Enantiomeric Enrichment of Sulfoxides by Preparative Flash Chromatography on an Achiral Phase

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Flash chromatography on silica gel of several sulfoxides of varying ee's shows a strong enantiomeric fractionation. For example (*R*)-methyl *p*-tolyl sulfoxide of 86% ee gives 99% ee (*R*) in the first fraction and 63% ee (*R*) in the last fraction, respectively, while (*R*)-ferrocenyl phenyl sulfoxide (65% ee) provides (*S*) enantiomer (79% ee) in the first fraction and (*R*) enantiomer (94% ee) in the last fraction. Various aspects of the phenomena are discussed. This method provides a simple procedure to obtain high ee for sulfoxides prepared by asymmetric synthesis of only modest enantioselectivity.

Chiral sulfoxides are extremely useful chiral auxiliaries in asymmetric synthesis.[1-4] For this purpose, it is of interest to prepare sulfoxides of various structural types. The conversion of chiral sulfinates to sulfoxides (the Andersen method[5,6]) is the normally preferred method of preparation of sulfoxides. Asymmetric oxidation of sulfides is also a useful and flexible route to sulfoxides, although ee's are seldom higher than 95%.[7-10] During recent efforts to optimize an oxidant system previously described (cumene hydroperoxide in the presence of the combination $Ti(O\text{-}i\text{-}Pr)_4$/diethyl tartarate/$H_2O$ = 1:2:1),[9] an isolation procedure was devised to cleanly recover and analyze the sulfoxide. Flash chromatography on silica gel was used to remove traces of sulfide and sulfone, as well as 2-phenyl-2-propanol. Evaluation of the enantiomeric excess had previously been performed by ^1H NMR with a chiral shift reagent or by measurement of the specific optical rotation of a representative sample and comparison with the maximum value.[1,9] In order to increase the accuracy of this measurement HPLC with a chiral phase (Daicel, Chiralcel OD-H) was utilized. Surprisingly, this technique gave poor reproducibility in the ee's, for example in the asymmetric oxidation of methyl *p*-tolyl sulfide, till it was realized that the results were strongly dependent on the fraction analyzed. The sulfoxide (0.82 g, 5.3 mmol) was obtained by flash chromatography[11] on a column of 4 cm diameter, filled with 50 g of silica gel (230–400 mesh). Elution by ethyl acetate allows the recovery of pure methyl *p*-tolyl sulfoxide in 14 fractions of 20 mL each. The ee's of these fractions were very different (entry 1, Table 1). We first suspected pollution by a contaminant, but this was excluded by mixing two enantiomerically pure enantiomers. The flash chromatography was repeated on this mixture and again gave a well-defined dispersion of the ee's (entry 5, Table 1). In order to exclude the possibility of partial racemization of the sulfoxide during the flash chromatography, a sample of enantiopure sulfoxide was treated in the same conditions. All of the fractions retained 100% ee. Clearly, we were faced with a rare case of *fractionation of enantiomers* by chromatography on an *achiral phase*. There exist only a few reports on such phenomena. The first in 1983 by Cunny *et al.* involved HPLC analysis of ^{14}C-labeled nicotine.[12] Giil-Av found in 1984 that several partially resolved dipeptides gave different ee's in the various fractions during chromatography on silica.[13] In 1985 Dreiding *et al.* reported that a chiral hydrindandione also gave a dispersion of ee's (chromatography on silica gel).[14] Hara *et al.* investigated in 1987 the similar chromatographic behavior of a mixture of ^{14}C-labeled racemic *N*-acetylvaline *tert*-butyl ester with the unlabeled (*S*)-enantiomer on silica gel.[15] In 1989, Matusch used (aminopropyl)silica gel as the stationary phase for separation of the excess enantiomer of 1,1'-binaphthol, 1-anthryl-2,2,2-trifluoroethanol, *N*-benzoylalanine methyl ester, a benzodiazepine, and chloromezanone.[16] Finally, Carman described in 1991 an additional example of the enantiomeric fractionation of a cineole derivative on silica gel.[17] All authors proposed various hypotheses such as auto-association of solute in the mobile phase with generation of diastereomeric agglomerates of different mobilities, or the formation of diastereomeric auto-associations on the stationary phase.

Scheme 1 presents a graphical representation of results with methyl *p*-tolyl sulfoxide (86% ee). It is obvious that enrichment of ee occurs in the first fractions (99% ee) while depletion (up to 73% ee) happens in the last fractions. In order to see if this represents a fixed composition of the slow-moving fraction a sample of 20% ee was investigated under the same conditions (entry 6, Table 1). The general trends were similar: highest ee's at the beginning (37% ee), lowest values at the end (18% ee). A chromatography of methyl *p*-tolyl sulfoxide (85.5% ee) in which the amount

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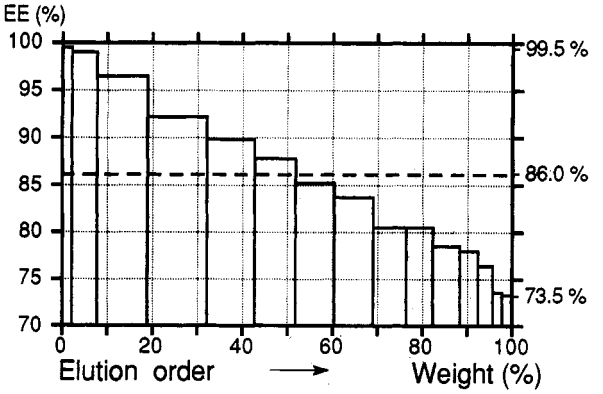
Table 1. Enantiomeric Enrichment of Sulfoxides by Flash Chromatography

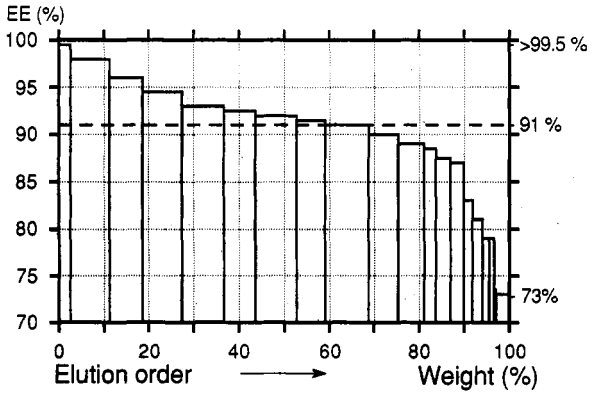
			first fraction		last fraction	
entry	sulfoxide[a]	ee (%)[b]	ee (%)	weight (%)	ee (%)	weight (%)
1	*p*-Tol-S(O)-Me[c]	86.0 (*R*)	99.5 (*R*)	2.19	73.5 (*R*)	2.19
2	*p*-Tol-S(O)-Me[c,d]	86.0 (*R*)	91.0 (*R*)	21.90	80.5 (*R*)	2.50
3	*p*-Tol-S(O)-Me	85.0 (*R*)	99.5 (*R*)	0.75	77.0 (*R*)	4.89
4	*p*-Tol-S(O)-Me	82.0 (*S*)	89.0 (*S*)	3.00	70.0 (*S*)	0.80
5	*p*-Tol-S(O)-Me[c]	80.0 (*R*)	99.5 (*R*)	0.70	63.0 (*R*)	1.54
6	*p*-Tol-S(O)-Me[c]	20.0 (*R*)	37.0 (*R*)	3.31	18.0 (*R*)	18.46
7	*p*-Tol-S(O)-Me	100 (*R*)	100 (*R*)	–	100 (*R*)	–
8	Fc-S(O)-Me[e]	90.5 (*R*)	99.5 (*R*)	2.27	82.0 (*R*)	7.91
9	Fc-S(O)-Ph[e]	65.0 (*R*)	79.0 (*S*)	7.38	94.0 (*R*)	9.78
10	Bn-S(O)-^{t}Bu	44.5 (*S*)	53.0 (*S*)	3.10	42.0 (*S*)	29.50
11	Bn-S(O)-^{t}Bu[f]	30.0 (*S*)	37.5 (*S*)	14.20	27.5 (*S*)	17.40
12	*p*-Tol-S(O)-Me[c,g]	85.5 (*R*)	93.0 (*R*)	2.81	72.0 (*R*)	0.80
13	*p*-Tol-S(O)-Me[c,h]	85.5 (*R*)	89.5 (*R*)	8.44	80.0 (*R*)	0.50
14	*p*-Tol-S(O)-Me[c,i]	91.0 (*R*)	99.5 (*R*)	2.19	73.0 (*R*)	2.70

[a] If not indicated otherwise, the sulfoxides are prepared by asymmetric oxidation[21] (see Experimental Section). After hydrolysis the crude sulfoxide is separated from cumic alcohol, sulfide, and sulfone by flash chromatography on ~10 g silica gel/mmol of sulfoxide and elution by EtOAc in fractions of 20 mL each, except for the last two (40 and 100 mL). [b] Measured by HPLC on Chiralcel OD-H (Diacel). [c] Prepared by mixing the two enantiopure sulfoxides. [d] Flash chromatography on Al_2O_3. [e] Fc stands for ferrocenyl. Chromatography with larger fractions and other eluent (see Experimental Section). [f] 50 g silica gel/mmol of sulfoxide. [g] 30 g silica gel/mmol of sulfoxide. [h] 4.5 g silica gel/mmol of sulfoxide. [i] 20 g reverse-phase silica/mmol of sulfoxide, fractions of 5 mL.

Scheme 1. Flash Chromatography of (*R*)-*p*-Tolyl Methyl Sulfoxide (86.0% ee) on Silica Gel (elution by AcOEt, fractions of 20 mL)

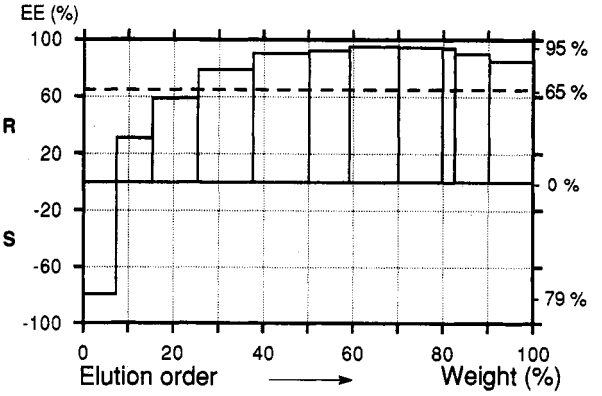


Scheme 2. Flash Chromatography of (*R*)-*p*-tolyl Methyl Sulfoxide (91.0% ee) on Reverse-Phase Silica (elution by AcOEt, fractions of 5 mL)

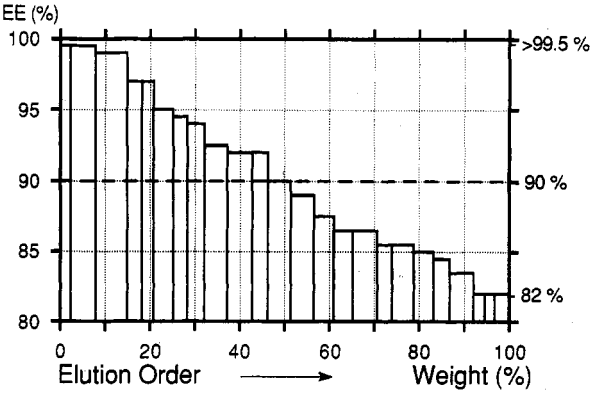


of silica gel was increased three times with respect to the above flash chromatography conditions does not improve the efficiency of the enantiomeric enrichment (entry 12, Table 1). A decrease of the amount of silica gel (two times) was also not beneficial (entry 13, Table 1). We checked the behavior of (*R*)-methyl *p*-tolyl sulfoxide (91% ee) on reverse-phase flash chromatography (reverse-phase silica[18]), using ethyl acetate as eluent. The elution is faster than on silica gel and the flash chromatography needs

Scheme 3. Flash Chromatography of (*R*)-Ferrocenyl Phenyl Sulfoxide (65.0% ee) on Silica Gel (elution under nitrogen by AcOEt/cyclohexane = 1:1, fractions of 40 mL)



Scheme 4. Flash Chromatography of (*R*)-Ferrocenyl Methyl Sulfoxide (90.5% ee) on Silica Gel (elution under nitrogen by AcOEt/ether = 1:1, fractions of 20 mL)



smaller fractions, but the fractionation of ee occurs in a similar way like on silica gel (entry 14, Table 1 and Scheme 2).

An interesting observation has been made for ferrocenyl phenyl sulfoxide (65% ee in *R* configuration): chroma-

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tography on silica gel and elution by ethyl acetate provided repeatedly in the first fraction a sulfoxide with 79% ee (*S* configuration, the *minor enantiomer*) while the last fraction gave the sulfoxide with 94% ee (*R*) (entry 9, Table 1 and Scheme 3).

A reasonable explanation of the ee enrichment in the first fractions is the occurrence of stronger associations of racemic sulfoxide on the stationary phase. An alternate explanation is that sulfoxides are associated in the mobile phase, therefore giving rise to diastereomeric entities of different chromatographic mobilities. It has been found that certain sulfoxides are associated in aprotic solvents as dimers or oligomers.[19,20] The important splitting of ee observed on reverse-flash chromatography (Scheme 2) gives some support to the contribution of labile autoassociation of sulfoxides in the mobile phase (ethyl acetate) which is the same as in the flash chromatography on silica gel. The faster migration of the minor enantiomer, as found for ferrocenyl phenyl sulfoxide, can be explained by a coating of the stationary phase[22] by some of the chiral sulfoxide (without modification of the initial ee) combined with a chromatography of the remaining sulfoxide on this chiral support.

The splitting of enantiomeric excess by flash chromatography on silica gel is not specific to methyl *p*-tolyl sulfoxide and to ferrocenyl phenyl suloxide. The same behavior was found with methyl ferrocenyl sulfoxide (Scheme 4, entry 8, Table 1) and benzyl *tert*-butyl sulfoxide (entries 10, 11, Table 1), the increase in ee being observed at the beginning of the elution. Finally a similar effect, although less pronounced, was observed on alumina, as found for methyl *p*-tolyl sulfoxide (entry 2, Table 1).

The enantiomeric change by chromatography on silica gel is frequent for sulfoxides but it is not general; for example, ferrocenyl *p*-tolyl sulfoxide and ferrocenyl *tert*-butyl sulfoxide gave no enantiomeric modification.

In conclusion, our findings have two important consequences: (i) Evaluation of the enantioselectivity of an asymmetric synthesis of sulfoxides requires great care in the workup and isolation to avoiding fractionation of enantiomers.

(ii) As previously pointed for other cases,[13,14] flash chromatography represents a simple preparation procedure for amplification of the enantiomeric excess of a partially resolved sulfoxide (which does not need to be a crystalline compound). This increases the value of asymmetric syntheses of sulfoxides giving 80–90% ee, allowing isolation of samples with ee's greater than 99%. We are currently investigating if the same phenomena is observed with phosphine oxides or with other classes of polar or apolar compounds.

Experimental Section

Apparatus. The recordings of ^{1}H NMR and ^{13}C NMR spectra,[9] the determination of optical rotations,[9] and the HPLC on a chiral phase[23] were obtained as described previously. The melting points are uncorrected.

Chemicals. Dichloromethane was distilled over P_2O_5 and stored under argon. Ti(OiPr)$_4$ and (+)- and (−)-DET were distilled before used. Cumene hydroperoxide (80%) was obtained from Aldrich and stored over molecular sieves. Silica gel (chromagel 60, 230–400 mesh) and alumina 90 "aktiv" (70–230 mesh, activity 1 without H_2O) were purchased from Merck. Reverse-phase silica was prepared according to ref 15, by treatment of silica gel by octadecyltrichlorosilane (ODS).

Flash Chromatography. It was used in the usual conditions,[11] as previously described for purification of sulfoxides.[8,9,21]

Sulfides and Sulfoxides. Methyl *p*-tolyl sulfide, *n*-benzyl *tert*-butyl sulfoxide, and the corresponding sulfoxides are known compounds. Ferrocenyl *tert*-butyl sulfide, ferrocenyl *tert*-butyl sulfoxide, and ferrocenyl *p*-tolyl sulfoxide were recently prepared.[23] The following new sulfides and sulfoxides were prepared as described below:

Ferrocenyl Methyl Sulfide. The reaction was carried out during 3 h by treating 7 mmol of dimethyl disulfide (0.6 mL) with 7 mmol of ferrocenyllithium[21] in THF. The mixture was poured into 50 mL of 2 M NaOH and extracted with Et_2O (3 × 50 mL). The combined organic layers were dried, and the solvent was evaporated under vacuum. The residue was loaded onto a silica gel column (300 g) and eluted with cyclohexane. The flash chromatography in cyclohexane afforded 1.06 g (4.57 mmol, 65%) of sulfide: ^{1}H NMR ($CDCl_3$) δ 4.28 (m, 3 H), 4.17 (s 6 H), 2.26 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 92.0, 71.5, 69.3, 68.5, 20.5. Anal. Calcd for $C_{11}H_{12}FeS$:C, 56.94; H, 5.34; S, 13.71. Found: C, 56.91; H, 5.21; S, 13.81.

Ferrocenyl *p*-Tolyl Sulfide. The reaction was carried out during 12 h by treating 7 mmol of di-*p*-tolyl disulfide (1.72 g) with 7 mmol of ferrocenyllithium in THF. The flash chromatography in cyclohexane afforded 1.6 g (5.18 mmol, 74%) of sulfide: ^{1}H NMR ($CDCl_3$) δ 6.95 (s, 4 H, Ph), 4.4–4.45 (m, 4 H, Fc), 4.35 (s 5 H), 2.25 (s, 3 H); SM (DCI/NH^{4+}) *m/z* (rel inten) 326 (9), 309 (100), 189 (22). Anal. Calcd for $C_{17}H_{16}FeS$: C, 66.24; H, 5.32; S, 10.40. Found: C, 66.47; H, 5.22; S, 10.14.

Ferrocenyl Phenyl Sulfide. The reaction of 10 mmol of ferrocenyllithium with 15 mmol of diphenyl disulfide (3.26 g) in THF gave the sulfide in 2 h. The flash chromatography in cyclohexane afforded 1.29 g (4.36 mmol, 36%): ^{1}H NMR ($CDCl_3$) δ 7.05–7.12 (m, 5 H), 4.32–4.4 (m, 4 H), 4.25 (s 5 H); ^{13}C NMR ($CDCl_3$) δ 140.1, 128.6, 125.7, 124.8, 89.3, 74.9, 70.5, 69.3, 66.3. Anal. Calcd for $C_{16}H_{14}FeS$:C, 65.30; H, 4.80. Found: C, 65.75; H, 5.39.

The general method used[9,21] for the oxidation of all sulfides will be exemplified with ferrocenyl methyl sulfide.

Ferrocenyl Methyl Sulfoxide. A solution of (*R,R*)-diethyl tartrate (1.4 mL, 8 mmol), titanium tetraisopropoxide (1.2 mL, 4 mmol), and water (72 μL, 4 mmol) in dichloromethane was stirred at −23 °C under argon. Ferrocenyl methyl sulfide (0.9 g, 3.9 mmol) was added and stirring was continued for an additional 20 min. Then, cumene hydroperoxide (1.5 mL, 8 mmol) was added dropwise and the whole system was kept 18 h at −23 °C (unstirred). The mixture was added to a solution of ferrous sulfate heptahydrate (9 g, 30 mmol), citric acid (3 g, 14 mmol), water (100 mL), dioxane (50 mL), and ether (50 mL). The two-phase mixture was stirred for 15 min and then transferred to a separatory funnel and extracted with Et_2O (3 × 50 mL). The combined organic layers were treated with NaOH (2 M, 50 mL). The two-phase mixture was stirred vigorously for 60 min to remove DET. After the separation, the organic layers were dried over $MgSO_4$ and concentrated to give the crude product. Flash chromatography was performed on silica gel (~50 g per mmol of initial sulfide) by elution with ethyl acetate/ether (1/1) as previously described (on a column of 6 cm diameter and 20 cm height). Cumene hydroperoxide as well as remaining sulfide and traces of sulfone were quickly removed in the first fractions. The sulfoxide part comes well separated. Each fraction of 40 mL (except for the last two: 80 and 160 mL) allowed recovery of pure ferrocenyl methyl sulfoxide: 506 mg (2.3 mmol), 52% yield, and 90.0% ee (*R*). All the ee's have been determined by HPLC on Chiralcel OD-H (Table 2). All the recovered sulfoxide was recrystallized in a mixture of ether/hexane (1:1) to give the enantiopure sulfoxide: $[\alpha]_D$ = −184° (*c* = 0.50; $CHCl_3$). (*R*)

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Table 2. Enantiomeric Enrichment (ee) of Ferrocenyl Methyl Sulfoxide in Flash Chromatography Fractions 1-23

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
weight (mg)	11.5	28.5	35.5	16.7	12.8	22.3	15.9	19.8	25.1	28.1	18.2	25.3	26.3	22.3	21.6	27.5	16.7	24.5	21.9	18.3	9.6	17.4	40.0
ee (%)	99.5	99.5	99.0	97.0	97.0	95.0	94.5	94.0	92.0	92.0	92.0	90.0	89.0	87.5	86.5	86.5	85.0	85.0	85.0	84.5	83.5	83.5	82.0

Configuration is assigned by using the model of asymmetric induction previously described in the oxidation of sulfides:[9] mp = 98–99 °C; ^{1}H NMR ($CDCl_3$) δ 4.37–4.69 (m, 9 H), 2.74 (s, 3 H); MS (DCI/NH^{4+}) *m/z* (rel inten) 249 (100), 233 (16), 186 (7). Anal. Calcd for $C_{11}H_{12}FeSO$: C, 53.25; H, 4.88. Found: C, 53.75; H, 5.03.

Ferrocenyl Phenyl Sulfoxide. An amount of 3.4 mmol of ferrocenyl phenyl sulfide (1.0 g) has been oxidized in 41 h by the general procedure to produce, after flash chromatography under argon (50 g of silica gel/mmol of initial sulfide, ethyl acetate/cyclohexane, 1/2) with 40 mL in each fraction except for the last two (100 and 200 mL), 0.809 g (2.71 mmol) of sulfoxide (77% yield), ee = 65% (*R*). The product was recrystallized in a mixture of ether/hexane (1:1) and gave the enantiopure sulfoxide: $[\alpha]_D$ = −182 °C (*c* = 0.61; $CHCl_3$). (*R*) Configuration is assigned by using the model of asymmetric induction previously described in the oxidation of sulfides:[9] mp = 128–130 °C; ^{1}H NMR ($CDCl_3$) δ 7.37 (m, 2 H), 7.4 (m, 3 H), 4.2–4.6 (m, 9 H); ^{13}C NMR ($CDCl_3$) δ 140.1, 130.5, 128.9, 124.2, 87.6, 70.0, 69.8, 67.9, 66.4, 65.1. Anal. Calcd for $C_{16}H_{14}FeSO$: C, 61.95; H, 4.55; S, 10.34. Found: C, 62.45; H, 4.88; S, 10.28.

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