Electronic Supplementary Information (ESI)

Dynamic Resolution of Lithiated *ortho*-Trifluoromethyl Styrene Oxide and the Effect of Chiral Diamines on the Barrier to Enantiomerisation

Rosmara Mansueto, Filippo Maria Perna, Antonio Salomone, Saverio Florio and Vito Capriati*

Dipartimento di Farmacia - Scienze del Farmaco, Università di Bari "Aldo Moro", Consorzio Interuniversitario Nazionale "Metodologie e Processi Innovativi di Sintesi" C.I.N.M.P.I.S. Via E. Orabona 4, I-70125 Bari, Italy

Table of Contents

1. General Information

Tetrahydrofuran (THF), diethyl ether, toluene and hexane were freshly distilled under a nitrogen atmosphere: THF and diethyl ether over sodium/benzophenone ketyl, toluene and hexane over calcium hydride. For the ^{1}H and ^{13}C NMR spectra (^{1}H NMR 400 or 600 MHz; ^{13}C NMR 100 or 150 MHz), $CDCl_3$ was used as the solvent. GC-MS spectrometry analyses were performed on a gas chromatograph (dimethylsilicon capillary column, 30 m, 0.25 mm i.d.) equipped with a mass selective detector operating at 70 eV (EI). Elemental analyses were performed by using a Carlo Erba CHNS-O EA1108-Elemental Analyzer. Analytical thin layer chromatography (TLC) was carried out on precoated 0.25 mm thick plates of Kieselgel 60 F254; visualization was accomplished by UV light (254 nm) or by spraying with a solution of 5 % (w/v) ammonium molybdate and 0.2 % (w/v) cerium(III) sulfate in 100 ml 17.6 % (w/v) aq. sulphuric acid and heating to 473 K for some time until blue spots appear. All reactions involving air-sensitive reagents were performed under nitrogen in oven-dried glassware using syringe-septum cap technique. Lithiation-electrophilic trapping reactions were performed in a diethyl ether /liquid N_2 (–120 °C), acetone/liquid N_2 (– 90 °C) or acetone/dry ice (–78 °C) cold bath. Racemic oxirane **1** was prepared by the Corey–Chaykovsky epoxidation procedure[1] starting from the corresponding benzaldehyde derivative, whereas oxirane **10** was obtained according to the methodology of Durst and co-workers.[2] Optically active epoxides (*R*)-**1** (e.r. 95:5, 15% yield) and (*R*)-**10** (e.r. 98:2, 20% yield) were synthesized by means of Jacobsen's hydrolytic kinetic resolution[3] starting from the corresponding racemic mixtures.

Oxiranes **1**,[4] **2a**4 and **10**[5] are known compounds and their characterization match the literature reports.

---

[1] E. J. Corey and M. Chaykovsky *J. Am. Chem. Soc.* 1965, **87**, 1353.

[2] E. Akguen, M. B. Glinski, K. L. Dhawan and T. Durst, *J. Org. Chem.* 1981, **46**, 2730.

[3] S. E. Schaus, B. D. Brandes, J. F. Larrow, M. Tokunaga, K. B. Hansen, A. E. Gould, M. E. Furrow and E. N. Jacobsen, *J. Am. Chem. Soc.* 2002, **124**, 1307.

[4] J. Deregnaucourt, A. Archelas, F. Barbirato, J.-M. Paris and R. Furstoss, *Adv. Synth. Catal.* 2007, **349**, 1405.

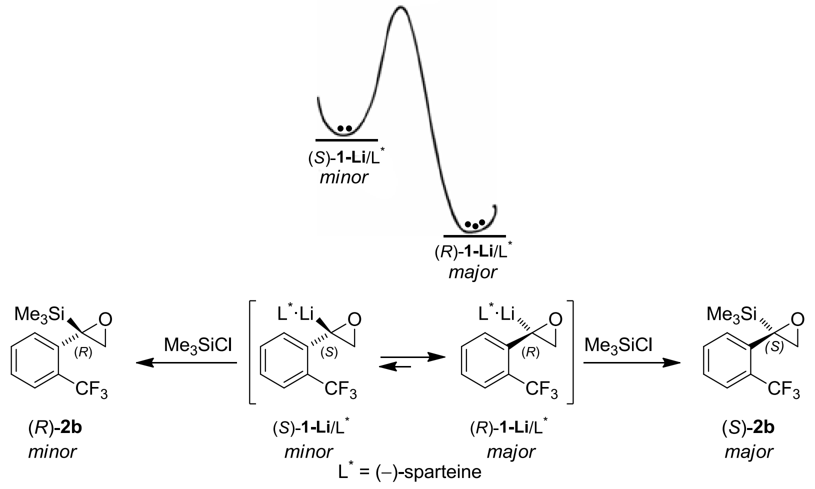
[5] (*a*) S. A. Weissman, K. Rossen and P. J. Reider, *Org. Lett.* 2001, **3**, 2513; (*b*) S. A. Weissman, K. Rossen and P. J. Reider, *Org. Lett.* 2005, **7**, 2803.

2. General Procedure for the Dynamic Thermodynamic Resolution (DTR) of 1-Li

To a solution of oxirane **1** (1 mmol) and (–)-sparteine **3** (1.2 mmol) in 10 mL of dry hexane (or pentane), at –78 °C and under N_2, *s*-BuLi (1.2 mmol of a 1.4 M cyclohexane solution) was added dropwise. The resulting yellowish mixture was stirred for 30 min at the above temperature before being quenched with the electrophile (5 mmol) (neat if liquid or diluted in 2 mL of hexane if solid). After additional stirring for 30 min at –78 °C, the reaction vessel was warmed up to room temperature. Then, a solution of sat. aq. NH_4Cl (3 mL) was added and the reaction mixture was poured into 20 mL of water and extracted with Et_2O (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel (AcOEt/petroleum ether) to afford oxiranes [D]-**1, 2a-d.**

3. Stereochemical Aspects of the DTR of 1-Li

Since the enantiomerisation of enantio-enriched (*R*)-**1-Li** occurs slowly in an apolar solvent such as hexane and in the presence of TMEDA (see Eyring plot, page S5), retention times (calculated by GC or HPLC analysis, see Section 8) of enantio-enriched products **2a-d** (obtained upon quenching in hexane/TMEDA (*R*)-**1-Li** with the corresponding electrophiles) were compared with those of the same products prepared by DTR in hexane(pentane)/(–)-sparteine. Assuming that the reaction of (*R*)-**1-Li** with electrophiles proceeds with retention of configuration at the benzylic carbon atom (in accordance with what observed in the α-functionalisation of lithiated styrene oxide derivatives),[6] the major enantiomer of the products **2a-d** (and thus the most stable diastereomeric **1-Li**/(–)-sparteine complex) was assigned the *R* configuration (Scheme S1). The change in the absolute configuration at the benzylic carbon in product **2b** was only due to a change in the relative priority of the substituent groups (Scheme S1).



Scheme S1

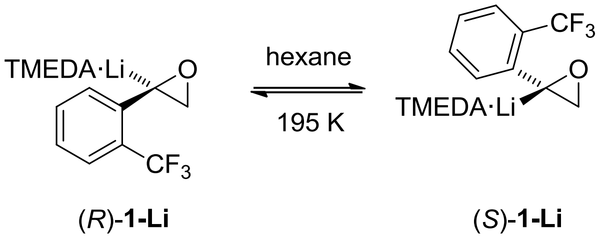
---

[6] V. Capriati, S. Florio and R. Luisi *Chem. Rev.* 2008**, 108,** 1918.

4. Experimental Procedure Using a Sacrificial Electrophile

To a solution of oxirane **1** (1 mmol) and (–)-sparteine **3** (1.2 mmol) in 10 mL of dry pentane, at –78 °C and under N_2, *s*-BuLi (1.2 mmol of a 1.4 M cyclohexane solution) was added dropwise and the resulting yellowish mixture was stirred for 15 min. Then, the reaction vessel was cooled to –120 °C and acetone (0.2 mmol diluted in 2 mL of pentane) was slowly added. The mixture was stirred for additional 5 min at –120 °C and, after this time, CH_3OD (5 equiv) was added all at once. Upon warming up to room temperature, the mixture was poured into 20 mL of water and extracted with Et_2O (3 × 10 mL). The organic layers were combined, dried (Na_2SO_4) and evaporated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (AcOEt/petroleum ether 1/9) to afford oxiranes **2d** (15 % yield, e.r. 52:48, *R*:*S*) and [D]-**1** (75 % yield, e.r. 82:18, *R*:*S*) (see Table 1 in the main text).

5. Eyring Plot and Free Energy Barrier for Enantiomerisation of 1-Li in Hexane/TMEDA



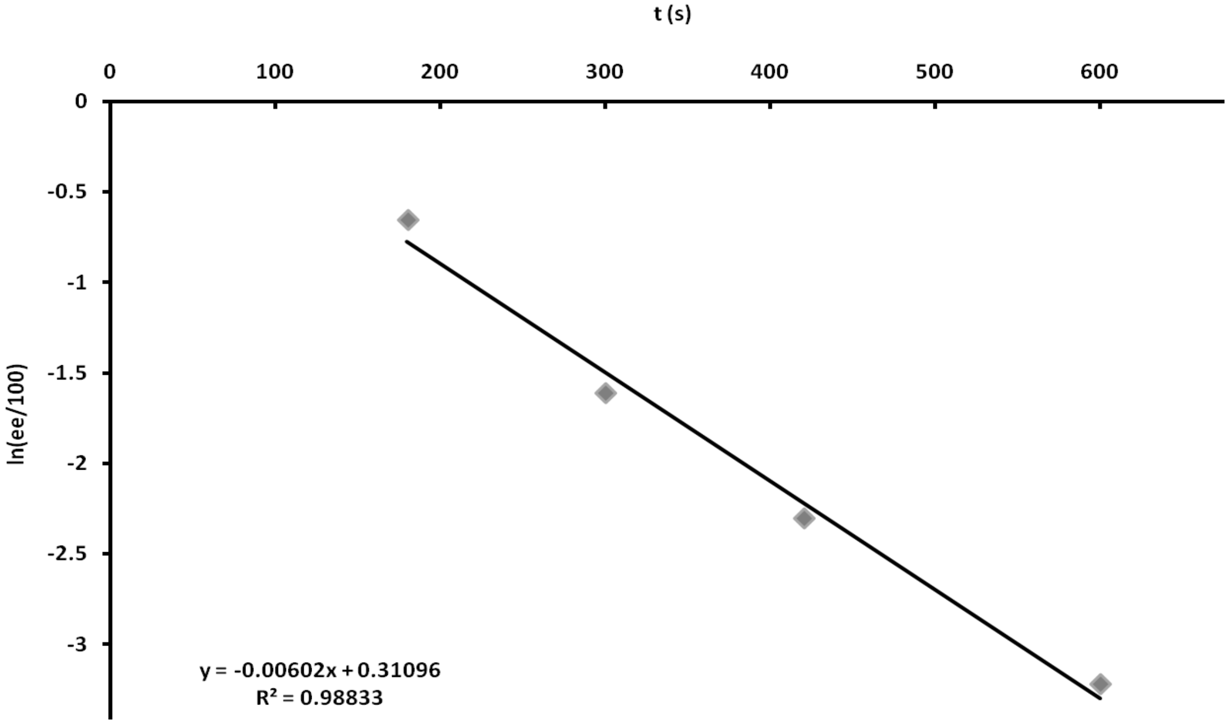
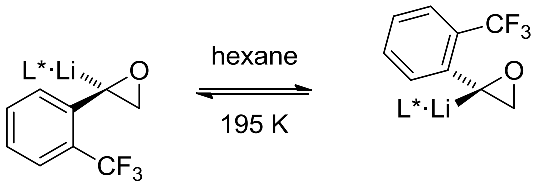


Figure S1. Plot of ln(ee/100) vs delay time at 195 K in lithiation–deuteration exchange on *ortho*-trifluoromethylstyrene oxide (*R*)-**1** in hexane/TMEDA.

Table S1. Inversion barrier, racemisation half-life and enantiomerisation rate constant for lithiated *ortho*-trifluoromethylstyrene oxide **1-Li** in hexane/TMEDA at 195 K.

ee	t (sec)	k_{enant} (s^{-1})	$\Delta G^{\neq}$ (kcal/mol)	$t_{1/2\ rac}$ (sec)
52	180	3.01 x 10^{-3}	13.5 ±0.1	115
20	300			
10	420			
4	600			

6. Eyring Plot and Free Energy Barriers for Enantiomerisation of 1-Li in Hexane/(–)-Sparteine



(*R*)-**1-Li**/L*

(*S*)-**1-Li**/L*

L* = (–)-sparteine

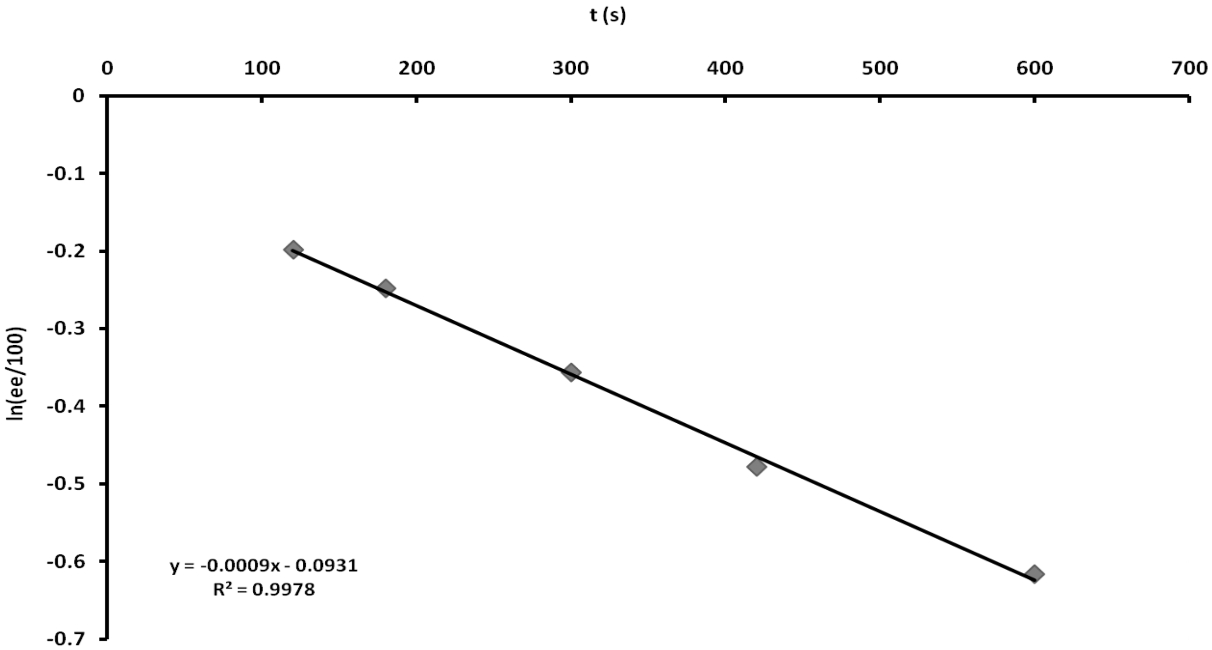
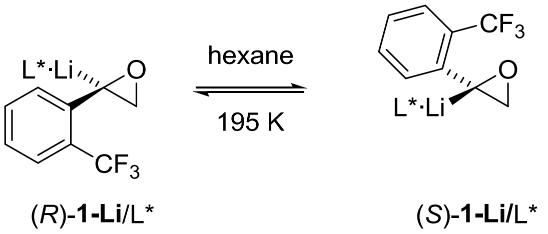


Figure S2: Plot of Ln(ee/100) vs delay time at 195 K in lithiation–deuteration exchange on *ortho*-trifluoromethylstyrene oxide (*R*)-**1** in hexane/(–)-sparteine.

Table S2. Inversion barriers and enantiomerisation rate constants for lithiated *ortho*-trifluoromethylstyrene oxide **1-Li** in hexane/(–)-sparteine at 195 K.

ee	t (sec)	$k_{S\rightarrow R}$ (s^{-1})	$\Delta G_{S\rightarrow R}^{\neq}$ (kcal/mol)	$k_{R\rightarrow S}$ (s^{-1})	$\Delta G_{R\rightarrow S}^{\neq}$ (kcal/mol)
82	120	6.81×10^{-4}	14.1 ±0.1	2.03×10^{-4}	14.5 ±0.1
78	180				
70	300				
62	420				
54	600				

7. Eyring Plot and Free Energy Barriers for Enantiomerisation of 1-Li in Hexane/(+)-Sparteine Surrogate



L*= (+)-sparteine surrogate

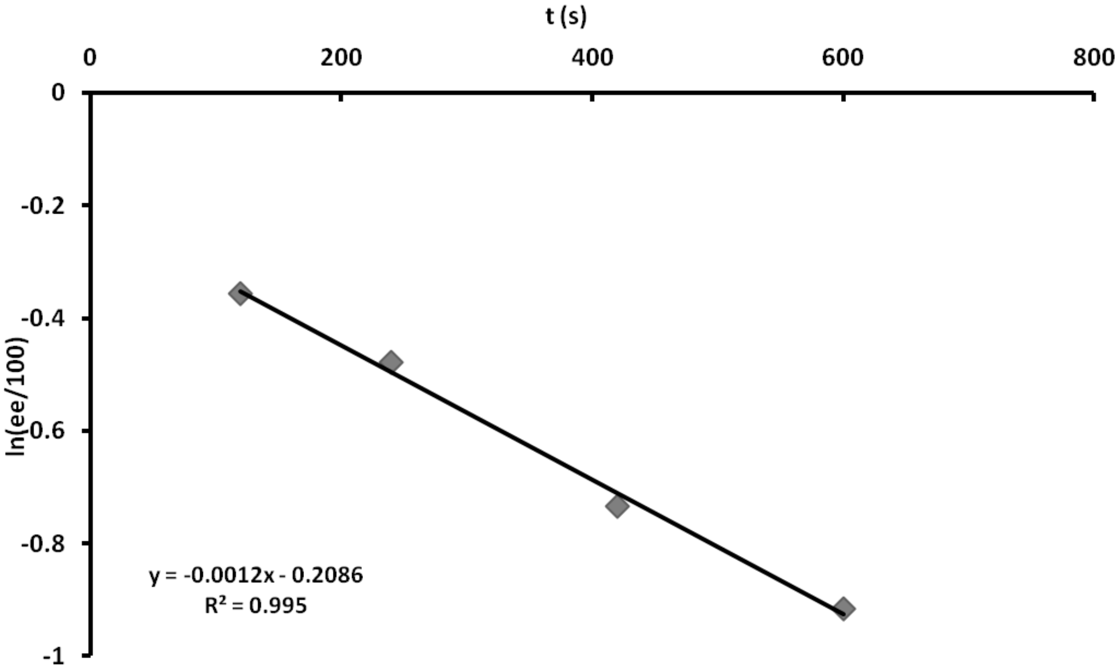


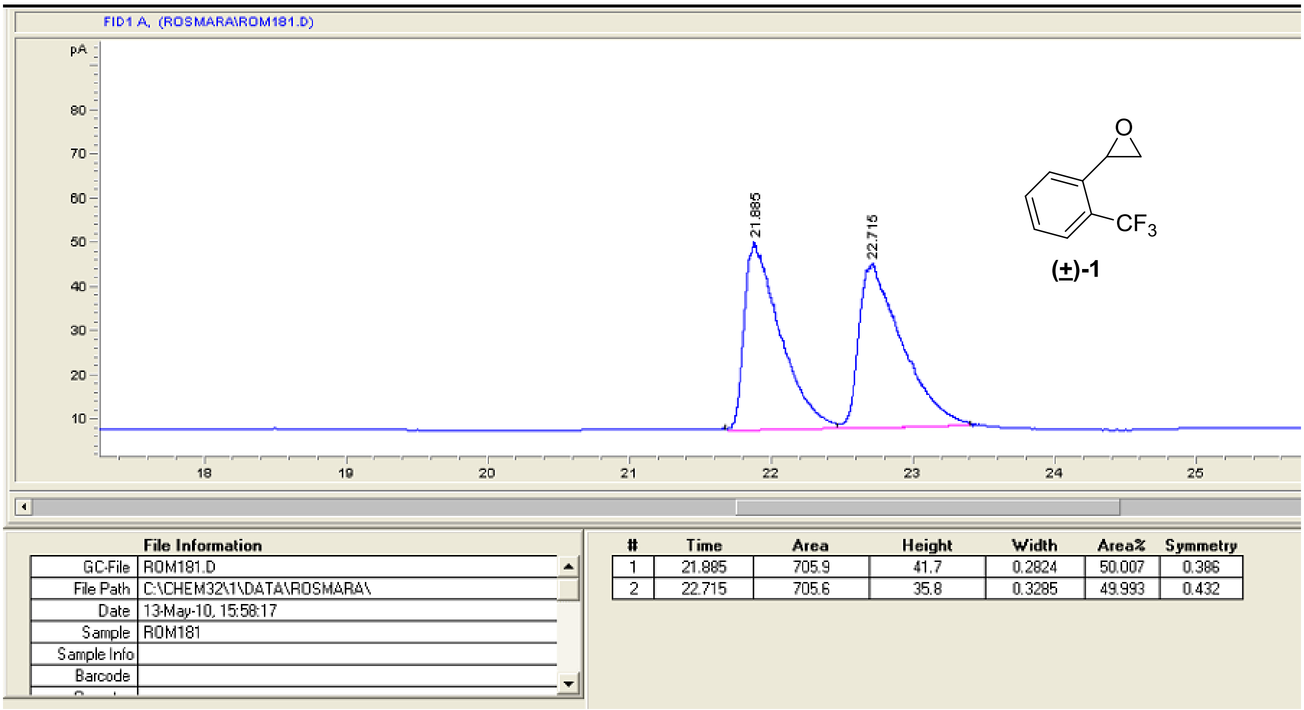
Figure S3: Plot of Ln(ee/100) vs delay time at 195 K in lithiation–deuteration exchange on *ortho*-trifluoromethylstyrene oxide **1** in hexane/(+)-sparteine surrogate.

Table S3. Inversion barriers and enantiomerisation rate constants for lithiated *ortho*-trifluoromethylstyrene oxide **1-Li** in hexane/(+)-sparteine surrogate at 195 K.

ee	t (sec)	$k_{R\rightarrow S}$ (s^{-1})	$\Delta G_{R\rightarrow S}^{\neq}$ (kcal/mol)	$k_{S\rightarrow R}$ (s^{-1})	$\Delta G_{S\rightarrow R}^{\neq}$ (kcal/mol)
70	120	8.37×10^{-4}	14.0 ±0.1	3.59×10^{-4}	14.3 ±0.1
62	240				
48	420				
40	600				

8. Determination of Enantiomeric Ratios of Compounds 1, 2a–d, and 10

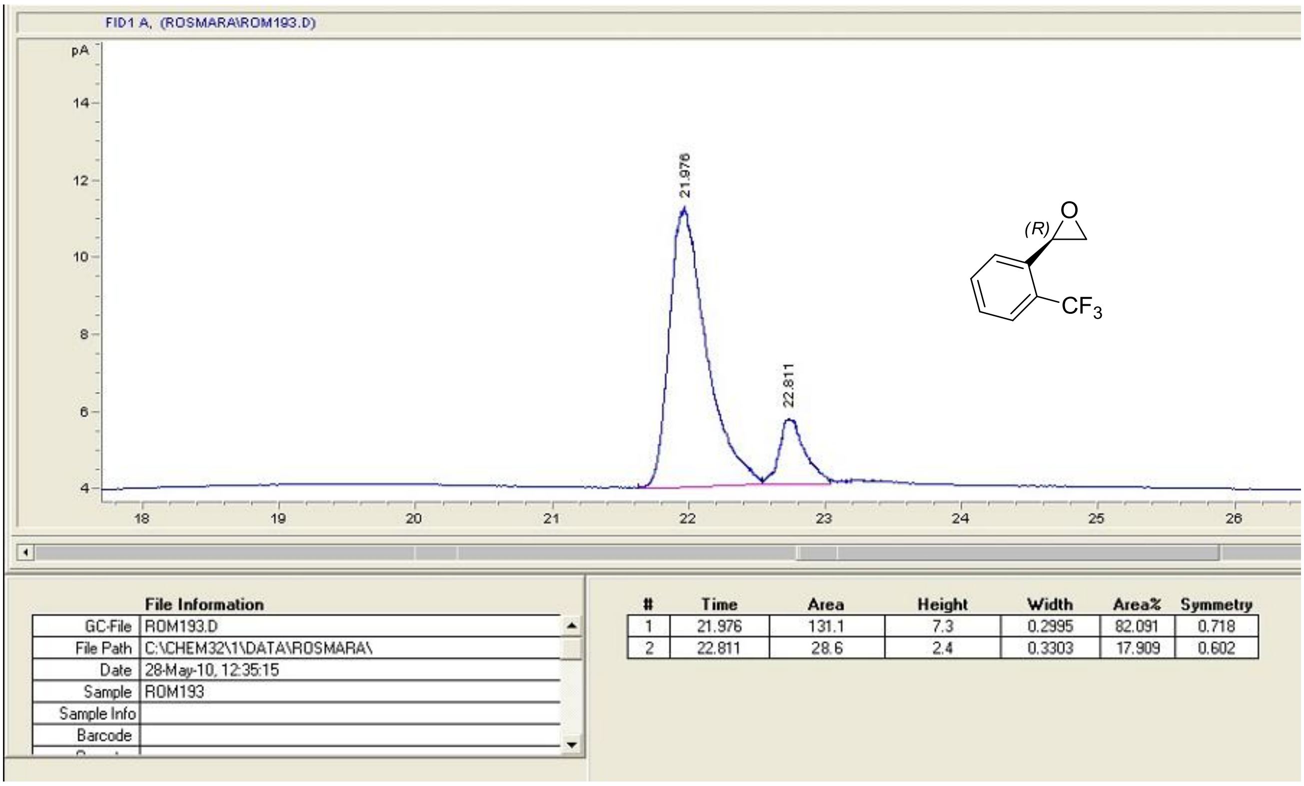
Enantiomeric ratios were determined as follows. In the case of compounds **1**, **2a**–**c** and **10**, by GC analysis employing a Chirasil-DEX CB column (250-0.25 mm, column head pressure 18 psi, He flow rate 2 mL min^{-1}): oven temperature 75 °C for [D]-**1** [(*R*): $t_{R\ \mathit{major}}$ = 21.9 min; (*S*): $t_{R\ \mathit{minor}}$ = 22.7 min]; oven temperature 75 °C for **2a** [(*R*): $t_{R\ \mathit{major}}$ = 17.3 min; (*S*): $t_{R\ \mathit{minor}}$ = 17.8 min]; oven temperature 70 °C for **2b** [(*S*): $t_{R\ \mathit{major}}$ = 81.9 min; (*R*): $t_{R\ \mathit{minor}}$ = 85.3 min]; oven temperature 100 °C for **2c** [(*R*) : $t_{R\ \mathit{minor}}$ = 58.5 min; (*S*): $t_{R\ \mathit{major}}$ = 60.5 min]; oven temperature 70 °C for **10** [(*R*): $t_{R\ \mathit{major}}$ = 14.8 min; (*S*): $t_{R\ \mathit{minor}}$ = 15.4 min]. In the case of compound **2d**, by HPLC analysis employing a Daicel Chiralcel OD-H column: 250-4.6 mm, *n*-hexane/*i*-PrOH 90:10, flow rate 0.5 mL min^{-1}, λ = 260 nm; (*R*): $t_{R\ \mathit{minor}}$ = 9.7 min; (*S*): $t_{R\ \mathit{major}}$ = 10.2 min.



File Information

GC-File	ROM181.D
File Path	C:\CHEM32\1\DATA\ROSMARA\
Date	13-May-10, 15:58:17
Sample	ROM181
Sample Info	
Barcode	

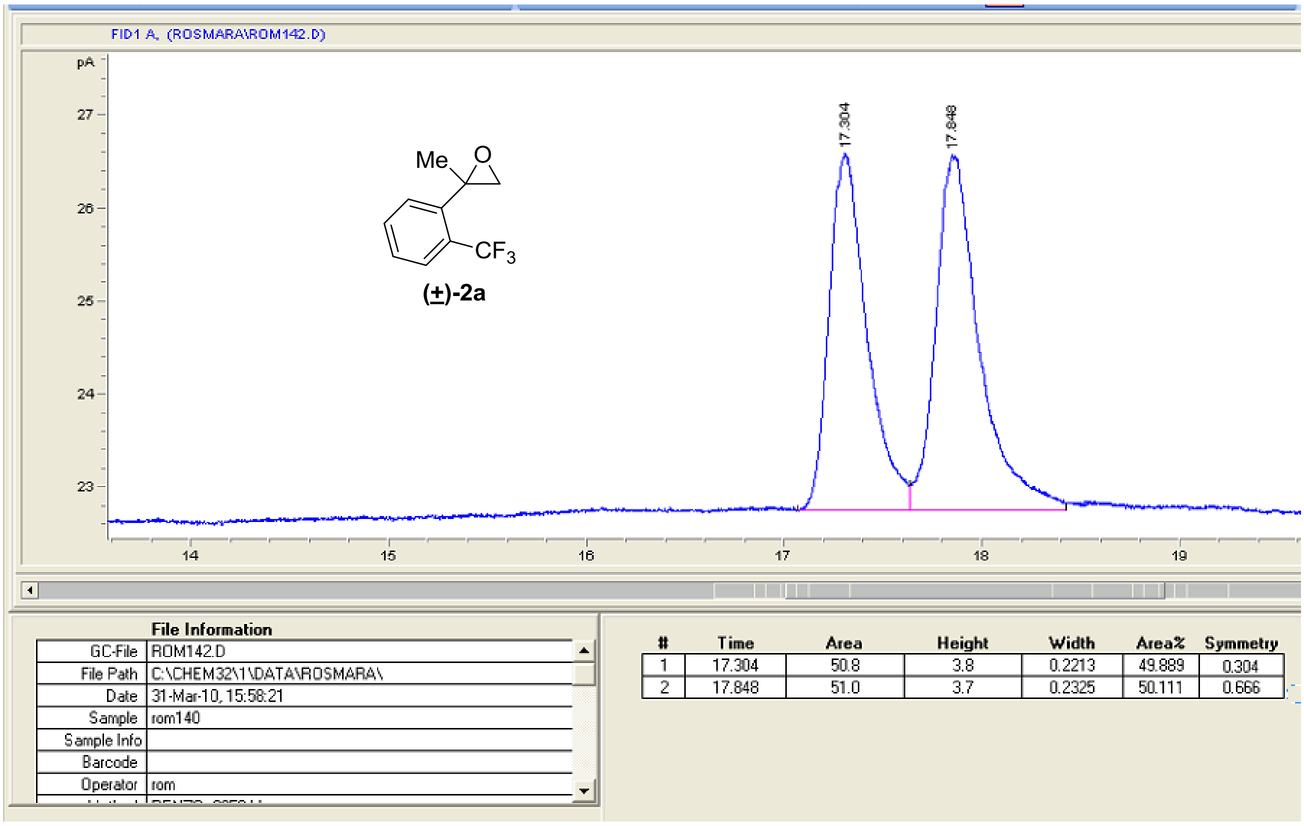
#	Time	Area	Height	Width	Area%	Symmetry
1	21.885	705.9	41.7	0.2824	50.007	0.386
2	22.715	705.6	35.8	0.3285	49.993	0.432



File Information

GC-File	ROM193.D
File Path	C:\CHEM32\1\DATA\ROSMARA\
Date	28-May-10, 12:35:15
Sample	ROM193
Sample Info	
Barcode	

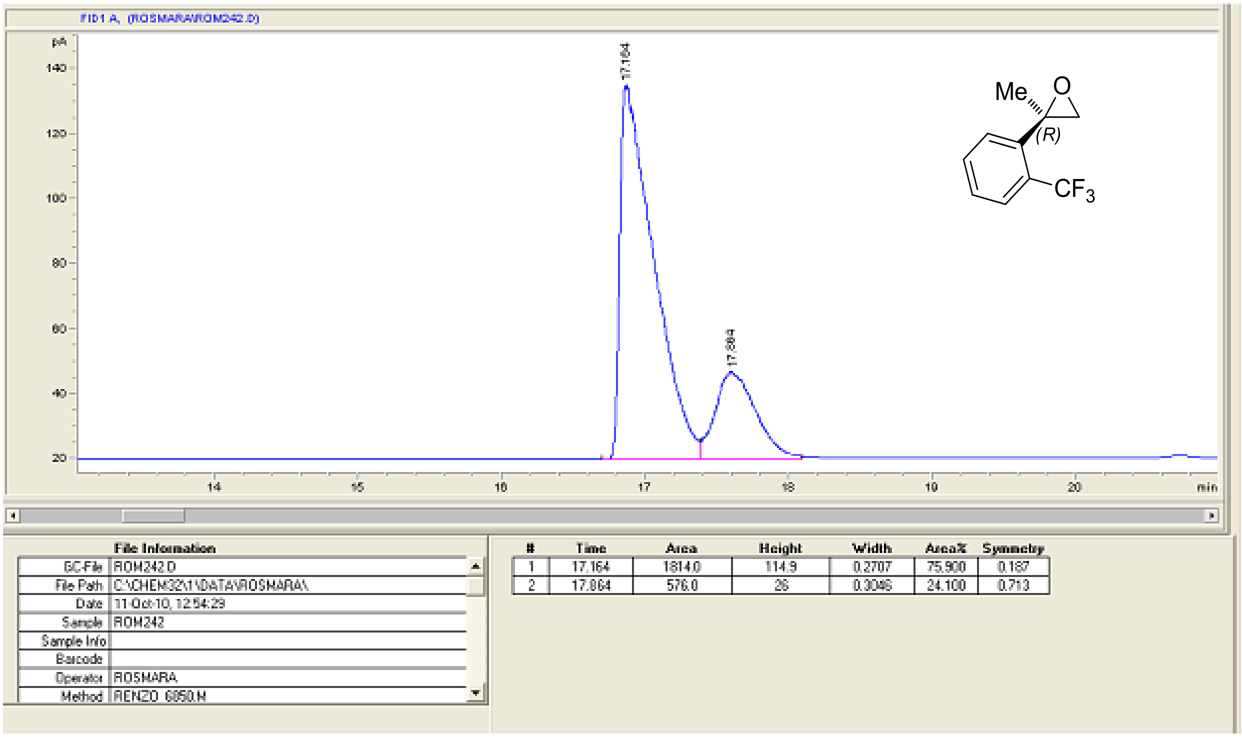
#	Time	Area	Height	Width	Area%	Symmetry
1	21.976	131.1	7.3	0.2995	82.091	0.718
2	22.811	28.6	2.4	0.3303	17.909	0.602



File Information

GC-File	ROM142.D
File Path	C:\CHEM32\1\DATA\ROSMARA\
Date	31-Mar-10, 15:58:21
Sample	rom140
Sample Info	
Barcode	
Operator	rom

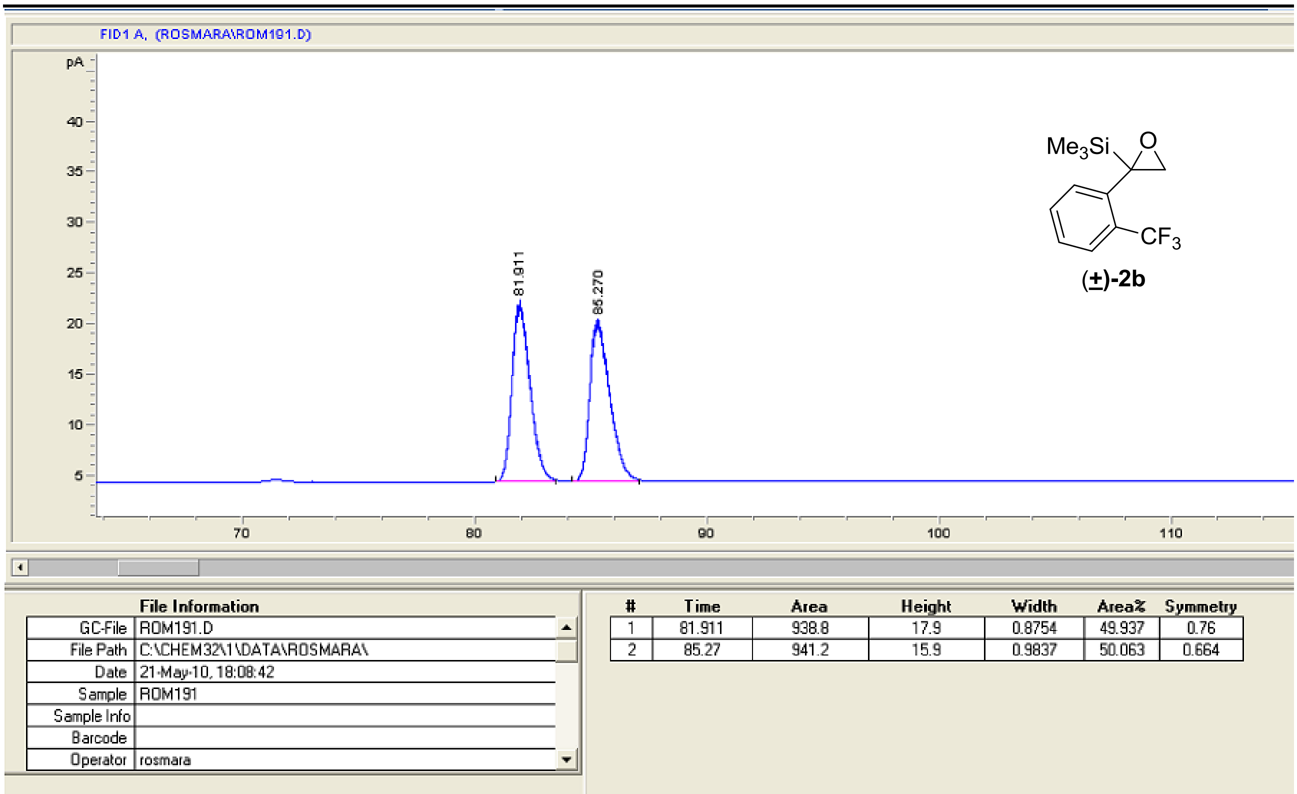
#	Time	Area	Height	Width	Area%	Symmetry
1	17.304	50.8	3.8	0.2213	49.889	0.304
2	17.848	51.0	3.7	0.2325	50.111	0.666



File Information

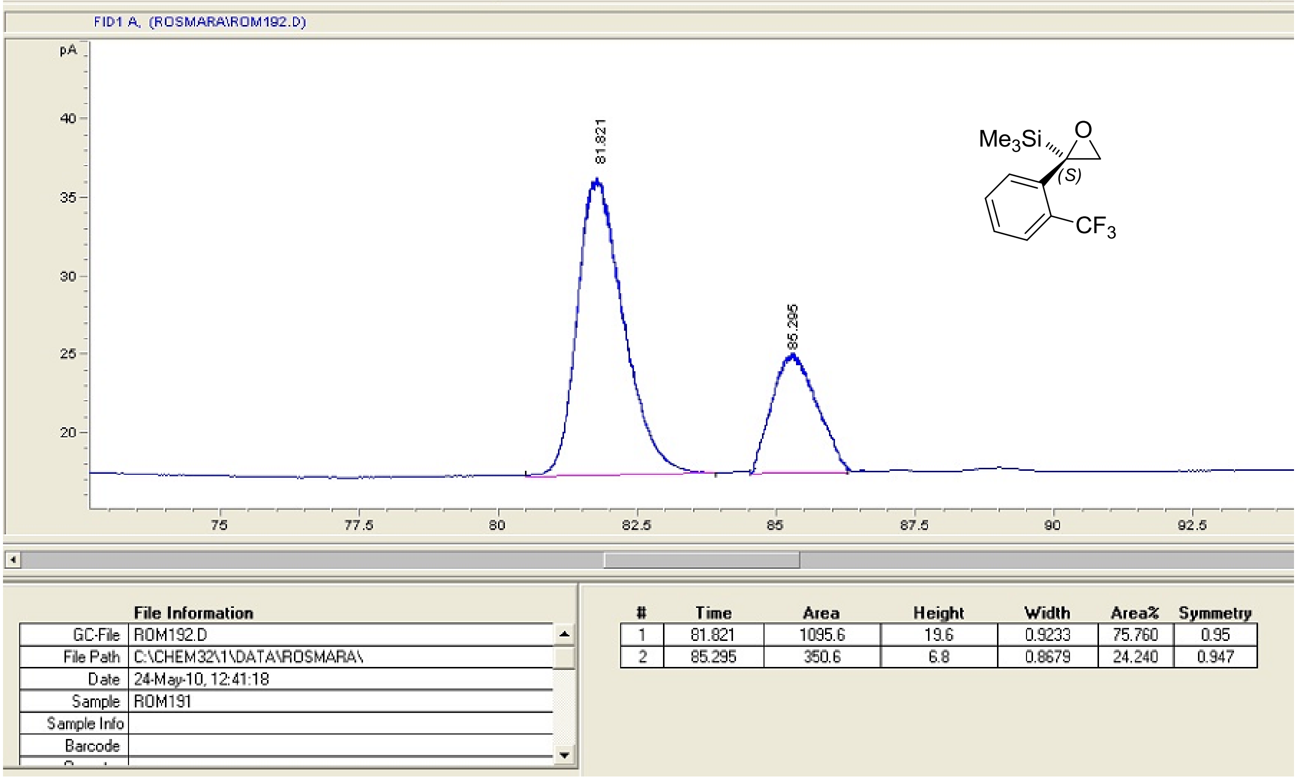
GC-File	ROM242.D
File Path	C:\CHEM32\1\DATA\ROSMARA\
Date	11-Oct-10, 12:54:29
Sample	ROM242
Sample Info	
Barcode	
Operator	ROSMARA
Method	RENZO_6850.M

#	Time	Area	Height	Width	Area%	Symmetry
1	17.164	1814.0	114.9	0.2707	75.900	0.187
2	17.864	576.0	26	0.3046	24.100	0.713



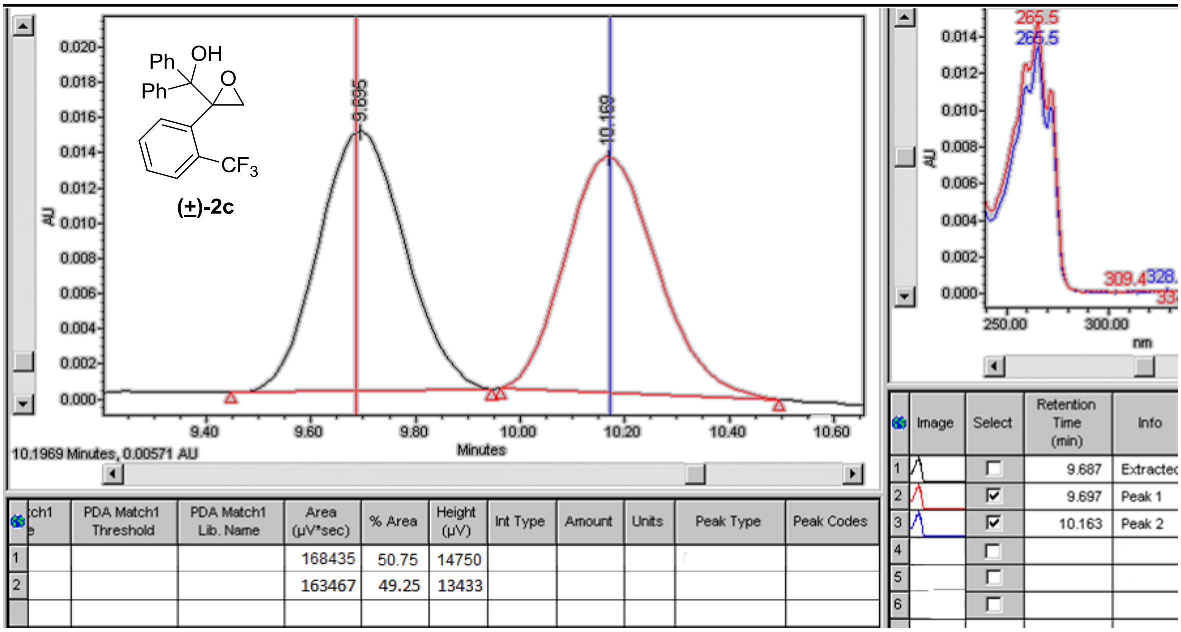
	File Information
GC-File	ROM191.D
File Path	C:\CHEM32\1\DATA\ROSMARA\
Date	21-May-10, 18:08:42
Sample	ROM191
Sample Info	
Barcode	
Operator	rosmara

#	Time	Area	Height	Width	Area%	Symmetry
1	81.911	938.8	17.9	0.8754	49.937	0.76
2	85.27	941.2	15.9	0.9837	50.063	0.664



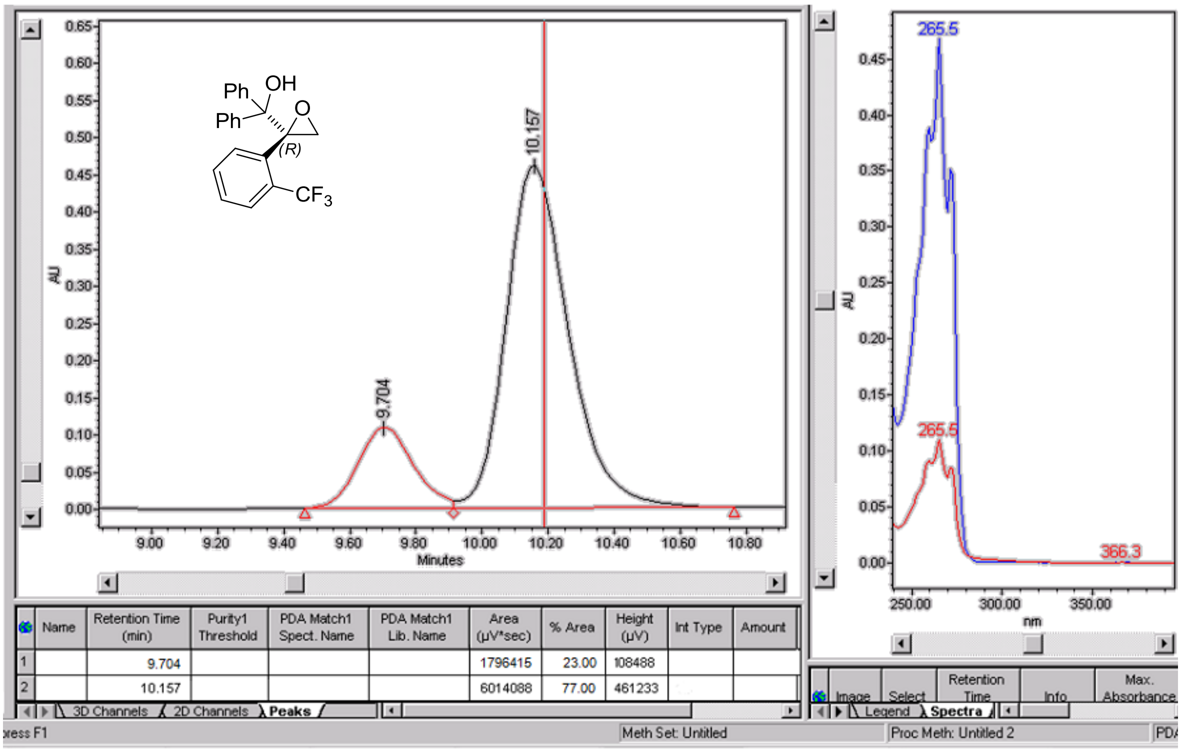
	File Information
GC-File	ROM192.D
File Path	C:\CHEM32\1\DATA\ROSMARA\
Date	24-May-10, 12:41:18
Sample	ROM191
Sample Info	
Barcode	

#	Time	Area	Height	Width	Area%	Symmetry
1	81.821	1095.6	19.6	0.9233	75.760	0.95
2	85.295	350.6	6.8	0.8679	24.240	0.947

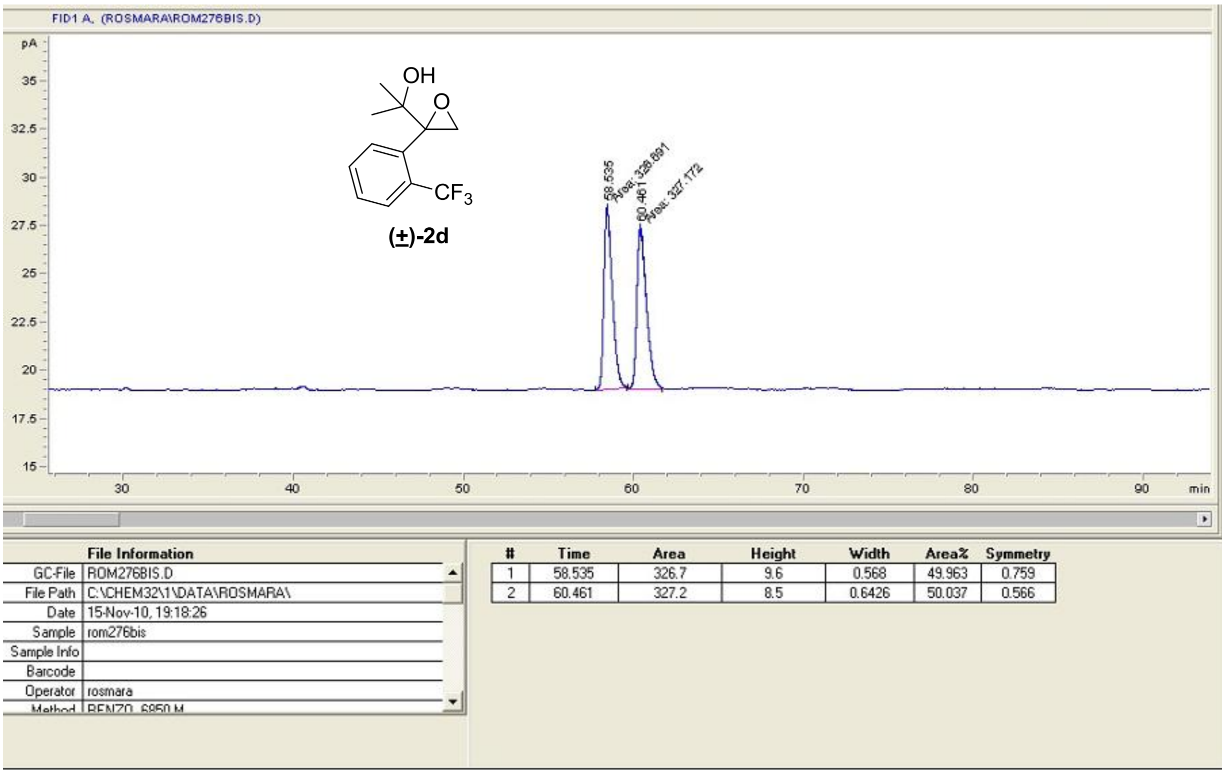


ch1	PDA Match1 Threshold	PDA Match1 Lib. Name	Area (µV*sec)	% Area	Height (µV)	Int Type	Amount	Units	Peak Type	Peak Codes
1			168435	50.75	14750					
2			163467	49.25	13433					

	Image	Select	Retention Time (min)	Info
1		☐	9.687	Extracted
2		☑	9.697	Peak 1
3		☑	10.163	Peak 2
4		☐		
5		☐		
6		☐		

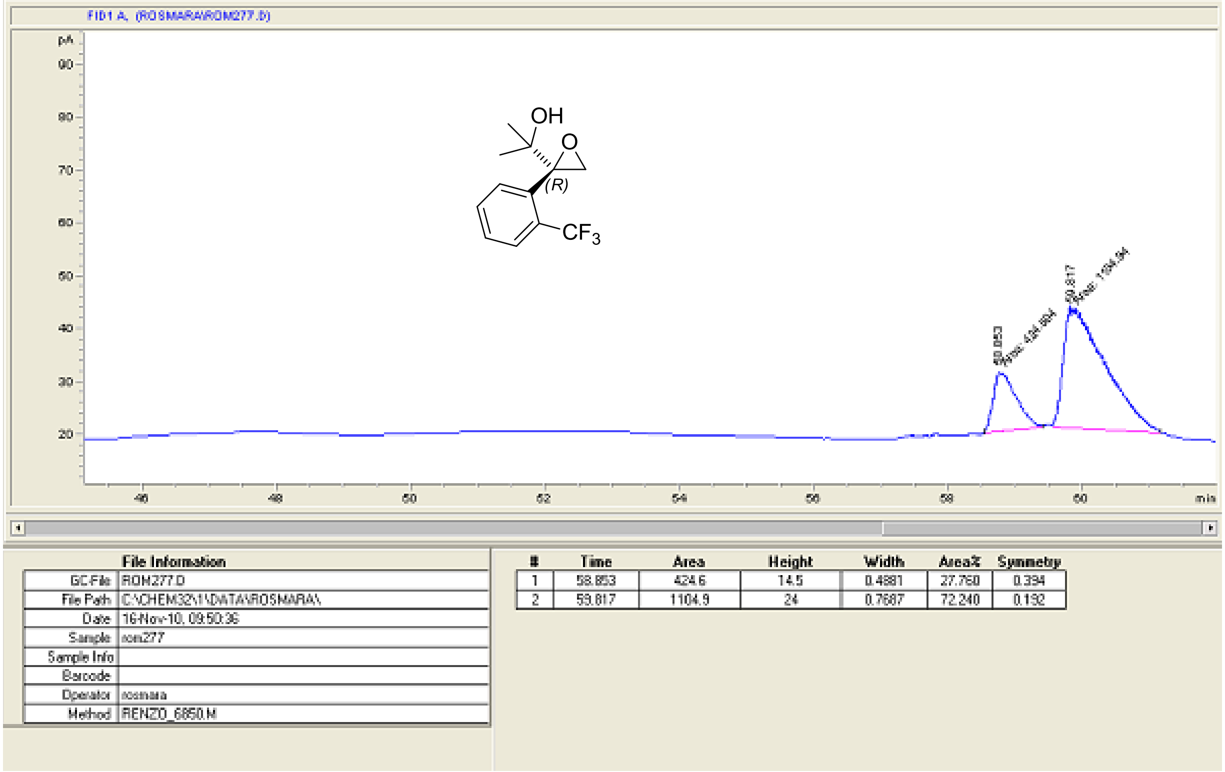


	Name	Retention Time (min)	Purity1 Threshold	PDA Match1 Spect. Name	PDA Match1 Lib. Name	Area (µV*sec)	% Area	Height (µV)	Int Type	Amount
1		9.704				1796415	23.00	108488		
2		10.157				6014088	77.00	461233		



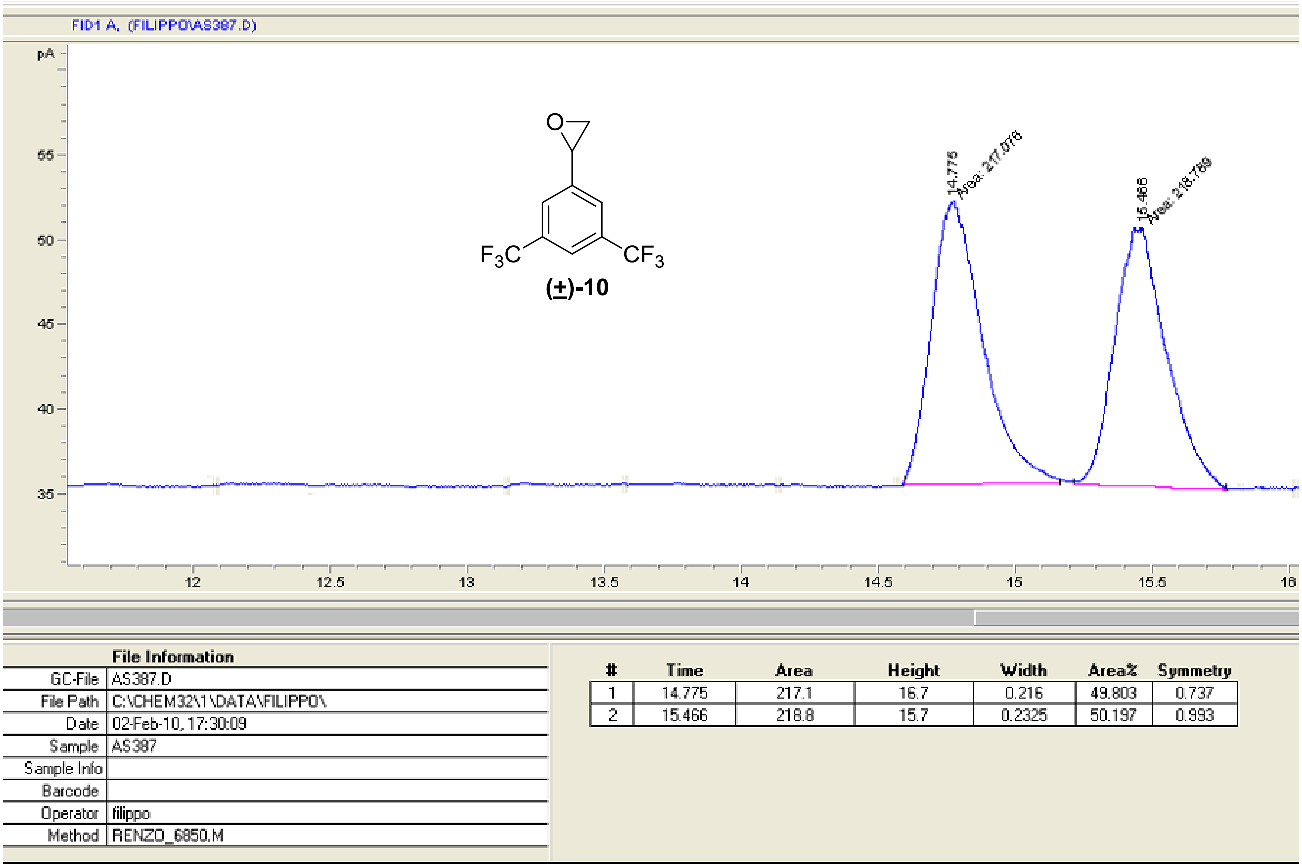
File Information	
GC-File	ROM276BIS.D
File Path	C:\CHEM32\1\DATA\ROSMARA\
Date	15-Nov-10, 19:18:26
Sample	rom276bis
Sample Info	
Barcode	
Operator	rosmara
Method	RENZO_6850.M

#	Time	Area	Height	Width	Area%	Symmetry
1	58.535	326.7	9.6	0.568	49.963	0.759
2	60.461	327.2	8.5	0.6426	50.037	0.566



File Information	
GC-File	ROM277.D
File Path	C:\CHEM32\1\DATA\ROSMARA\
Date	16-Nov-10, 09:50:36
Sample	rom277
Sample Info	
Barcode	
Operator	rosmara
Method	RENZO_6850.M

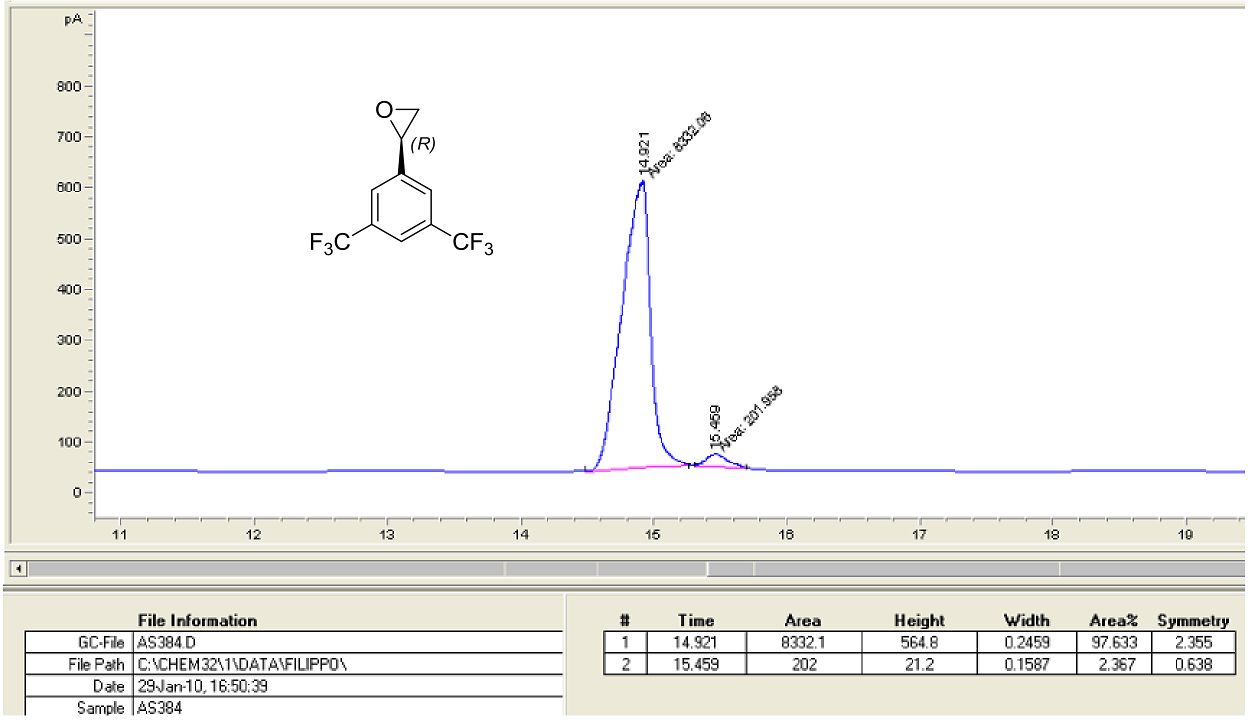
#	Time	Area	Height	Width	Area%	Symmetry
1	58.853	424.6	14.5	0.4881	27.760	0.394
2	59.817	1104.9	24	0.7687	72.240	0.192



File Information

GC-File	AS387.D
File Path	C:\CHEM32\1\DATA\FILIPPO\
Date	02-Feb-10, 17:30:09
Sample	AS387
Sample Info	
Barcode	
Operator	filippo
Method	RENZO_6850.M

#	Time	Area	Height	Width	Area%	Symmetry
1	14.775	217.1	16.7	0.216	49.803	0.737
2	15.466	218.8	15.7	0.2325	50.197	0.993

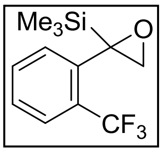


File Information

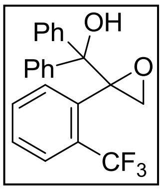
GC-File	AS384.D
File Path	C:\CHEM32\1\DATA\FILIPPO\
Date	29-Jan-10, 16:50:39
Sample	AS384

#	Time	Area	Height	Width	Area%	Symmetry
1	14.921	8332.1	564.8	0.2459	97.633	2.355
2	15.459	202	21.2	0.1587	2.367	0.638

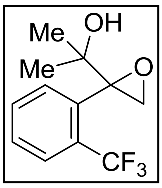
9. Characterization and Spectral Data of Compounds 2b-d



Trimethyl[1-(2-trifluoromethylphenyl)epoxyethyl]silane (2b): 70%, yellow oil. **^{1}H NMR** ($CDCl_3$, 400 MHz): 0.03 (s, 9 H), 3.05 (d, *J* = 5.1 Hz, 1 H), 3.12 (d, *J* = 5.1 Hz, 1 H), 7.33-7.59 (m, 4 H). **^{13}C NMR** ($CDCl_3$, 150 MHz) δ: -3.6, 52.8, 54.8, 124.5 (q, $^1J_{C\text{-}F}$ = 274.0 Hz), 126.2, 127.0, 129.9, 131.5, 140.0. **GC-MS** (70 eV) *m/z* (%): 260 (9, M^+), 191 (74), 149 (90), 129 (98), 77 (100). **FT-IR** (film) cm^{-1}: 843, 1035, 1124, 1316, 2924, 2960. **Elemental analysis** calcd (%) for $C_{12}H_{15}F_3OSi$: C, 55.36; H, 5.81 found: C, 55.52; H, 5.93.

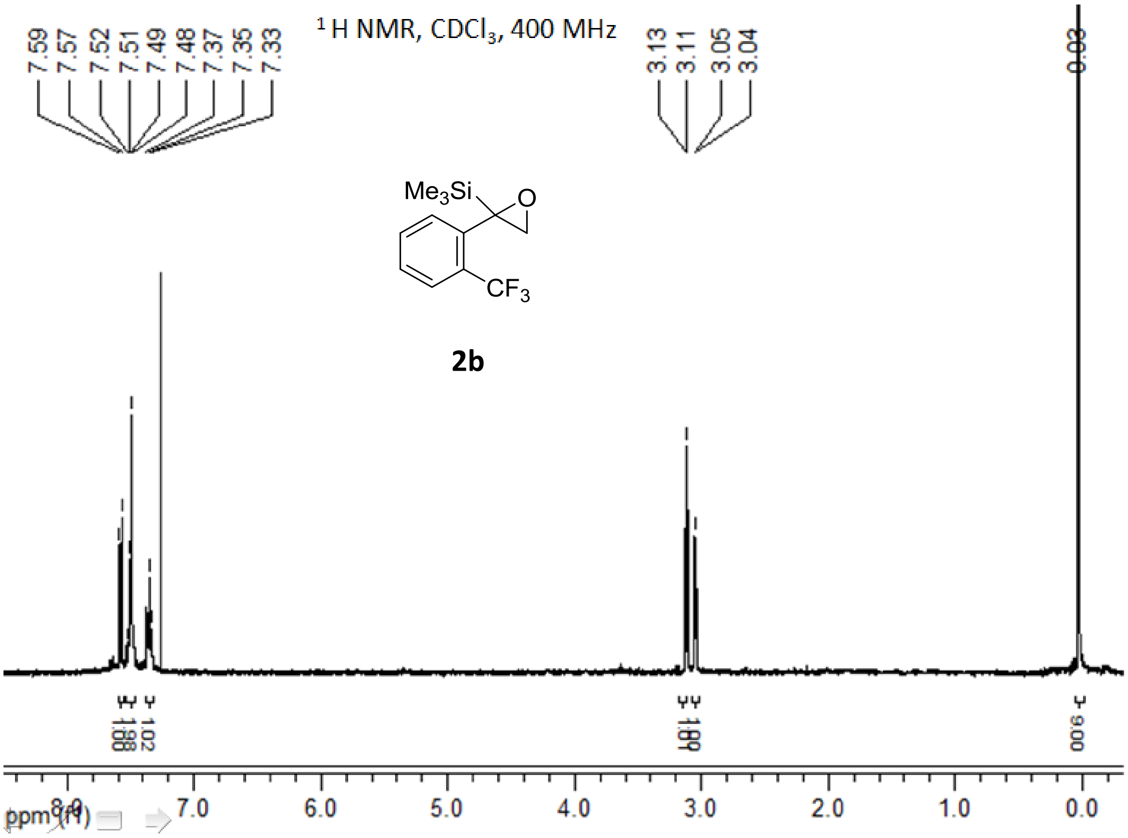


1,1-Diphenyl-2-(2-trifluoromethylphenyl)-2,3-epoxy-1-propanol (2c): (75%), waxy solid. **^{1}H NMR** (DMSO-*d*$_6$, 600 MHz) δ: 2.52 (d, *J* = 4.2 Hz , 1 H), 2.69(d, *J* = 4.2 Hz , 1 H), 6.20 (bs, 1 H), 7.10-7.70 (m, 14 H). **^{13}C NMR** ($CDCl_3$, 150 MHz) δ: 51.9, 64.2, 78.7, 124.6 (q, $^1J_{C\text{-}F}$ = 274.0 Hz), 126.8, 127.3, 127.5, 127.6, 127.9, 128.4, 129.8 (q, $^2J_{C\text{-}F}$ = 30.7 Hz), 130.7, 131.7, 135.2, 141.9, 142.8. **GC-MS** (70 eV) *m/z* (%): 352 (20, M^+- H_2O), 183 (100), 165 (57), 105 (75), 77 (3). **FT-IR** (film) cm^{-1}: 701, 770, 1037, 1108, 1315, 1448, 3468. **Elemental analysis** calcd (%) for $C_{22}H_{17}F_3O_2$: C, 71.34; H, 4.63 found: C, 71.52; H, 4.70.

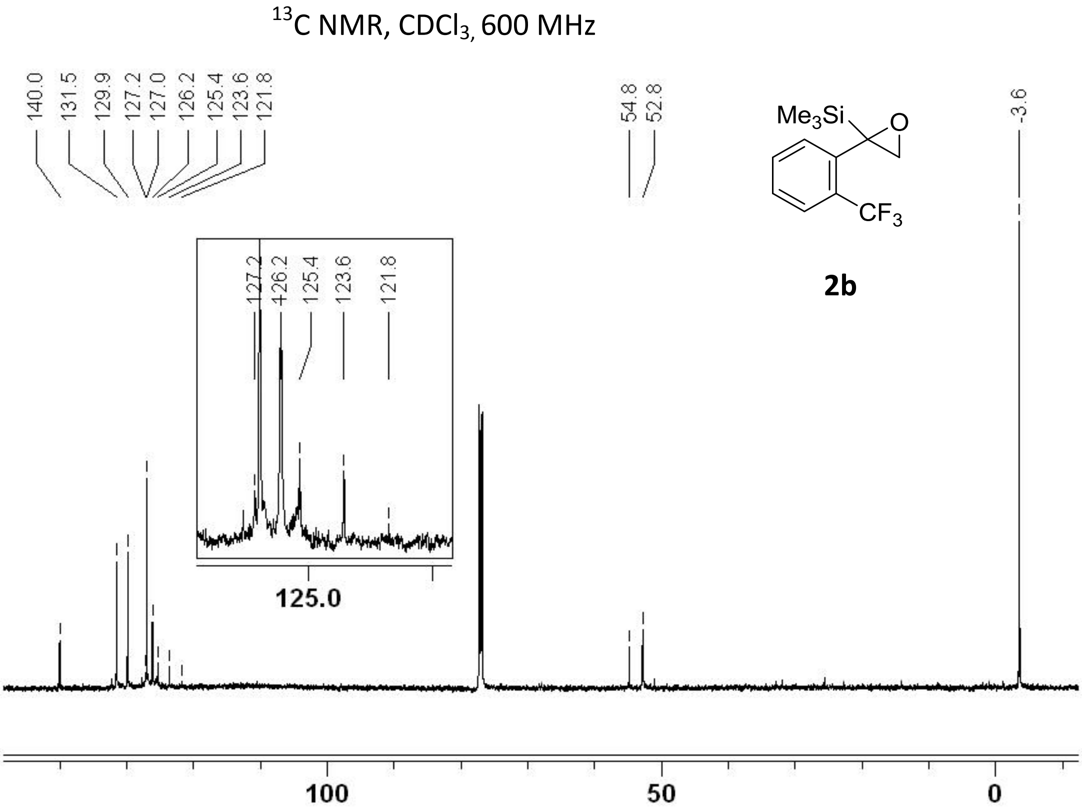


2-Methyl-3-(2-trifluoromethylphenyl)-3,4-epoxy-2-butanol (2d): (90%), yellow oil. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ: 1.25 (s, 3 H), 1.27 (s, 3 H), 2.02 (bs, 1 H), 3.04 (d, *J* = 4.6 Hz, 1 H), 3.50 (d, *J* = 4.6 Hz, 1 H), 7.46–7.75 (m, 4 H). **^{13}C NMR** ($CDCl_3$, 600 MHz) δ: 25.4, 26.9, 53.3, 64.1, 71.3, 124.5 (q, $^1J_{C\text{-}F}$ = 274.0 Hz), 128.6 (q, $^2J_{C\text{-}F}$ = 30.0 Hz), 128.5, 131.1, 131.9, 135.6. **GC-MS** (70 eV) *m/z* (%): 188 (20), 168 (100), 140 (43), 129 (98), 59 (55). **FT-IR** (film) cm^{-1}: 770, 1036, 1119, 1175, 1315, 2984, 3468. **Elemental analysis** calcd (%) for $C_{12}H_{13}F_3O_2$: C, 58.54; H, 5.32 found: C, 58.71; H, 5.66.

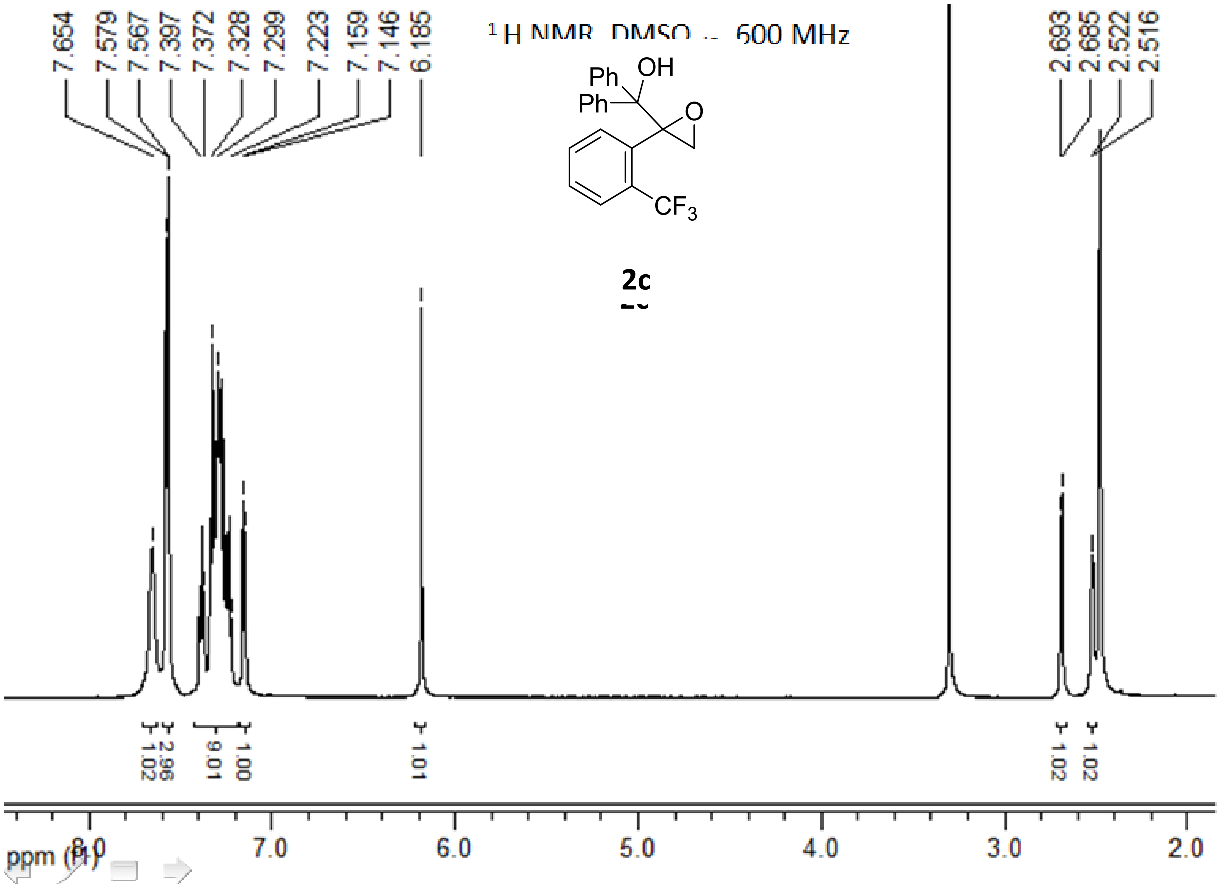
10. ^{1}H and ^{13}C NMR Spectra of Compounds 2b-d



2b



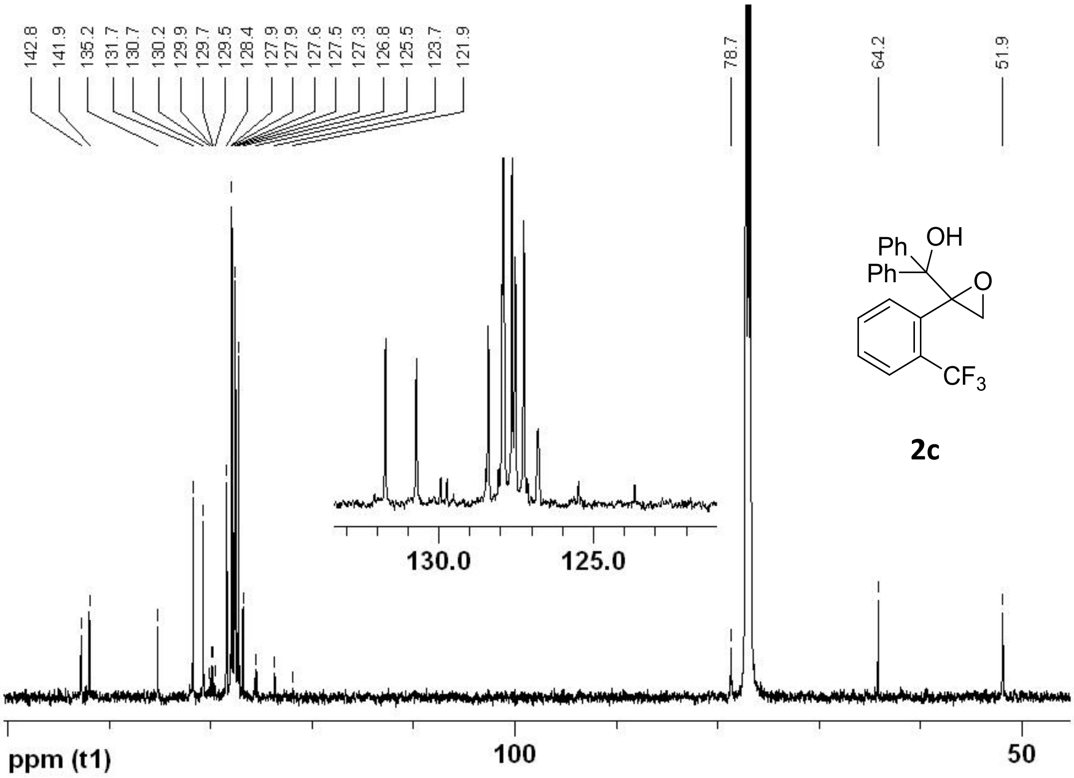
2b



^{1}H NMR, DMSO-d_6, 600 MHz

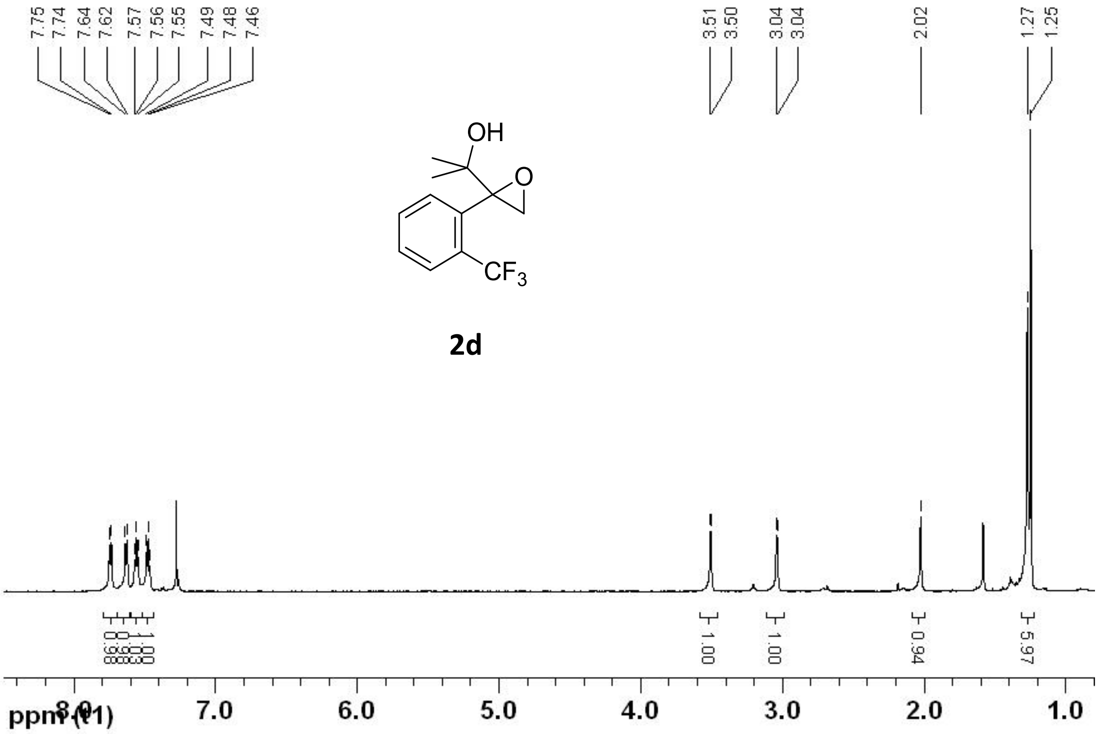
2c

^{13}C NMR, CDCl$_3$, 600 MHz



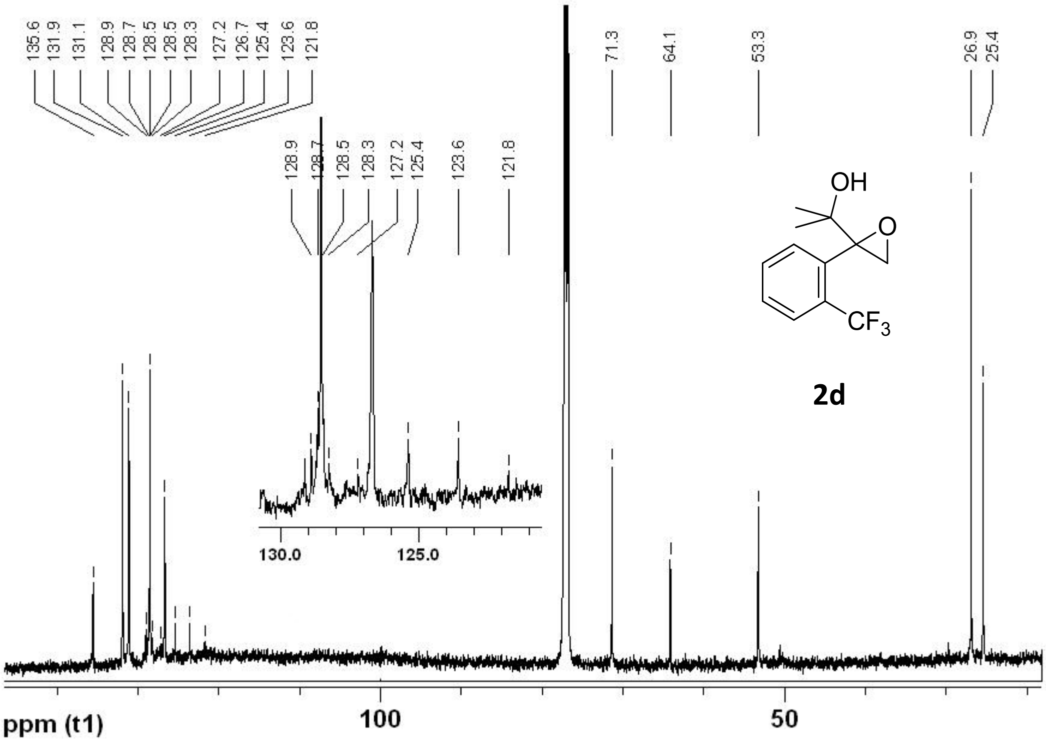
2c

^{1}H NMR, CDCl$_3$, 600 MHz



2d

^{13}C NMR, CDCl$_3$, 150 MHz



2d