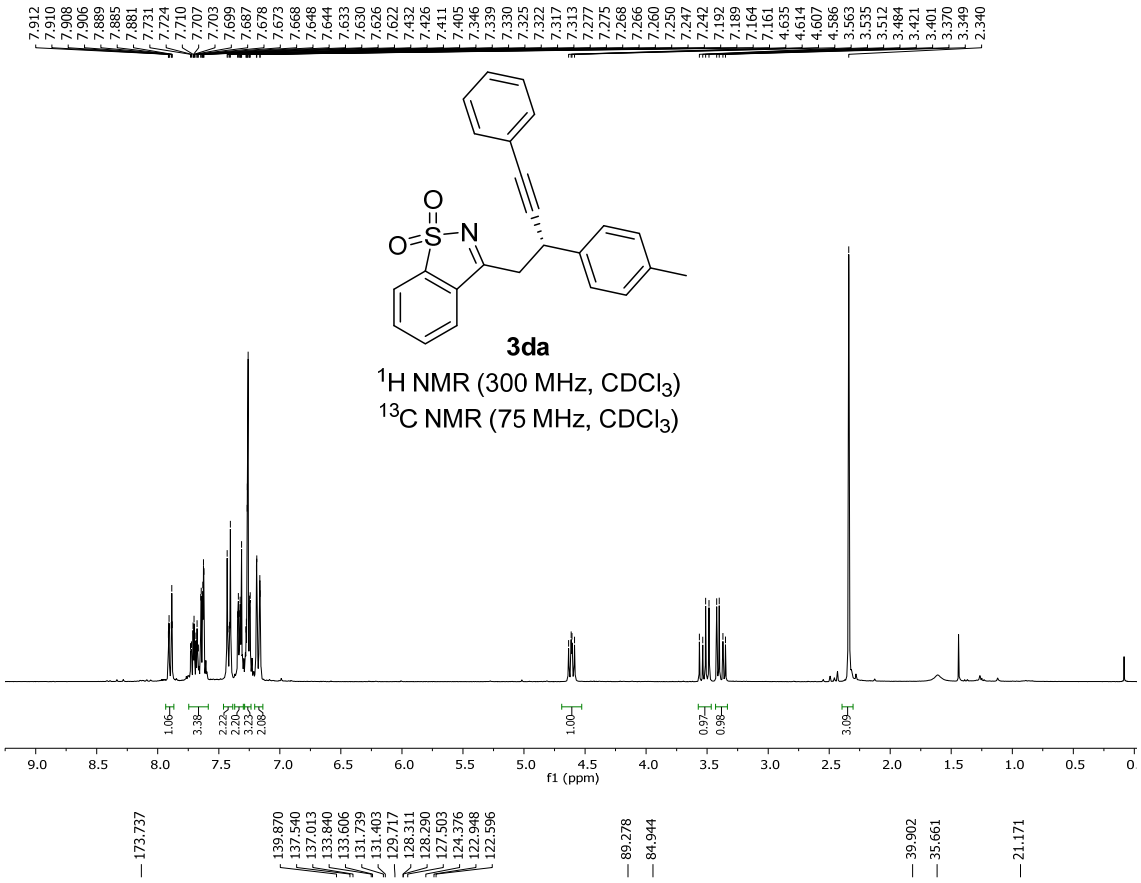
Retention Time	Area	Area Percent
18,41	226501385	51,117
25,19	216600530	48,883

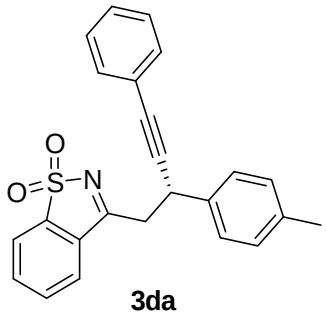
Enantioselective reaction:



9: 245 nm, 4 nm Results

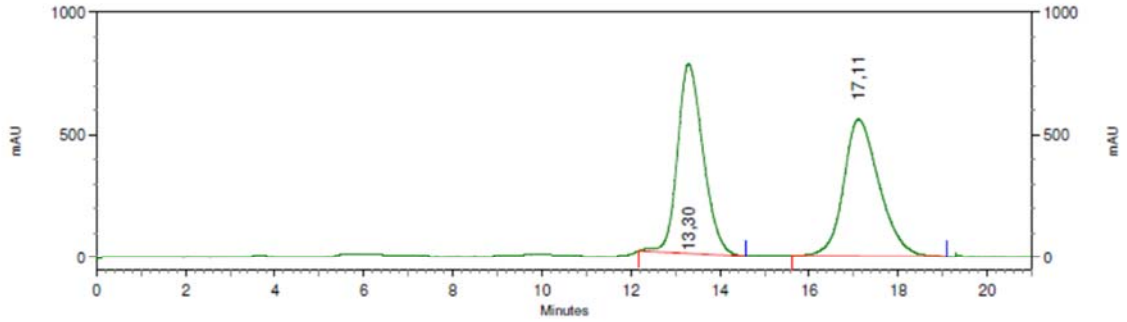
Retention Time	Area	Area Percent
18,69	12734908	33,621
25,52	25142819	66,379


7.912
7.910
7.908
7.906
7.889
7.885
7.881
7.731
7.724
7.710
7.707
7.703
7.699
7.687
7.678
7.673
7.668
7.648
7.644
7.633
7.630
7.626
7.622
7.432
7.426
7.411
7.405
7.346
7.339
7.330
7.325
7.322
7.317
7.313
7.277
7.275
7.268
7.266
7.260
7.250
7.247
7.242
7.192
7.189
7.164
7.161
4.635
4.614
4.607
4.586
3.563
3.535
3.512
3.484
3.421
3.401
3.370
3.349
2.340
O
O=S–N
3da
1H NMR (300 MHz, CDCl3)
13C NMR (75 MHz, CDCl3)
1.06
3.38
2.22
2.20
3.23
2.08
1.00
0.97
0.98
3.09
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
f1 (ppm)
173.737
139.870
137.540
137.013
133.840
133.606
131.739
131.403
129.717
128.311
128.290
127.503
124.376
122.948
122.596
89.278
84.944
39.902
35.661
21.171
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)



3da

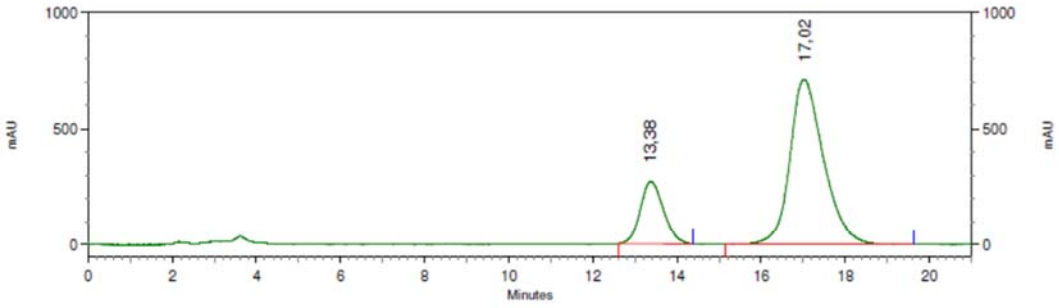
Racemic or near racemic mixture:



6: 242 nm, 4 nm Results

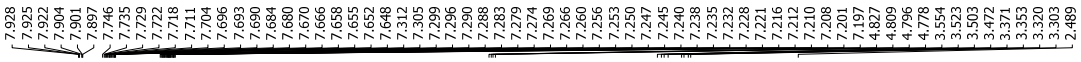
Retention Time	Area	Area Percent
13,30	123855977	49,833
17,11	124683675	50,167

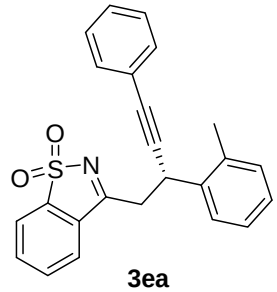
Enantioselective reaction:



9: 245 nm, 4 nm Results

Retention Time	Area	Area Percent
13,38	41865095	20,701
17,02	160369460	79,299

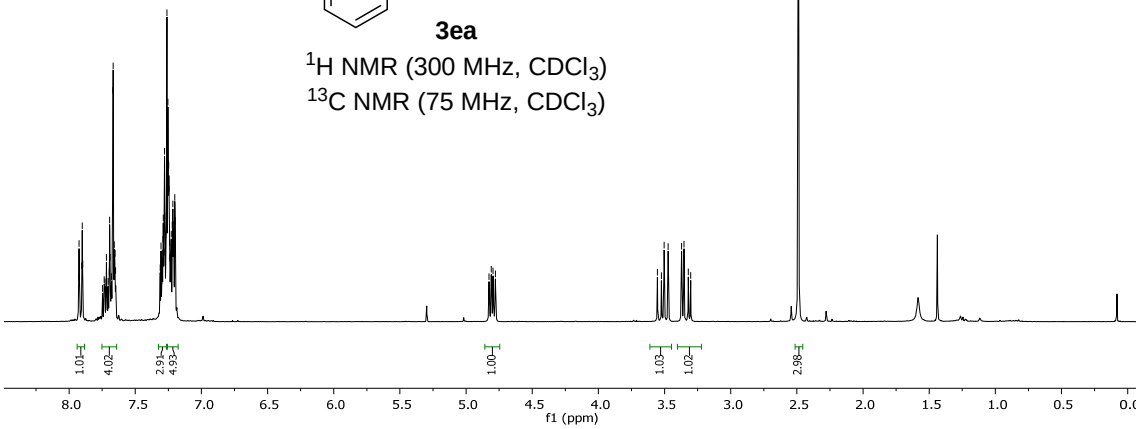


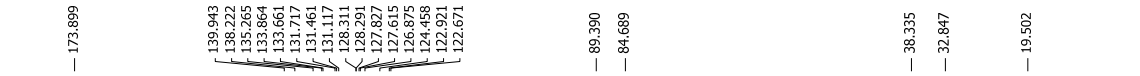


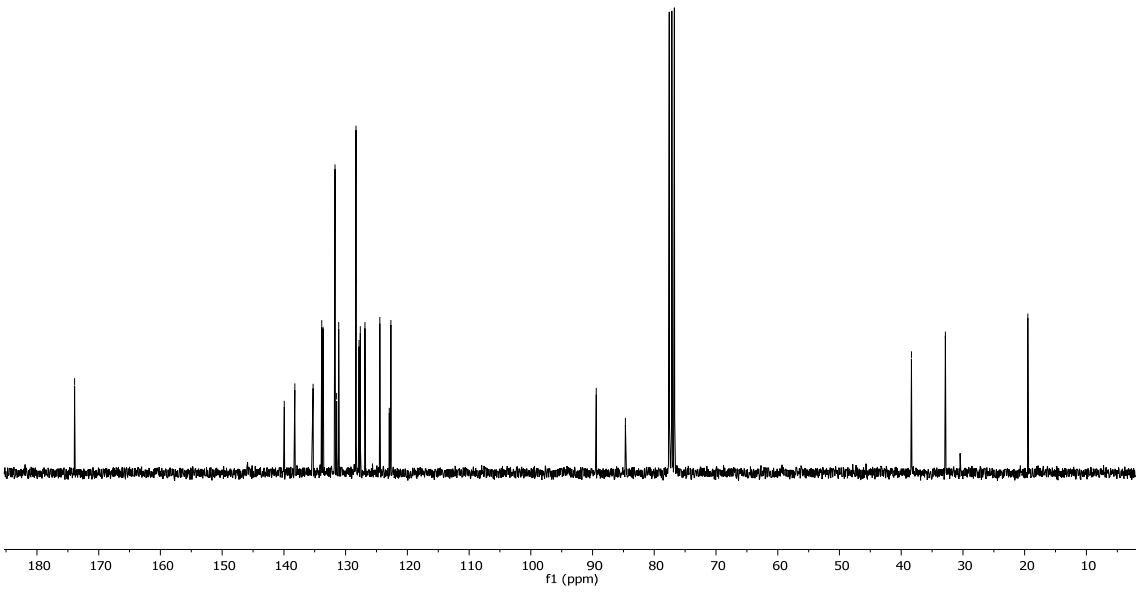
3ea

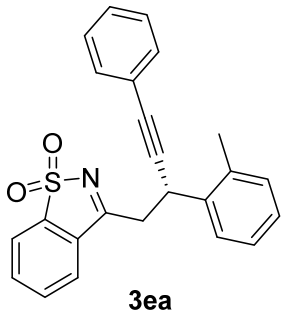
^{1}H NMR (300 MHz, $CDCl_3$)

^{13}C NMR (75 MHz, $CDCl_3$)



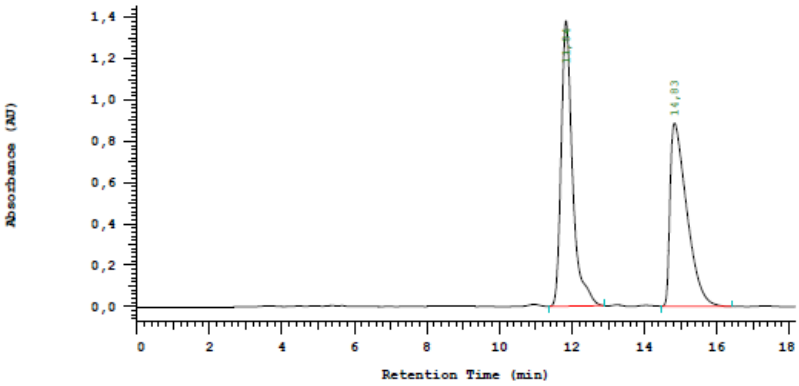






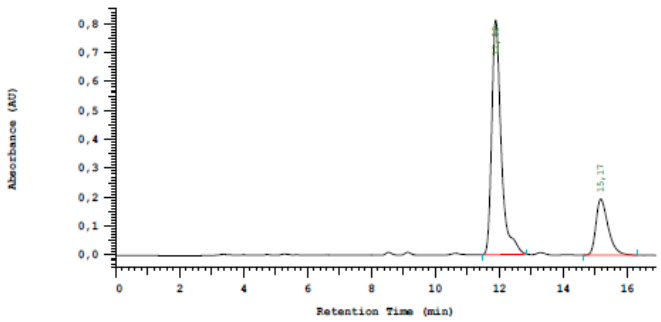
3ea

Racemic or near racemic mixture:

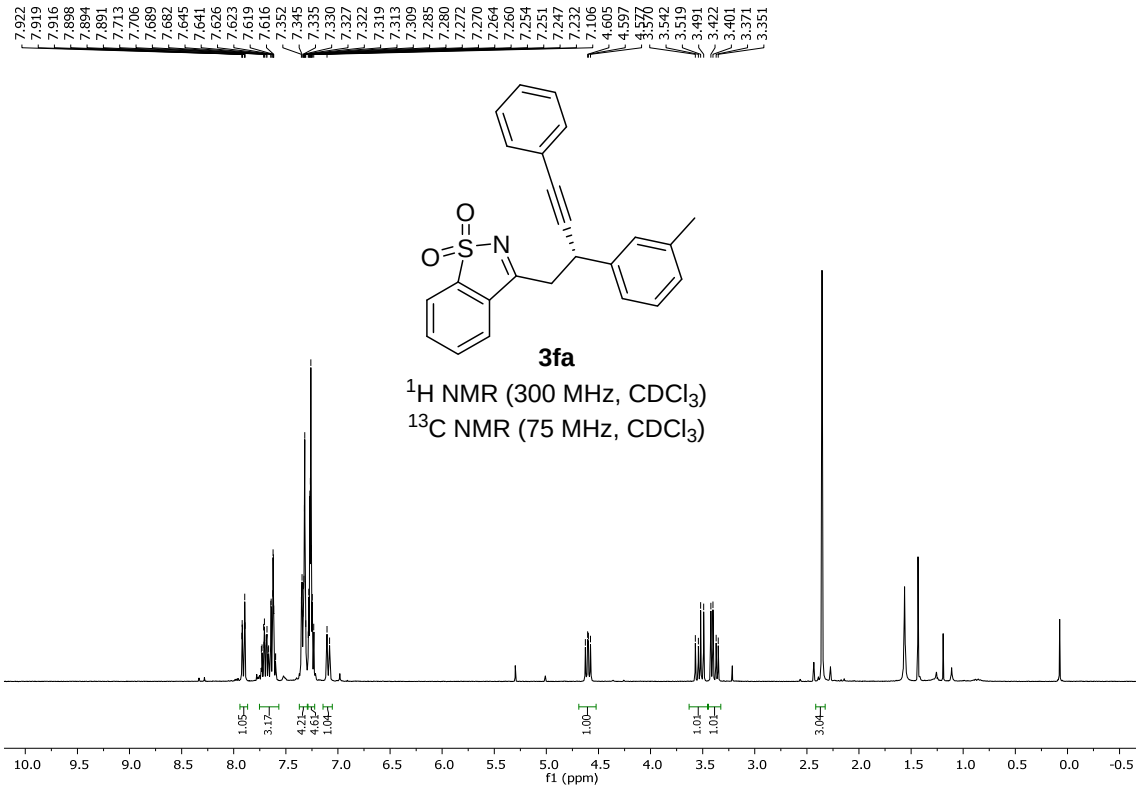


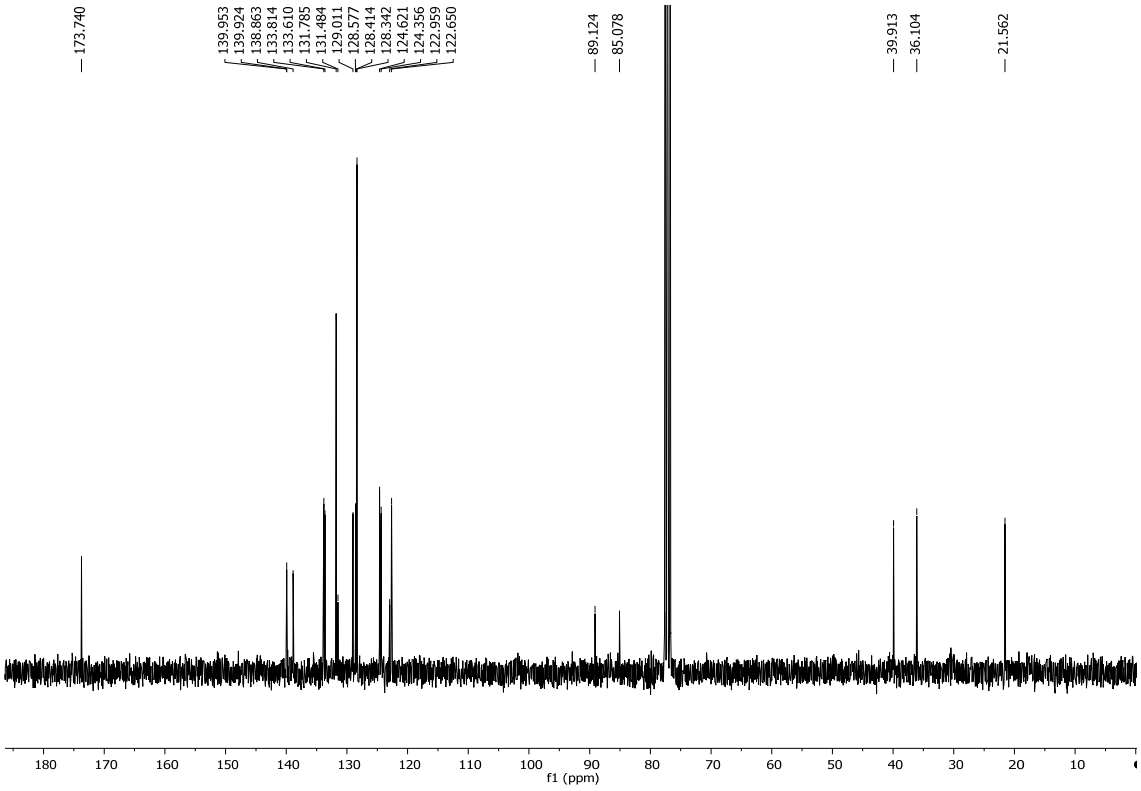
No.	RT	Area	Area %	Name
1	11,84	15064120	51,403	
2	14,83	14241760	48,597	
		29305880	100,000	

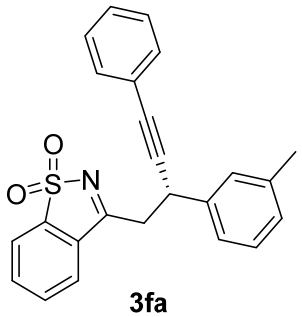
Enantioselective reaction:



No.	RT	Area	Area %	Name
1	11,89	8333409	76,387	
2	15,17	2576065	23,613	
		10909474	100,000	

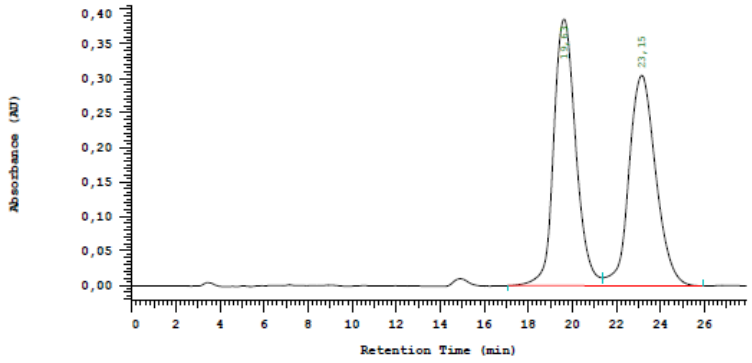

7.922
7.919
7.916
7.898
7.894
7.891
7.713
7.706
7.689
7.682
7.645
7.641
7.626
7.623
7.619
7.616
7.352
7.345
7.335
7.330
7.327
7.322
7.319
7.313
7.309
7.285
7.280
7.272
7.270
7.264
7.260
7.254
7.251
7.247
7.232
7.106
4.605
4.597
4.577
3.570
3.542
3.519
3.491
3.422
3.401
3.371
3.351
O
O=S-N
3fa
1H NMR (300 MHz, CDCl3)
13C NMR (75 MHz, CDCl3)
1.05
3.17
4.21
4.62
1.04
1.00
1.01
1.01
3.04
f1 (ppm)


173.740
139.953
139.924
138.863
133.814
133.610
131.785
131.484
129.011
128.577
128.414
128.342
124.621
124.356
122.959
122.650
89.124
85.078
39.913
36.104
21.562
f1 (ppm)



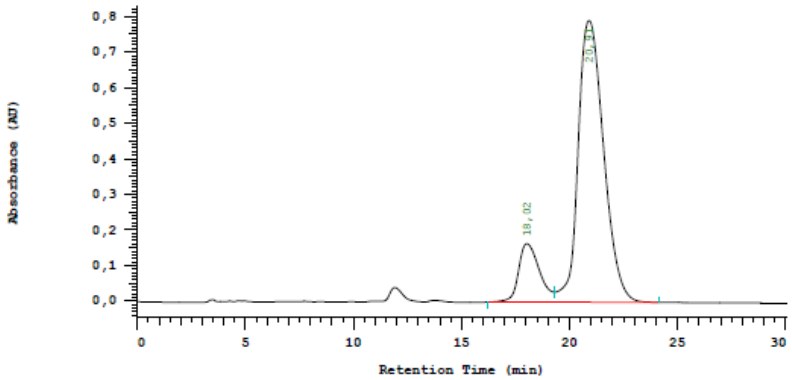
3fa

Racemic or near racemic mixture:

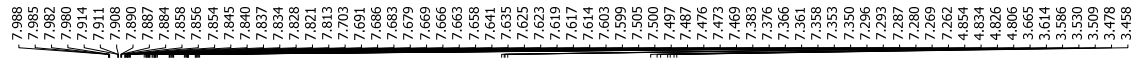


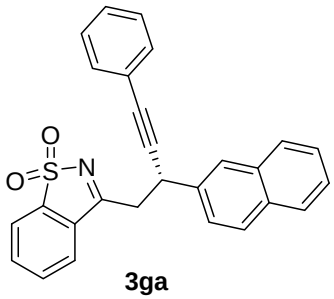
No.	RT	Area	Area %	Name
1	19,63	13434774	50,975	
2	23,15	12921004	49,025	
		26355778	100,000	

Enantioselective reaction:



No.	RT	Area	Area %	Name
1	18,02	5525730	14,557	
2	20,91	32433190	85,443	
		37958920	100,000	

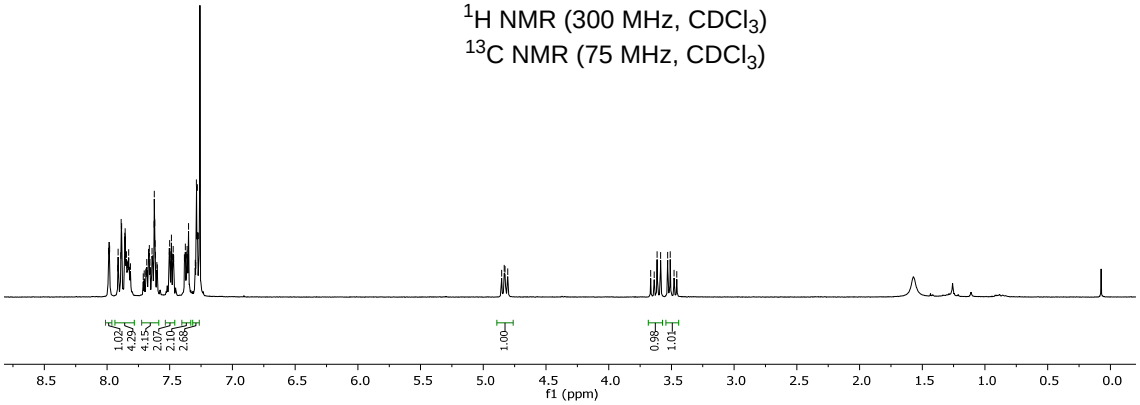


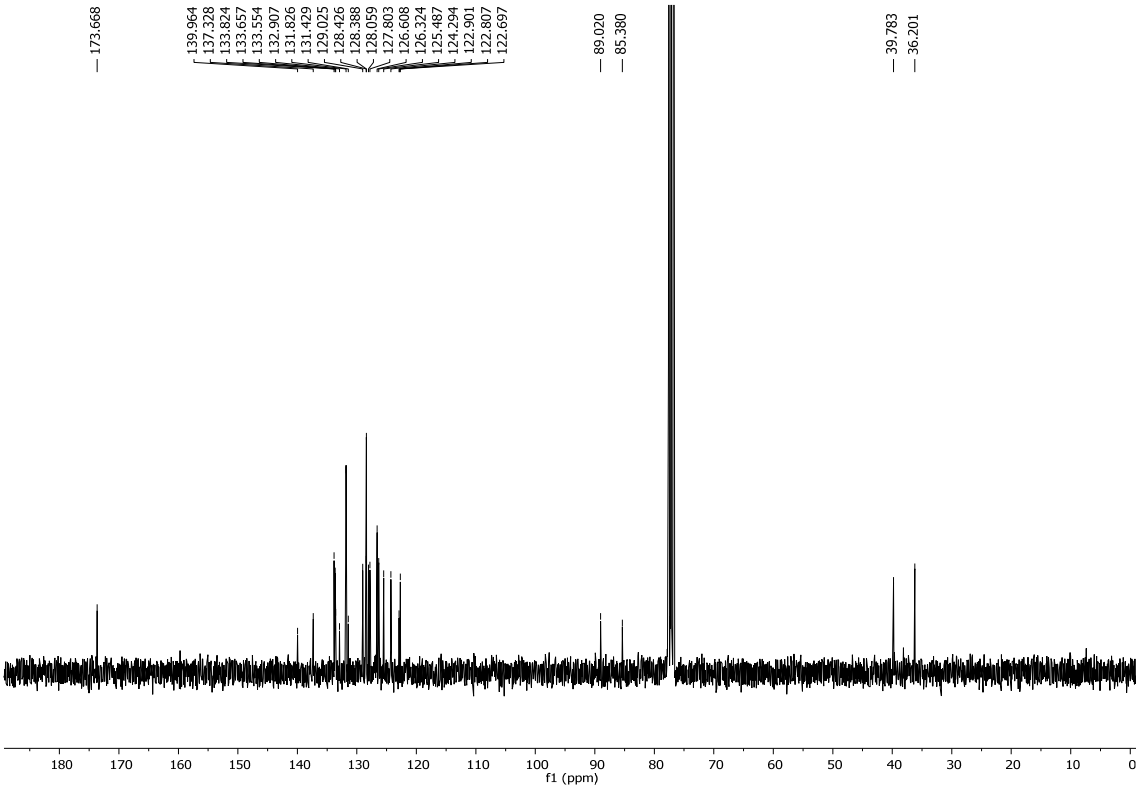


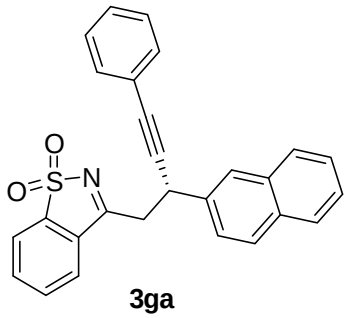
3ga

^{1}H NMR (300 MHz, $CDCl_3$)

^{13}C NMR (75 MHz, $CDCl_3$)

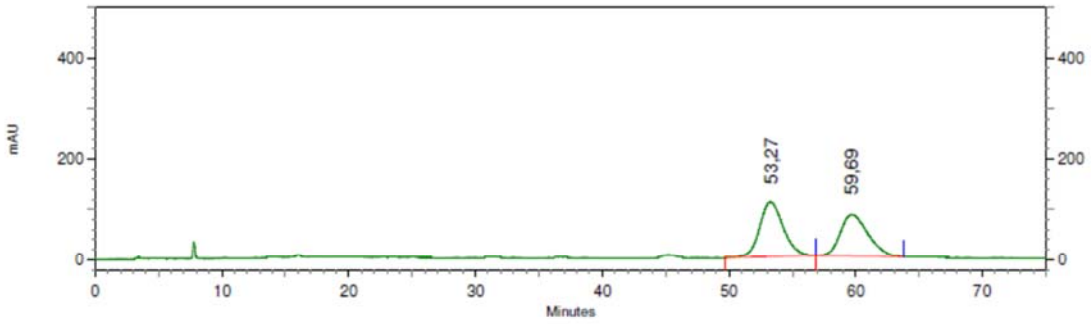






3ga

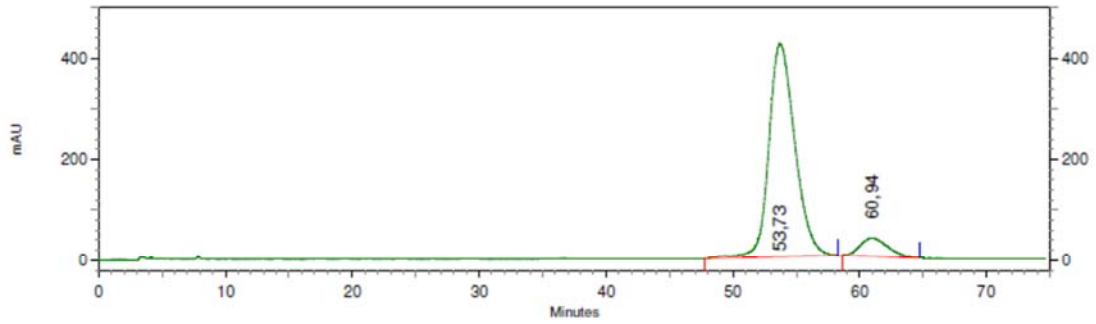
Racemic or near racemic mixture:



15: 245 nm, 4 nm
Results

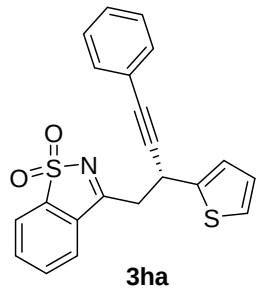
Retention Time	Area	Area Percent
53,27	56801629	53,042
59,69	50285828	46,958

Enantioselective reaction:



15: 245 nm, 4 nm
Results

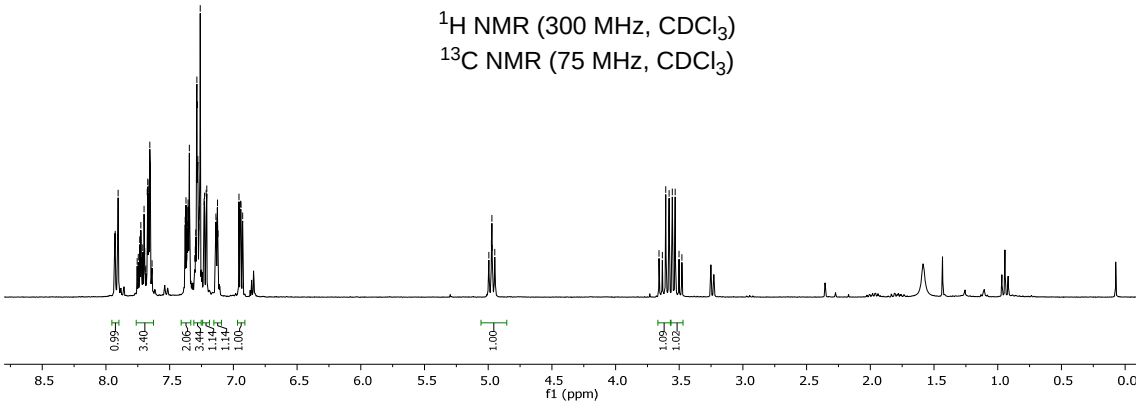
Retention Time	Area	Area Percent
53,73	241294007	91,489
60,94	22446536	8,511

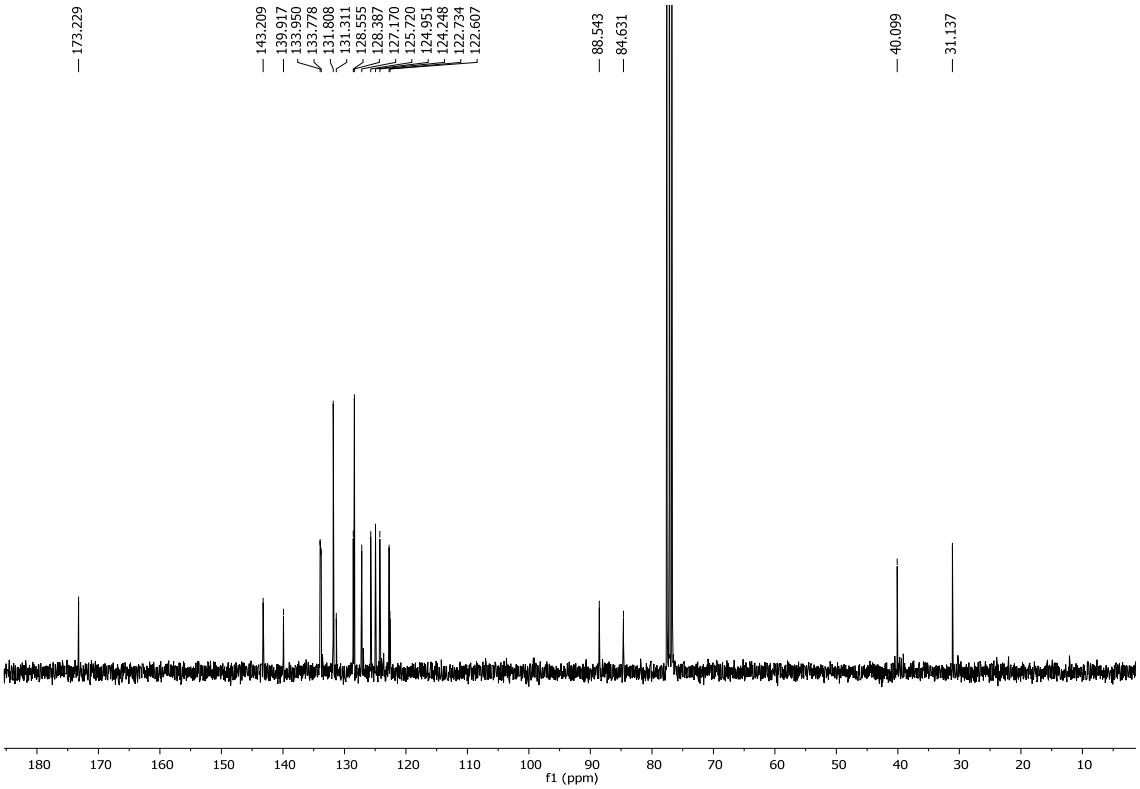


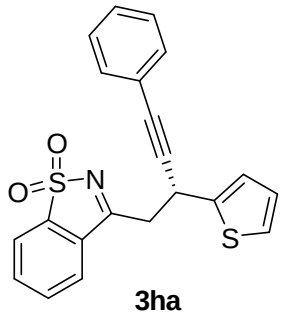
3ha

^{1}H NMR (300 MHz, $CDCl_3$)

^{13}C NMR (75 MHz, $CDCl_3$)

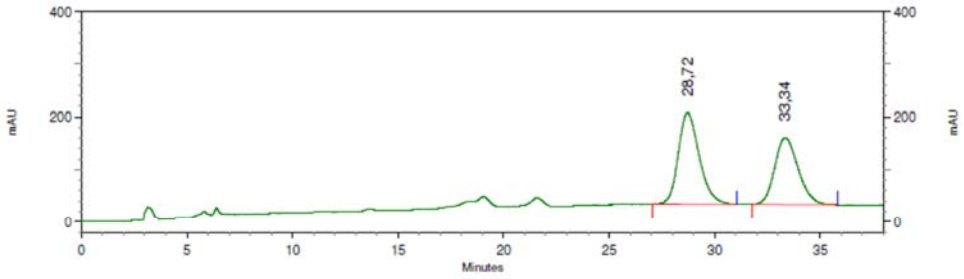






3ha

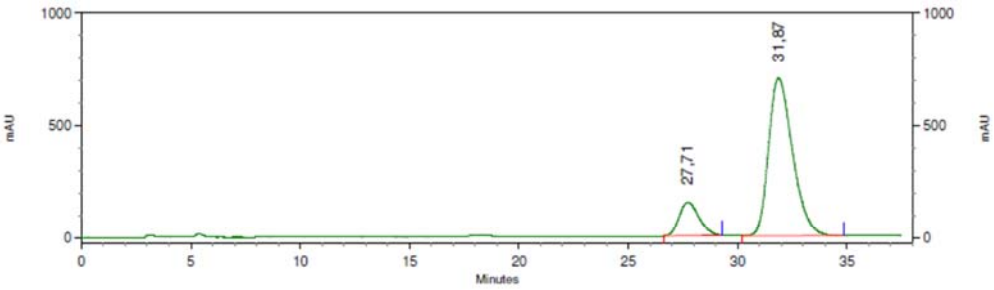
Racemic or near racemic mixture:



19: 221 nm, 4 nm
Results

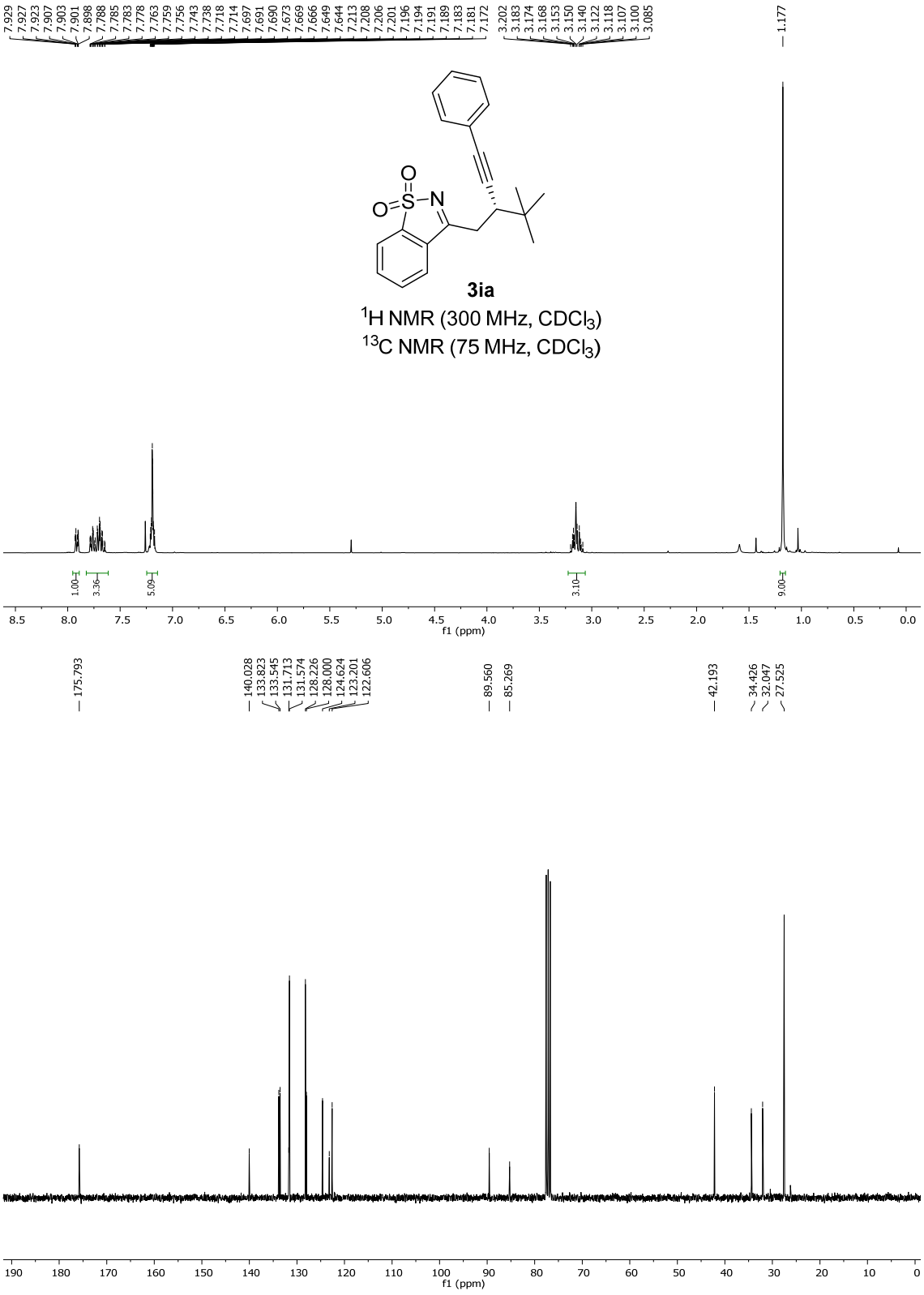
Retention Time	Area	Area Percent
28,72	48245961	54,991
33,34	39488857	45,009

Enantioselective reaction:



15: 245 nm, 4 nm
Results

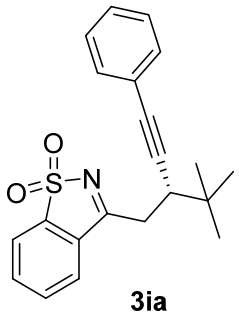
Retention Time	Area	Area Percent
27,71	38403186	15,138
31,87	215287629	84,862



3ia

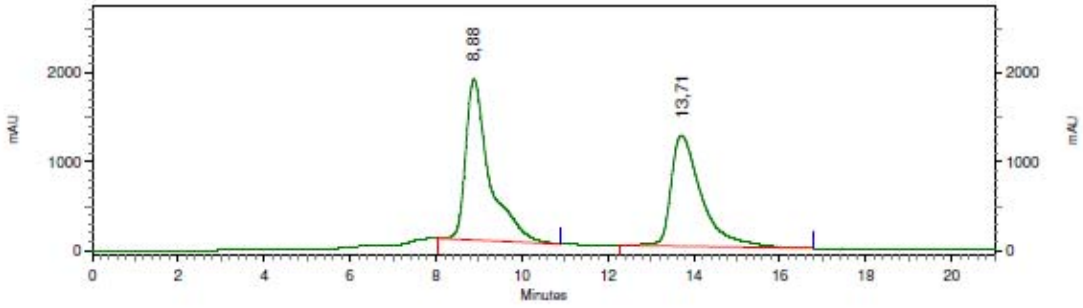
^{1}H NMR (300 MHz, $CDCl_3$)

^{13}C NMR (75 MHz, $CDCl_3$)



3ia

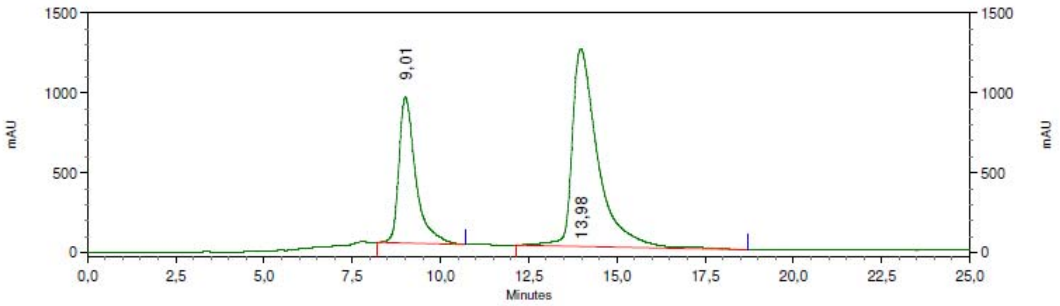
Racemic or near racemic mixture:



9: 243 nm, 4 nm Results

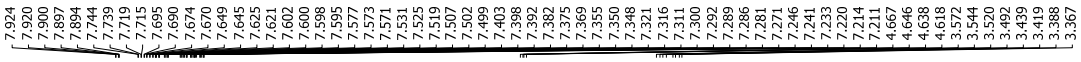
Retention Time	Area	Area Percent
8,88	278579960	53,092
13,71	246131441	46,908

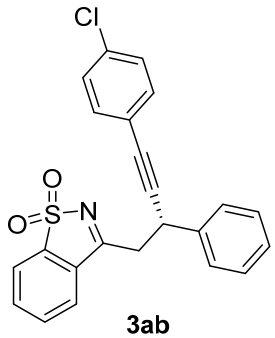
Enantioselective reaction:



9: 250 nm, 4 nm Results

Retention Time	Area	Area Percent
9,01	121004060	32,470
13,98	251664079	67,530

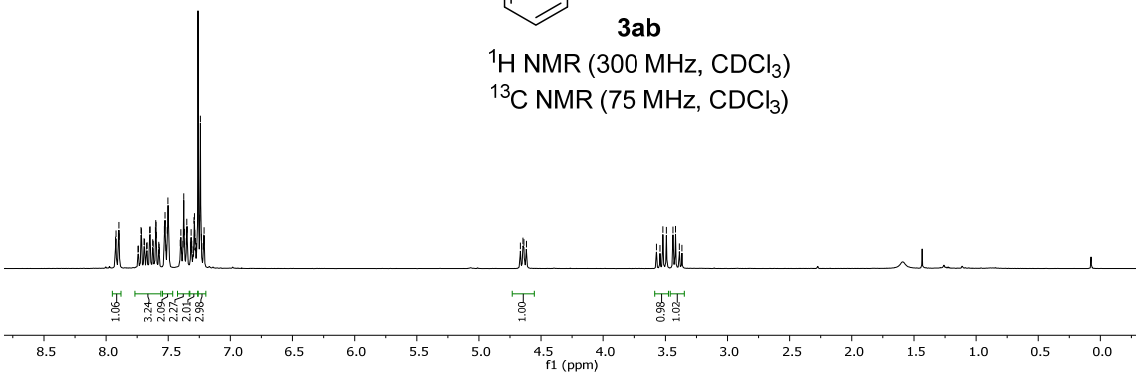


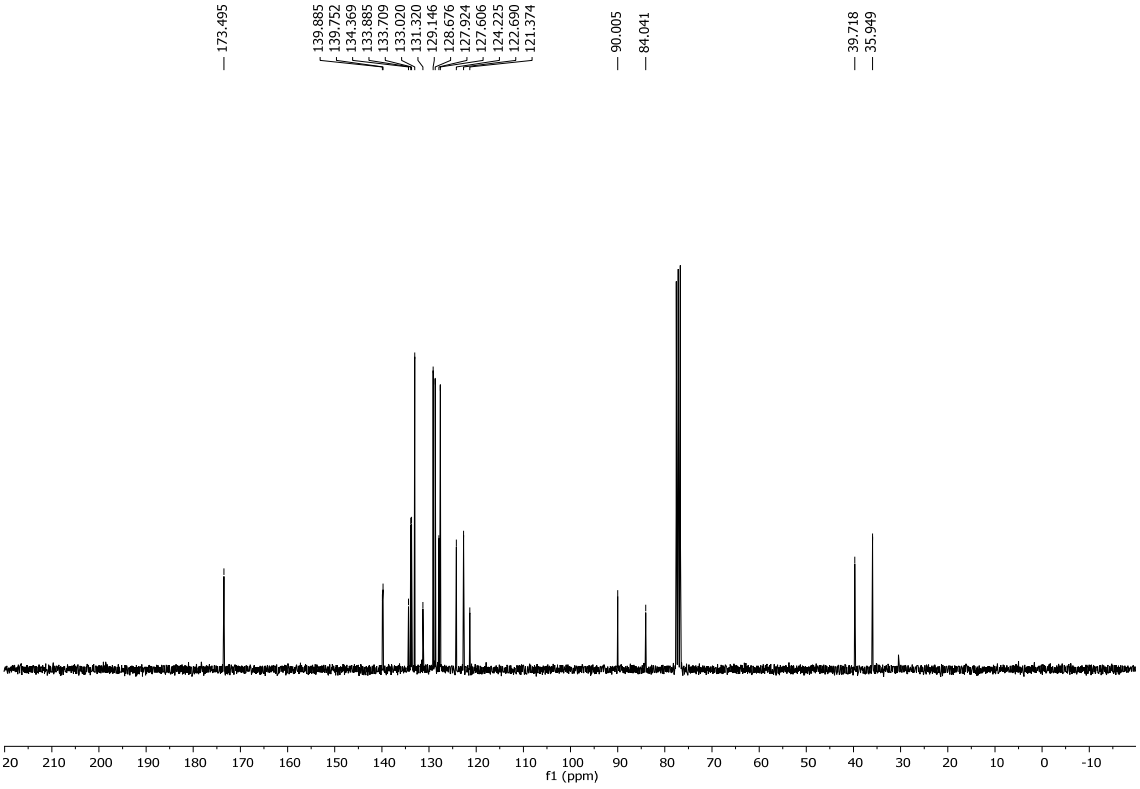


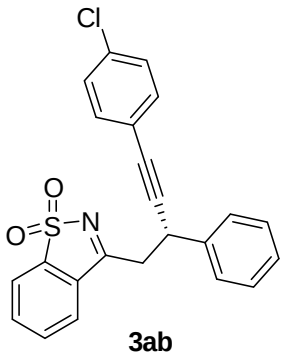
3ab

^{1}H NMR (300 MHz, $CDCl_3$)

^{13}C NMR (75 MHz, $CDCl_3$)

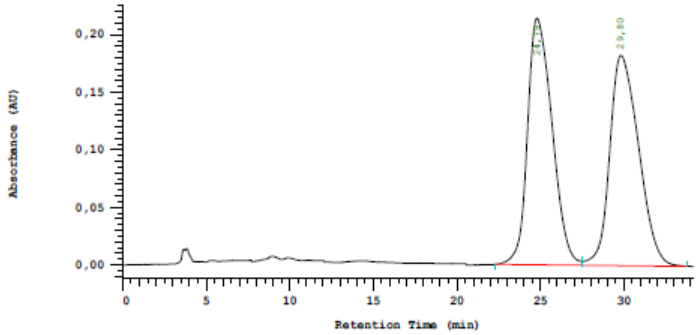






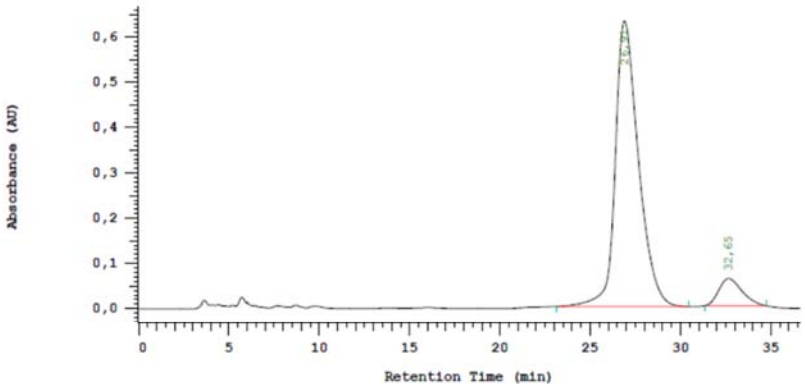
3ab

Racemic or near racemic mixture:

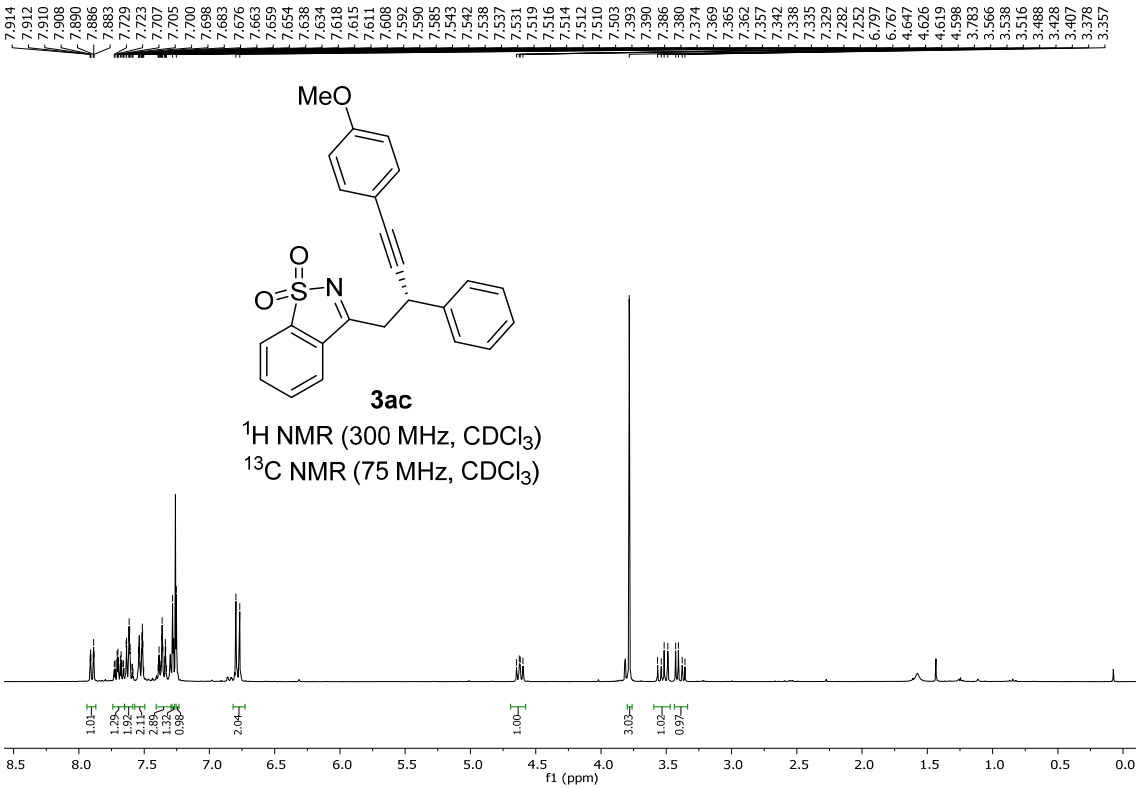


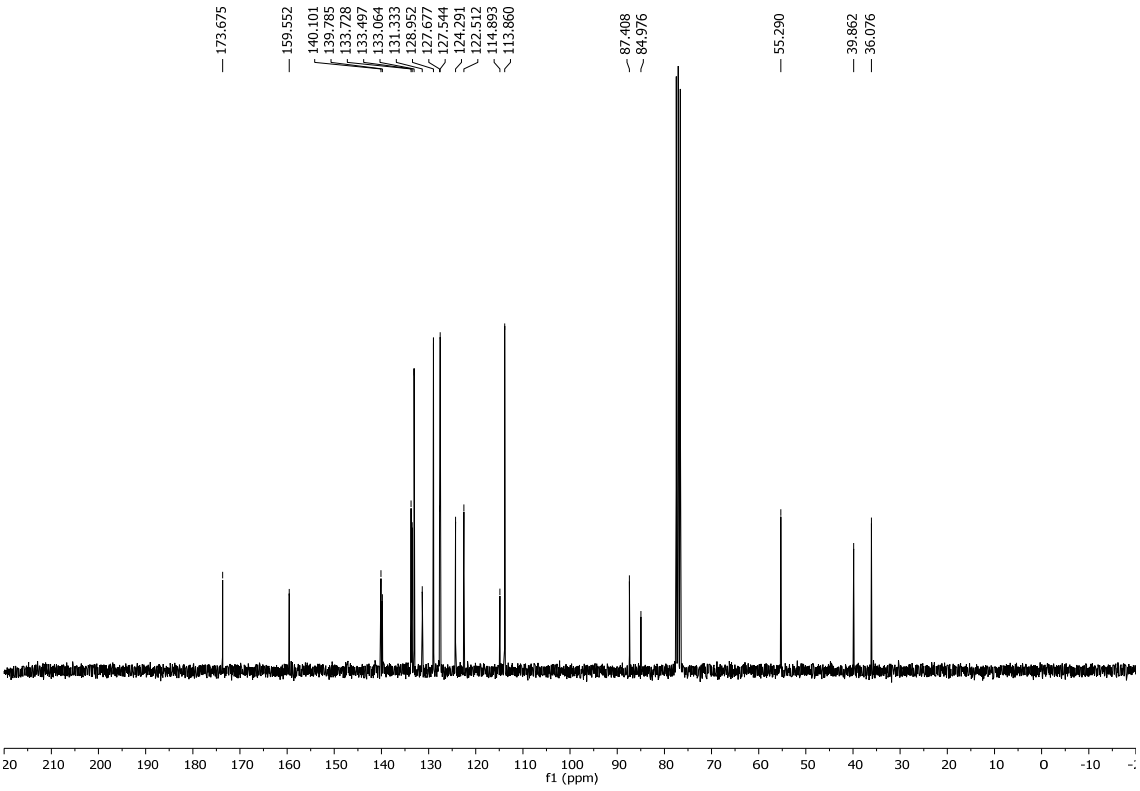
No.	RT	Area	Area %	Name
1	24,79	10927720	49,898	
2	29,80	10972194	50,102	
		21899914	100,000	

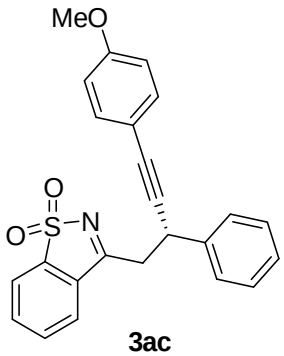
Enantioselective reaction:



No.	RT	Area	Area %	Name
1	26,91	28149638	91,326	
2	32,65	2673610	8,674	
		30823248	100,000	

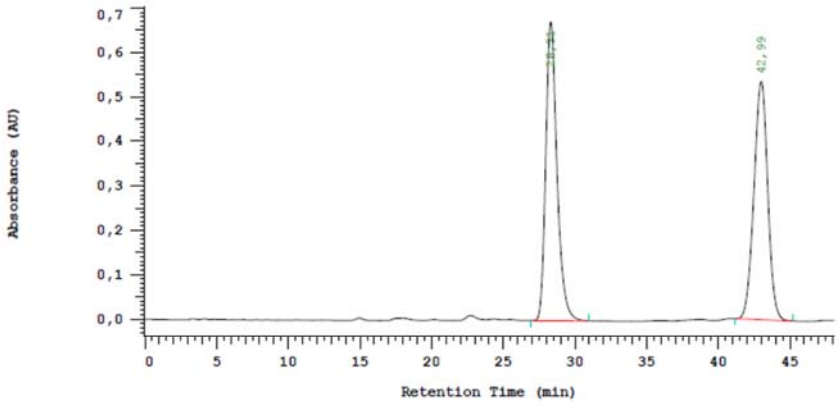

MeO
O
O=S=N
3ac
1H NMR (300 MHz, CDCl3)
13C NMR (75 MHz, CDCl3)
f1 (ppm)


f1 (ppm)



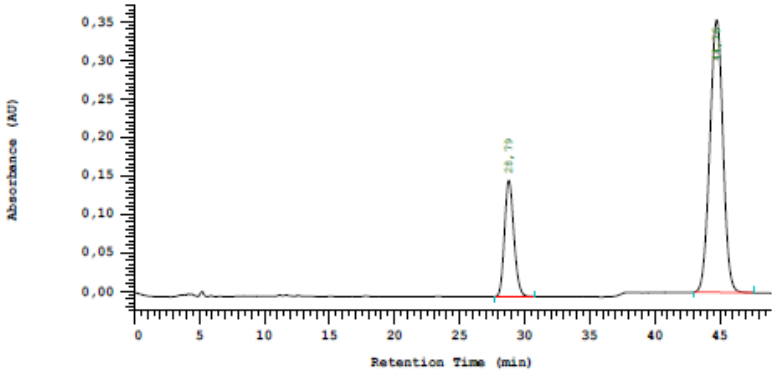
3ac

Racemic or near racemic mixture:

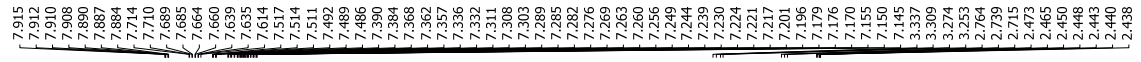


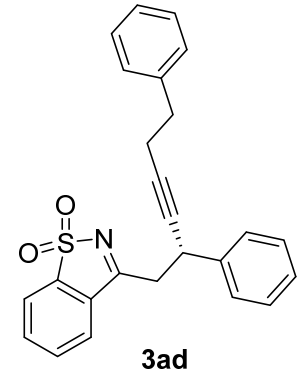
No.	RT	Area	Area %	Name
1	28,31	18141489	50,342	
2	42,99	17895059	49,658	
		36036548	100,000	

Enantioselective reaction:



No.	RT	Area	Area %	Name
1	28,79	3738144	23,344	
2	44,76	12274864	76,656	
		16013008	100,000	

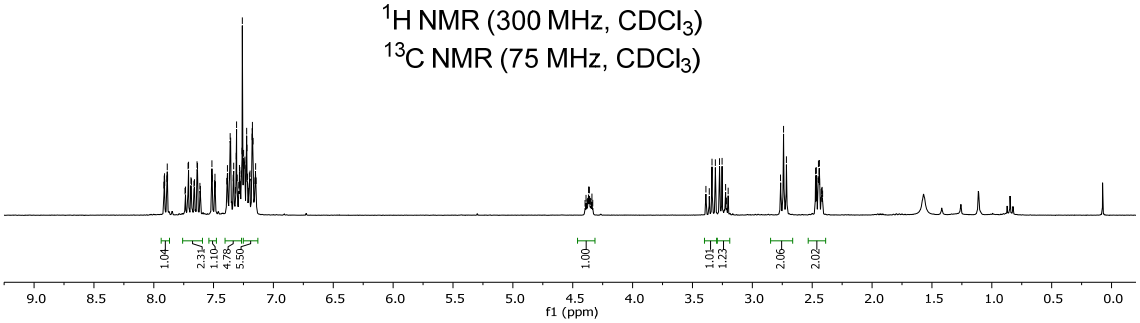


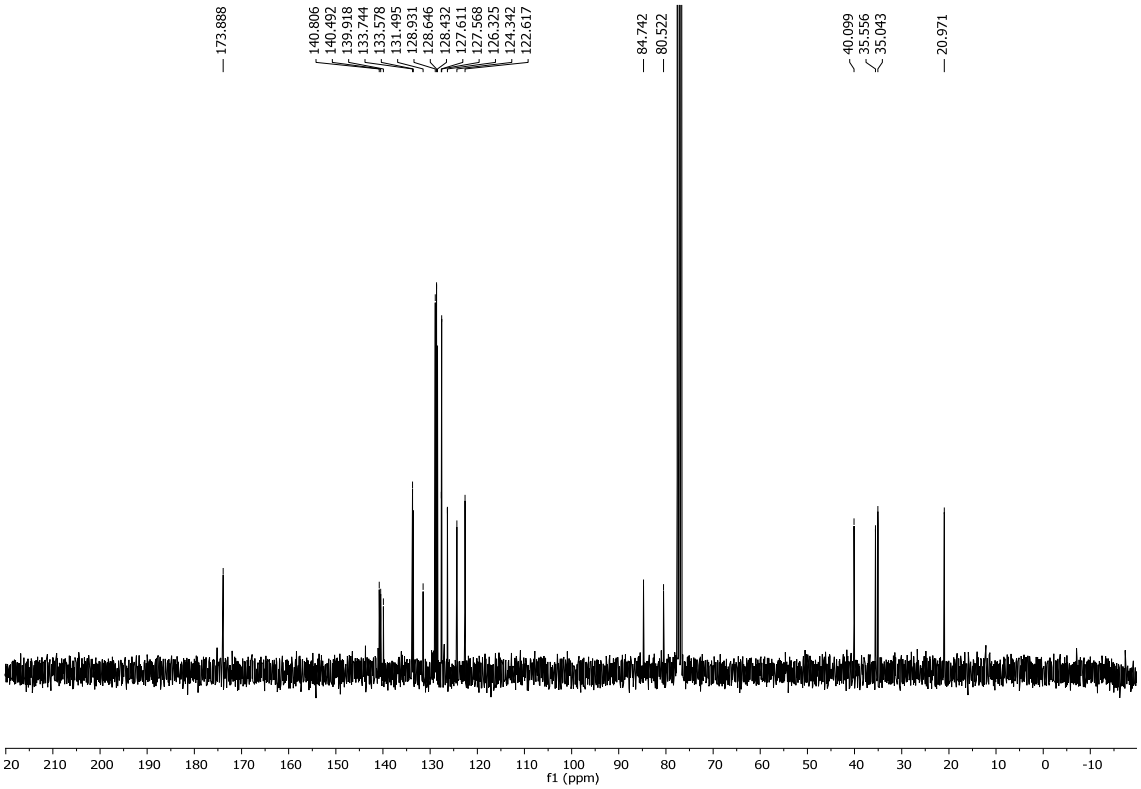


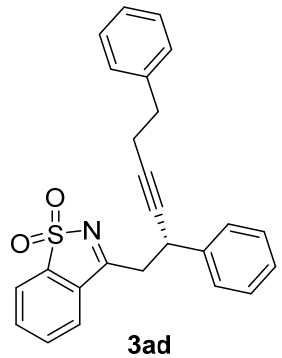
3ad

^{1}H NMR (300 MHz, $CDCl_3$)

^{13}C NMR (75 MHz, $CDCl_3$)

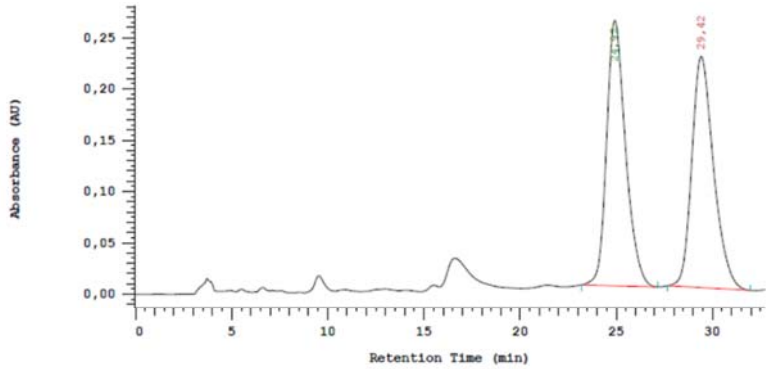






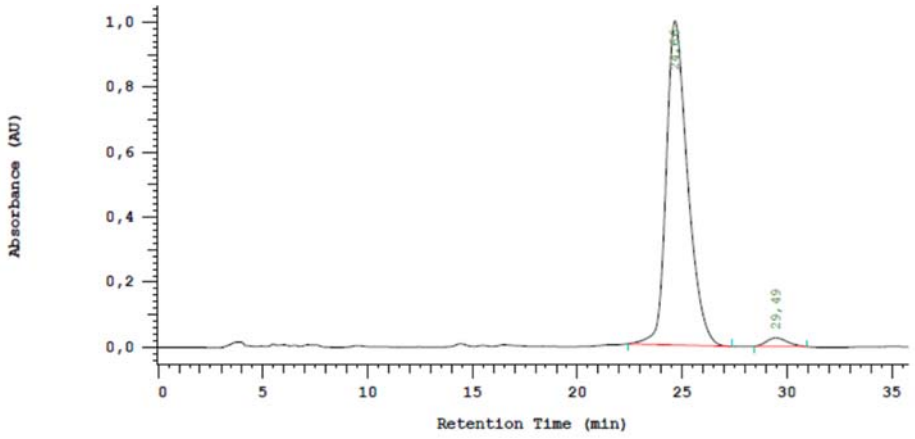
3ad

Racemic or near racemic mixture:

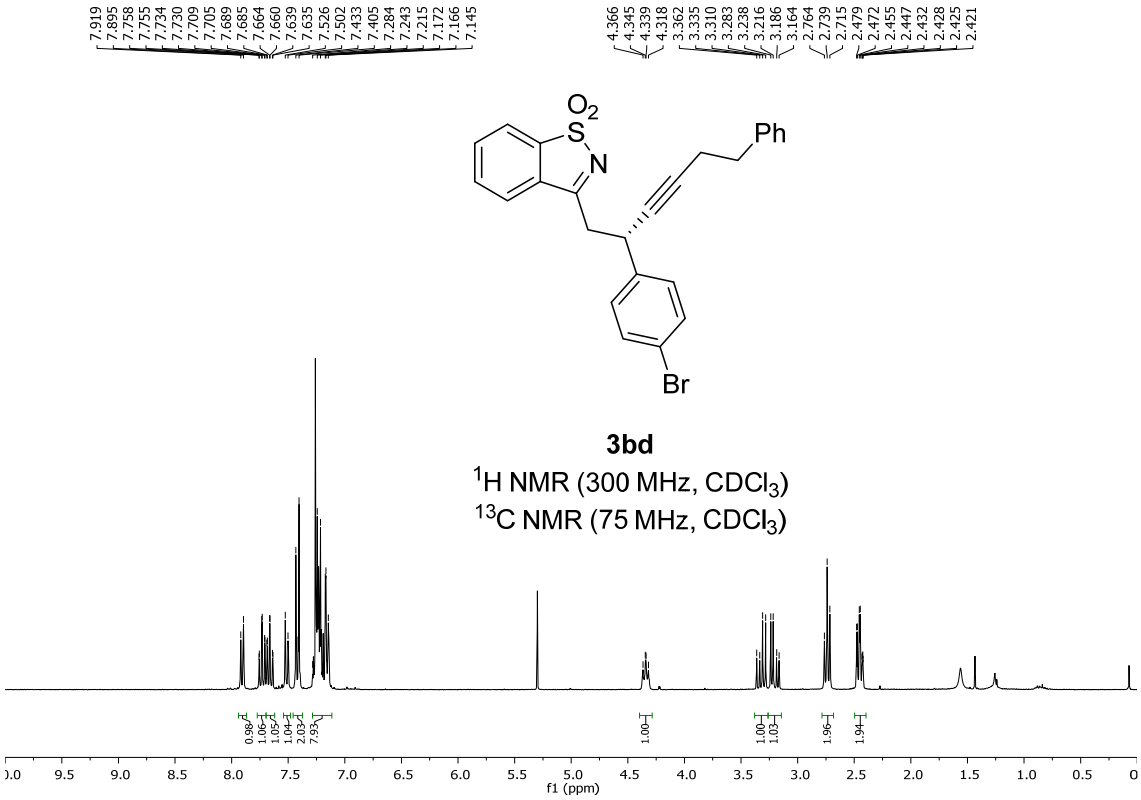


No.	RT	Area	Area %	Name
1	24,92	8841550	50,014	
2	29,42	8836630	49,986	
		17678180	100,000	

Enantioselective reaction:



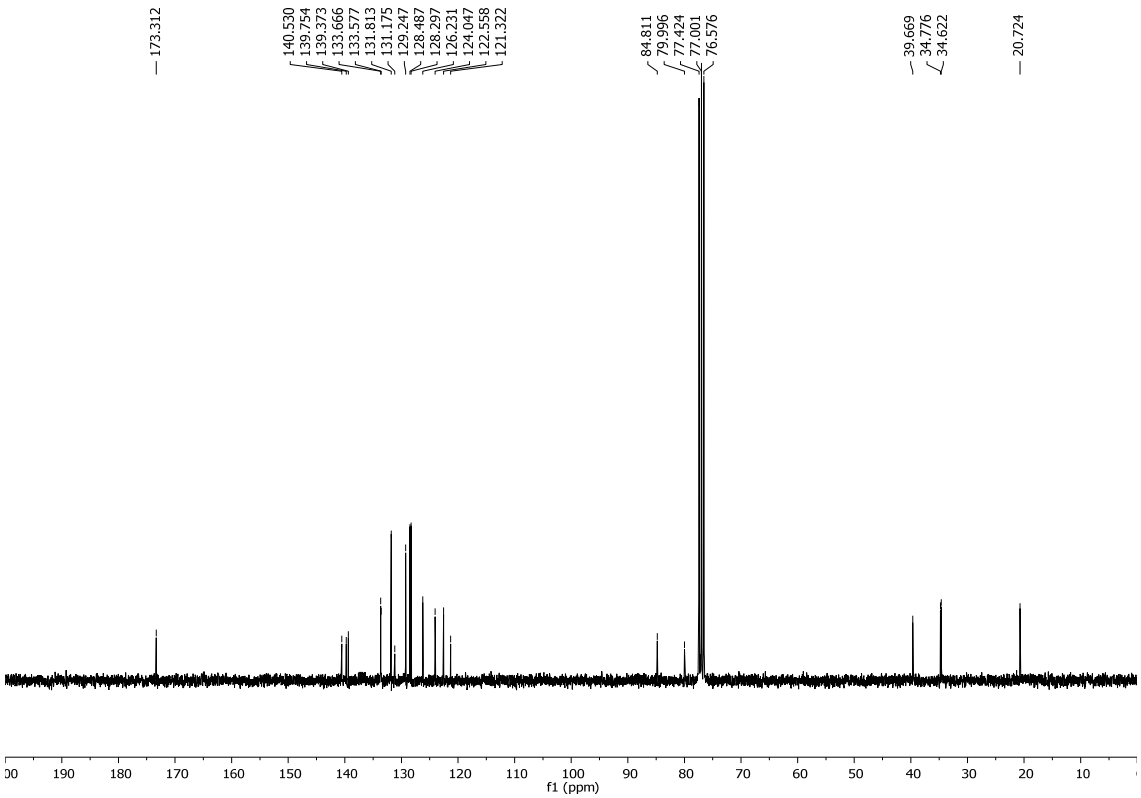
No.	RT	Area	Area %	Name
1	24,66	35156310	97,459	
2	29,49	916560	2,541	
		36072870	100,000	

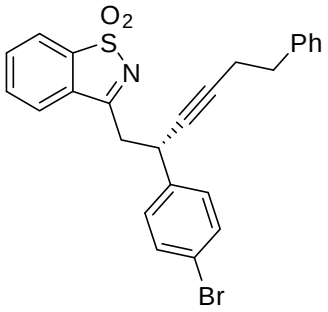


3bd

^{1}H NMR (300 MHz, $CDCl_3$)

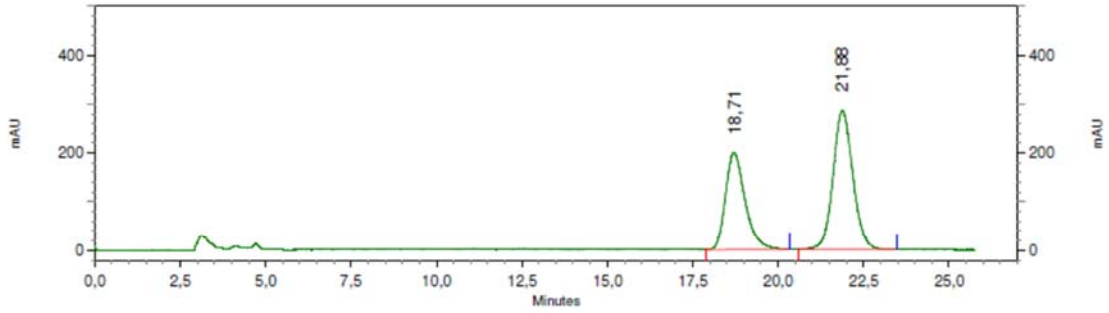
^{13}C NMR (75 MHz, $CDCl_3$)





3bd

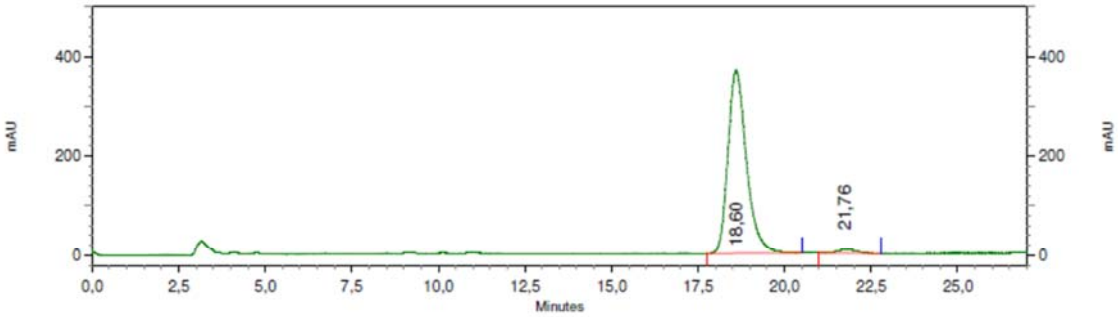
Racemic or near racemic mixture of enantiomers:



18: 220 nm, 4 nm
Results

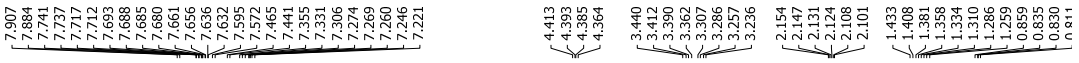
Retention Time	Area	Area Percent
18,71	32020989	40,880
21,88	46308719	59,120

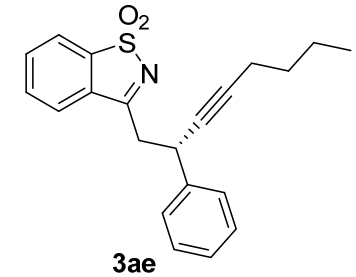
Enantioselective reaction:



18: 220 nm, 4 nm
Results

Retention Time	Area	Area Percent
18,60	55020959	97,752
21,76	1265305	2,248

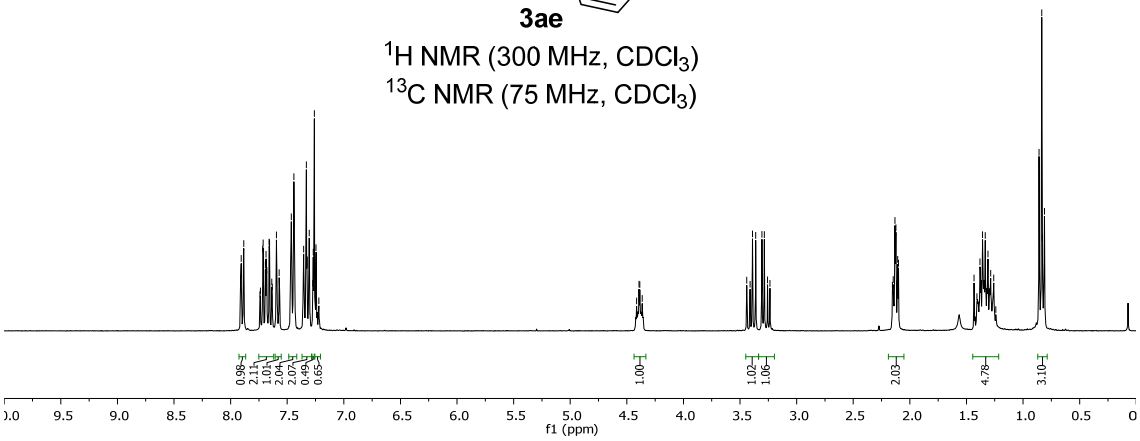


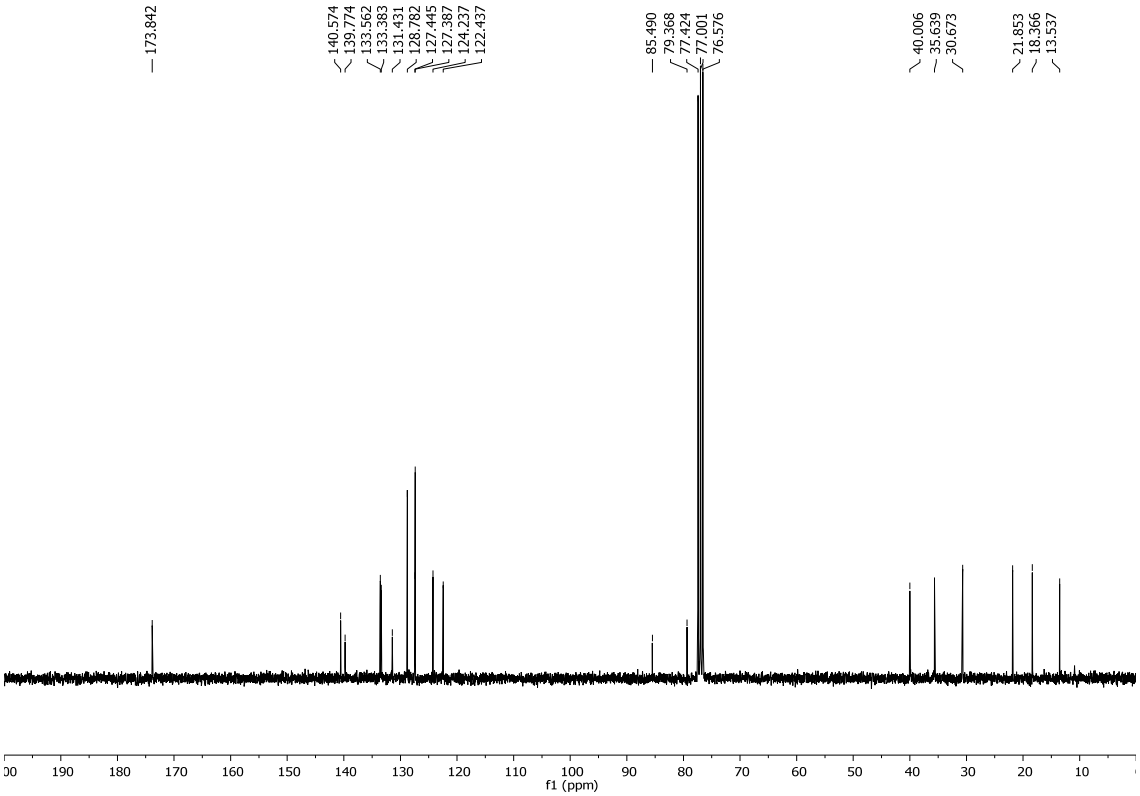


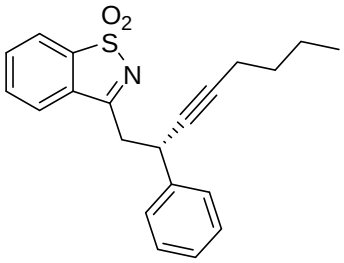
3ae

^{1}H NMR (300 MHz, $CDCl_3$)

^{13}C NMR (75 MHz, $CDCl_3$)

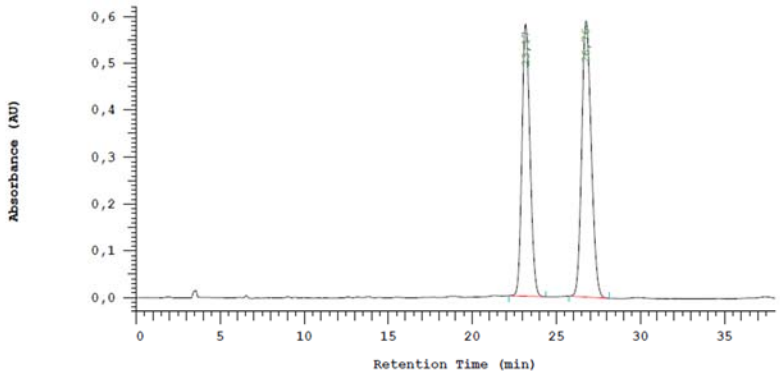






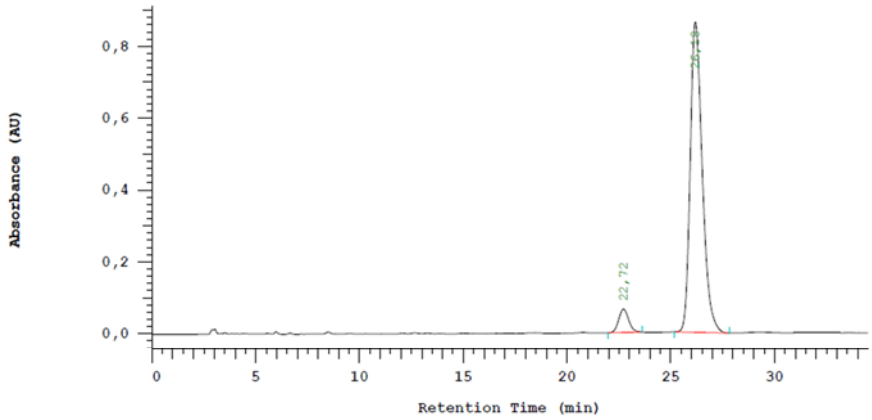
3ae

Racemic or near racemic mixture of enantiomers:

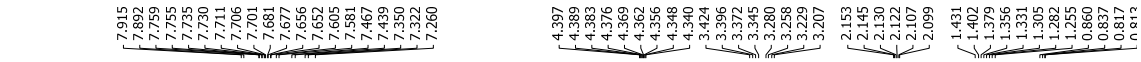


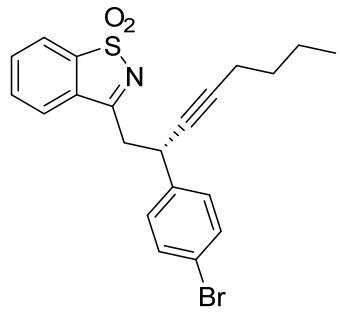
No.	RT	Area	Area %	Name
1	23,17	9625744	45,583	
2	26,76	11491329	54,417	
		21117073	100,000	

Enantioselective reaction:



No.	RT	Area	Area %	Name
1	22,72	1081550	5,898	
2	26,18	17256240	94,102	
		18337790	100,000	

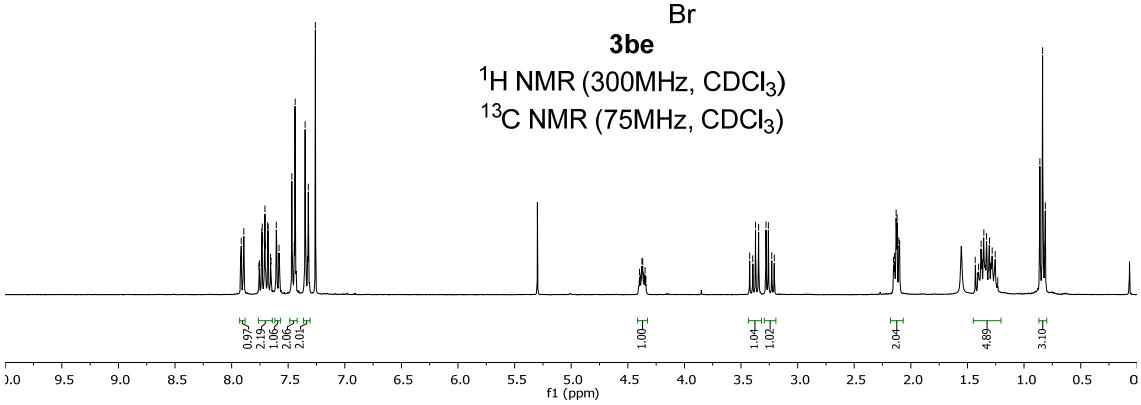


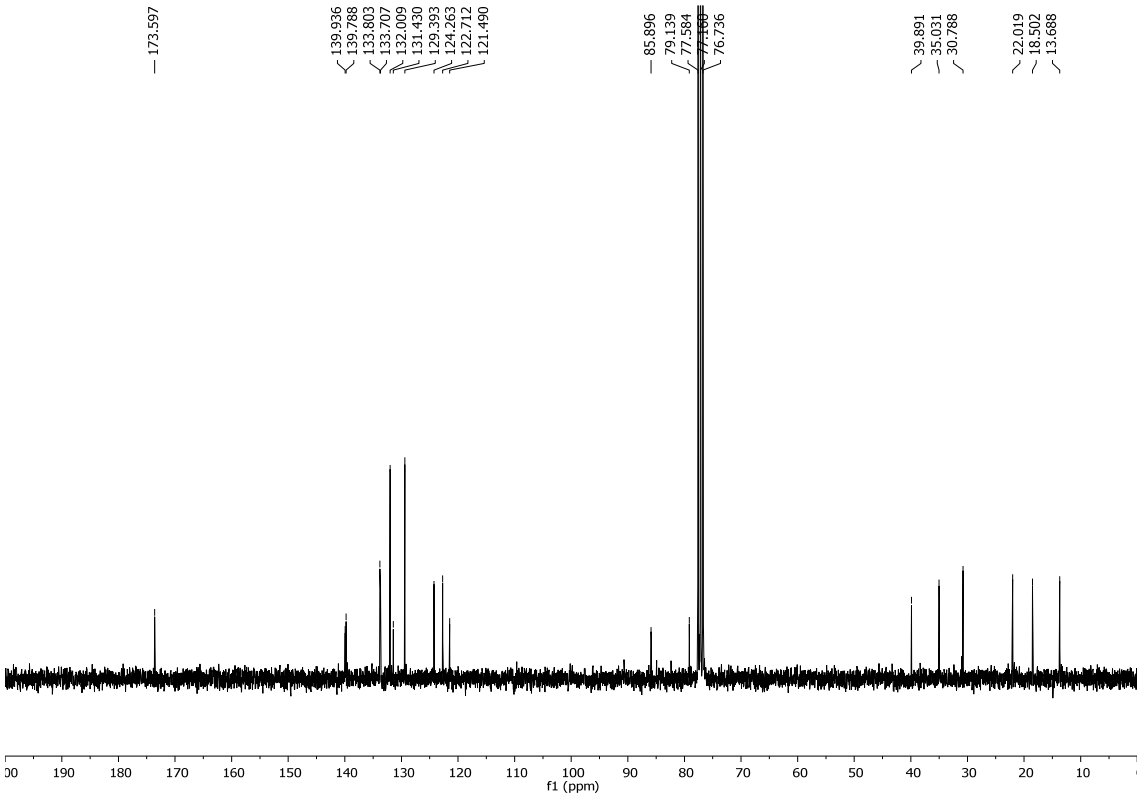


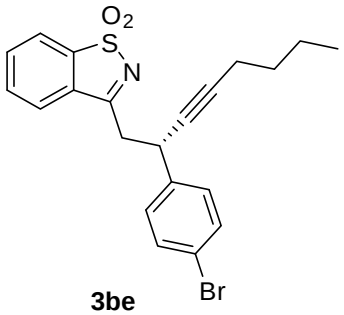
3be

^{1}H NMR (300MHz, $CDCl_3$)

^{13}C NMR (75MHz, $CDCl_3$)

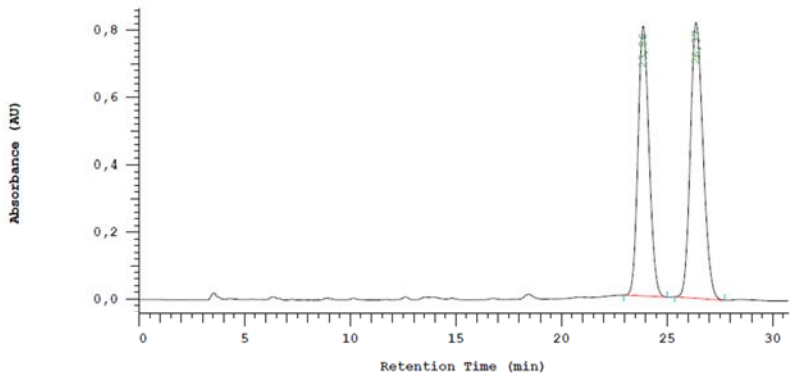






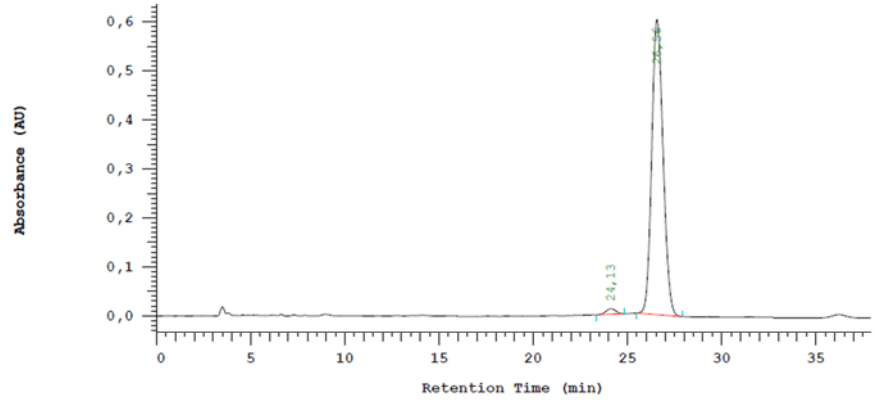
3be

Racemic or near racemic mixture of enantiomers:

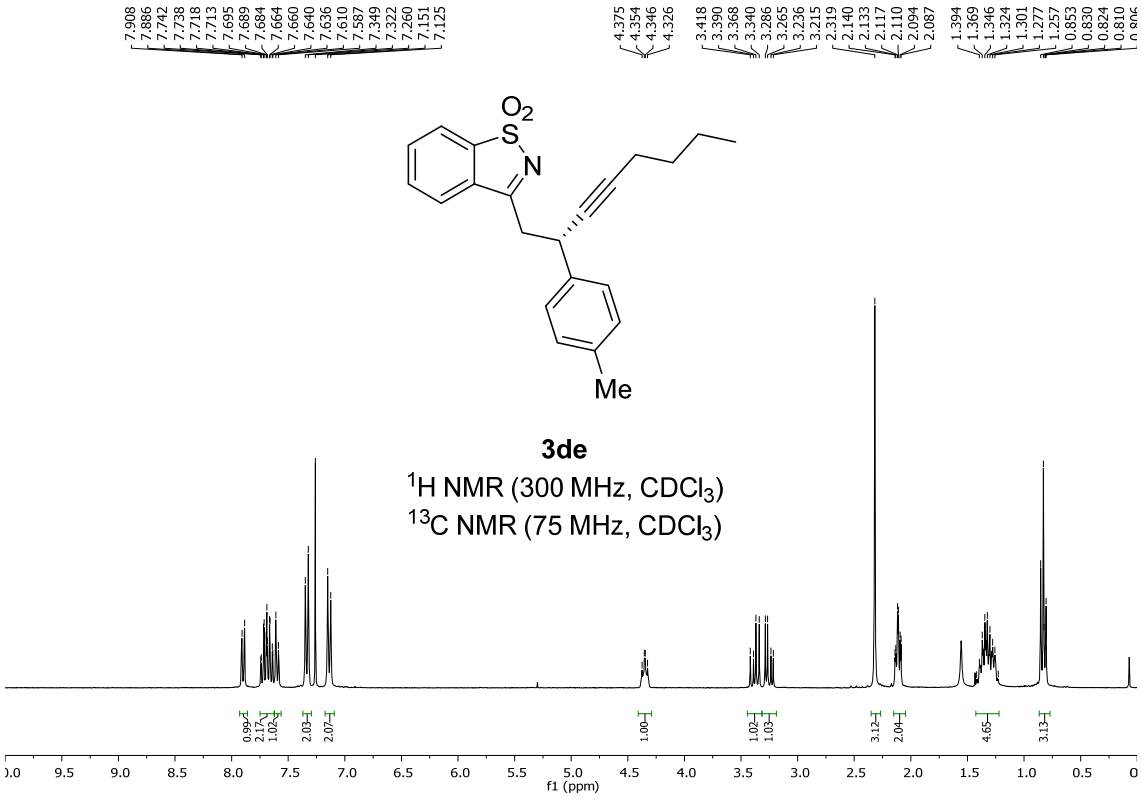


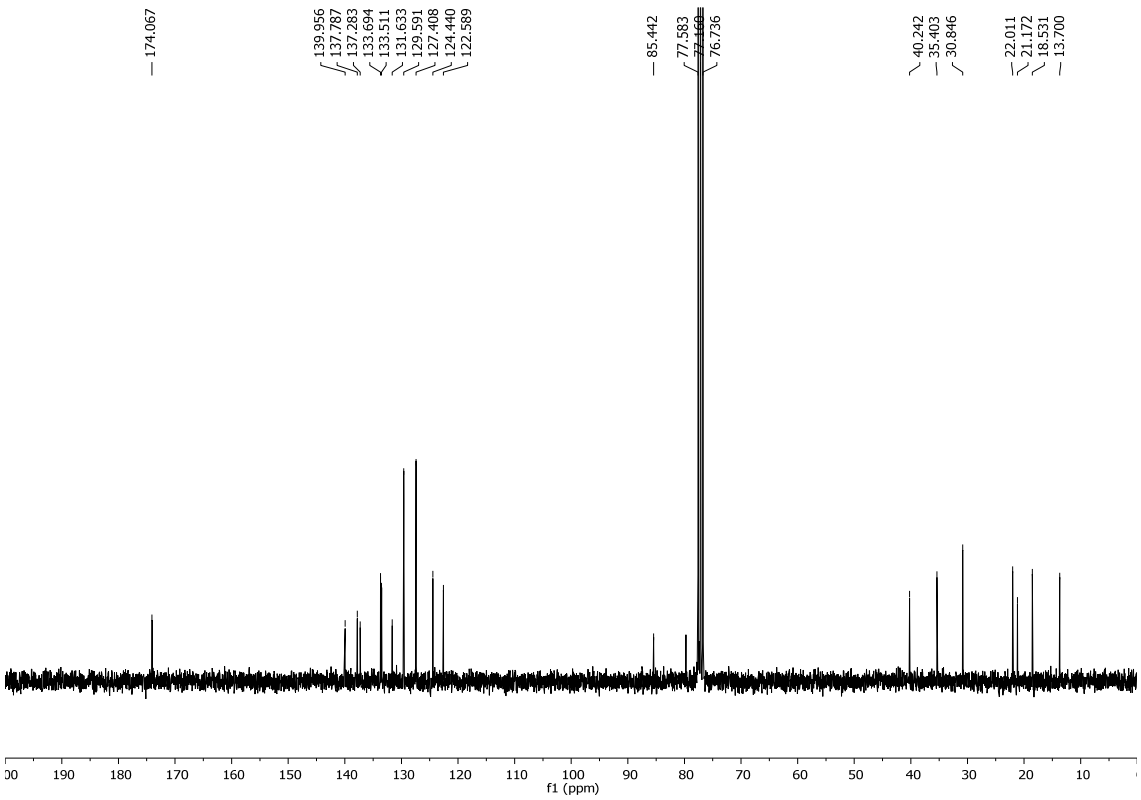
No.	RT	Area	Area %	Name
1	23,86	14572449	46,186	
2	26,37	16979510	53,814	
		31551959	100,000	

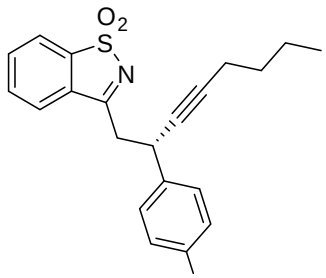
Enantioselective reaction:



No.	RT	Area	Area %	Name
1	24,13	198690	1,570	
2	26,56	12454504	98,430	
		12653194	100,000	

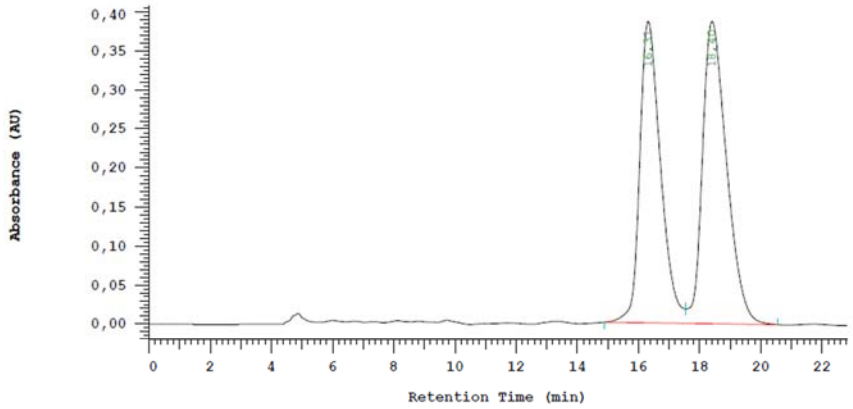

7.908
7.886
7.742
7.738
7.718
7.713
7.695
7.689
7.684
7.664
7.660
7.640
7.636
7.610
7.587
7.349
7.322
7.260
7.151
7.125
4.375
4.354
4.346
4.326
3.418
3.390
3.368
3.340
3.286
3.265
3.236
3.215
2.319
2.140
2.133
2.117
2.110
2.094
2.087
1.394
1.369
1.346
1.324
1.301
1.277
1.257
0.853
0.830
0.824
0.810
O2
S
N
Me
3de
1H NMR (300 MHz, CDCl3)
13C NMR (75 MHz, CDCl3)
0.99
2.17
1.02
2.03
2.07
1.00
1.02
1.03
3.12
2.04
4.65
3.13
f1 (ppm)


174.067
139.956
137.787
137.283
133.694
133.511
131.633
129.591
127.408
124.440
122.589
85.442
77.583
77.160
76.736
40.242
35.403
30.846
22.011
21.172
18.531
13.700
f1 (ppm)



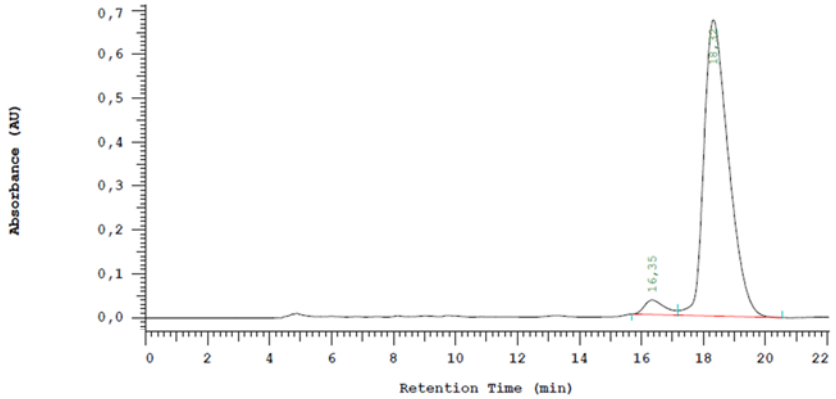
3de Me

Racemic or near racemic mixture of enantiomers:

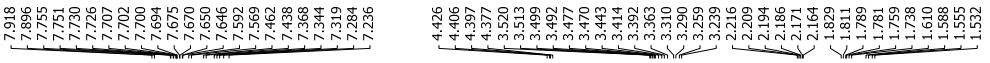


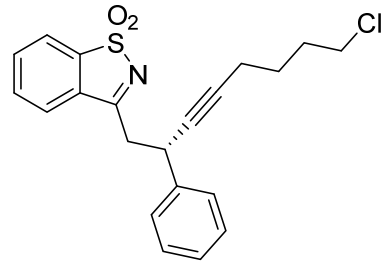
No.	RT	Area	Area %	Name
1	16,31	9140336	46,224	
2	18,40	10633608	53,776	
		19773944	100,000	

Enantioselective reaction:



No.	RT	Area	Area %	Name
1	16,35	755407	3,894	
2	18,32	18645662	96,106	
		19401069	100,000	

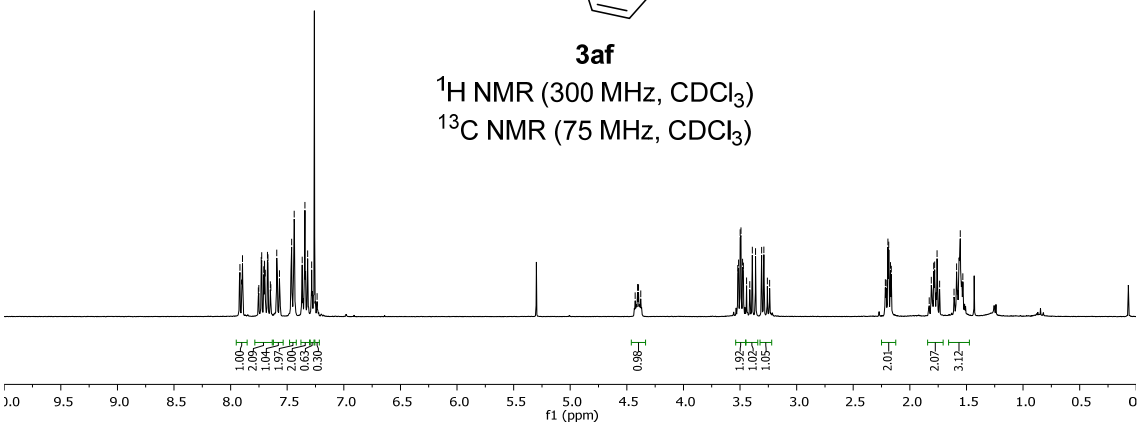


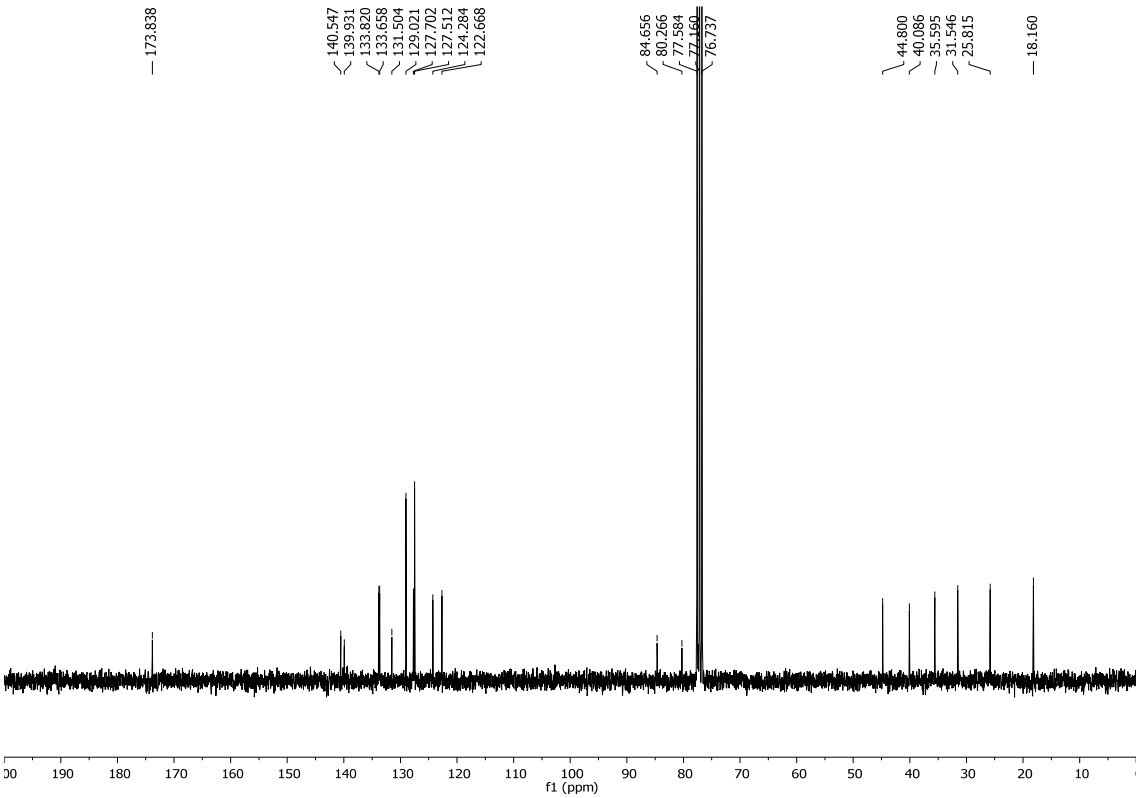


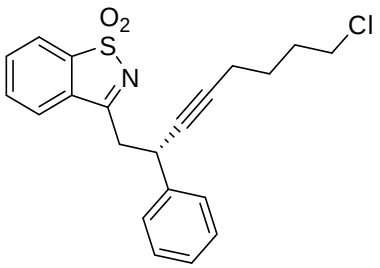
3af

^{1}H NMR (300 MHz, $CDCl_3$)

^{13}C NMR (75 MHz, $CDCl_3$)

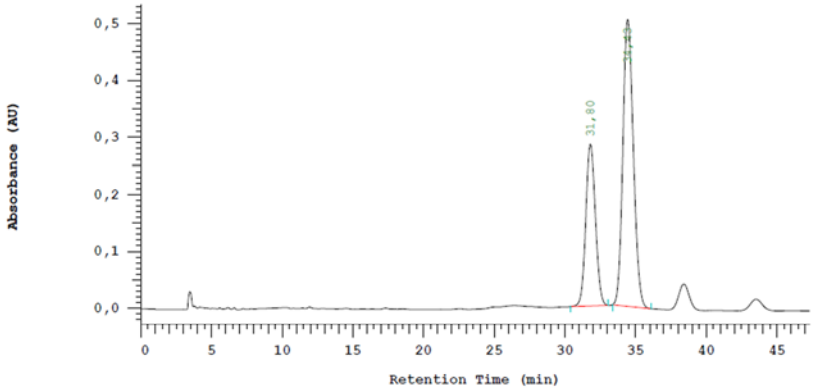






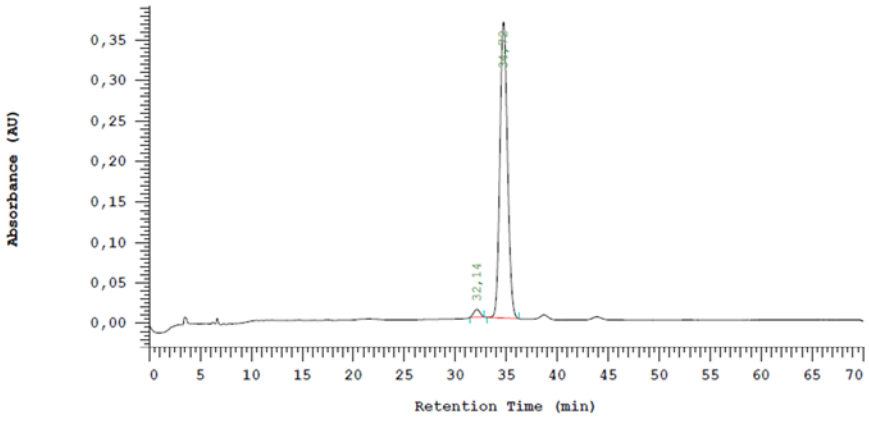
3af

Racemic or near racemic mixture of enantiomers:

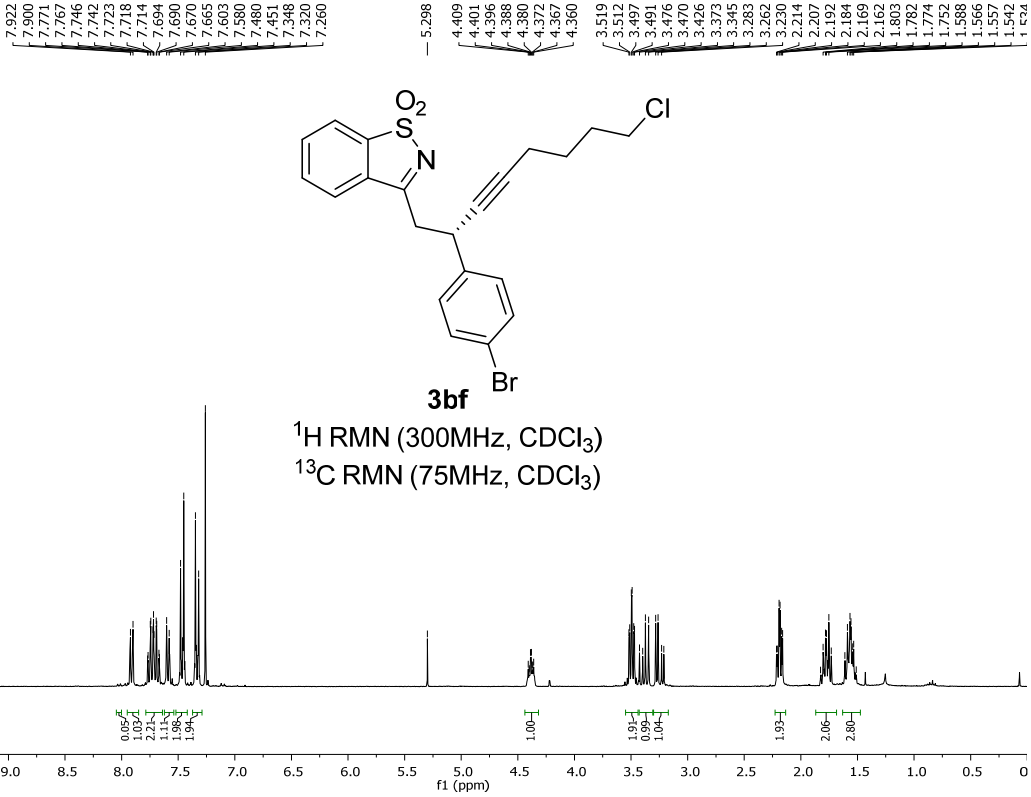


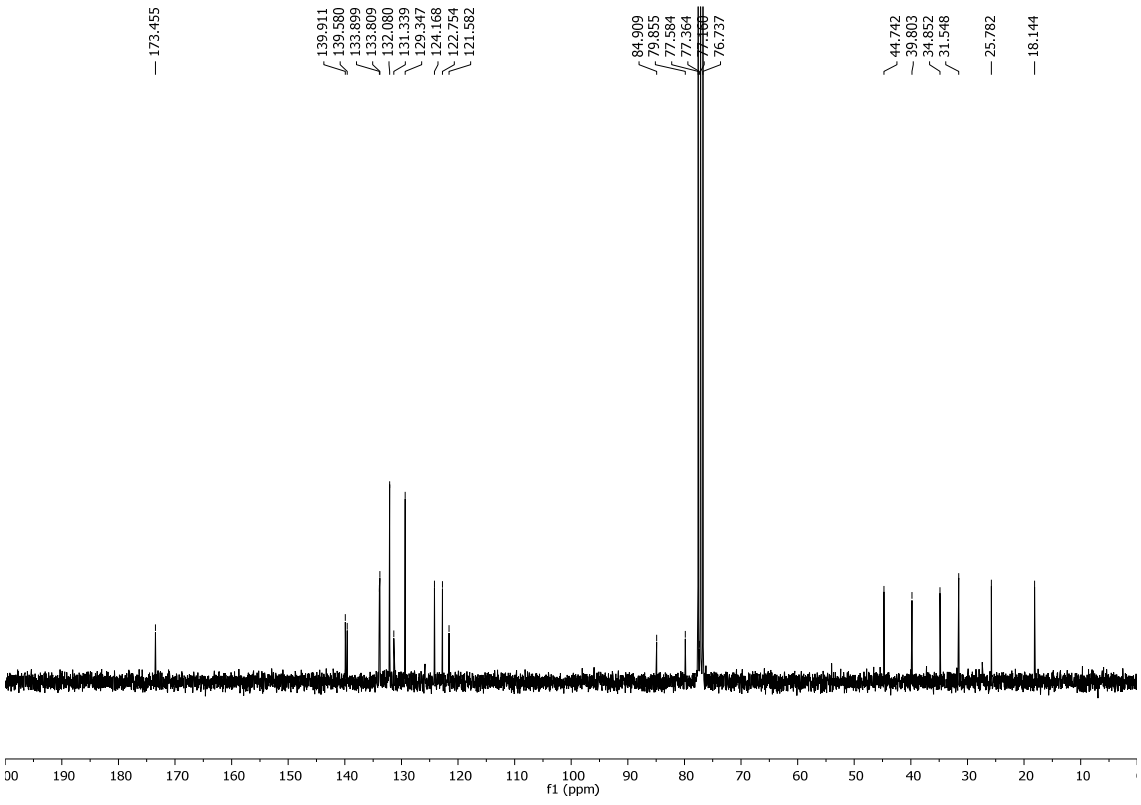
No.	RT	Area	Area %	Name
1	31,80	6645030	33,999	
2	34,43	12899800	66,001	
		19544830	100,000	

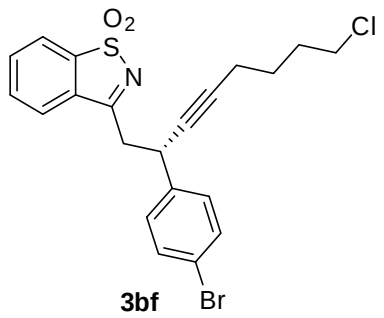
Enantioselective reaction:



No.	RT	Area	Area %	Name
1	32,14	199995	2,079	
2	34,72	9417889	97,921	
		9617884	100,000	

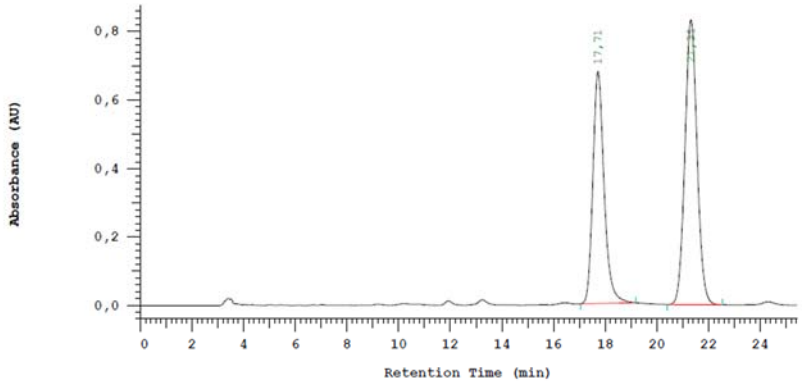

7.922
7.900
7.771
7.767
7.746
7.742
7.723
7.718
7.714
7.694
7.690
7.670
7.665
7.603
7.580
7.480
7.451
7.348
7.320
7.260
5.298
4.409
4.401
4.396
4.388
4.380
4.372
4.367
4.360
3.519
3.512
3.497
3.491
3.476
3.470
3.426
3.373
3.345
3.283
3.262
3.230
2.214
2.207
2.192
2.184
2.169
2.162
1.803
1.782
1.774
1.752
1.588
1.566
1.557
1.542
O2
S
N
Cl
Br
3bf
1H RMN (300MHz, CDCl3)
13C RMN (75MHz, CDCl3)
0.05
1.03
2.22
1.11
1.98
1.94
1.00
1.91
0.99
1.04
1.93
2.06
2.80
f1 (ppm)


173.455
139.911
139.580
133.899
133.809
132.080
131.339
129.347
124.168
122.754
121.582
84.909
79.855
77.584
77.364
76.737
44.742
39.803
34.852
31.548
25.782
18.144
f1 (ppm)



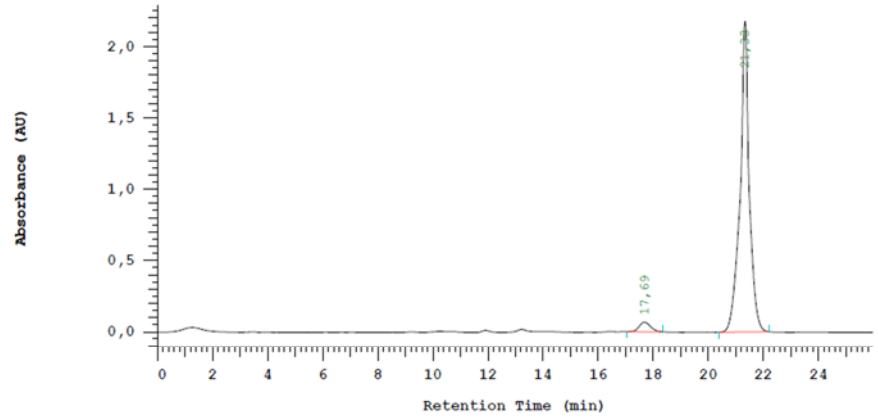
3bf

Racemic or near racemic mixture of enantiomers:

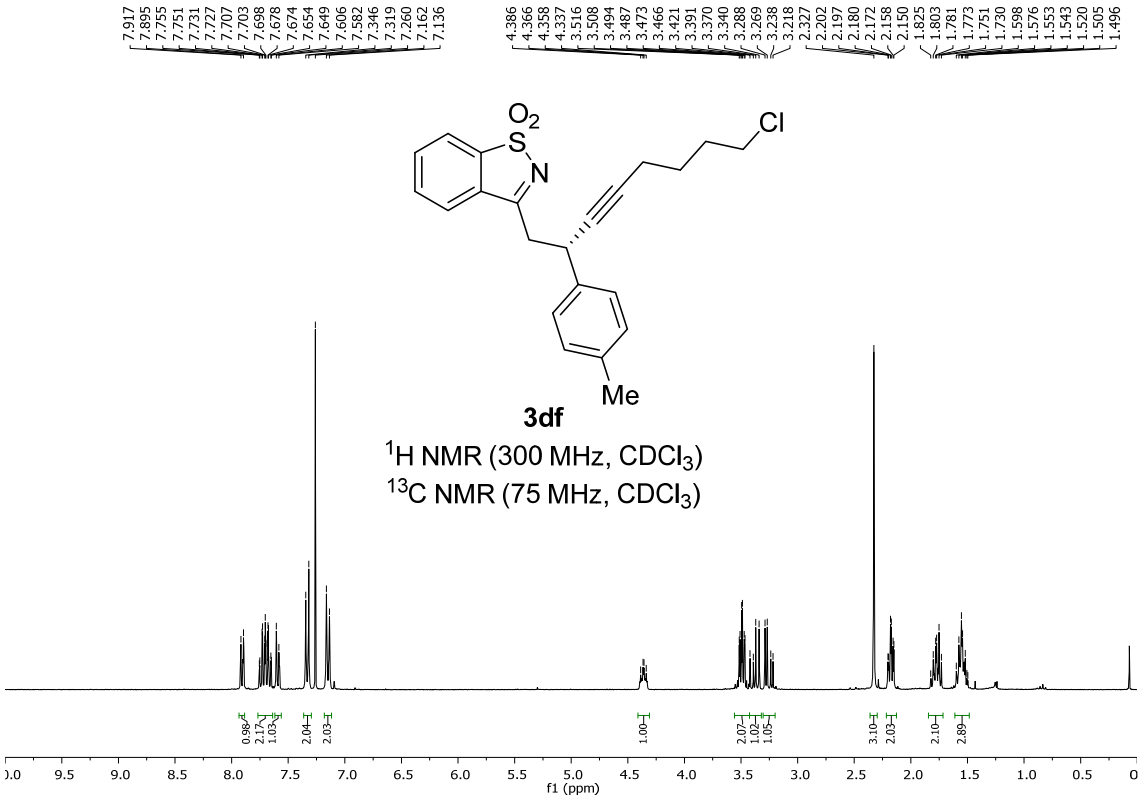


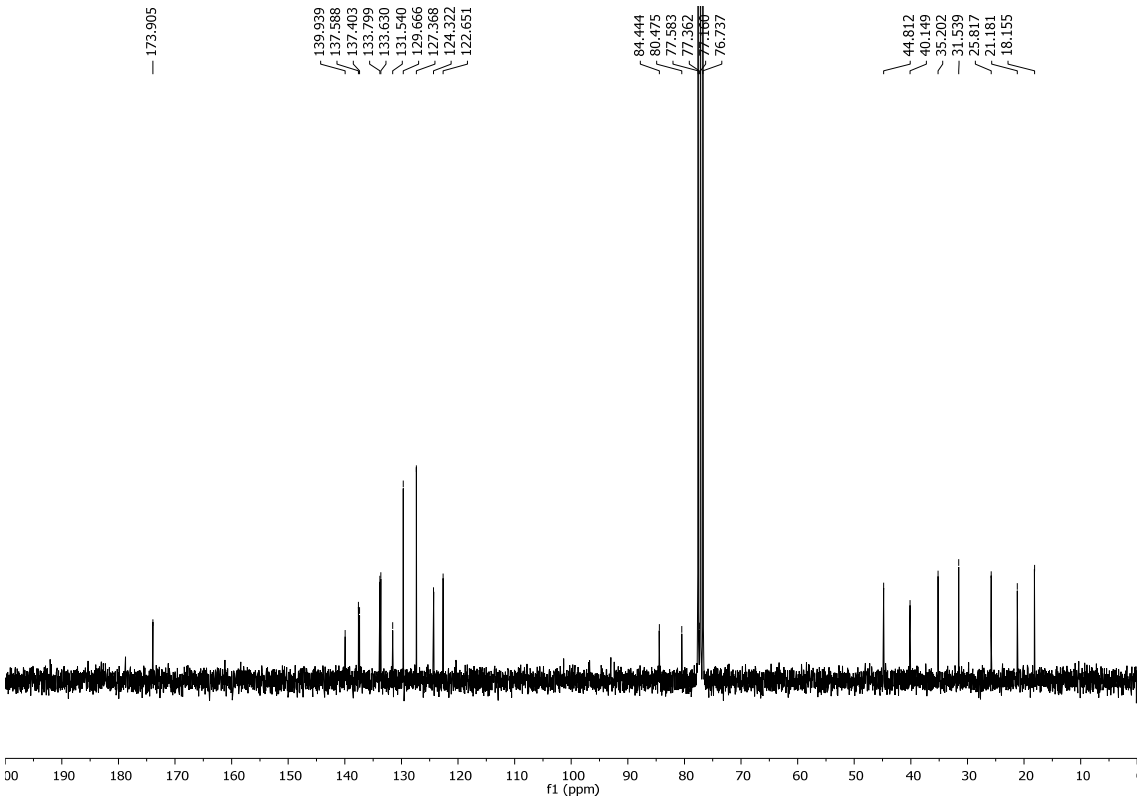
No.	RT	Area	Area %	Name
1	17,71	10183900	42,720	
2	21,31	13654979	57,280	
		23838879	100,000	

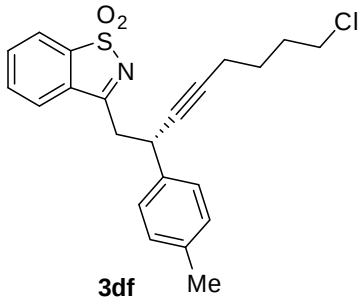
Enantioselective reaction:



No.	RT	Area	Area %	Name
1	17,69	950905	3,611	
2	21,33	25385980	96,389	
		26336885	100,000	

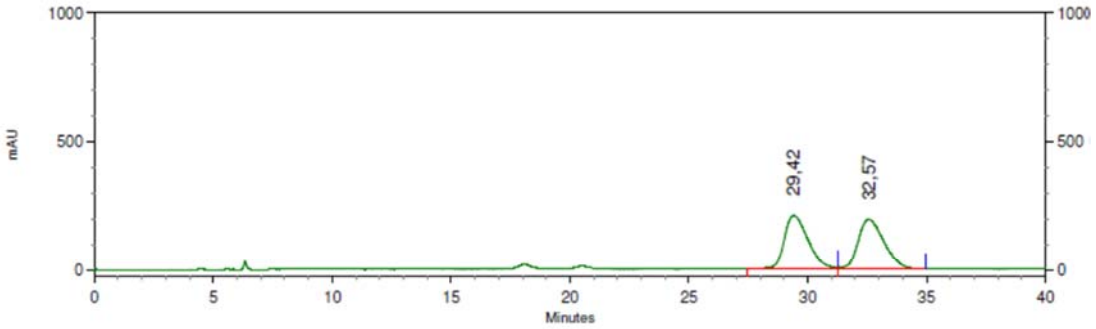

7.917
7.895
7.755
7.751
7.731
7.727
7.707
7.703
7.698
7.678
7.674
7.654
7.649
7.606
7.582
7.346
7.319
7.260
7.162
7.136
4.386
4.366
4.358
4.337
3.516
3.508
3.494
3.487
3.473
3.466
3.421
3.391
3.370
3.340
3.288
3.269
3.238
3.218
2.327
2.202
2.197
2.180
2.172
2.158
2.150
1.825
1.803
1.781
1.773
1.751
1.730
1.598
1.576
1.553
1.543
1.520
1.505
1.496
O2
S
N
Cl
Me
3df
1H NMR (300 MHz, CDCl3)
13C NMR (75 MHz, CDCl3)
0.98
2.17
1.03
2.04
2.03
1.00
2.07
1.02
1.05
3.10
2.03
2.10
2.89
f1 (ppm)


173.905
139.939
137.588
137.403
133.799
133.630
131.540
129.666
127.368
124.322
122.651
84.444
80.475
77.583
77.362
77.160
76.737
44.812
40.149
35.202
31.539
25.817
21.181
18.155
f1 (ppm)



3df

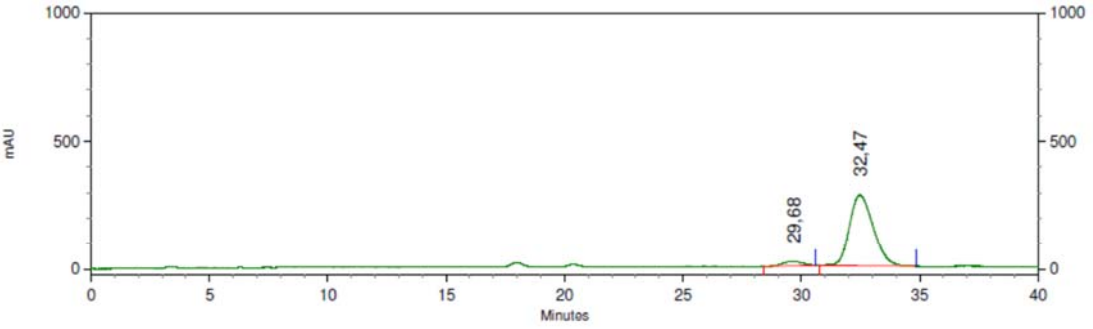
Racemic or near racemic mixture of enantiomers:



14: 259 nm, 4 nm
Results

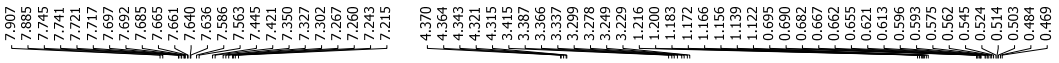
Retention Time	Area	Area Percent
29,42	58927730	49,702
32,57	59633840	50,298

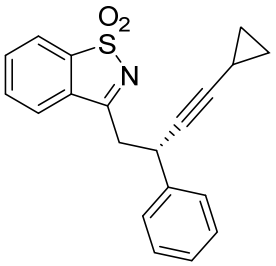
Enantioselective reaction:



2: 229 nm, 4 nm Results

Retention Time	Area	Area Percent
29,68	3881601	4,738
32,47	78050402	95,262

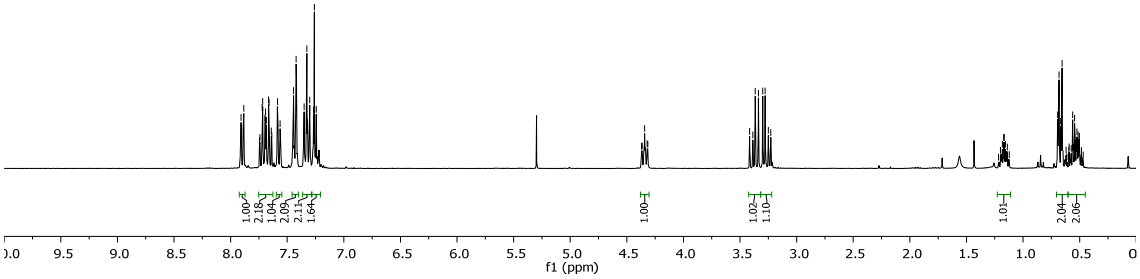


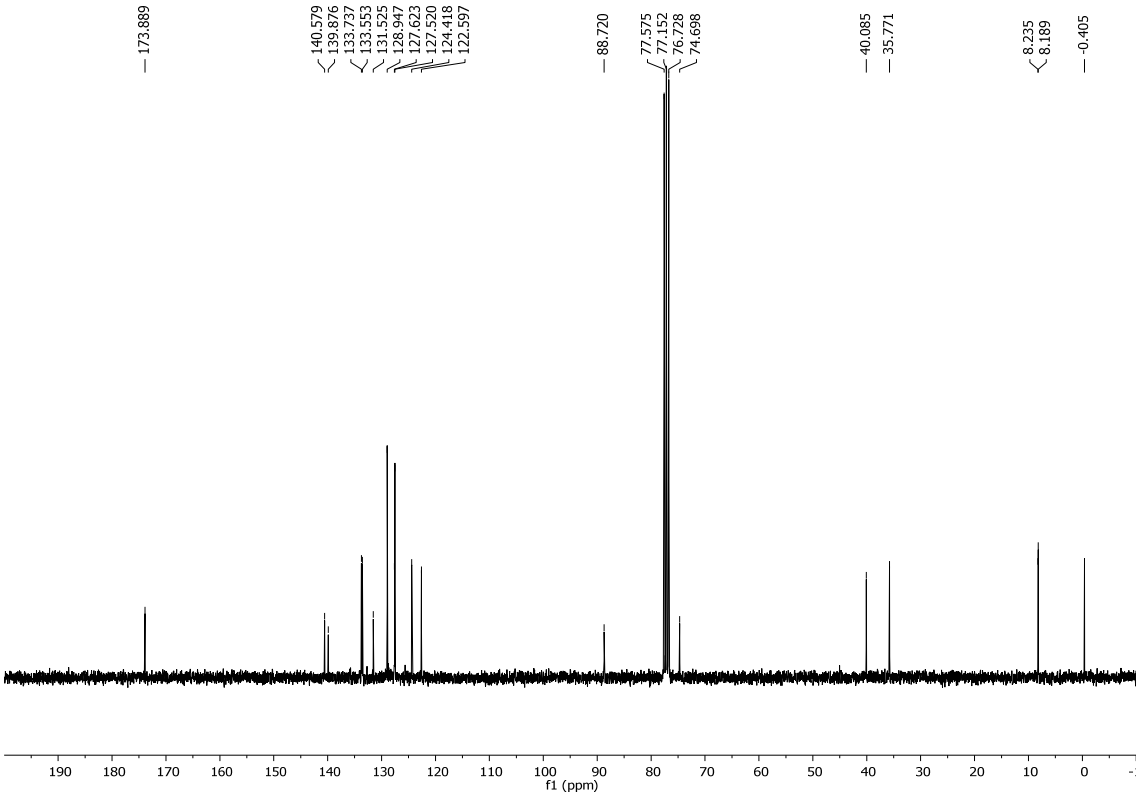


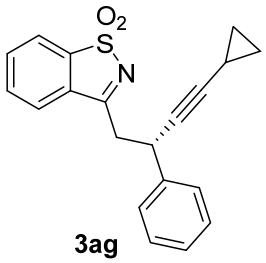
3ag

^{1}H NMR (300 MHz, $CDCl_3$)

^{13}C NMR (75 MHz, $CDCl_3$)

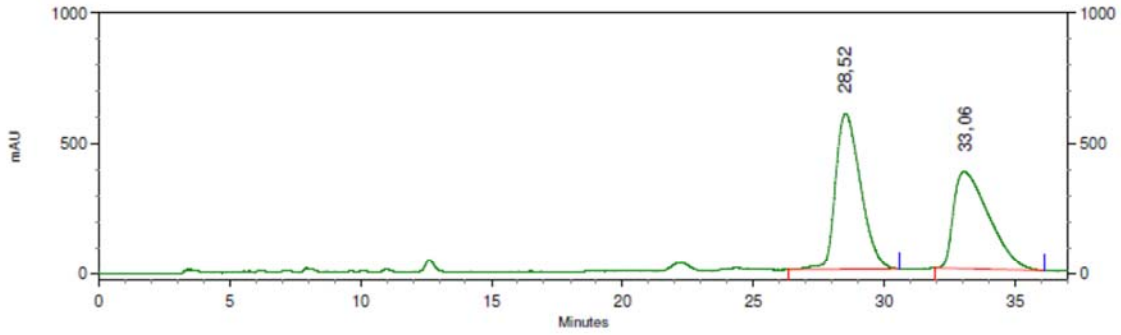






3ag

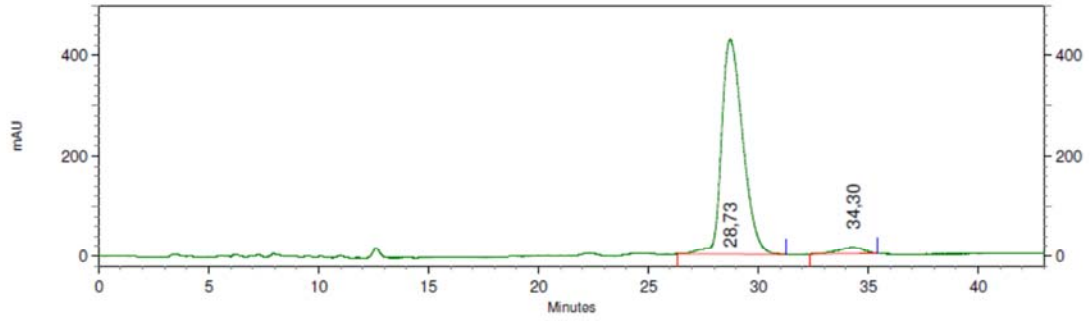
Racemic or near racemic mixture of enantiomers:



24: 242 nm, 4 nm
Results

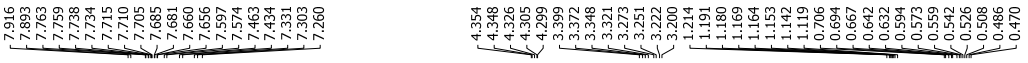
Retention Time	Area	Area Percent
28,52	160489802	53,135
33,06	141550470	46,865

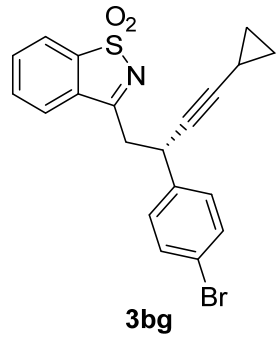
Enantioselective reaction:



24: 242 nm, 4 nm
Results

Retention Time	Area	Area Percent
28,73	115588387	96,368
34,30	4356850	3,632

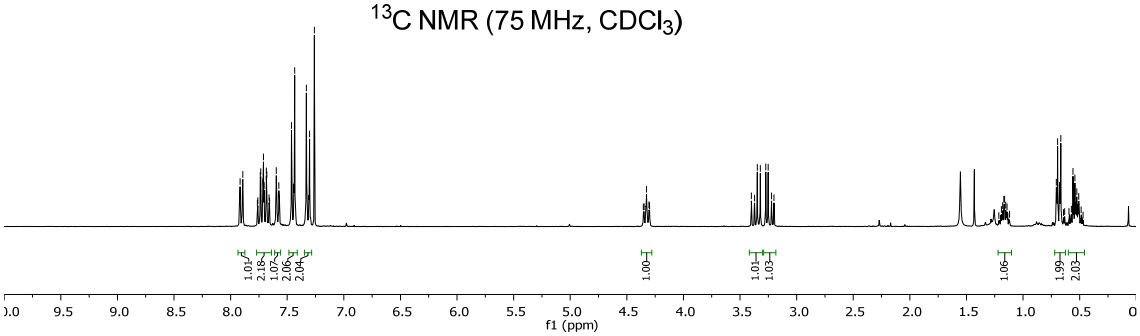


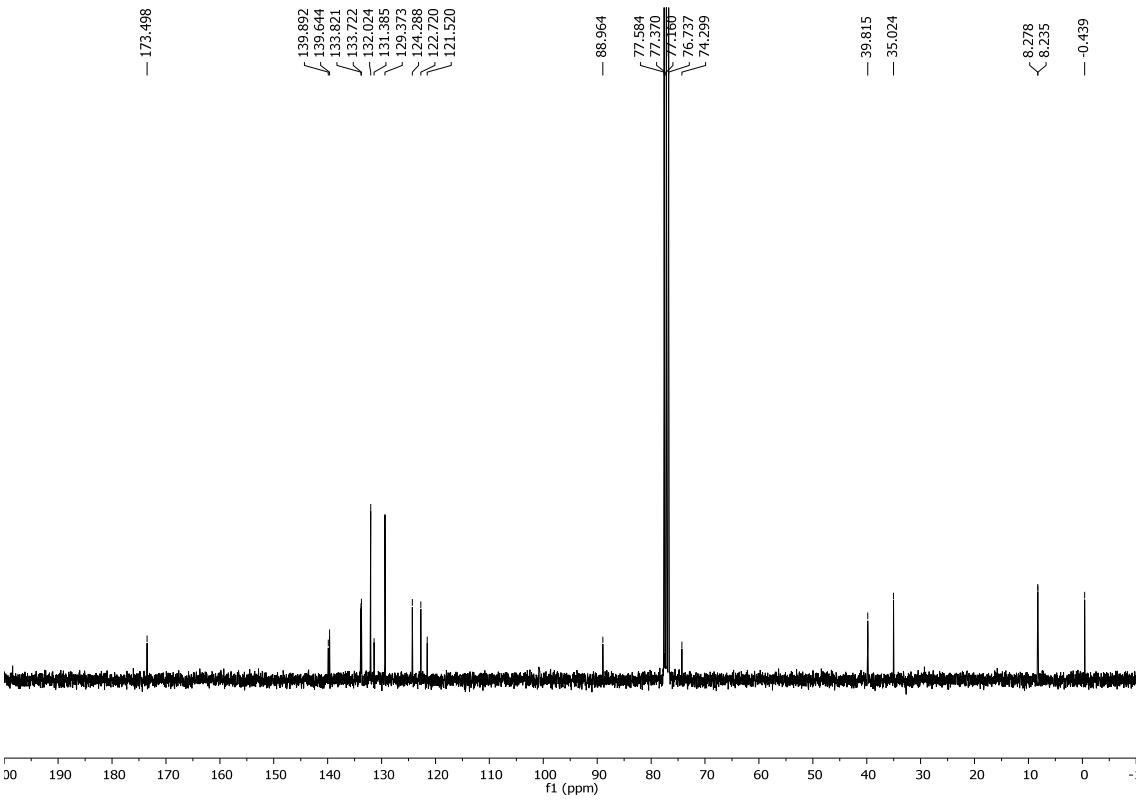


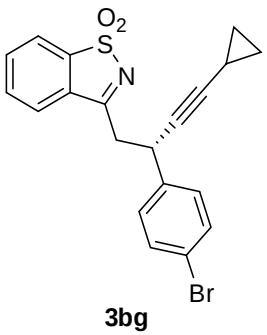
3bg

^{1}H NMR (300 MHz, $CDCl_3$)

^{13}C NMR (75 MHz, $CDCl_3$)

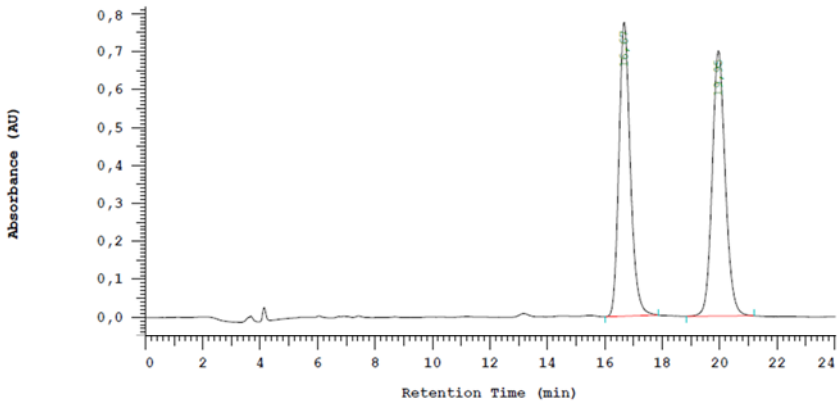






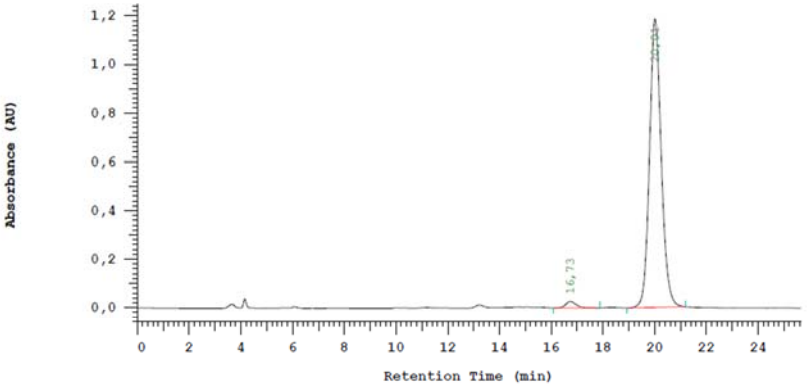
3bg

Racemic or near racemic mixture of enantiomers:

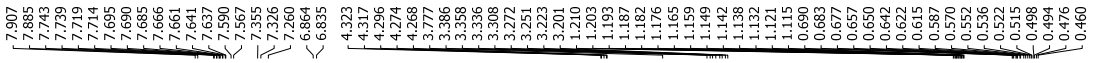


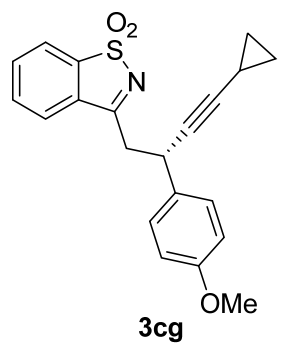
No.	RT	Area	Area %	Name
1	16,67	10639500	48,932	
2	19,95	11103820	51,068	
		21743320	100,000	

Enantioselective reaction:



No.	RT	Area	Area %	Name
1	16,73	370170	1,940	
2	20,01	18711820	98,060	
		19081990	100,000	

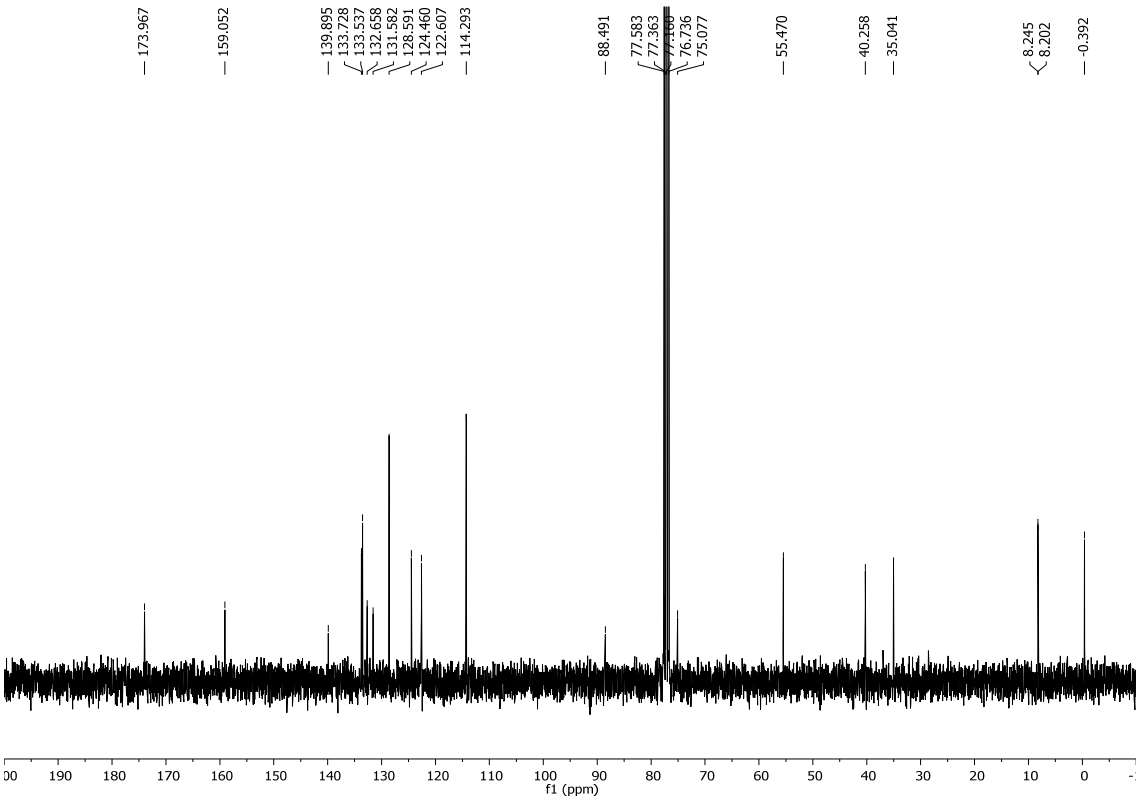


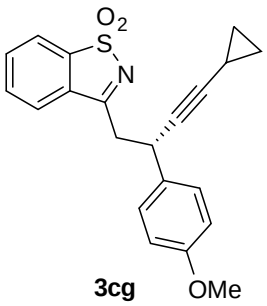


3cg

^{1}H NMR (300 MHz, $CDCl_3$)

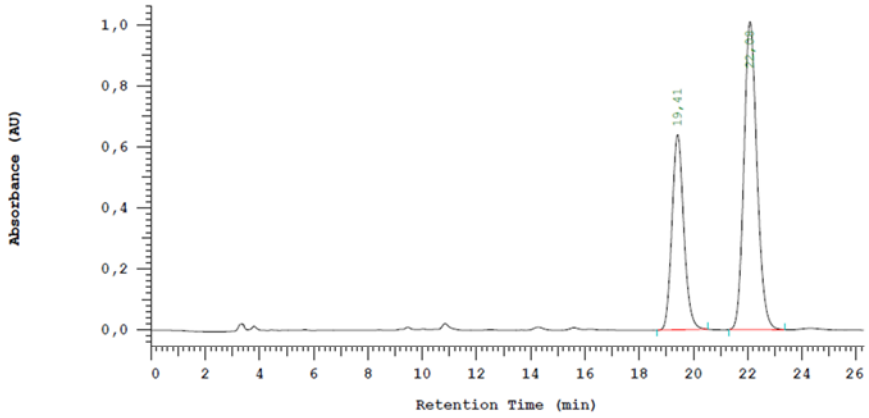
^{13}C NMR (75 MHz, $CDCl_3$)





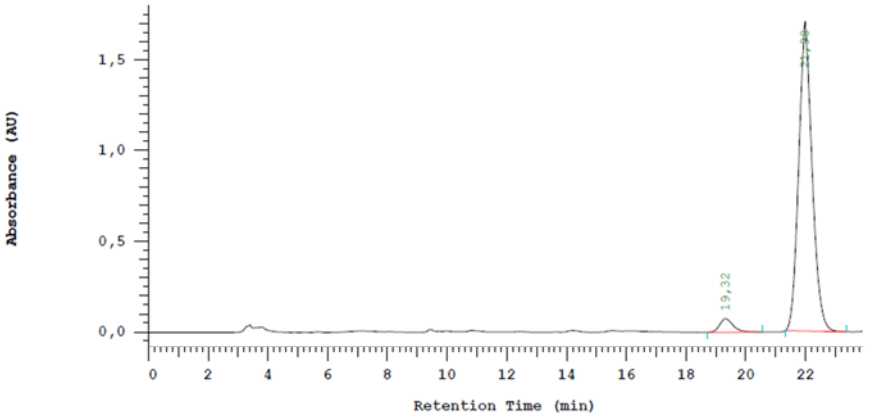
3cg

Racemic or near racemic mixture of enantiomers:

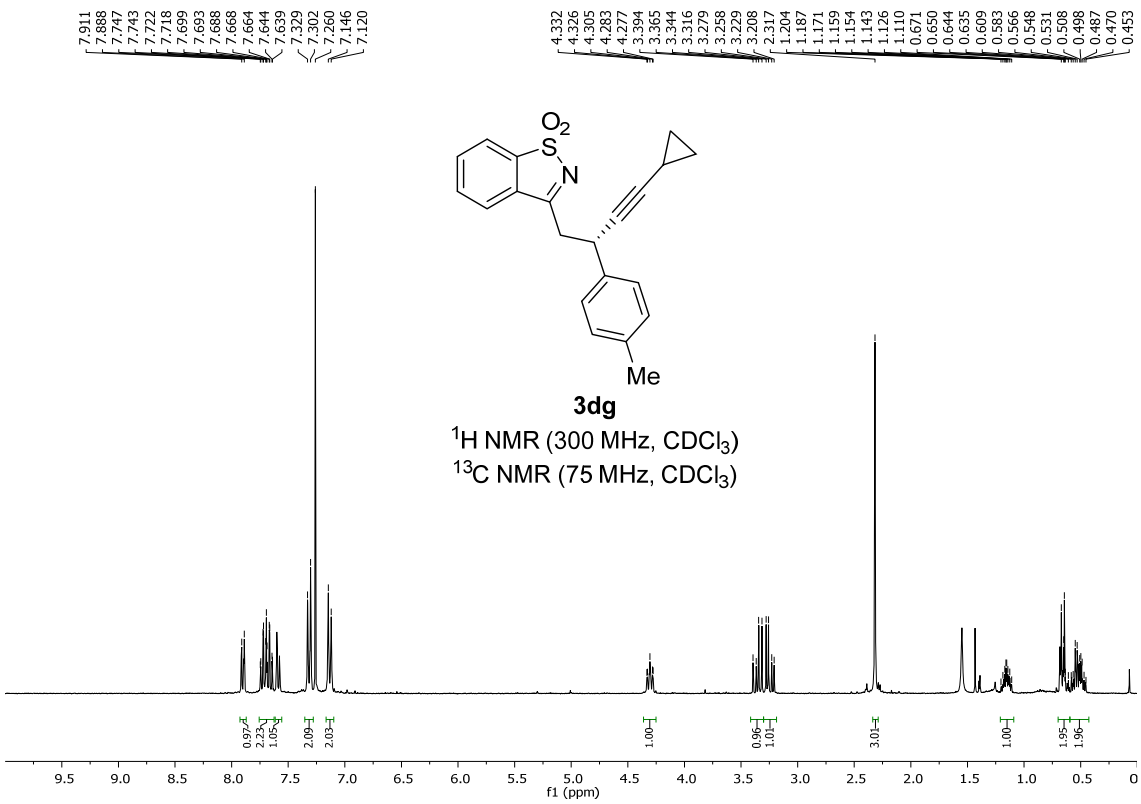


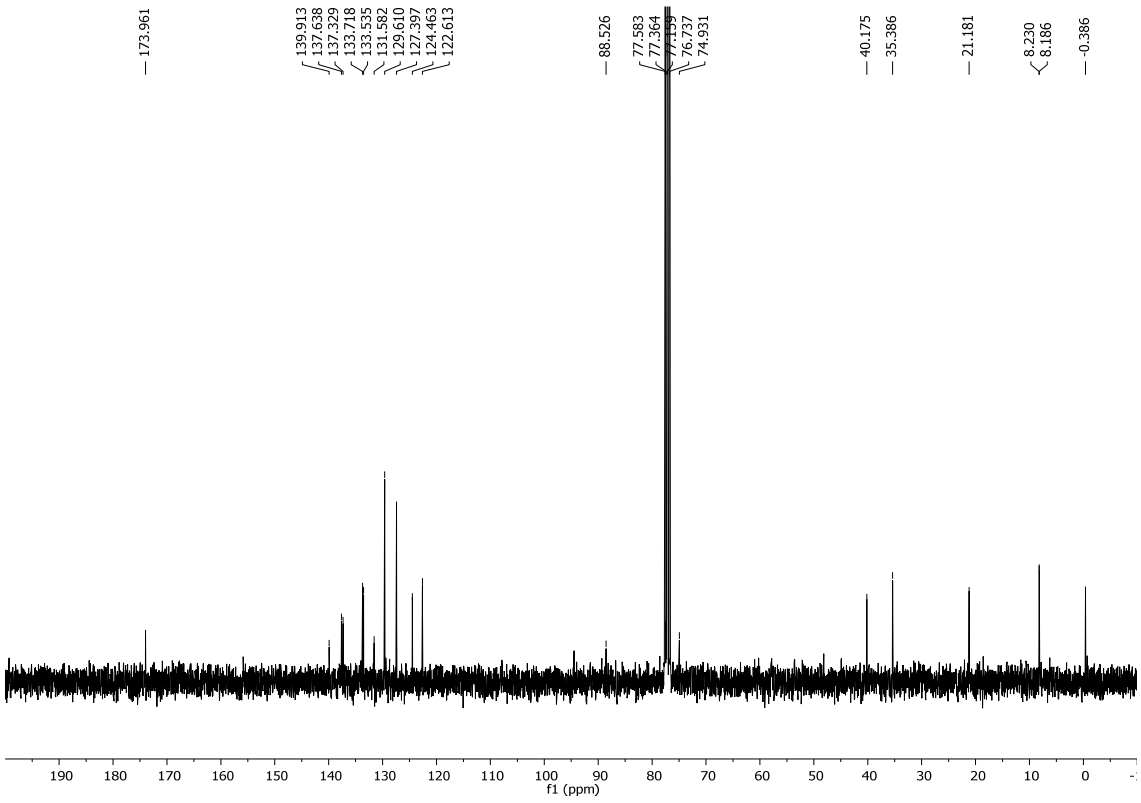
No.	RT	Area	Area %	Name
1	19,41	9640990	36,342	
2	22,08	16887315	63,658	
		26528305	100,000	

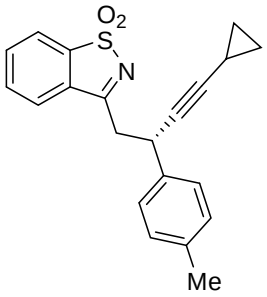
Enantioselective reaction:



No.	RT	Area	Area %	Name
1	19,32	1135975	4,145	
2	21,98	26272099	95,855	
		27408074	100,000	

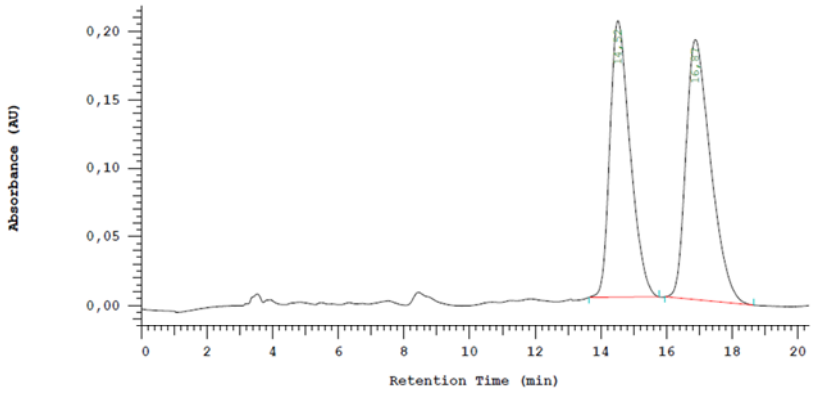

7.911
7.888
7.747
7.743
7.722
7.718
7.699
7.693
7.688
7.668
7.664
7.644
7.639
7.329
7.302
7.260
7.146
7.120
4.332
4.326
4.305
4.283
4.277
3.394
3.365
3.344
3.316
3.279
3.258
3.229
3.208
2.317
1.204
1.187
1.171
1.159
1.154
1.143
1.126
1.110
0.671
0.650
0.644
0.635
0.609
0.583
0.566
0.548
0.531
0.508
0.498
0.487
0.470
0.453
O2
S
N
Me
3dg
1H NMR (300 MHz, CDCl3)
13C NMR (75 MHz, CDCl3)
0.97
2.23
1.05
2.09
2.03
1.00
0.96
1.01
3.01
1.00
1.95
1.96
f1 (ppm)


173.961
139.913
137.638
137.329
133.718
133.535
131.582
129.610
127.397
124.463
122.613
88.526
77.583
77.364
77.139
76.737
74.931
40.175
35.386
21.181
8.230
8.186
-0.386
f1 (ppm)



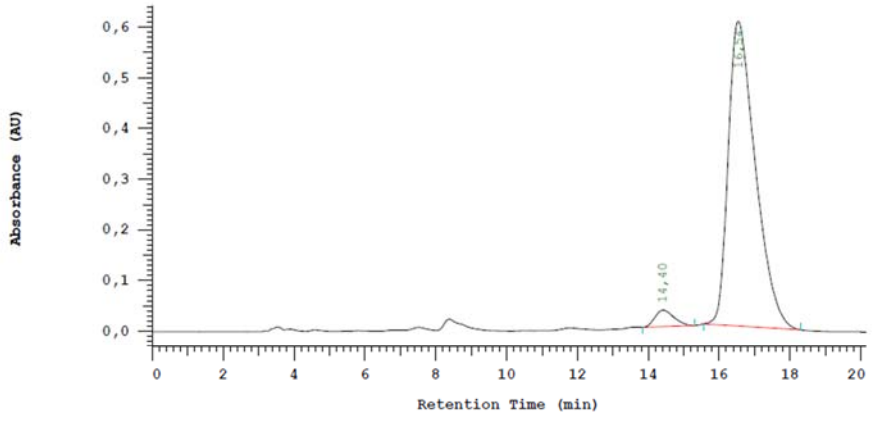
3dg

Racemic or near racemic mixture of enantiomers:

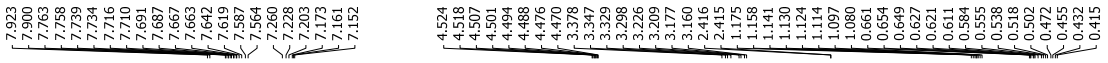


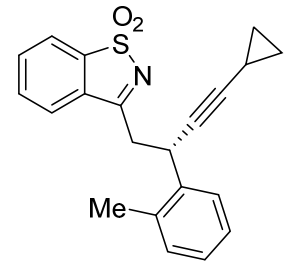
No.	RT	Area	Area %	Name
1	14,52	4322875	46,501	
2	16,87	4973360	53,499	
		9296235	100,000	

Enantioselective reaction:



No.	RT	Area	Area %	Name
1	14,40	599085	3,616	
2	16,54	15966884	96,384	
		16565969	100,000	

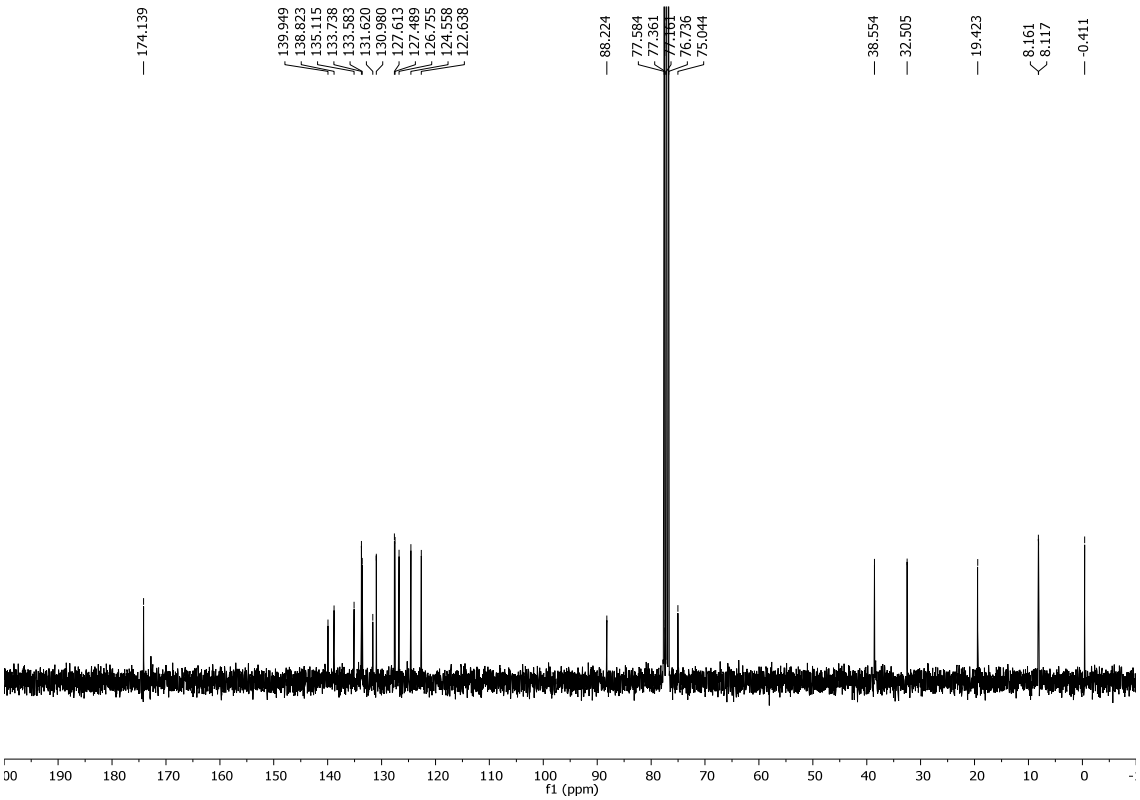


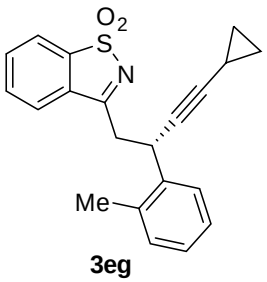


3eg

^{1}H NMR (300 MHz, $CDCl_3$)

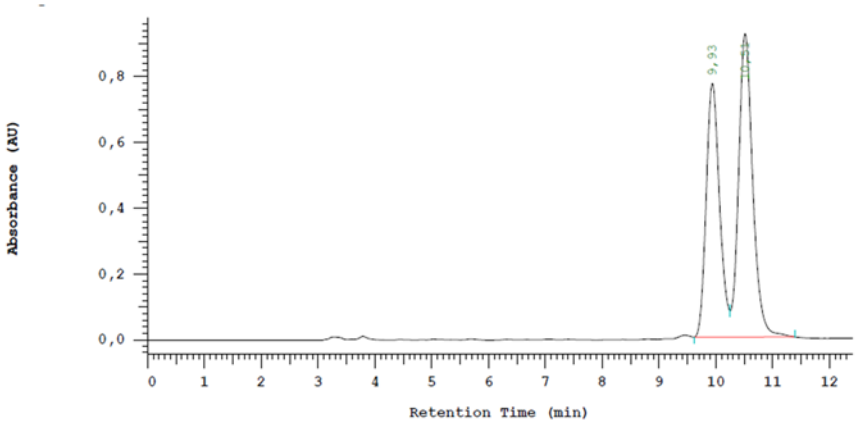
^{13}C NMR (75 MHz, $CDCl_3$)





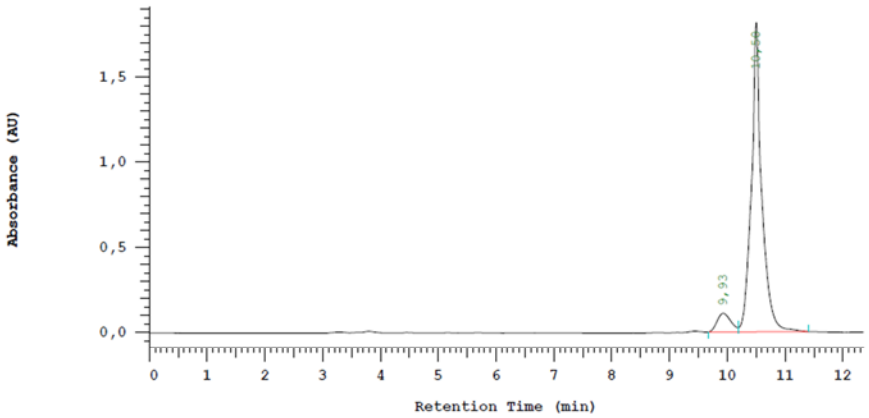
3eg

Racemic or near racemic mixture of enantiomers:

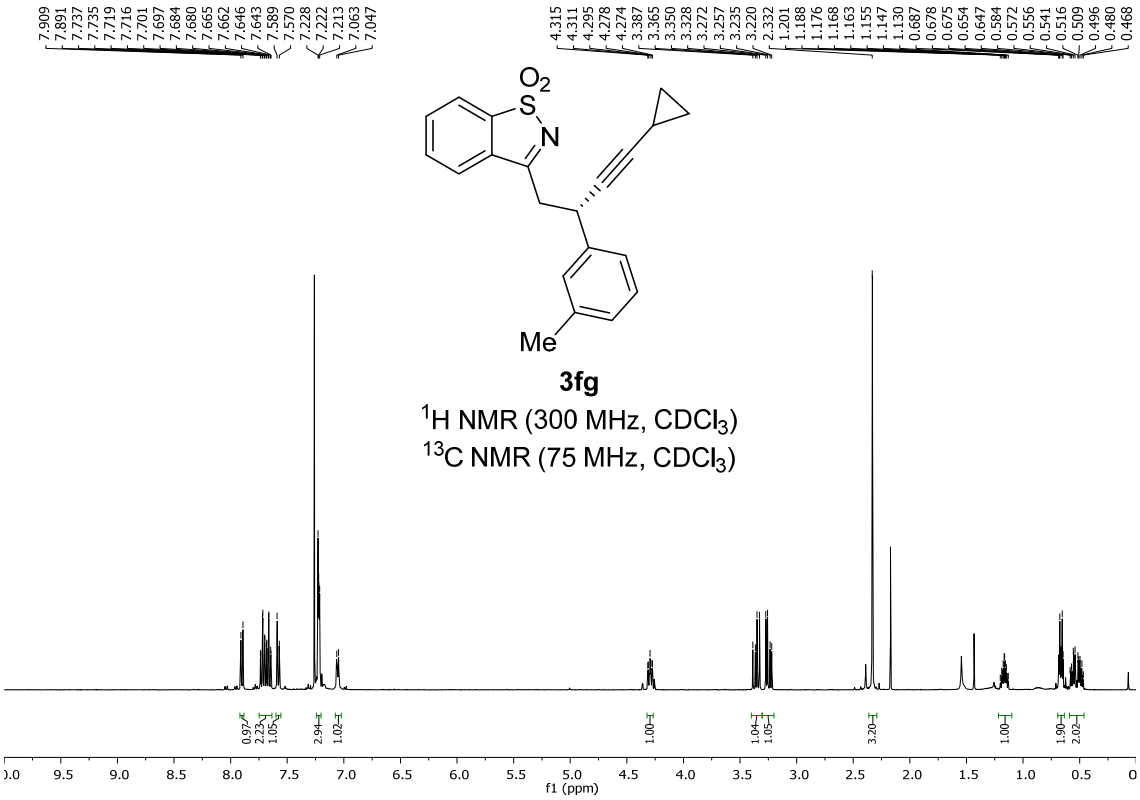


No.	RT	Area	Area %	Name
1	9,93	6282960	44,040	
2	10,51	7983640	55,960	
		14266600	100,000	

Enantioselective reaction:



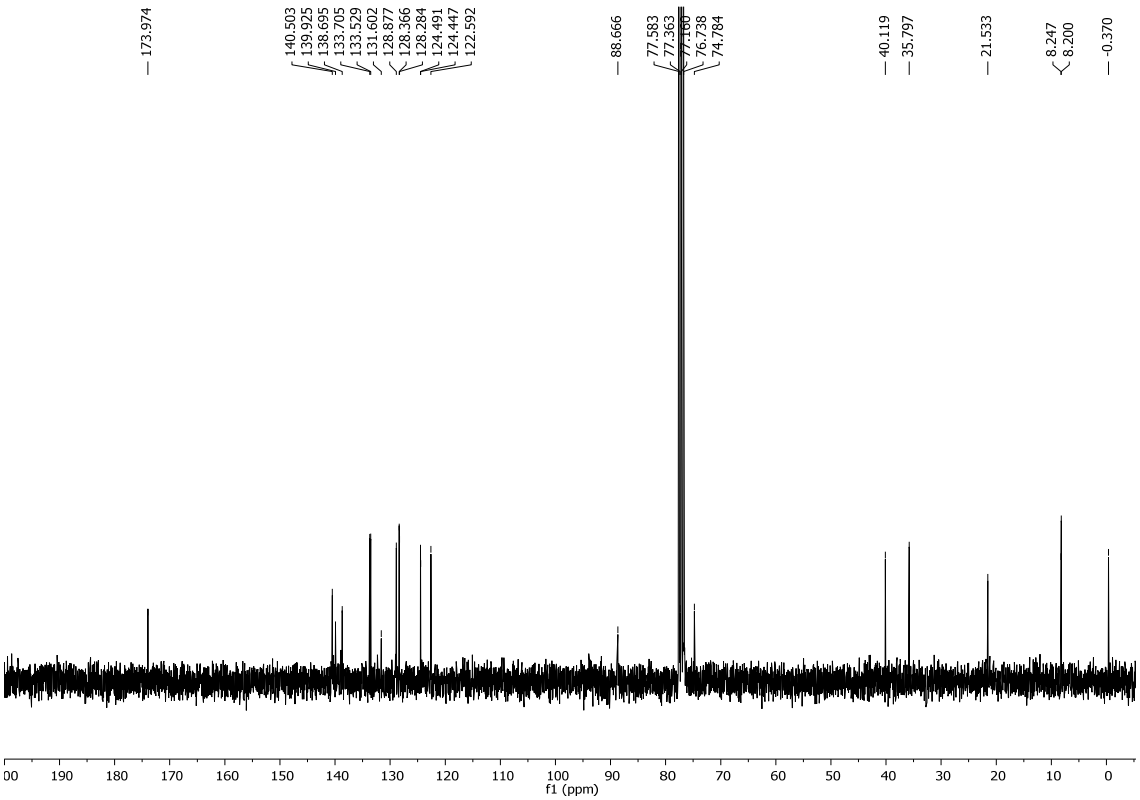
No.	RT	Area	Area %	Name
1	9,93	904102	7,378	
2	10,50	11350442	92,622	
		12254544	100,000	

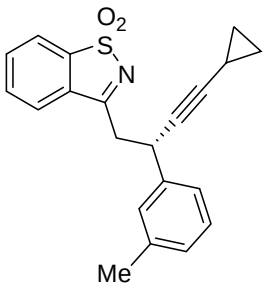


3fg

^{1}H NMR (300 MHz, $CDCl_3$)

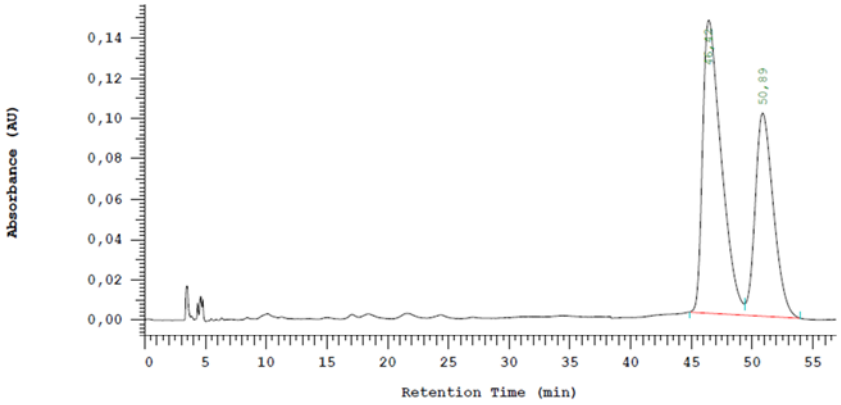
^{13}C NMR (75 MHz, $CDCl_3$)





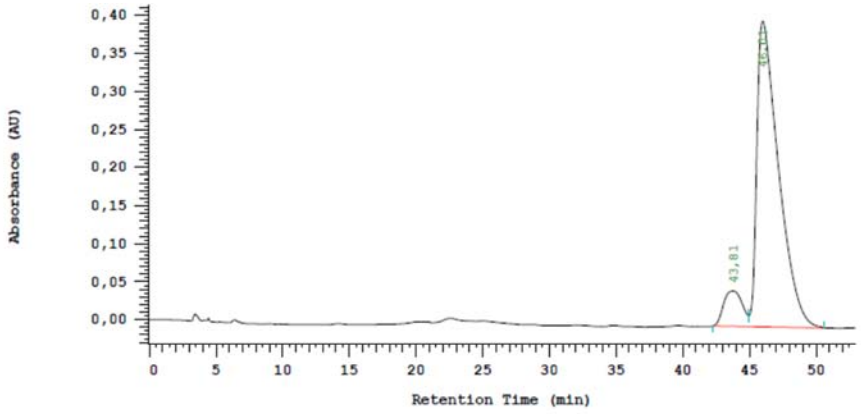
3fg

Racemic or near racemic mixture of enantiomers:

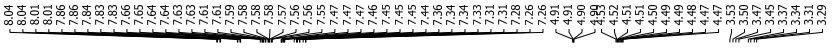


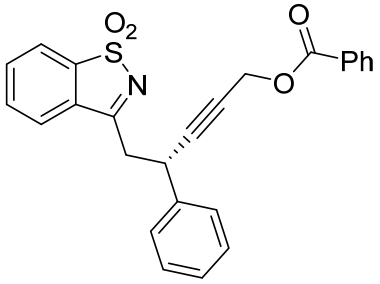
No.	RT	Area	Area %	Name
1	46,42	7748470	59,632	
2	50,89	5245439	40,368	
		12993909	100,000	

Enantioselective reaction:



No.	RT	Area	Area %	Name
1	43,81	2270362	9,139	
2	46,01	22571467	90,861	
		24841829	100,000	

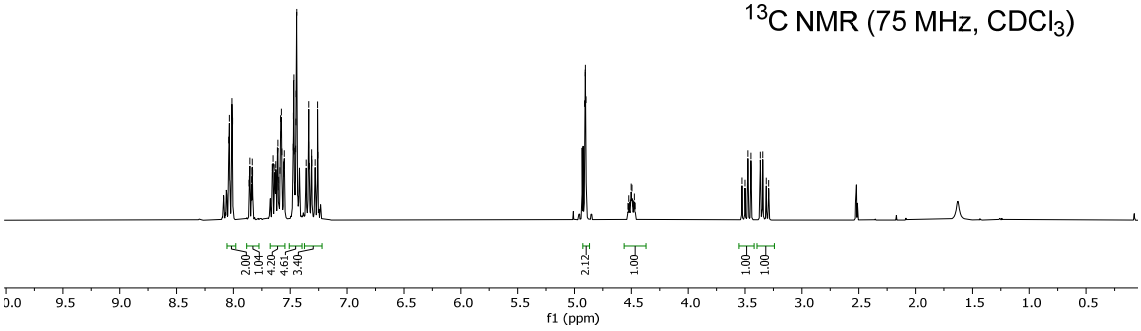


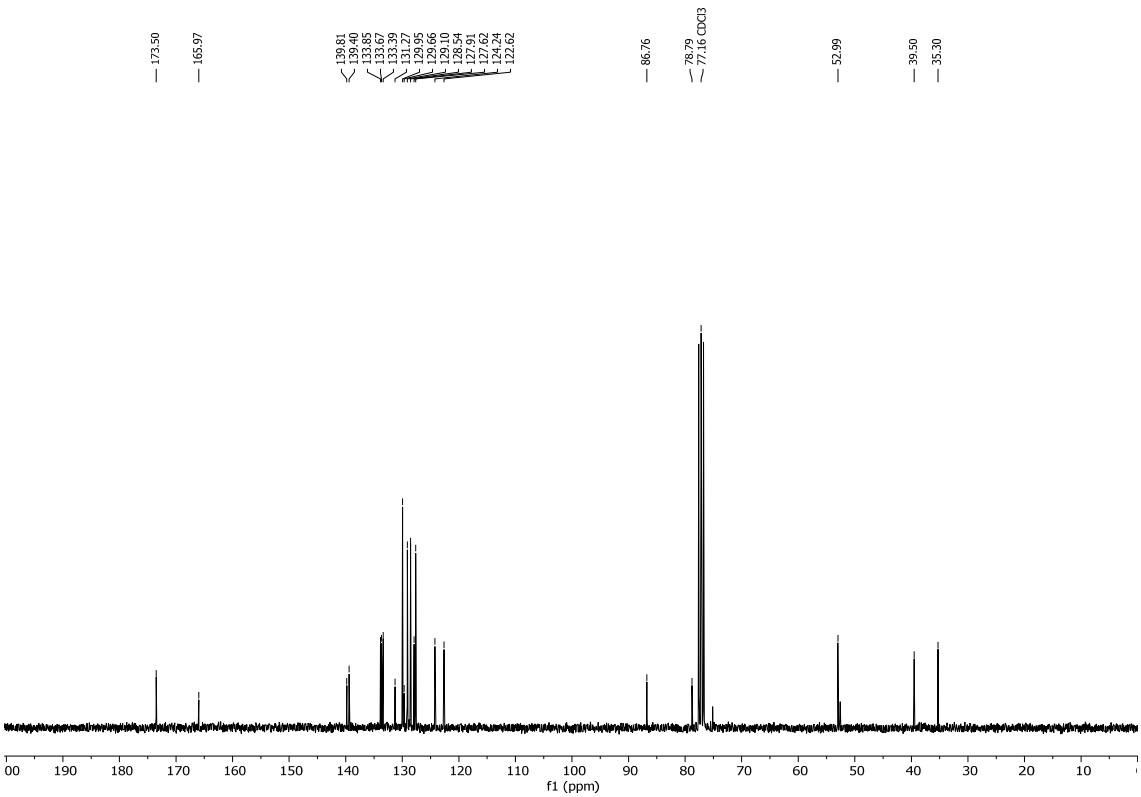


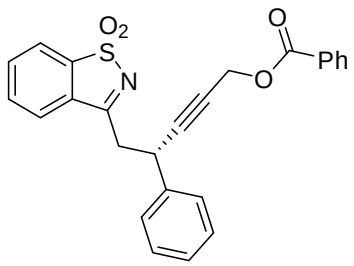
3ah

^{1}H NMR (300 MHz, $CDCl_3$)

^{13}C NMR (75 MHz, $CDCl_3$)

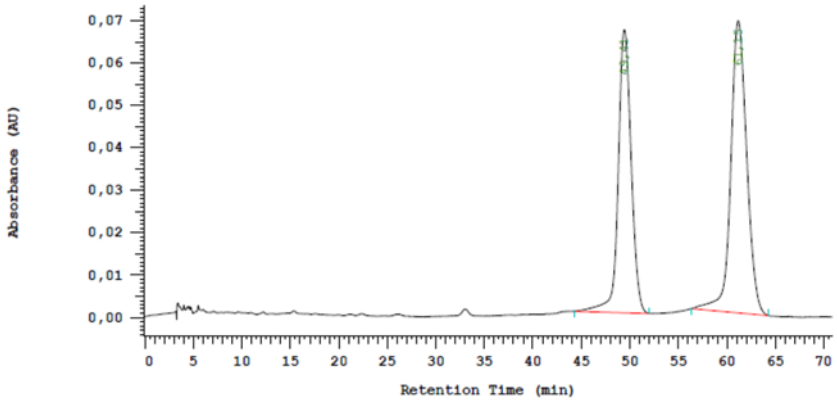






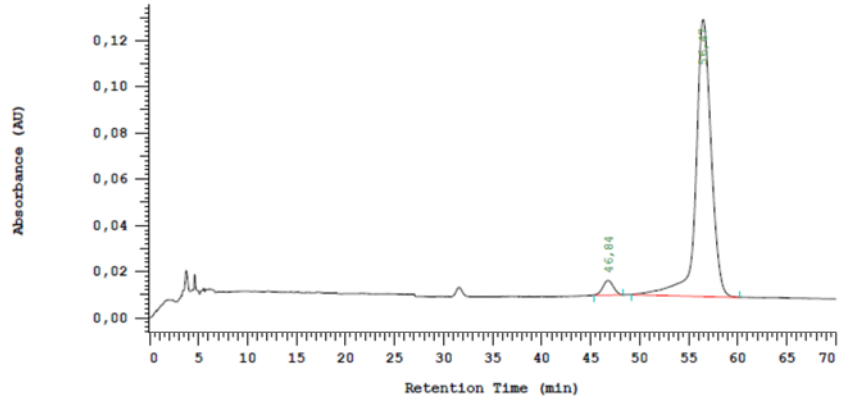
3ah

Racemic or near racemic mixture of enantiomers:

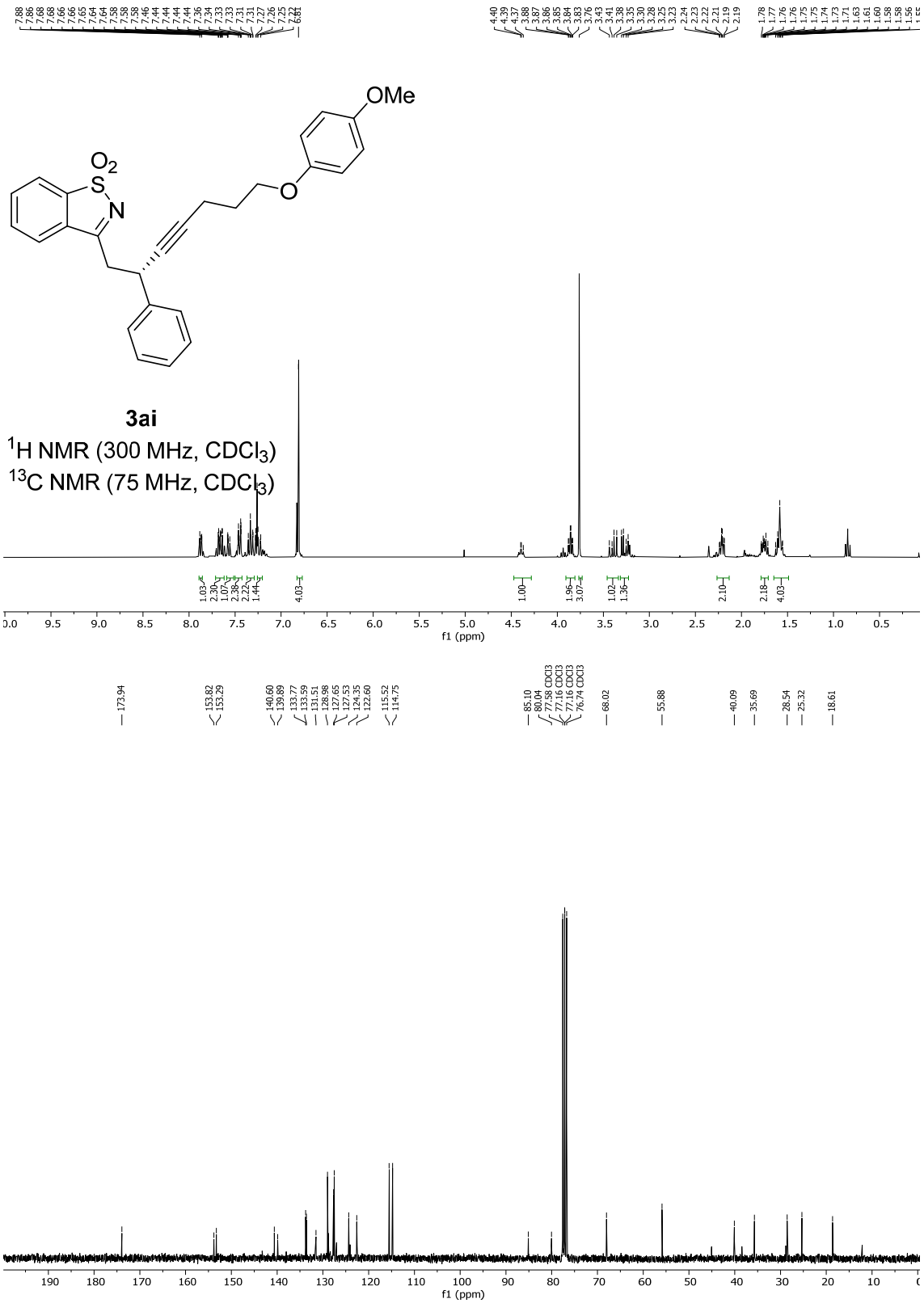


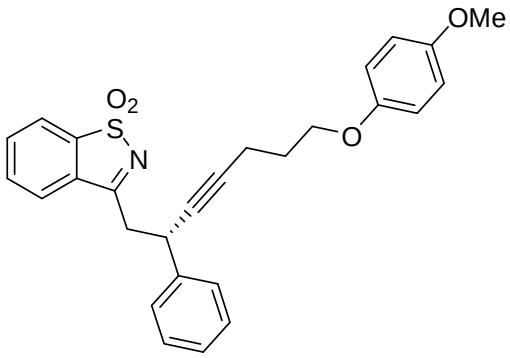
No.	RT	Area	Area %	Name
1	49,41	3065898	43,906	
2	61,15	3916918	56,094	
		6982816	100,000	

Enantioselective reaction:



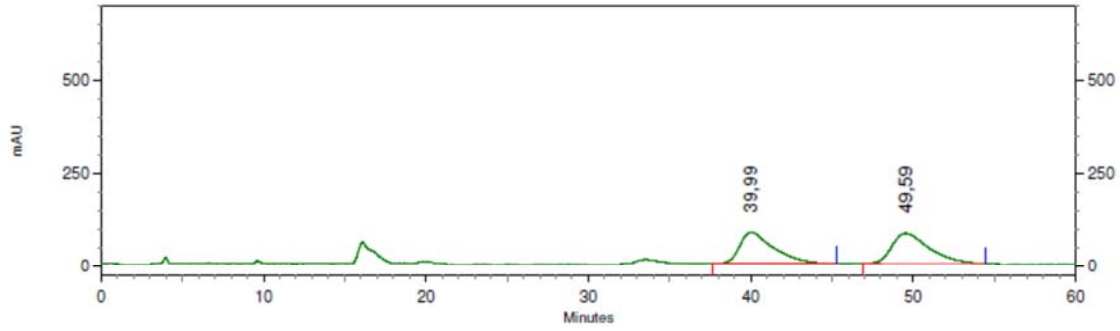
No.	RT	Area	Area %	Name
1	46,84	235995	3,513	
2	56,47	6481260	96,487	
		6717255	100,000	


OMe
O2
S
N
O
3ai
1H NMR (300 MHz, CDCl3)
13C NMR (75 MHz, CDCl3)
f1 (ppm)
f1 (ppm)



3ai

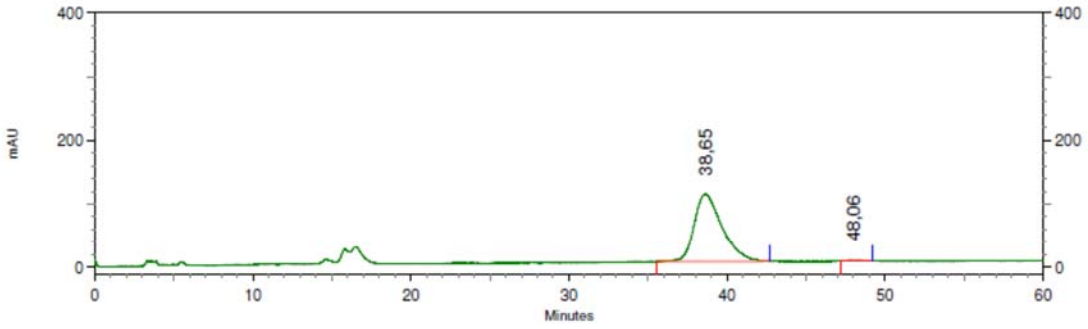
Racemic or near racemic mixture of enantiomers:



27: 236 nm, 4 nm
Results

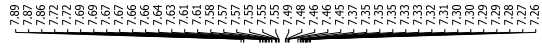
Retention Time	Area	Area Percent
39,99	50050186	48,478
49,59	53193265	51,522

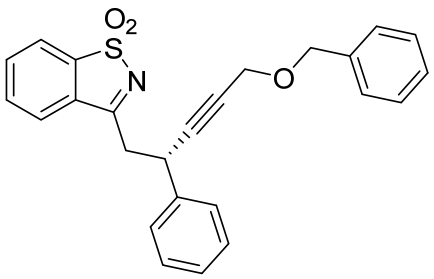
Enantioselective reaction:



2: 229 nm, 4 nm Results

Retention Time	Area	Area Percent
38,65	52724926	99,330
48,06	355486	0,670

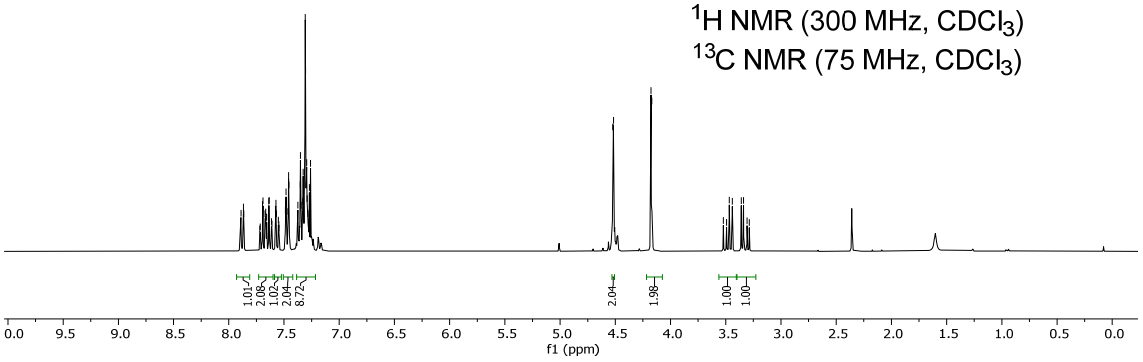


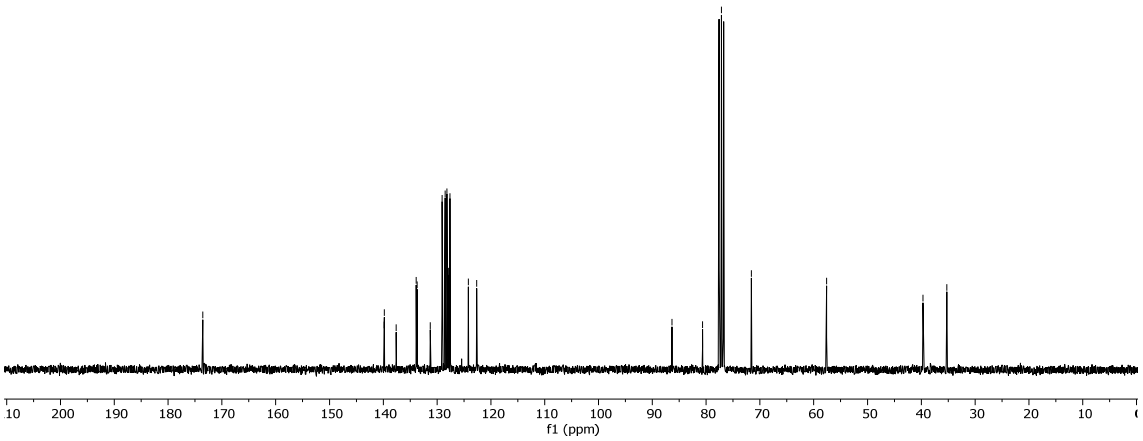


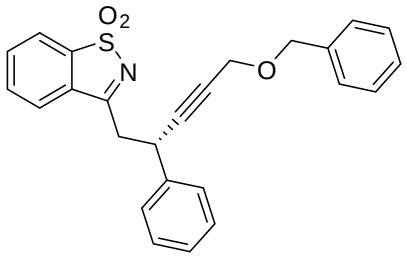
3aj

^{1}H NMR (300 MHz, $CDCl_3$)

^{13}C NMR (75 MHz, $CDCl_3$)

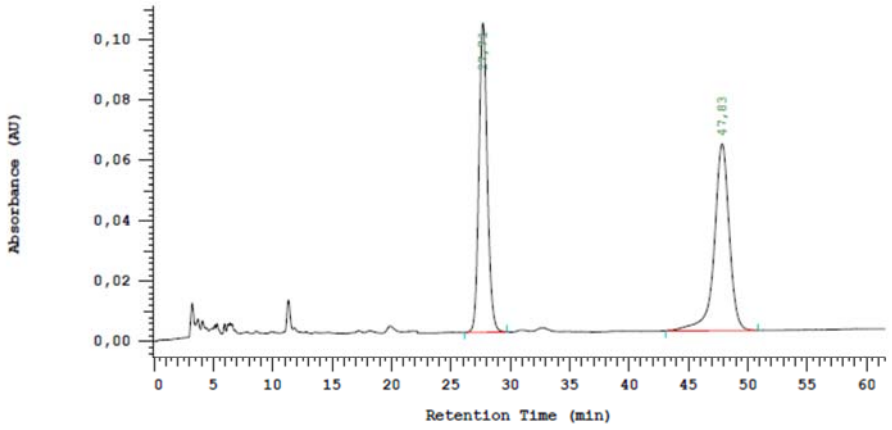






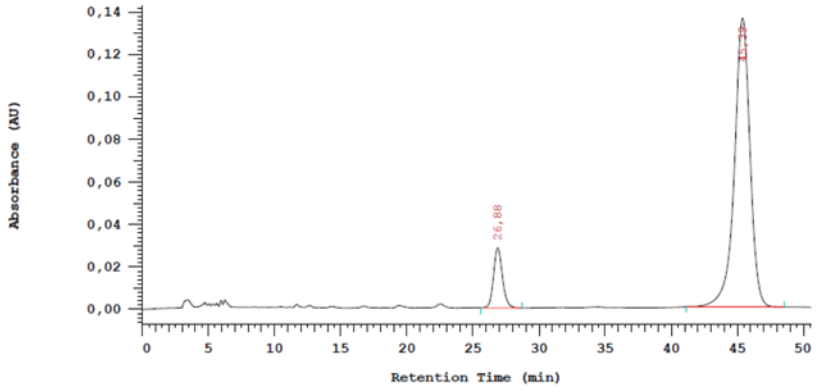
3aj

Racemic or near racemic mixture of enantiomers:

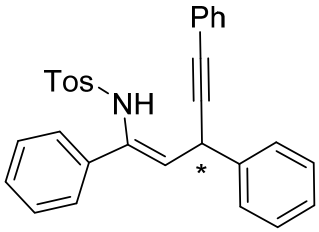


No.	RT	Area	Area %	Name
1	27,71	2482240	47,776	
2	47,83	2713290	52,224	
		5195530	100,000	

Enantioselective reaction:



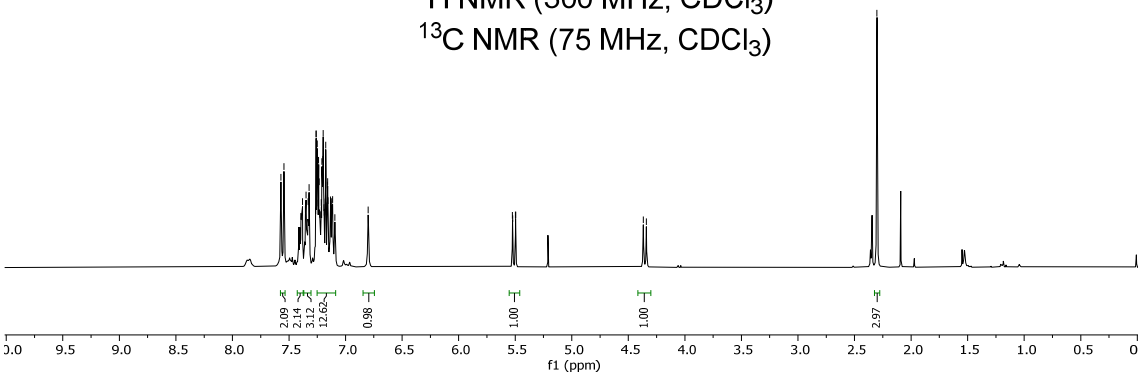
No.	RT	Area	Area %	Name
1	26,88	656695	10,549	
2	45,39	5568660	89,451	
		6225355	100,000	

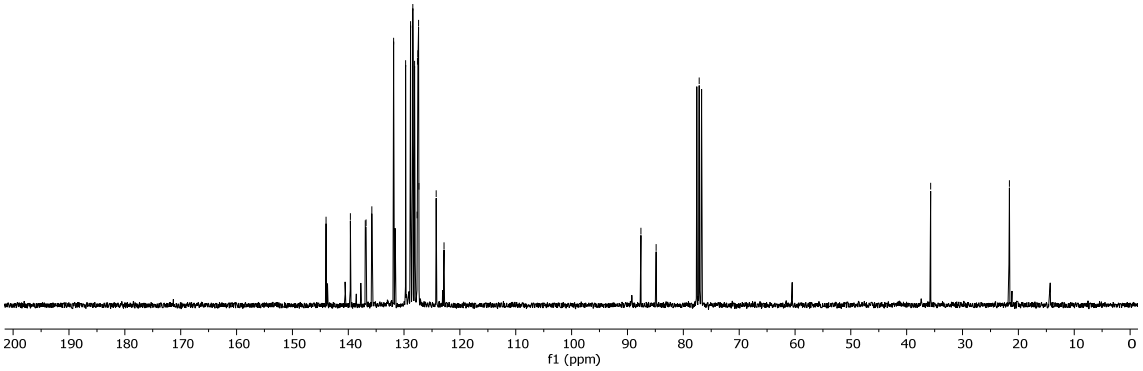


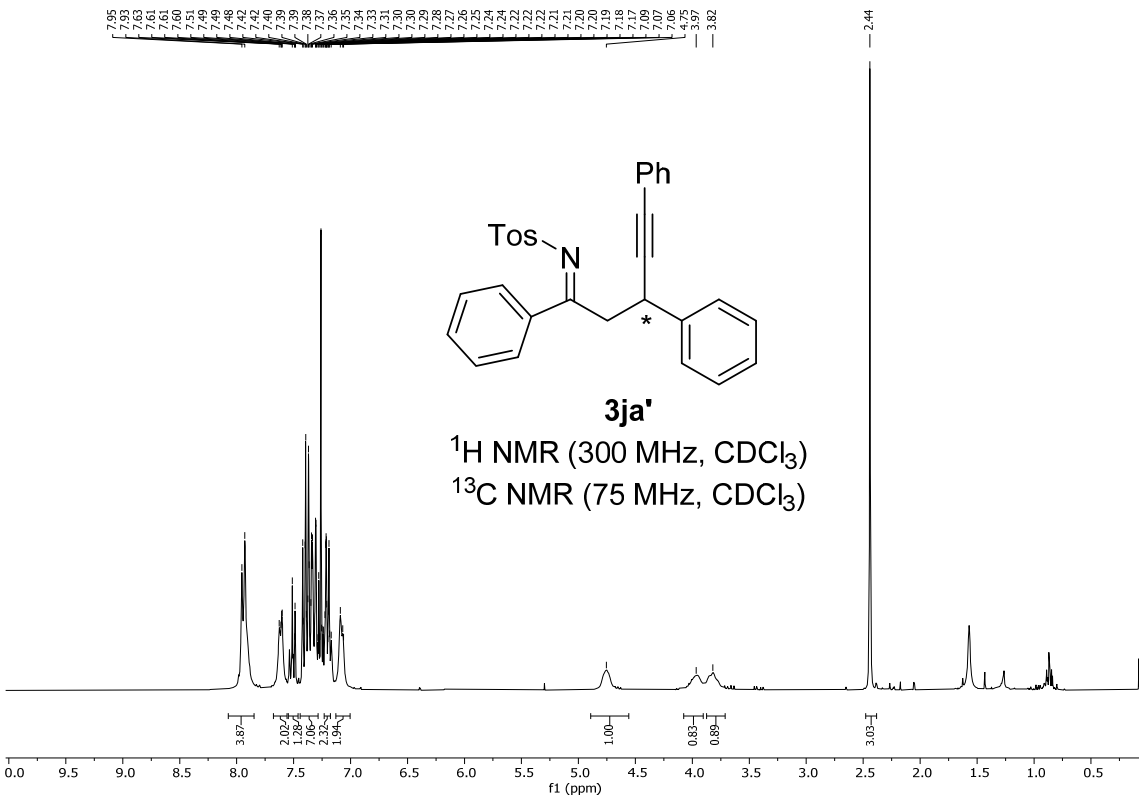
3ja

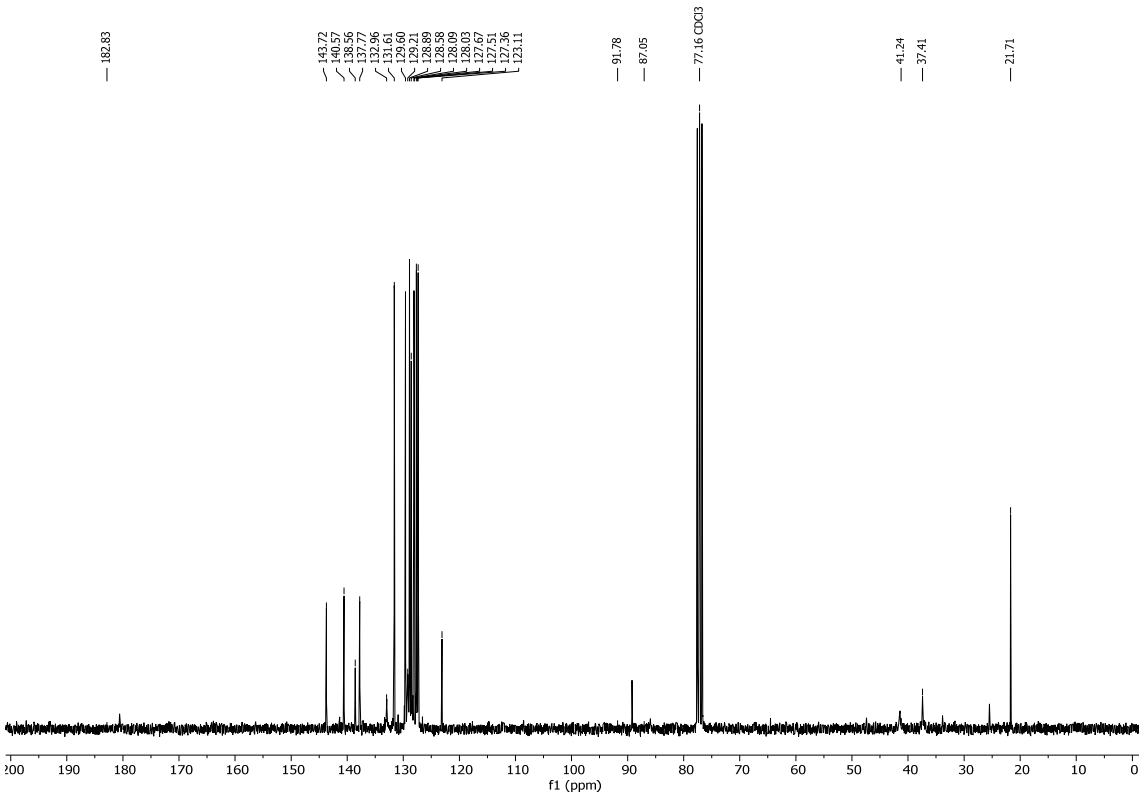
^{1}H NMR (300 MHz, $CDCl_3$)

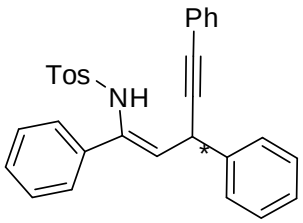
^{13}C NMR (75 MHz, $CDCl_3$)



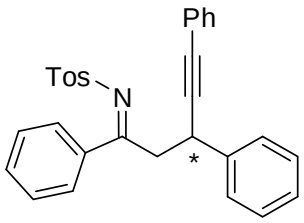



Ph
Tos
N
*
3ja'
1H NMR (300 MHz, CDCl3)
13C NMR (75 MHz, CDCl3)
f1 (ppm)


182.83
143.72
140.57
138.56
137.77
132.96
131.61
129.60
129.21
128.89
128.58
128.09
128.03
127.67
127.51
127.36
123.11
91.78
87.05
77.16 CDCl3
41.24
37.41
21.71
f1 (ppm)

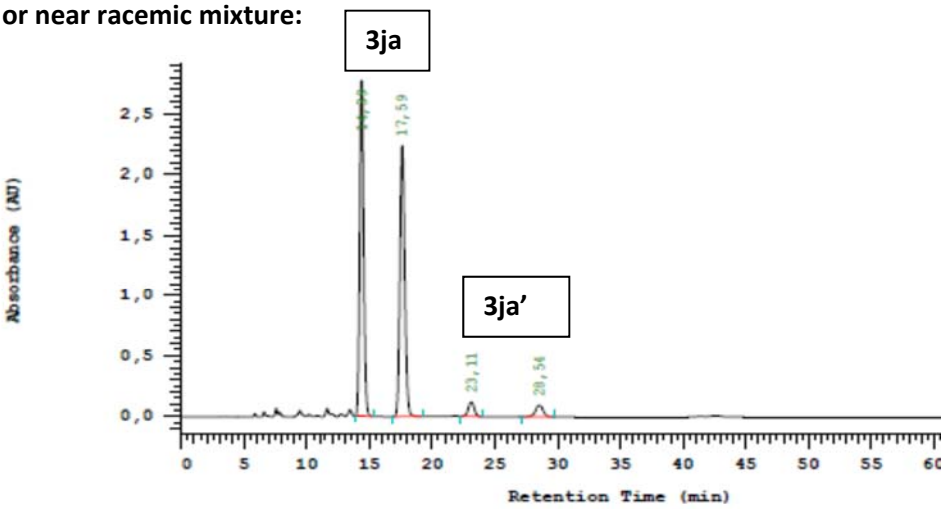


3ja



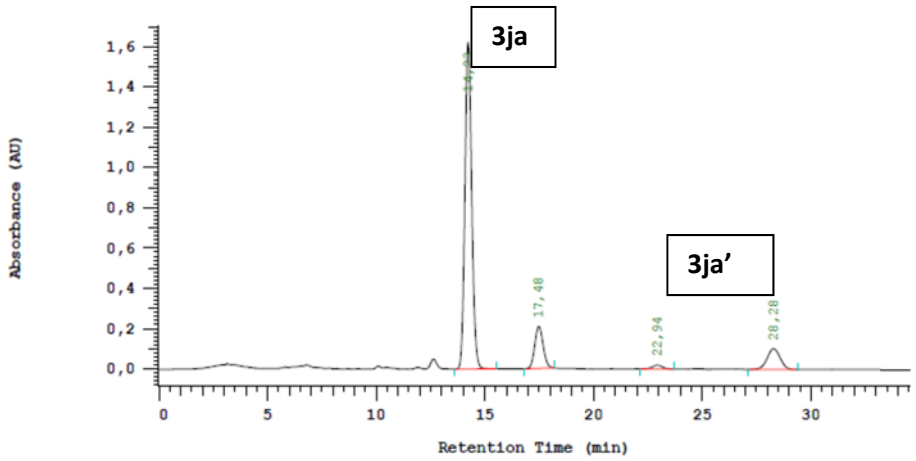
3ja'

Racemic or near racemic mixture:

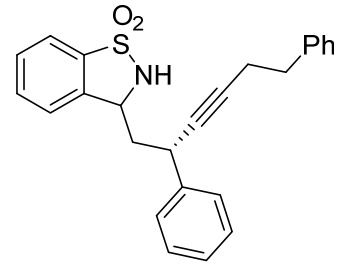


No.	RT	Area	Area %
1	14,39	28915600	46,944
2	17,59	28939929	46,984
3	23,11	1842060	2,991
4	28,54	1897840	3,081
		61595429	100,000

Enantioselective reaction:



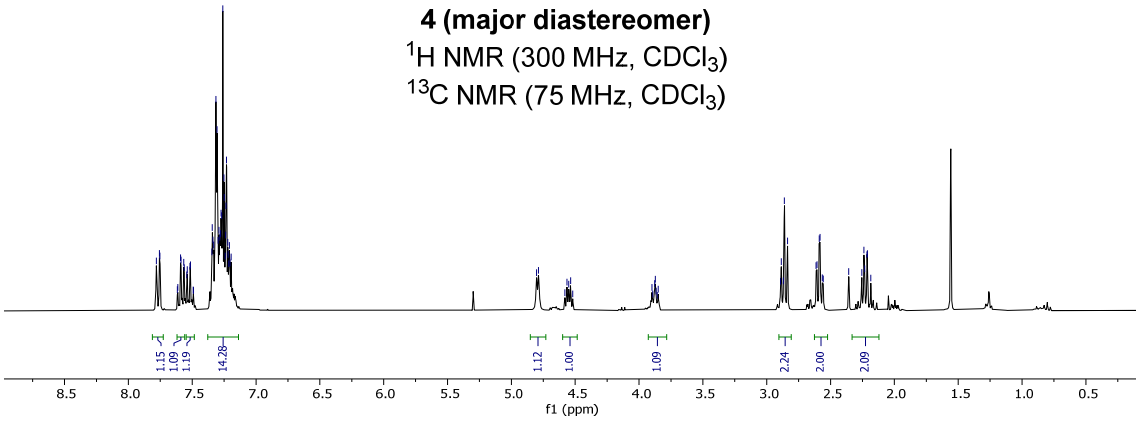
No.	RT	Area	Area %
1	14,23	17375590	77,056
2	17,48	2769410	12,282
3	22,94	303575	1,346
4	28,28	2100730	9,316
		22549305	100,000

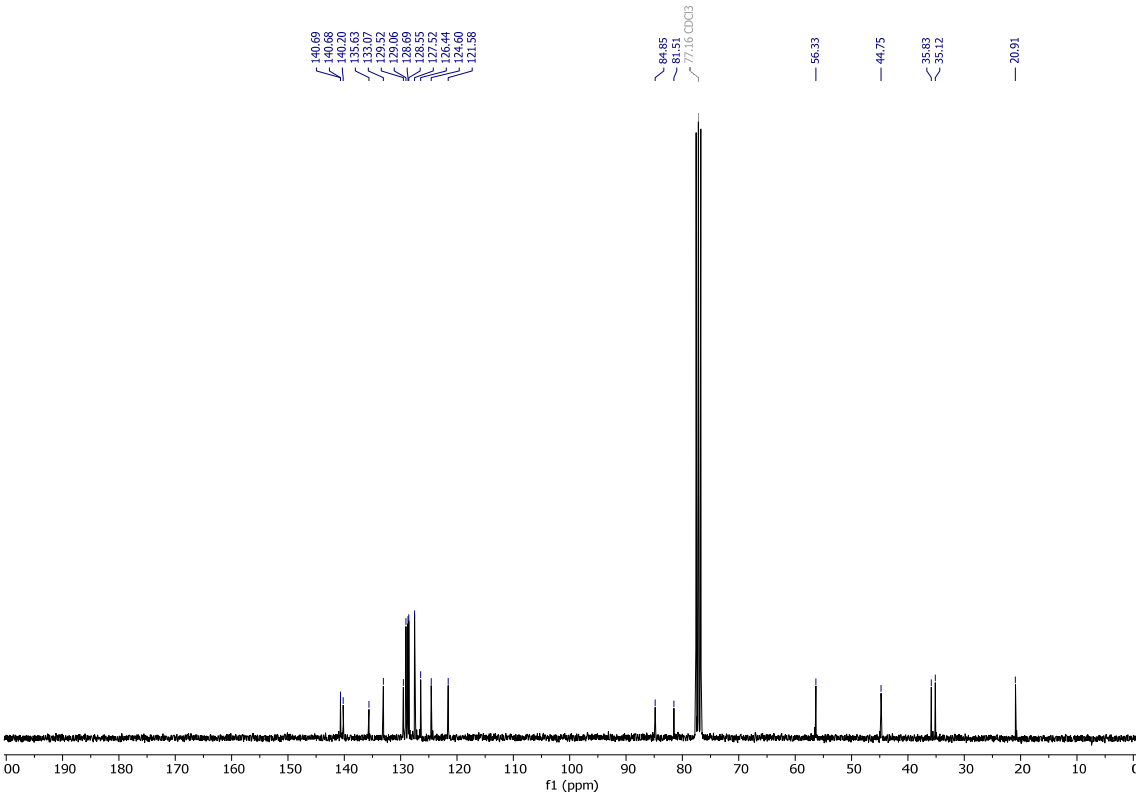


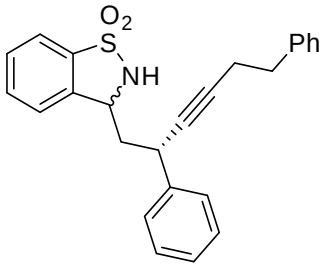
4 (major diastereomer)

^{1}H NMR (300 MHz, $CDCl_3$)

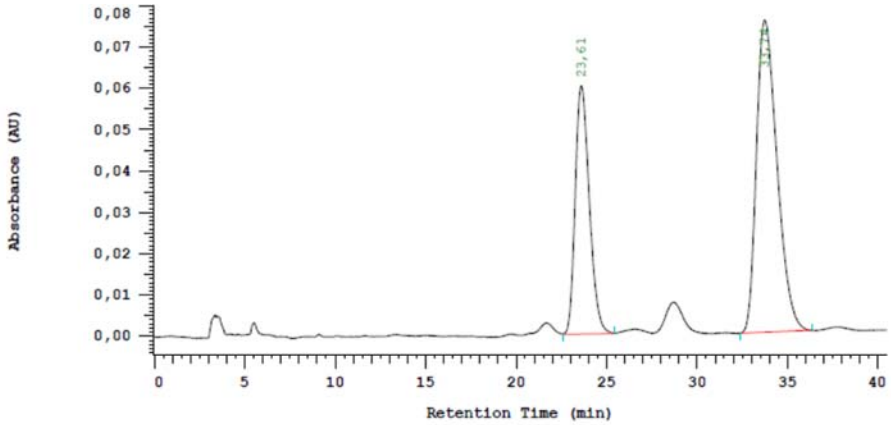
^{13}C NMR (75 MHz, $CDCl_3$)



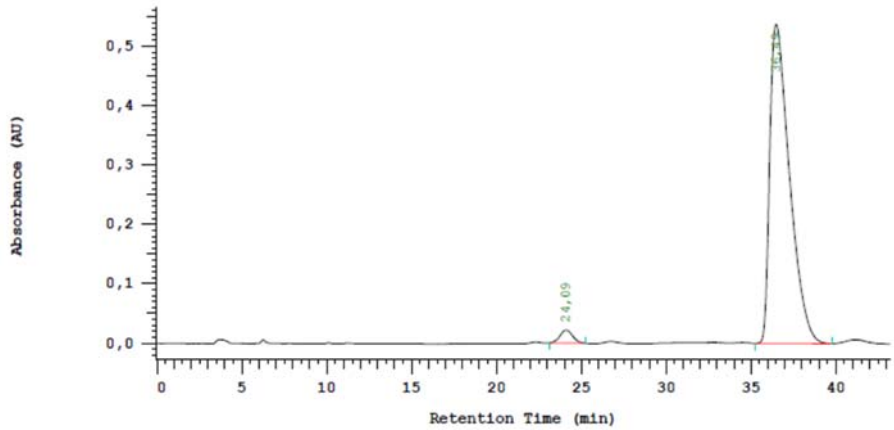




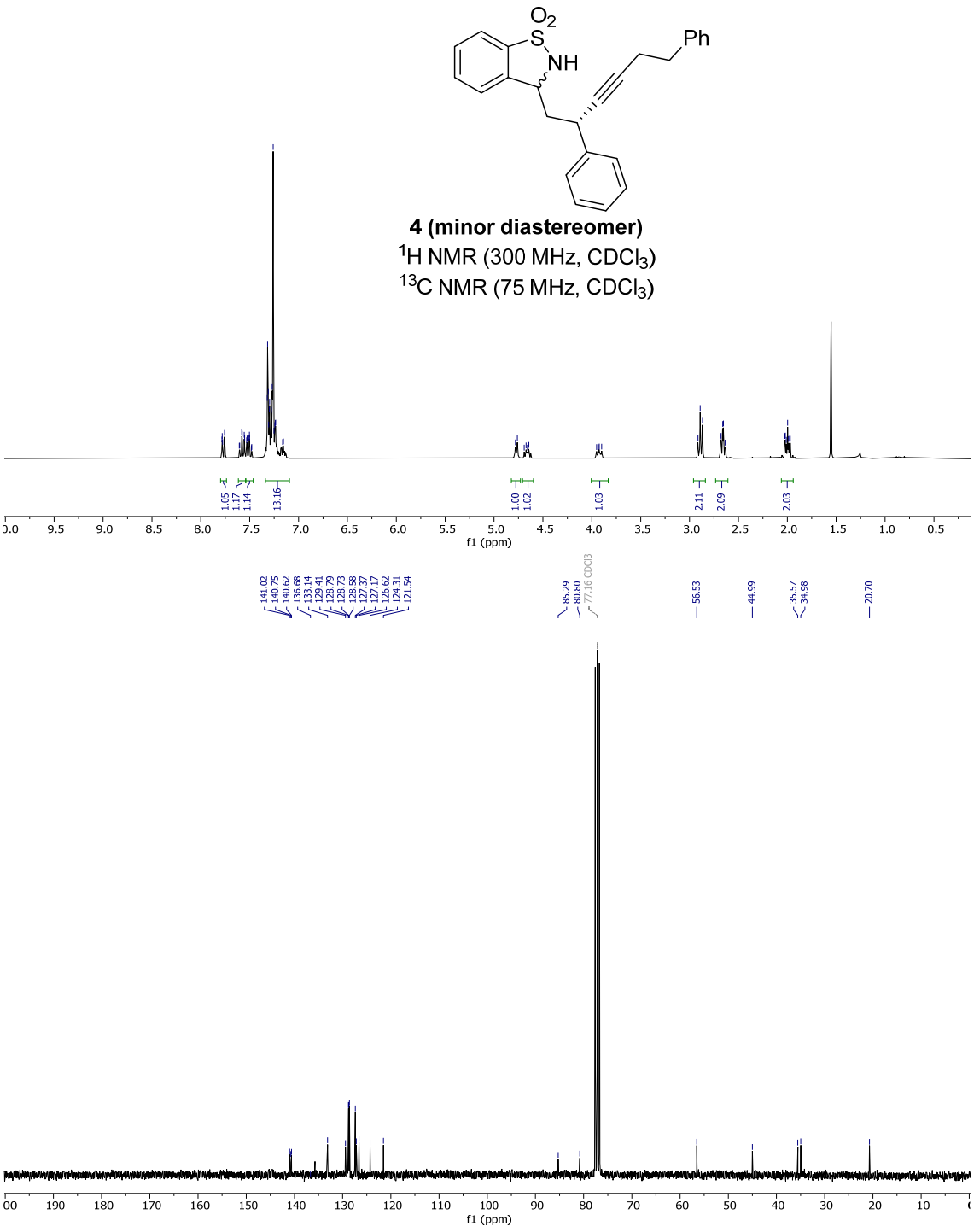
4 (major diastereomer)

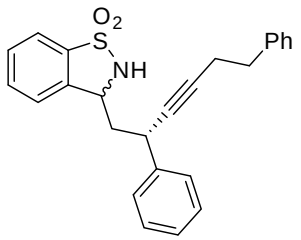


No.	RT	Area	Area %	Name
1	23,61	1612960	35,086	
2	33,74	2984210	64,914	
		4597170	100,000	

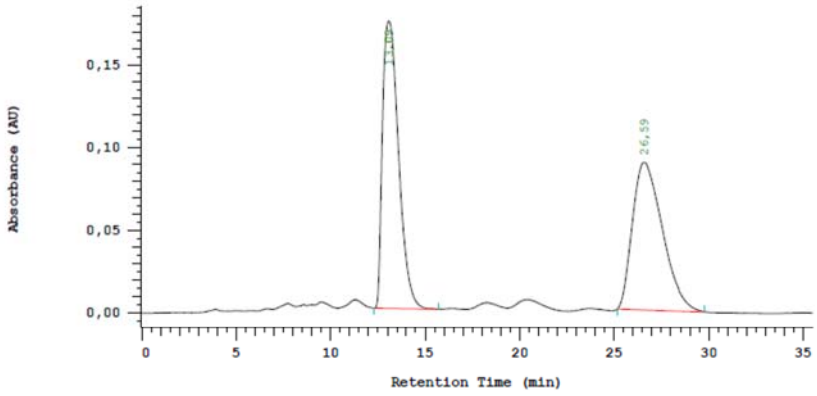


No.	RT	Area	Area %	Name
1	24,09	565220	2,549	
2	36,49	21606480	97,451	
		22171700	100,000	

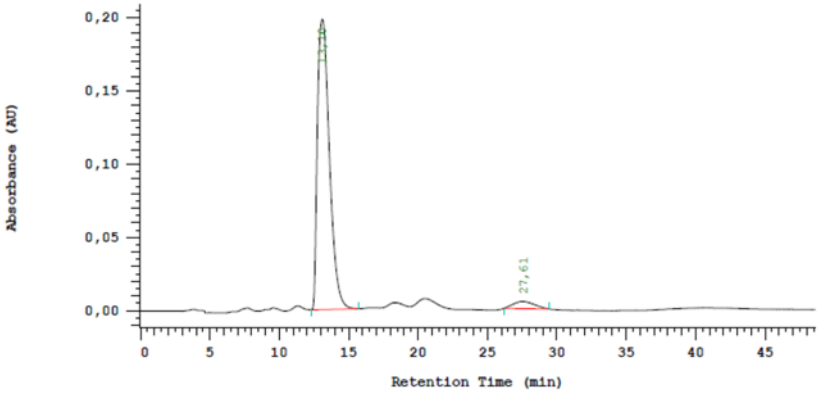

O2
S
NH
Ph
4 (minor diastereomer)
1H NMR (300 MHz, CDCl3)
13C NMR (75 MHz, CDCl3)
f1 (ppm)
f1 (ppm)



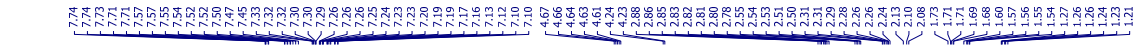
4 (minor diastereomer)

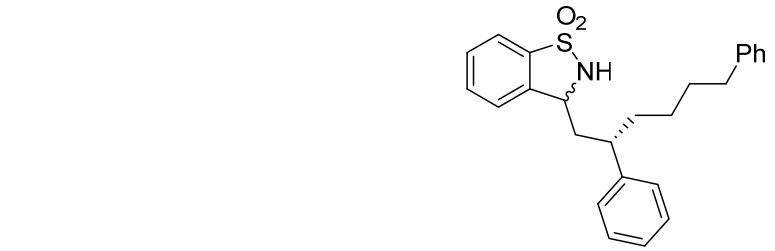


No.	RT	Area	Area %	Name
1	13,09	5131840	51,076	
2	26,59	4915550	48,924	enant. (+)
		10047390	100,000	



No.	RT	Area	Area %	Name
1	13,10	5936670	95,912	
2	27,61	253030	4,088	
		6189700	100,000	

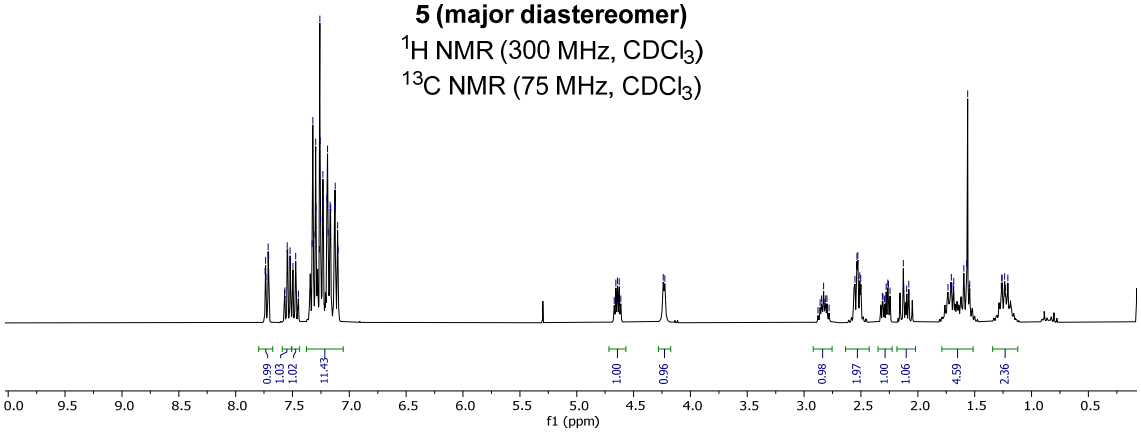


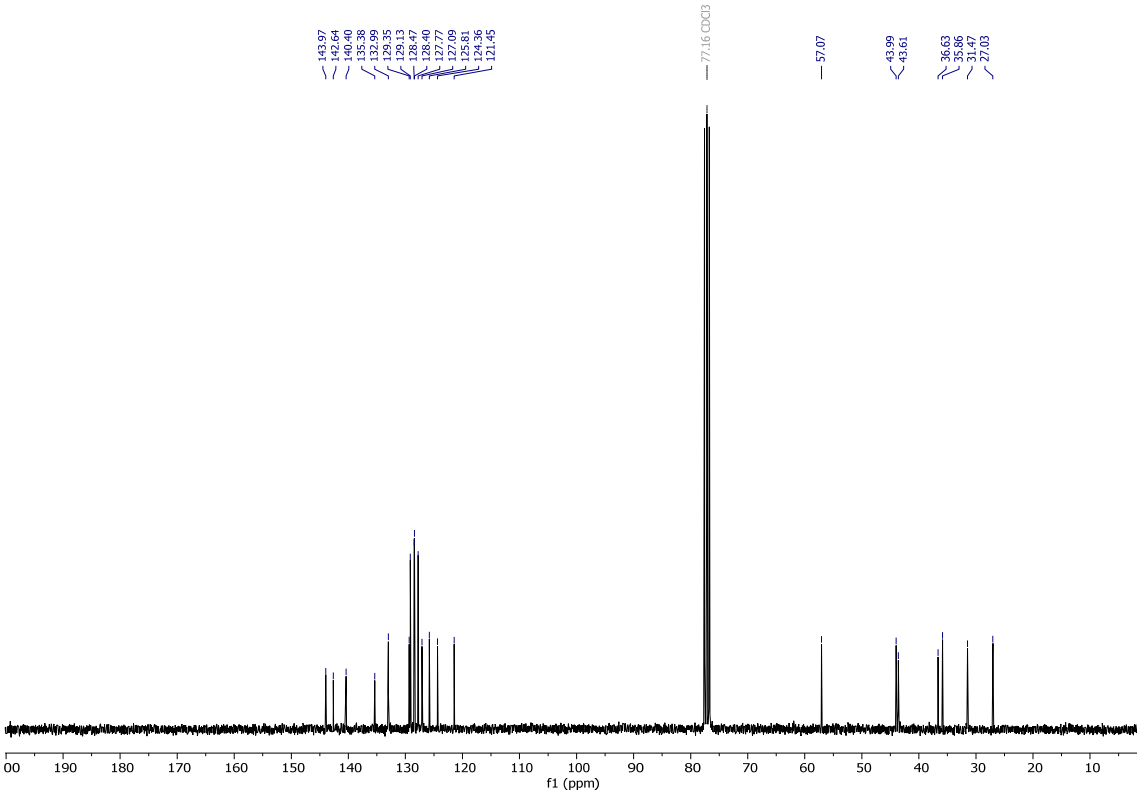


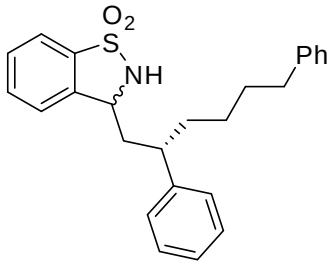
5 (major diastereomer)

^{1}H NMR (300 MHz, $CDCl_3$)

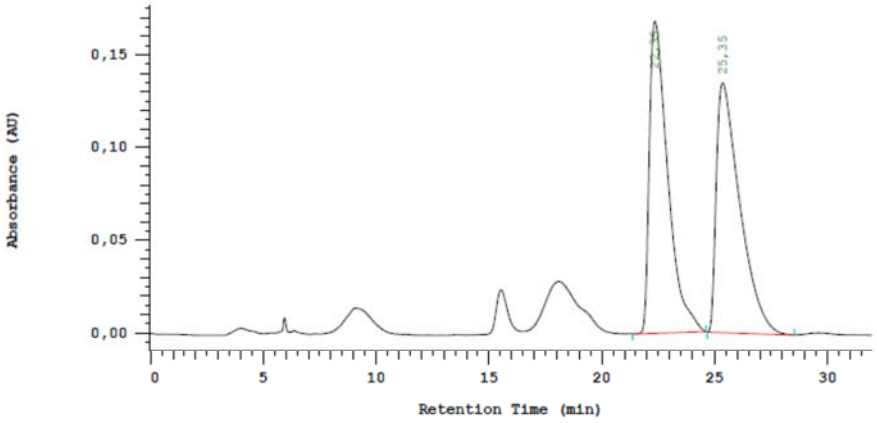
^{13}C NMR (75 MHz, $CDCl_3$)



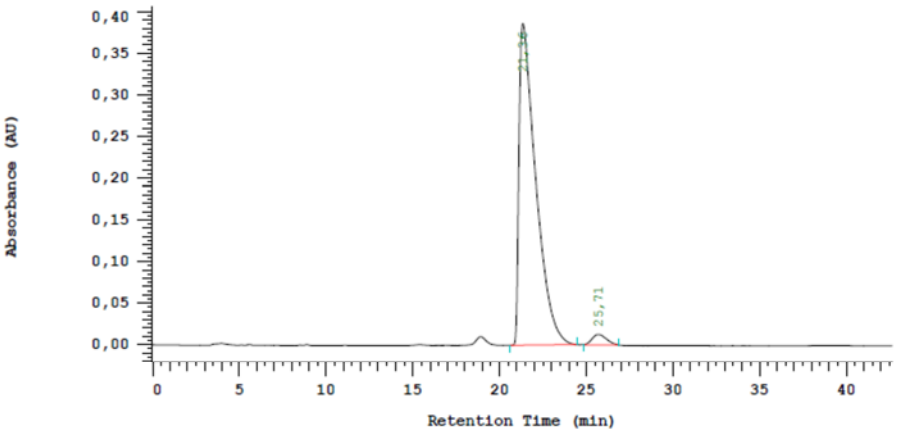




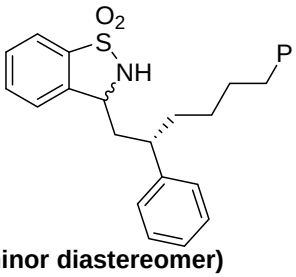
5 (major diastereomer)



No.	RT	Area	Area %	Name
1	22,35	4766030	49,562	
2	25,35	4850224	50,438	
		9616254	100,000	



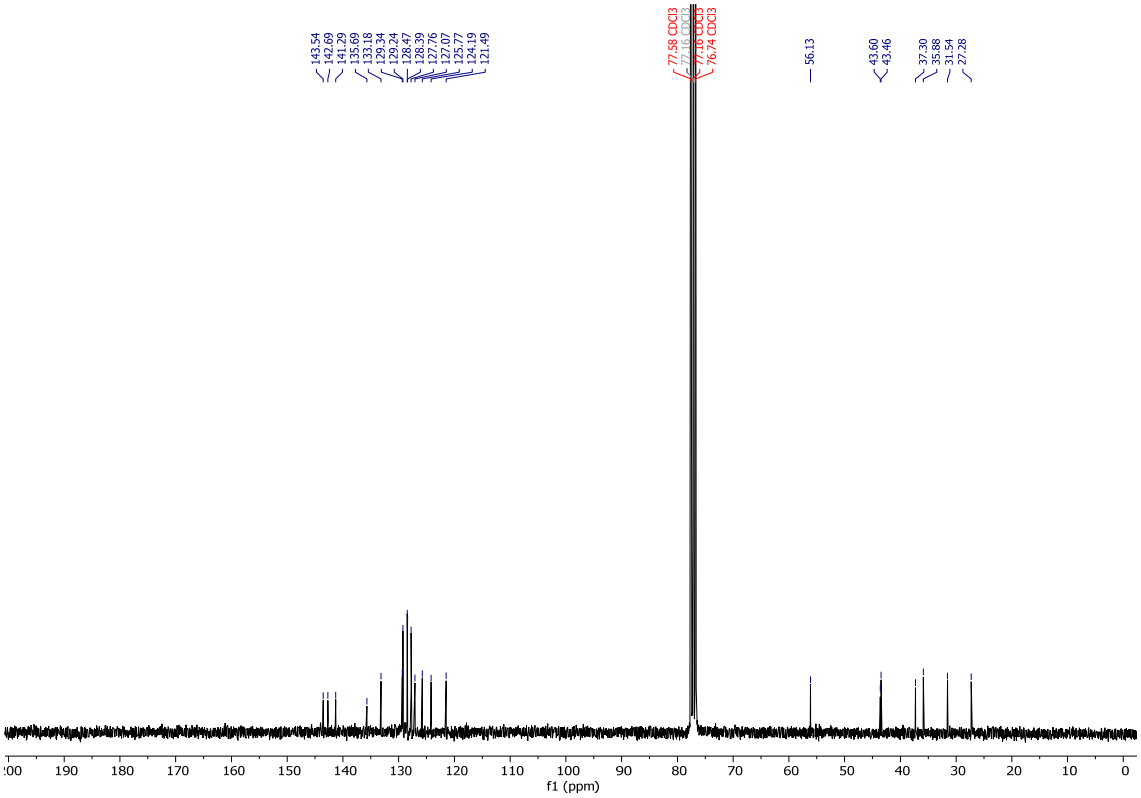
No.	RT	Area	Area %	Name
1	21,36	12941350	97,323	
2	25,71	355960	2,677	
		13297310	100,000	

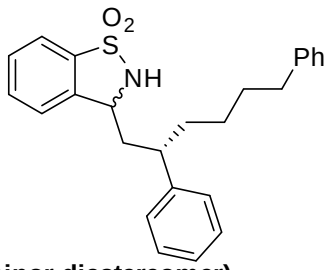


5 (minor diastereomer)

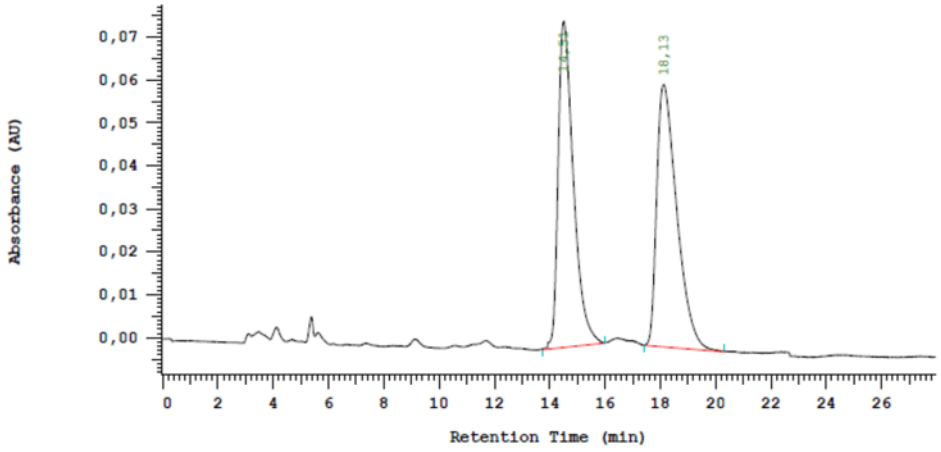
^{1}H NMR (300 MHz, $CDCl_3$)

^{13}C NMR (75 MHz, $CDCl_3$)

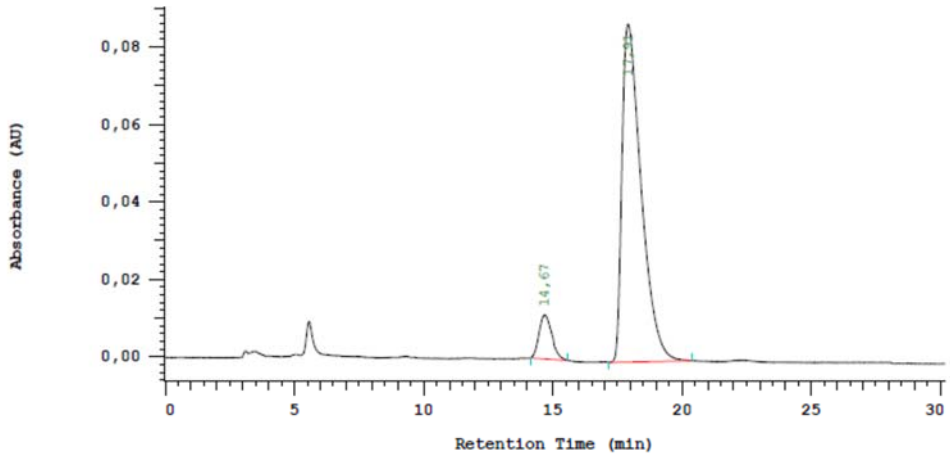




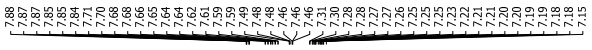
5 (minor diastereomer)

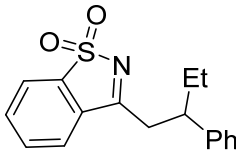


No.	RT	Area	Area %	Name
1	14,51	1451215	48,553	
2	18,13	1537740	51,447	
		2988955	100,000	



No.	RT	Area	Area %	Name
1	14,67	195100	8,005	
2	17,91	2242210	91,995	
		2437310	100,000	

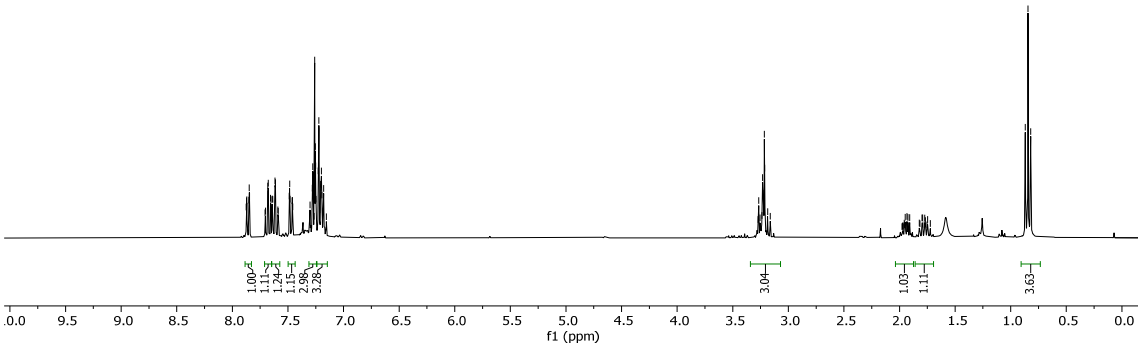


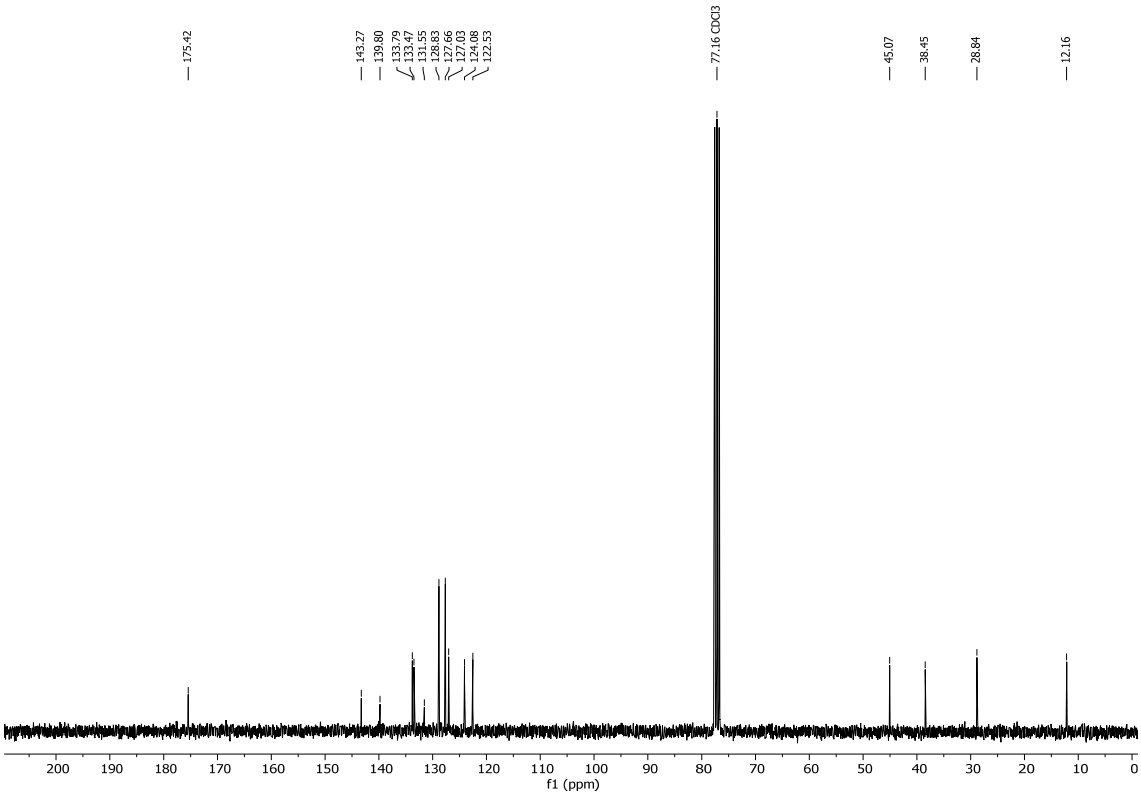


6

^{1}H NMR (300 MHz, $CDCl_3$)

^{13}C NMR (75 MHz, $CDCl_3$)





X-Ray Crystallography data for compound **3bg**: crystallized from hexane-EtOAc; $C_{20}H_{16}BrNO_2S$; Mr=414.31; monoclinic; space group=$P2_1$; a=7.4286(4), b=7.2641(3); c=17.1612(8) Å, β=96.473(2); V=929.15(8) Å^3; Z=2; ρ_{calcd}=1.495 Mg m^{-3}; μ=2.360 mm^{-1}; F(000)=420. A colorless crystal of 0.04x0.04x0.08 mm^3 was used; 3393 [R(int)=0.0504] independent reflections were collected on a Bruker S8 x-ray diffraction, equipped with a graphite monochromator and Mo Kα (λ = 0.71073 Å). The structure was solved by using direct methods with SHELXS-2014 and refined by using full matrix least squares on F^2 with SHELXL-2014. Non-hydrogen atoms were refined anisotropically, and hydrogen atoms were refined isotropically. Final R(ωR) values were R=0.0451 (0.1152). CCDC-1992564 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

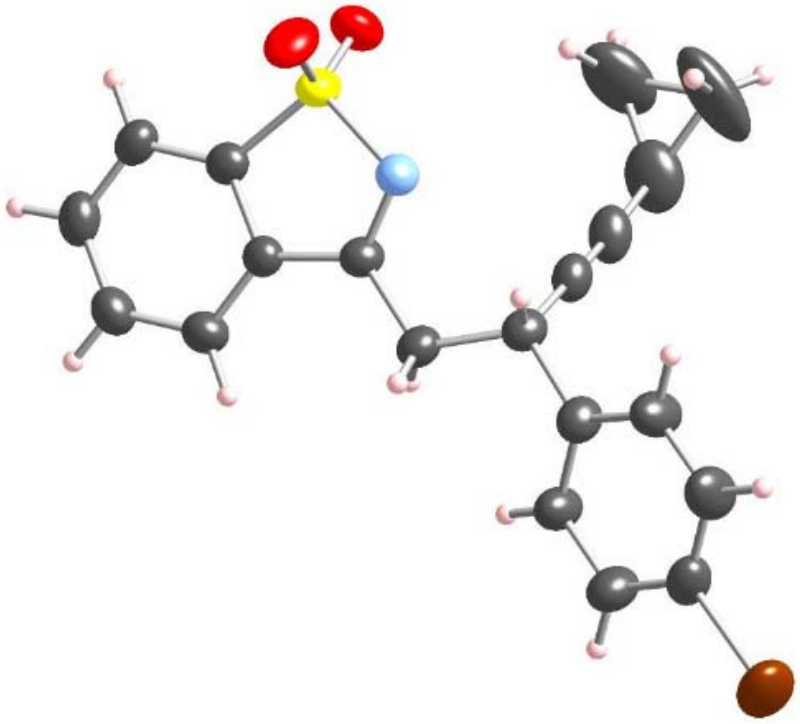


Figure S1. Ortep plot for the X-ray structure of compound **3bg**. The thermal ellipsoids are drawn at the 50% probability level. Flack parameter 0.017(6).