Supporting Information

Synthesis of (R)-Modafinil *via* Organocatalyzed and non-Heme Iron Catalyzed Sulfoxidation Using H_2O_2 as Environmentally Benign Oxidant

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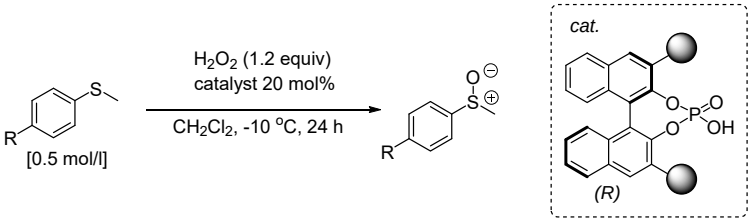
Table of Contents

1 General Information

All chemicals used for synthesis were purchased from commercial sources and were used without further purification. All solvents were purified by distillation using rotary evaporation or were purchased in HPLC-grade-quality. All BINOL-phosphates were prepared according to a literature procedure.[S1] Spectral data of the catalysts matches literature values.[S2,S3] All products were dried in high vacuum (up to 10^{-3} bar). Thin layer chromatography (TLC) was performed on pre-coated aluminum sheets ALUGRAM® SIL G/UV254 (0.2 mm silica gel with fluorescent indicator, MachereyNagel & Co). ^{1}H-NMR spectra were recorded at room temperature on a Bruker Avance 300 spectrometer operating at 300 MHz. All chemical shifts are given in the ppm-scale and refer to the nondeuterized proportion of the solvent. Enantiomeric excesses (*ee*) were determined using analytical high performance liquid chromatography (HPLC) performed on an Agilent Technologies 1200 Series equipment provided with Agilent ChemStation, Standard and preparative Autosampler, Diode Array and Multiple Wavelength Detector SL and a Thermostatted Column Compartment.

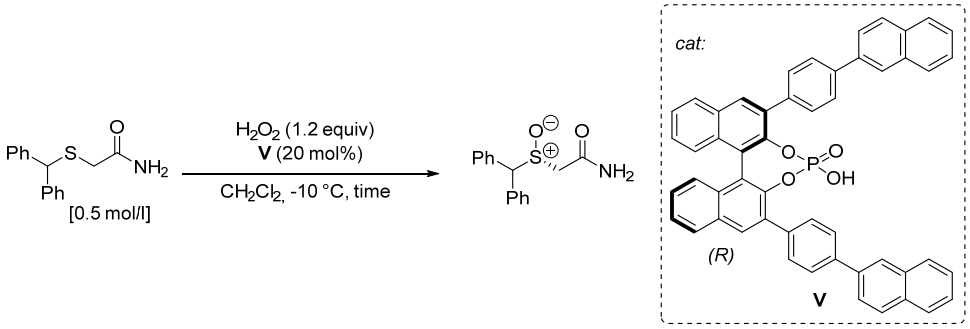
2 Experimental Procedures, Analytical and Spectroscopic Data

2.1 General Procedure for the Sulfoxidation towards Thioanisole



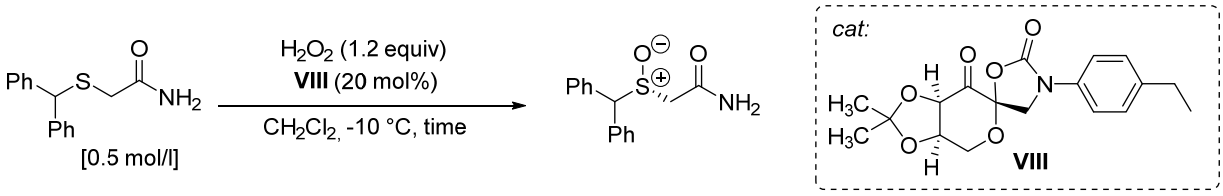
The corresponding BINOL-phosphate catalyst (0.048 mmol) was dissolved in CH_2Cl_2 (0.5 ml) at -10 °C. The sulfide (0.24 mmol) was added, followed by the addition of aqueous 30% H_2O_2 (1.2 equiv, 0.29 mmol, 29.4 µl) in one portion. The reaction mixture was stirred at room temperature for 24 h. The product was directly purified by column chromatography (SiO_2, EtOAc/PE 4:1). ^{1}H-NMR correlates well with that given in the literature.[S4,S5]

2.2 General Procedure for the Sulfoxidation towards *(R)*-Modafinil using BINOL-phosphate Catalyst V



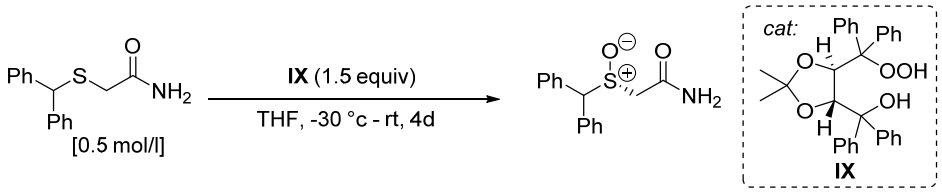
BINOL-phosphate **V** (0.048 mmol, 36 mg) was dissolved in CH_2Cl_2 (0.5 ml) at -10 °C, followed by the addition of aqueous 30% H_2O_2 (1.2 equiv, 0.29 mmol, 29.4 µl) in one portion. Then, the sulfide (0.24 mmol, 61.8 mg) was added to the reaction mixture, which was then stirred at -10 °C temperature for a certain time. The product was directly purified by column chromatography (SiO_2, EtOAc). ^{1}H-NMR correlates well with that given in the literature.[S6] The enantiomeric excess of the product was determined by chiral HPLC analysis (Daicel Chiralpak AS, flow 0.9 mL/min, *n*-hexane/*i*-PrOH 60:40, 25 °C, 31 bar).

2.3 Procedure for the Sulfoxidation towards *(R)*-Modafinil using Shi's N-Substituted Oxazolidinone Ketone VIII



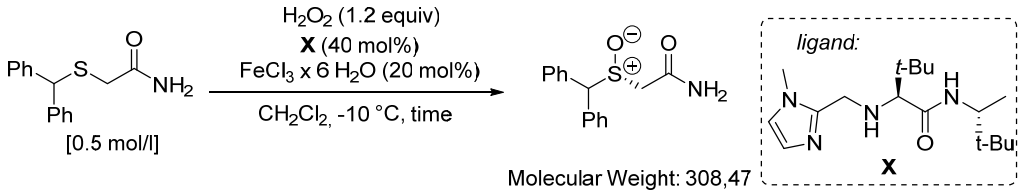
Shi's N-substituted oxazolidinone ketone (0.048 mmol, 16.7 mg) was dissolved in CH_2Cl_2 (0.5 ml) at -10 °C followed by the addition of aqueous 30% H_2O_2 (1.2 equiv, 0.29 mmol, 29.4 µl) in one portion. Then, the sulfide (0.24 mmol, 61.8 mg) was added to the reaction mixture, which was then stirred at -10 °C for a certain time. The product was directly purified by column chromatography (SiO_2, EtOAc). The enantiomeric excess of the product was determined by chiral HPLC analysis (Daicel Chiralpak AS, flow 0.9 mL/min, *n*-hexane/*i*-PrOH 60:40, 25 °C, 31 bar).

2.4 Procedure for the Sulfoxidation towards *(R)*-Modafinil using TADOOH



TADOOH (0.36 mmol, 173.7 mg) was dissolved in THF (0.5 ml) at -30 °C. Then, the sulfide (0.24 mmol, 61.8 mg) was added to the reaction mixture, which was then stirred at -30 °C for 3 days and additionally for 1 day at rt. The product was directly purified by column chromatography (SiO_2, EtOAc). The enantiomeric excess of the product was determined by chiral HPLC analysis (Daicel Chiralpak AS, flow 0.9 mL/min, *n*-hexane/*i*-PrOH 60:40, 25 °C, 31 bar).

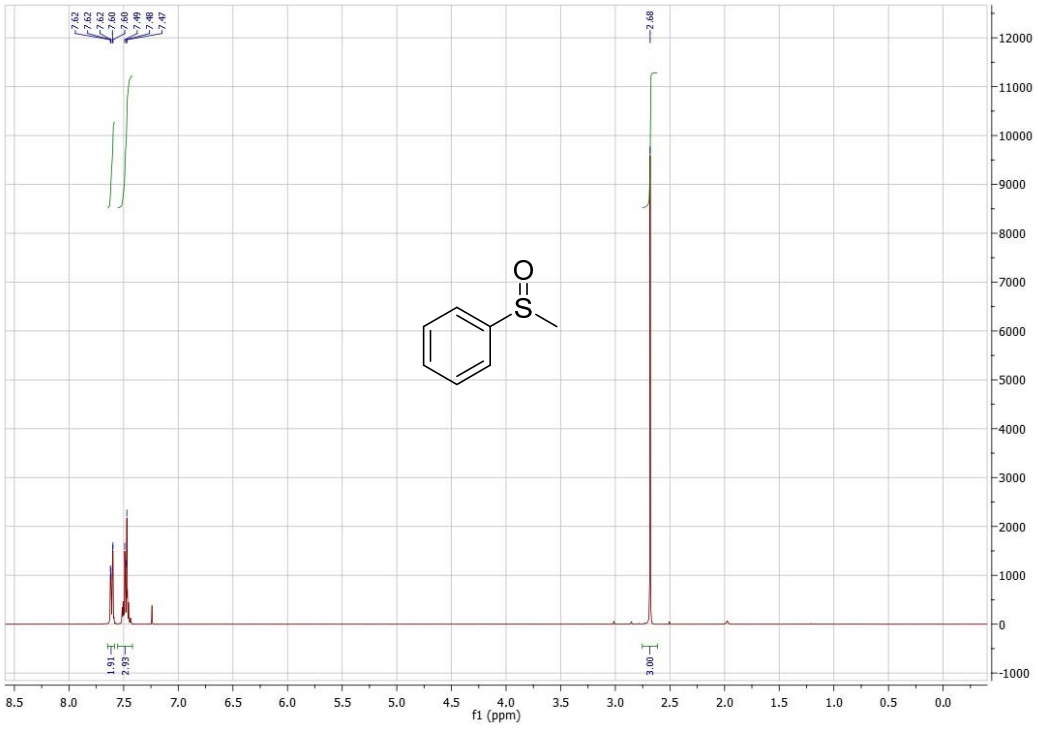
2.5 Procedure for the Sulfoxidation towards *(R)*-Modafinil using the Fe(III) and Dipeptide Based Chiral Ligand System



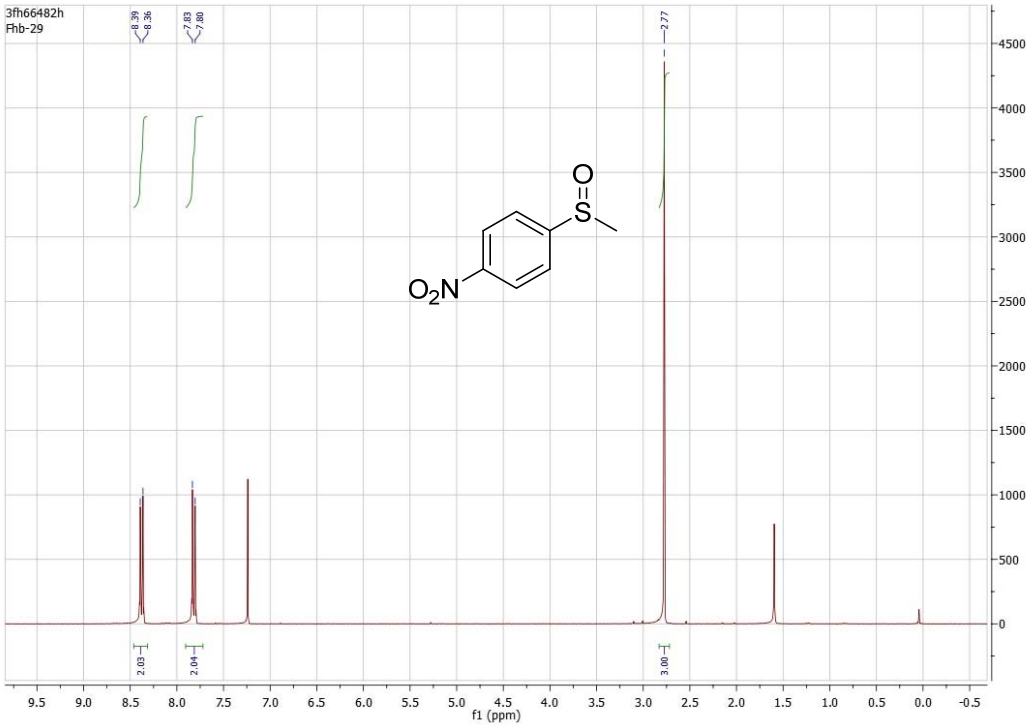
$FeCl_3$ * 6 H_2O (0.048 mmol, 13.0 mg) and the dipeptide based chiral ligand (0.096 mmol, 29.6 mg) were dissolved in CH_2Cl_2 (0.5 ml). The solution, which turned immediately dark violet, was stirred for 30 min. The sulfide (0.24 mmol, 61.8 mg) was added, followed by the addition of aqueous 30% H_2O_2 (1.2 equiv, 0.29 mmol, 29.4 µl). The reaction mixture was stirred at room temperature for 24 h. The product was directly purified by column chromatography (SiO_2, EtOAc/PE 4:1). The enantiomeric excess of the product was determined by chiral HPLC analysis (Daicel Chiralpak AS, flow 0.9 mL/min, *n*-hexane/*i*-PrOH 60:40, 25 °C, 31 bar).

3 Spectral Data

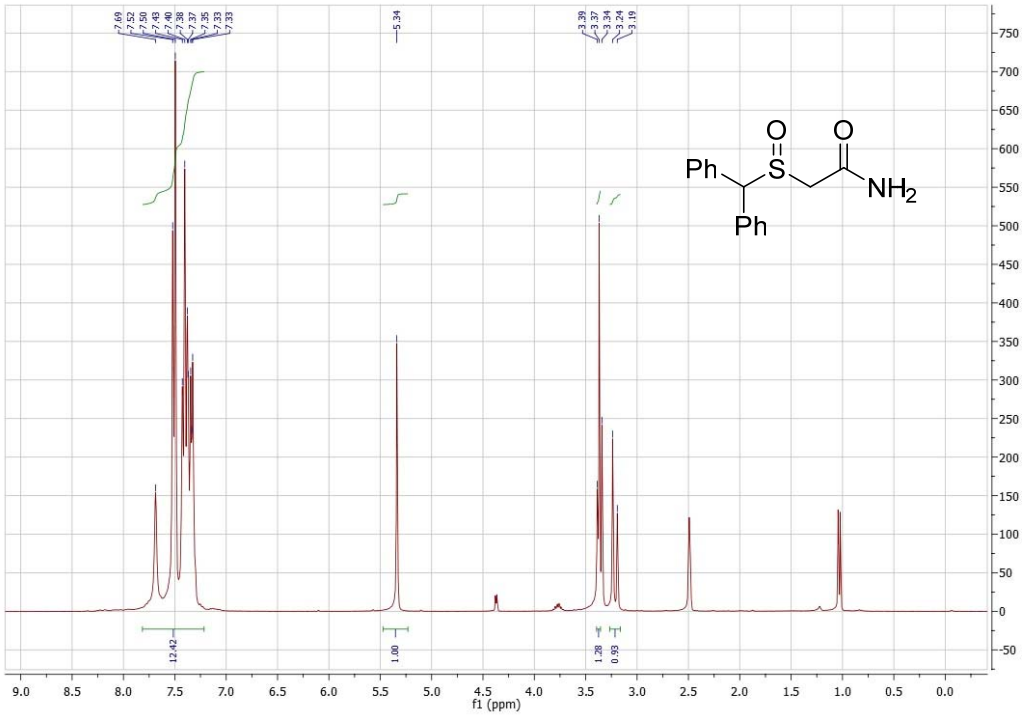
3.1 ^{1}H-NMR (300 MHz, $CDCl_3$) of (Methylsulfinyl)benzene (1a)



3.2 ^{1}H-NMR (300 MHz, $CDCl_3$) of 1-(Methylsulfinyl)-4-nitrobenzene (1b)

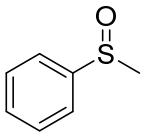


3.3 ^{1}H-NMR (300 MHz, $CDCl_3$) of 2-(Benzhydrylsulfinyl)acetamide (2)



4 HPLC data

(*S*)-(Methylsulfinyl)benzene (1a)

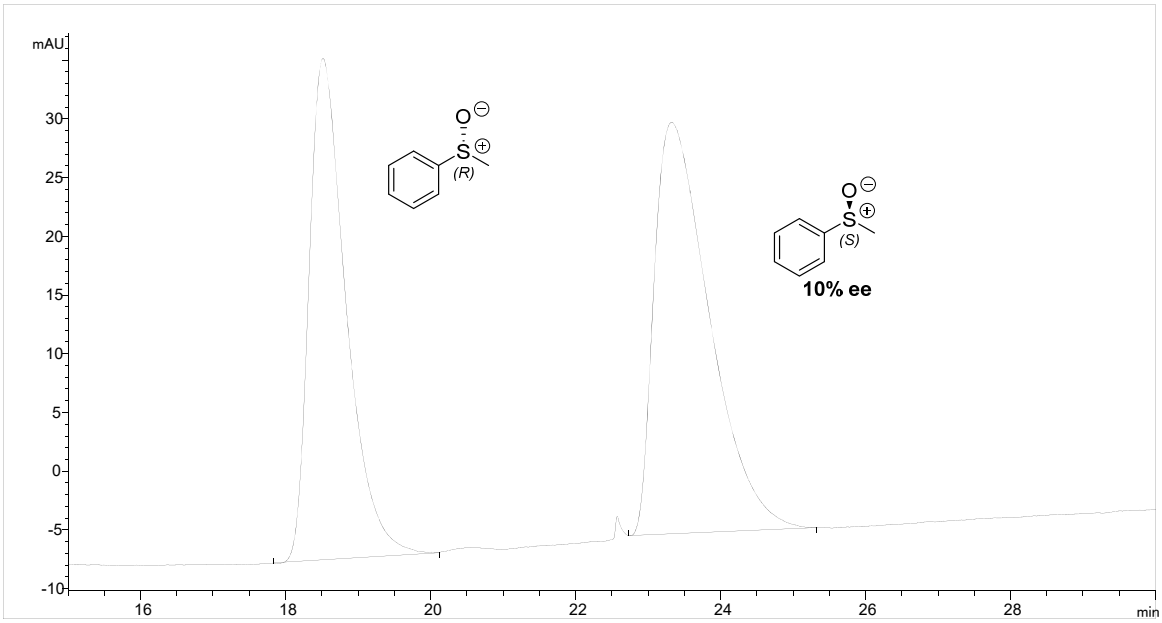


Daicel Chiralpak OD, *n*-hexane/*i*-PrOH = 93:7

Flow rate = 1.0 mL/min

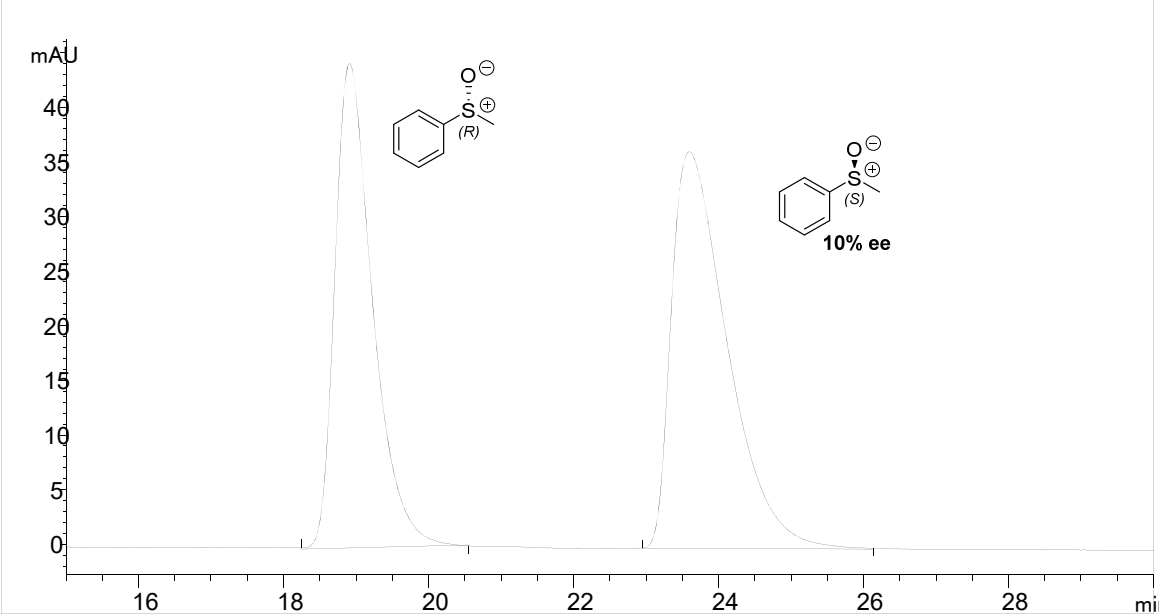
Processed Channel Descr. = PDA 254 nm

t_r = 18.5 min, t_r = 23.3 min (Table 1, entry 1)



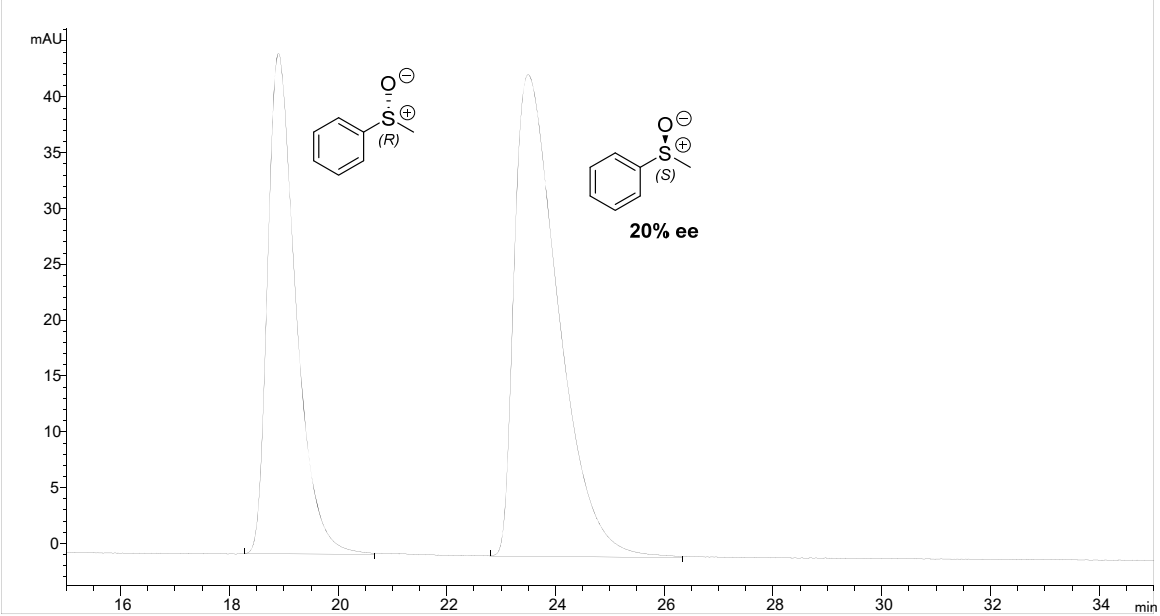
#	Time	Area	Height	Width	Area%	Symmetry
1	18.514	1519.1	42.7	0.5926	44.973	0.579
2	23.324	1858.6	35.1	0.8835	55.027	0.45

t_r = 18.9 min, t_r = 23.6 min (Table 1, entry 2)



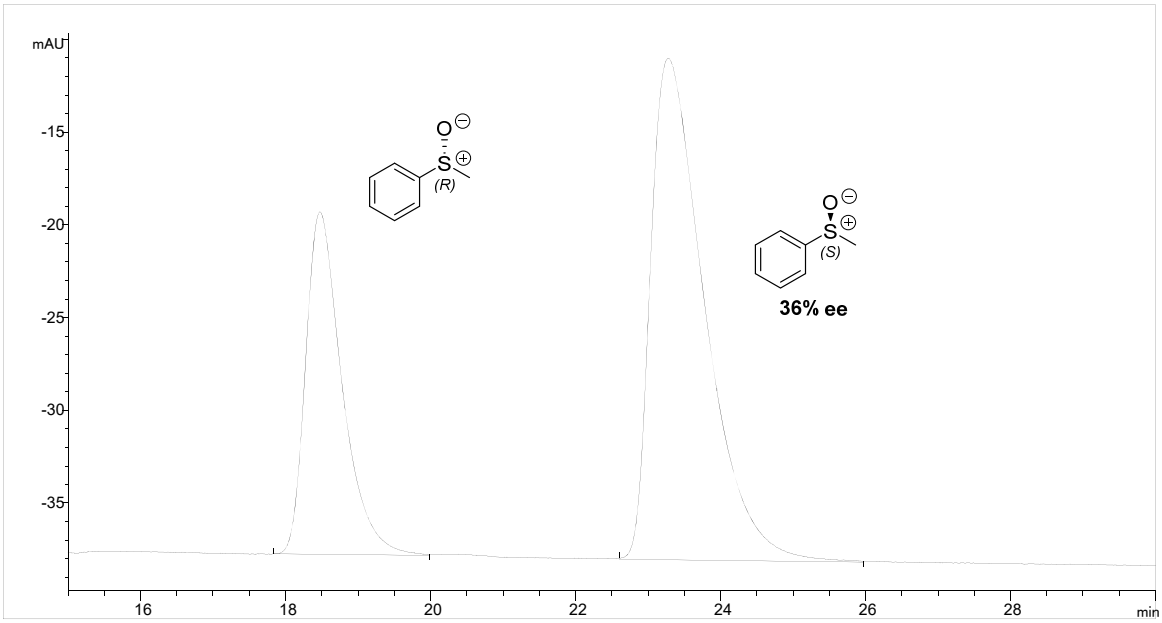
#	Time	Area	Height	Width	Area%	Symmetry
1	18.907	1602.4	44.3	0.6023	45.209	0.612
2	23.595	1942	36.3	0.8921	54.791	0.457

t_r = 18.9 min, t_r = 23.5 min (Table 1, entry 3)



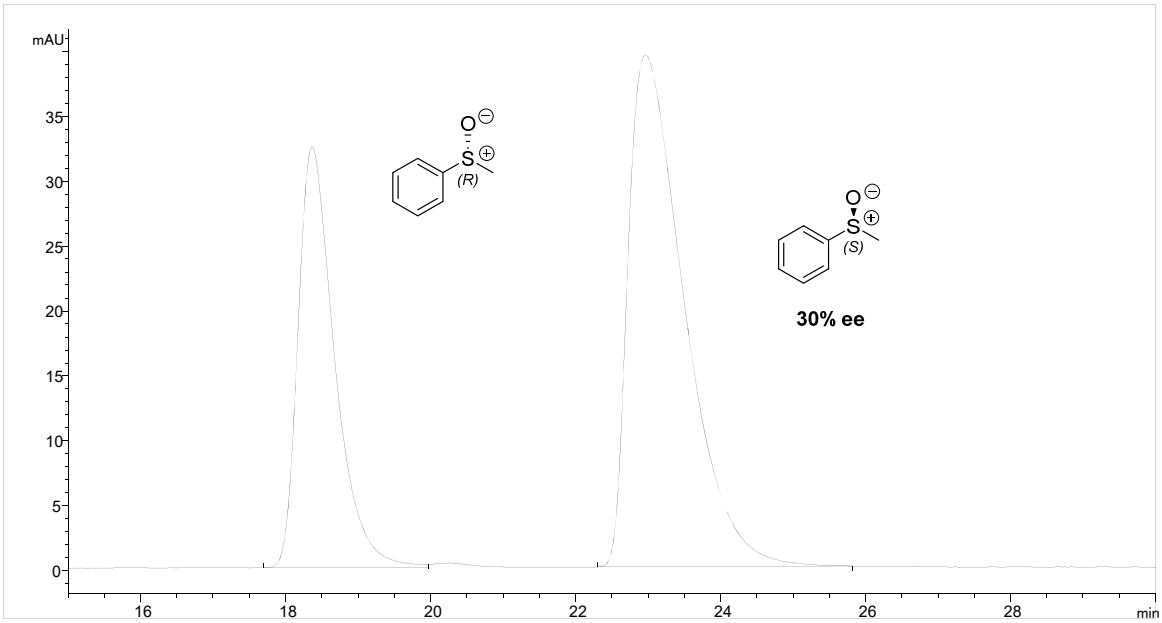
#	Time	Area	Height	Width	Area%	Symmetry
1	18.904	1622.9	44.8	0.6032	40.105	0.6
2	23.495	2423.7	43.2	0.9353	59.895	0.44

t_r = 18.5 min, t_r = 23.3 min (Table 1, entry 4)



	Time	Area	Height	Width	Area%	Symmetry
1	18.472	645.6	18.5	0.5825	31.594	0.624
2	23.279	1397.9	27	0.8614	68.406	0.474

t_r = 18.3 min, t_r = 23.0 min (Table 1, entry 6)



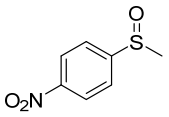
#	Time	Area	Height	Width	Area%	Symmetry
1	18.363	1139	32.4	0.585	34.995	0.602
2	22.962	2115.8	39.5	0.8937	65.005	0.434

(*S*)-1-(Methylsulfinyl)-4-nitrobenzene 1b

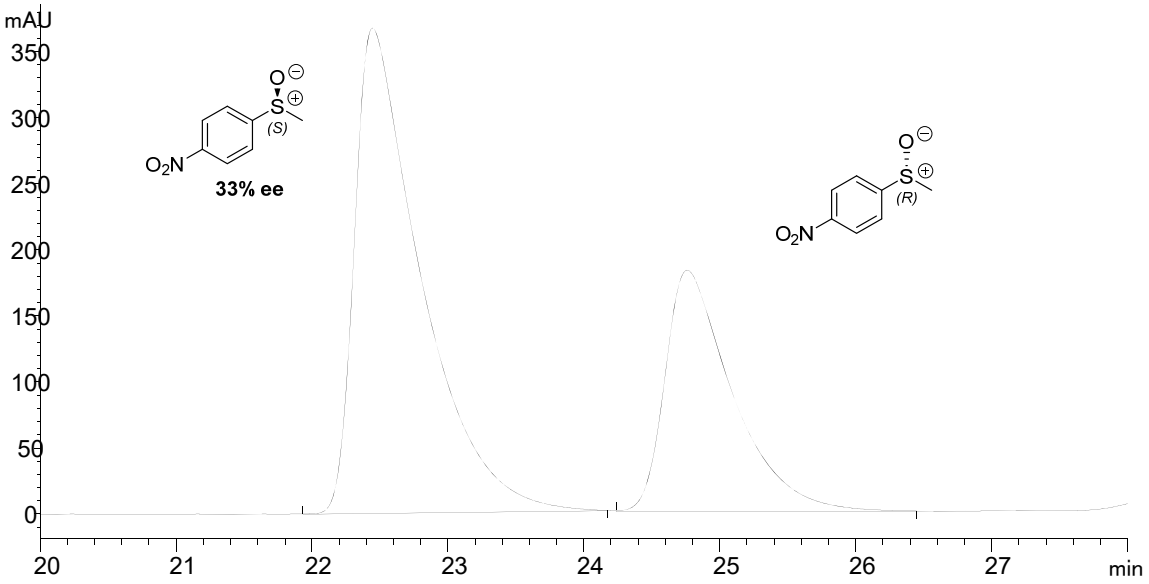
Daicel Chiralpak IA, *n*-hexane/*i*-PrOH = 90:10

Flow rate = 1.0 mL/min

Processed Channel Descr. = PDA 254 nm

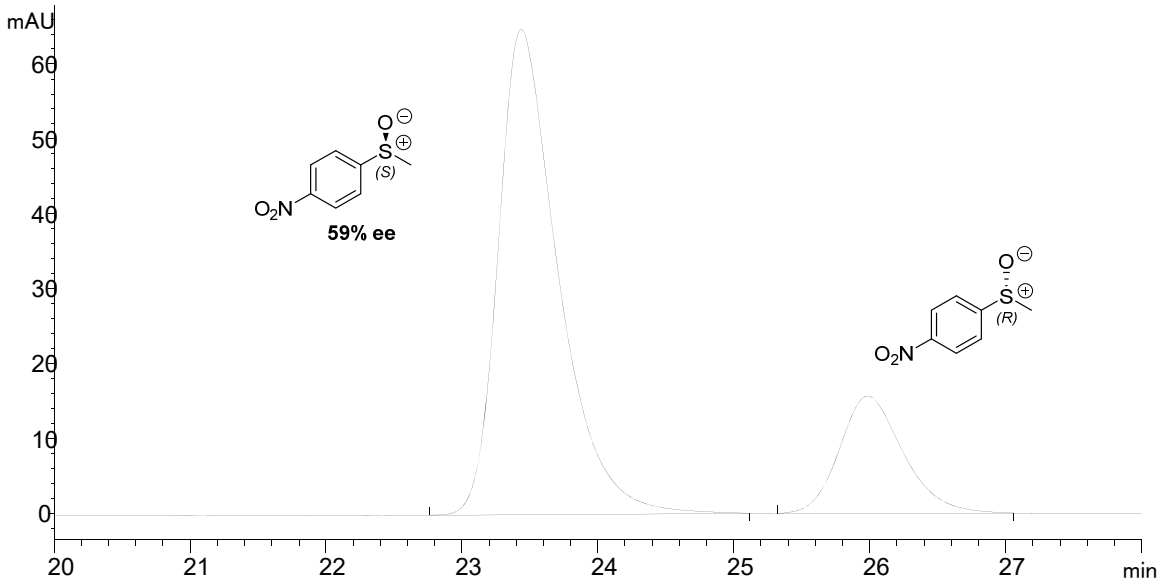


t_r = 22.4 min, t_r = 24.8 min (Table 1, entry 8)



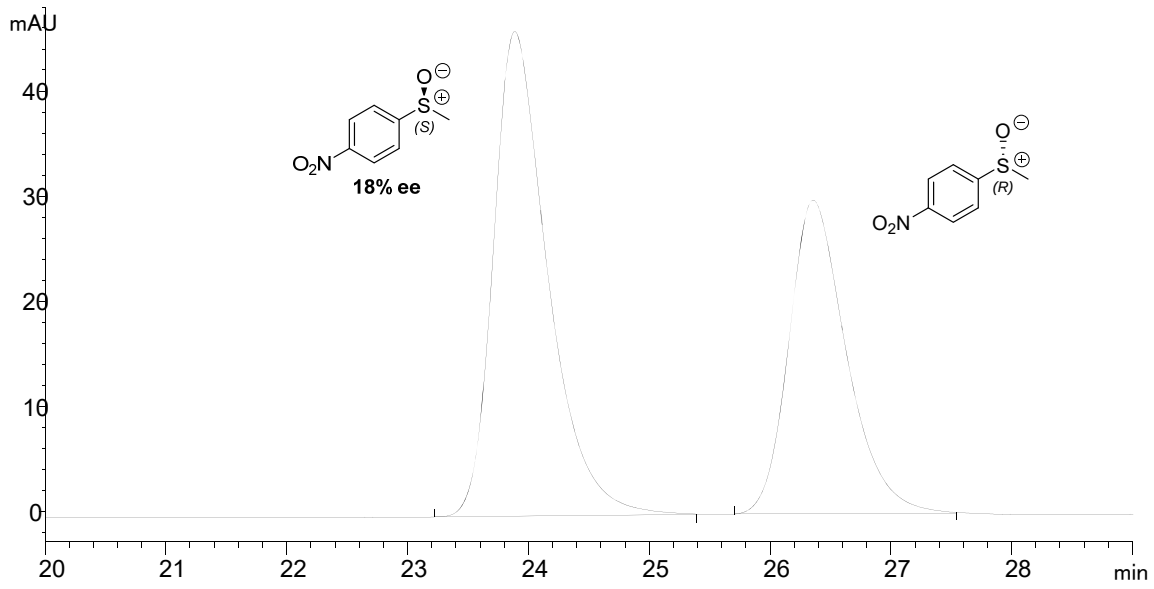
#	Time	Area	Height	Width	Area%	Symmetry
1	22.446	12504	367.8	0.5666	66.384	0.367
2	24.76	6331.8	182.8	0.5772	33.616	0.477

t_r = 23.4 min, t_r = 26.0 min; 59%. (Table 1, entry 9)



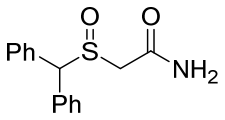
#	Time	Area	Height	Width	Area%	Symmetry
1	23.436	1995.4	64.8	0.5129	79.480	0.604
2	25.985	515.2	15.7	0.5471	20.520	0.773

t_r = 23.9 min, t_r = 26.4 min (Table 1, entry 10)



#	Time	Area	Height	Width	Area%	Symmetry
1	23.885	1447	46.1	0.5229	59.330	0.628
2	26.356	991.9	29.8	0.5541	40.670	0.712

(*R*)-2-(Benzhydrylsulfinyl)acetamide 2

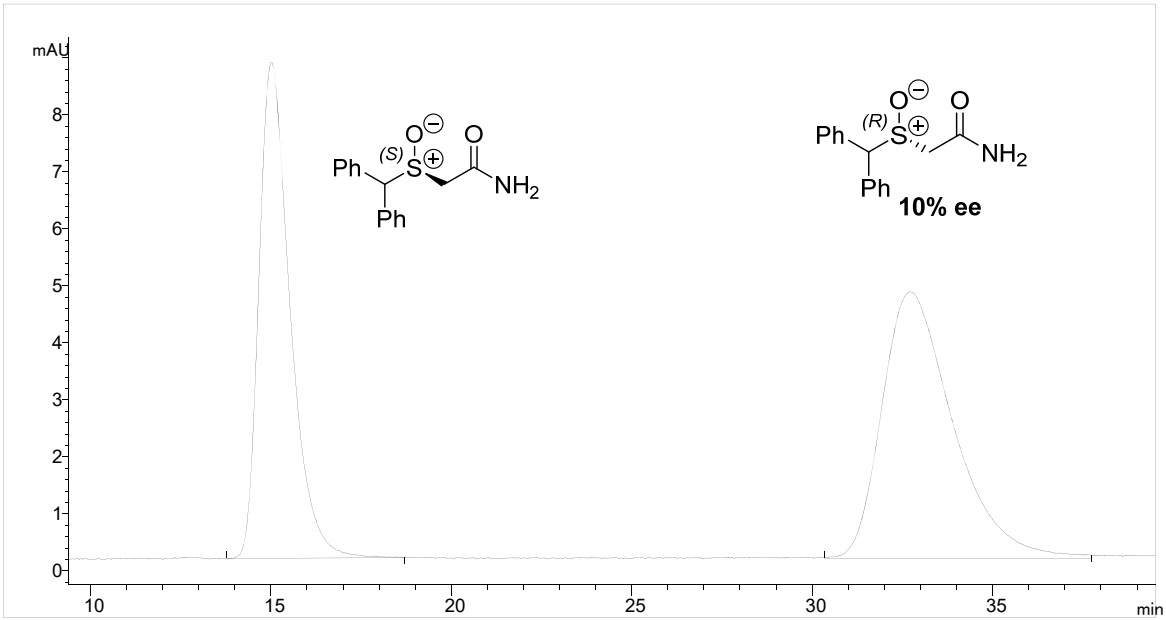


Daicel Chiralpak AS, *n*-hexane/*i*-PrOH = 60:40

Flow rate = 0.9 mL/min

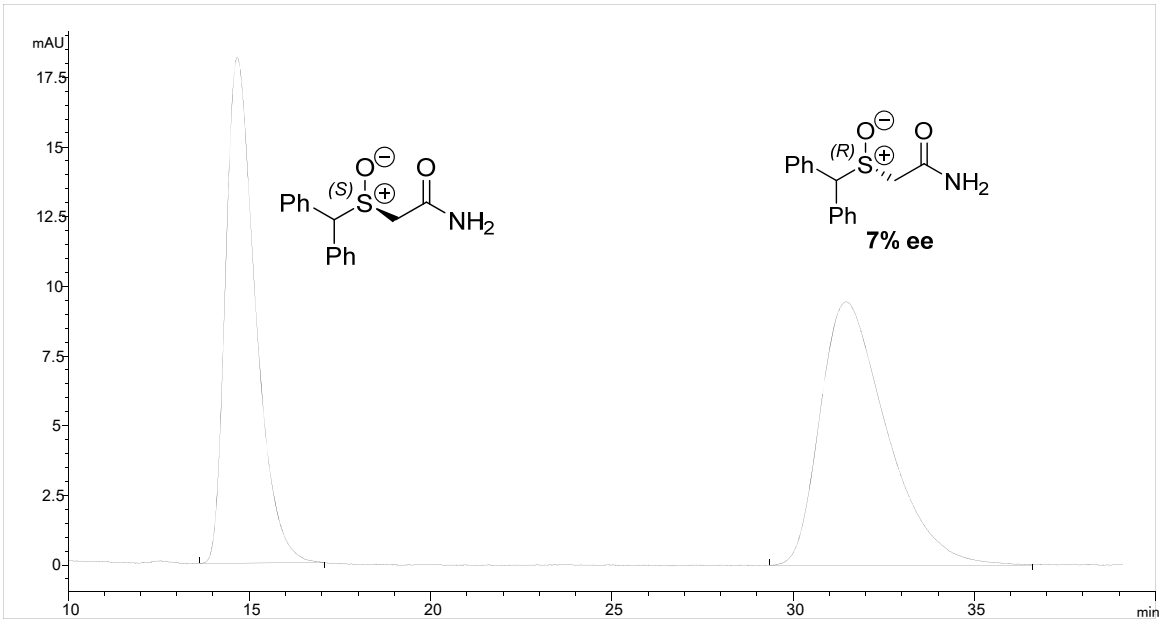
Processed Channel Descr. = PDA 254 nm

t_r = 15.0 min, t_r = 32.7 min (Table 1, entry 1)



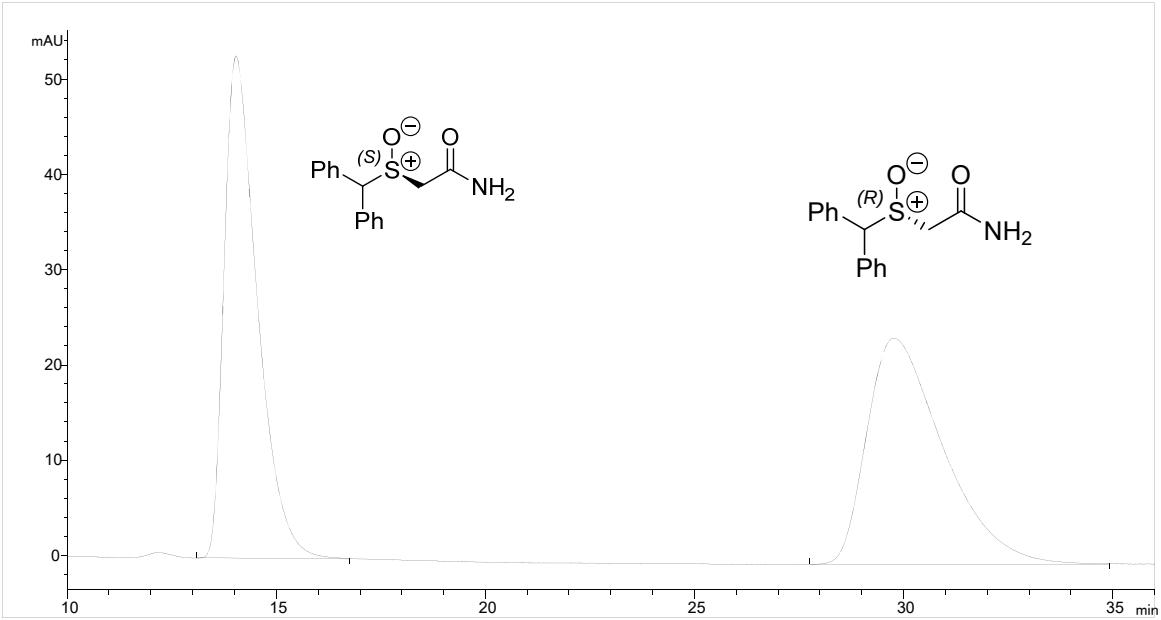
#	Time	Area	Height	Width	Area%	Symmetry
1	15.013	522.4	8.7	1.0008	44.939	0.637
2	32.713	640.1	4.7	2.2814	55.061	0.64

t_r = 14.7 min, t_r = 31.5 min (Table 1, entry 2)



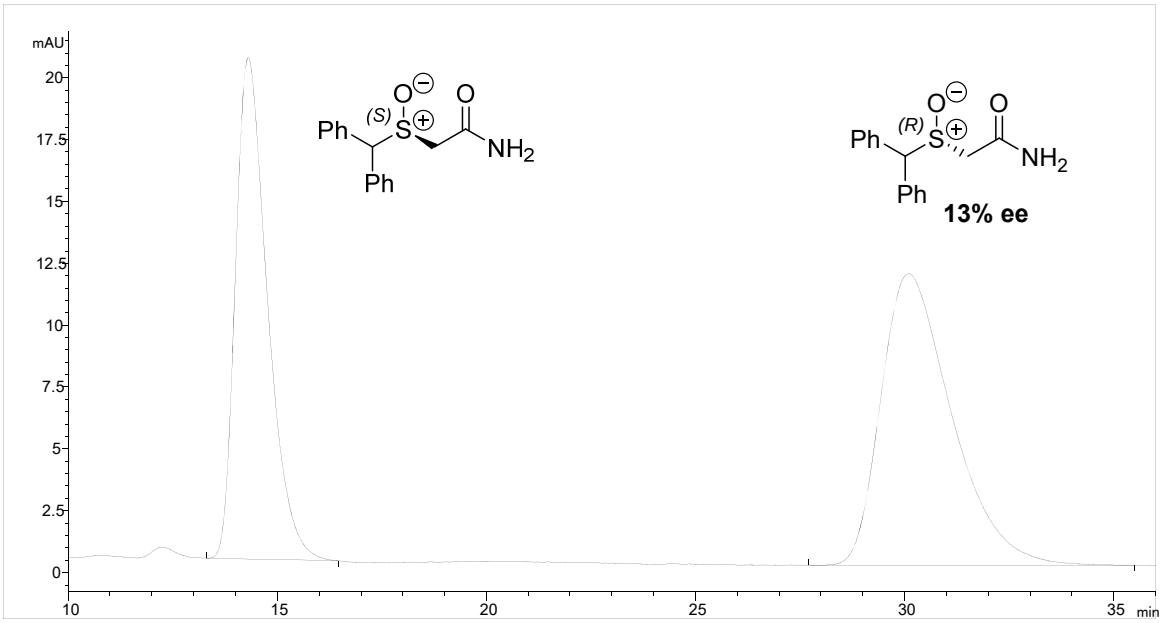
#	Time	Area	Height	Width	Area%	Symmetry
1	14.663	1039.6	18.2	0.9544	46.173	0.621
2	31.469	1211.9	9.5	2.1332	53.827	0.631

t_r = 14.0 min, t_r = 29.8 min (Table 1, entry 3)



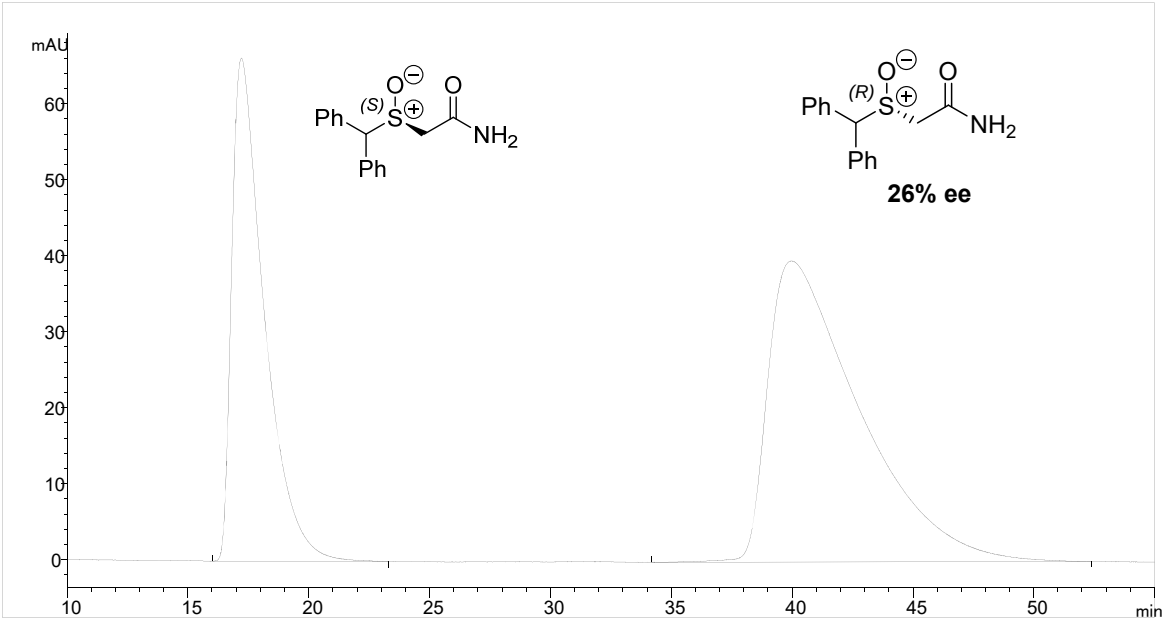
#	Time	Area	Height	Width	Area%	Symmetry
1	14.036	2911.6	52.7	0.9206	49.186	0.539
2	29.771	3008	23.7	2.1125	50.814	0.54

t_r = 14.3 min, t_r = 30.1 min (Table 1, entry 4)



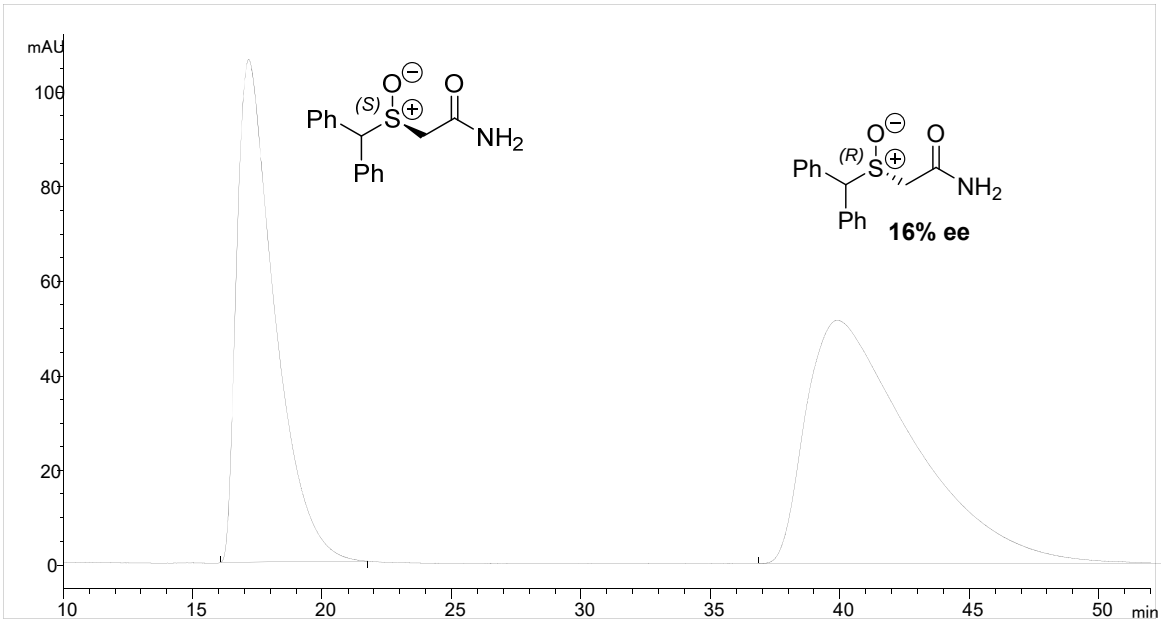
#	Time	Area	Height	Width	Area%	Symmetry
1	14.304	1080.3	20.3	0.8876	43.622	0.643
2	30.1	1396.3	11.8	1.9696	56.378	0.63

t_r = 17.2 min, t_r = 40.0 min (Table 1, entry 5)



#	Time	Area	Height	Width	Area%	Symmetry
1	17.208	6193.9	66.2	1.5593	37.222	0.408
2	39.969	10446.8	39.6	4.3929	62.778	0.34

t_r = 17.2 min, t_r = 39.9 min (Table 1, entry 6)



#	Time	Area	Height	Width	Area%	Symmetry
1	17.16	10815.5	106.4	1.6946	42.147	0.441
2	39.893	14845.9	51.5	4.8017	57.853	0.4

References

S1 Karmarkar SN, Kelkar SL, Wadia MS. *Synthesis* 1985:510-512.
S2 Ying A, Xu S, Liu S, Ni Y, Yang J, Wu C. *Ind. Eng. Chem. Res.* 2014;*53*:547-552.
S3 Lopchuk JM, Hughes RP, Gribble GW. *Org. Lett.* 2013;*15*:5218-5221.
S4 Lattanzi A, Bonadies F, Senatore A, Soriente A, Scettri A. *Tetrahedron: Asymmetry* 1997;*8*:2473-2478.
S5 Sturala J, Bohacova S, Chudoba J, Metelkova R, Cibulka R. *J. Org. Chem.* 2015;*80*:2676-2699.
S6 Chatterjie N, Stables JP, Wang H, Alexander GJ. *Neurochem. Res.* 2004;*29*:1481-1486.