The Free Internet Journal
for Organic Chemistry

Review

Archive for
Organic Chemistry

Arkivoc **2017**, part ii, 557-578

Self-disproportionation of enantiomers (SDE) of chiral sulfoxides, amides and thioamides via achiral chromatography

Józef Drabowicz,*[a,b] Aleksandra Jasiak,[a] Alicja Wzorek,*[c,d] Azusa Sato,[d,e] and Vadim A. Soloshonok[d,f]

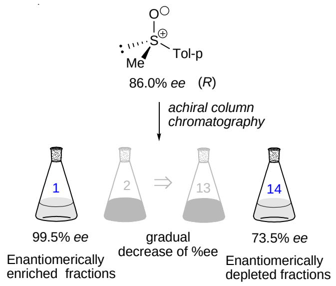
[a]Department of Heteroorganic Chemistry, Center of Molecular and Macromolecular Studies Polish Academy of Sciences, Sienkiewicza 112, 90-363 Łódź, Poland
[b]Institute of Chemistry, Environmental Protection and Biotechnology, Jan Długosz University in Częstochowa, Armii Krajowej 13/15, 42-201 Częstochowa, Poland
[c]Institute of Chemistry, Jan Kochanowski University in Kielce, Świętokrzyska 15G, 25-406 Kielce, Poland
[d]Department of Organic Chemistry I, Faculty of Chemistry, University of the Basque Country UPV/EHU Paseo Manuel Lardizábal 3, 20018 San Sebastián, Spain
[e]Department of Chemistry, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, 162-8666 Tokyo, Japan
[f]IKERBASQUE, Basque Foundation for Science, Alameda Urquijo 36-5, Plaza Bizkaia, 48011 Bilbao (Spain)
E-mail: drabow@gmail.com; awzorek@ujk.edu.pl

Dedicated to Prof. Jacek Młochowski on the occasion of his 80th anniversary

Received 08-07-2016 **Accepted** 09-16-2016 **Published on line** 02-07-2017

Abstract

This review presents a comprehensive, critical treatment of all the literature data related to the phenomenon of the SDE taking place during gravity-driven achiral chromatography of scalemic compounds bearing sulfoxide and thioamide functionalities. The discussion is focused on the SDE magnitude as a function of the structure iof the compound, composition of eluent and stationary phase, including some mechanistic details. An apparent possibility of application of the SDE phenomenon via achiral chromatography as a novel, emerging unconventional enantiomeric purification technique is also discussed.



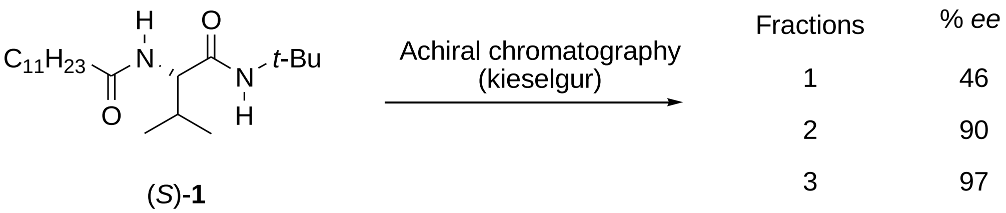
Keywords: Chiral sulfoxides, optically active thioamides, self-disproportionation of enantiomers (SDE), homochiral and heterochiral molecular associations, non-linear effects, achiral column chromatography, enantiomeric enrichment and depletion

DOI: https://doi.org/10.24820/ark.5550190.p009.829

Table of Contents

1. Introduction

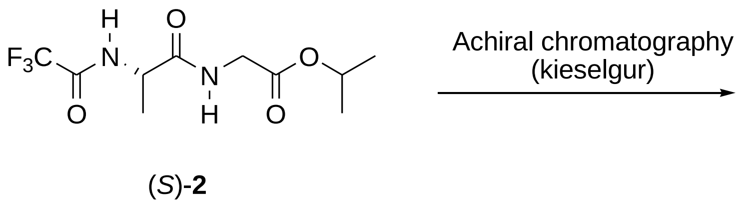
For a number of decades the possibility of spontaneous separation of enantiomerically enriched and enantiomerically depleted fractions during gravity-driven chromatography under achiral conditions was not considered at all. It was commonly accepted that such chromatographic purification of crude reaction products enriched in a particular enantiomer always gives a set of fractions in which the ratio of enantiomers remains is unchanged. The first doubts about the validity of this assumption were apparent in 1983 when Cundy and Crooks reported[1] the separation of an excess of ^{14}C-labeled (*S*)-(-)-nicotine enantiomer (second fraction) from the racemate (first fraction) on an achiral HPLC system. Almost independently Charles and Gil-Av in 1984[2] reported that achiral chromatography of valine-derived diamide (*S*)-**1** (Scheme 1) of 74% *ee* [using relatively weak eluent (*n*-hexane to *n*-hexane/EtOAc)] afforded fractions significantly enriched and correspondingly depleted in (*S*)-**1** enantiomer. They isolated the first fraction of (*S*)-**1** having only 46% *ee*, while the two subsequent fractions contained diamide (*S*)-**1** of considerably higher enantiomeric purity, as compared with the 74% *ee* of the starting sample. Furthermore, they showed that slightly changing the eluent composition, allowed the isolation of (*S*)-**1** in enantiomerically pure form.



(*S*)-**1**
74% *ee*

Scheme 1. Enantiomeric enrichment/depletion of diamide (*S*)-**1** during achiral chromatography on Kieselgur.

Moreover, they discovered[2] the opposite order of elution of enantiomerically enriched/depleted fractions in the chromatographic purification of dipeptide (*S*)-**2**. In this case the difference between the highest and lowest % *ee* of the eluted fractions was a somewhat less pronounced, resulting in an enrichment from 70.7% *ee* to 86.5% *ee* and in the corresponding depletion to 25% *ee* (Scheme 2).



(*S*)-**2**

70.7% *ee*

Fractions	% *ee*
1	86.5
2	60
3	25

Scheme 2. Enantiomeric enrichment/depletion of diamide (*S*)-**2** during achiral chromatography on Kieselgur.

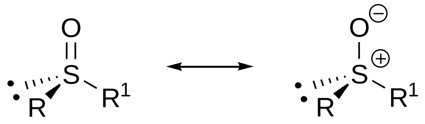
These authors also suggested that the phenomenon might not be limited to amino acid derivatives and could be applicable to various types of chiral compounds.[2] At the same time, considering the role of amino acids in the emergence of life, they put forward an idea that such processes could have occurred under prebiotic conditions, providing significant amounts of highly enantiomerically enriched compounds leading eventually to biological homochirality.[3] Soon thereafter, Dreiding et al. reported[4] that chromatography on silica gel of a chiral hydrindandione also gave fractions that showed dispersion of *ee*s. The similar chromatographic behaviour of a mixture of ^{14}C-labeled racemic *N*-acetylvaline *tert*-butyl ester with the unlabeled (*S*)-enantiomer on silica gel was described by Hara et al.[5] and for a cineole derivative by Carman.[6] With (aminopropyl)silica gel as the stationary phase the same chromatographic behaviour was observed for 1,1'-binaphthol, 1-anthryl-2,2,2-trifluoroethanol, *N*-benzoylalanine methyl ester, a benzodiazepine, and chloromezanone.[7]

It should be noted that this phenomenon is observed with HPLC,[2,4-11] medium-pressure liquid chromatography (MPLC),[12] and flash[13] and regular[14-16] chromatography. Before 2006 different definitions of this phenomenon were proposed in the literature: among them were "self-amplification of optical activity",[2] "enantiomer differentiation",[4] "autoseparation of enantiomers",[5] "separation of excess enantiomer",[6,8] "enantiomeric enrichment",[8-13,15-16] and "optical purification".[12] In 2006 one of us[17] suggested the use of the term "self-disproportionation of enantiomers" to describe the phenomenon.

Very recently, Soloshonok and Klika[18] presented a detailed rationale regarding the terminology related to the phenomenon self-disproportion of enantiomers (SDE) and discussed recently suggested alternative terms. Among a few terms proposed to describe this phenomenon, mentioned above, the maintenance of the acronym SDE has been advocated taking into account its qualities and the fact that its perceived shortcomings are invalid. This commentary also draws attention to the fact that this term can be readily applied to any process that exhibits the phenomenon of transforming a scalemic sample into fractions having different ratios of enantiomers in comparison to the enantiomeric composition of the starting sample, and is not restricted solely to chromatographic processes. Therefore, the term SDE refers to the end result, that is, the simultaneous formation of the correspondingly, to the same degree, enantiomerically enriched and depleted fractions, under achiral conditions.

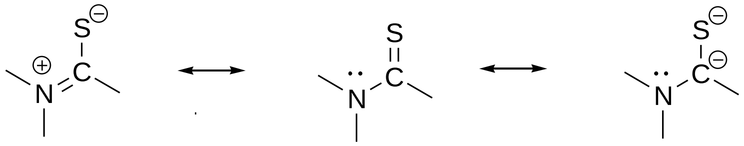
The most recognized case of SDE is a fractional crystallization of solids enriched in a particular enantiomer.[19] The SDE of chiral crystalline compounds results from the essential differences in the crystallographic structures of racemates and enantiomerically pure crystals (named as conglomerates), which are expressed as the Wallach rule.[3,20-21] It is obvious that racemates and conglomerates always show different physicochemical properties such as melting point, density, sublimation and solubility rates and these differences can be used for the purpose of enantiomeric purification. However, SDE via density gradient centrifugation[22] or SDE via sublimation[23-25] are far much less known, but can be quite successfully used for practical enantiomeric purifications.[26] It is also obvious that the well-defined preferences for dynamic homochiral/heterochiral molecular associations for chiral compounds in liquid state or in solution can be considered as the equivalent of the distinct crystallographic structures observed in the solid state. Therefore these preferences for homochiral/heterochiral dynamic molecular associations induce various nonlinear effects,[27-30] including SDE via chromatography.[17,31-35] Thus, when a solution of non-racemic compound is going through a chromatographic column, such dynamic homochiral/heterochiral molecular associations, having different mobility behaviour, as compared to the corresponding monomers, in the eluted material gradual decrease or increase of the given enantiomer is observed. Since such intermolecular interactions are the fundamental property of all organic compounds, the SDE phenomenon should occur always when a non-racemic sample is subjected to physicochemical phase-transitions or chromatography. But, the magnitude of the nonlinear effects is a function of the quality of the corresponding homochiral/heterochiral interactions, which in the vast majority of cases are based on H-bonding,[31,33,36-37] π-stacking[1,38] or dipole-dipole interactions[4,39] and therefore heavily depends on the structure of a particular chiral compound. In practical terms, the easiness of SDE observation depends on its magnitude under particular chromatographic conditions. Under standard conditions of gravity-driven column chromatography, the difference between enantiomerically-enriched and –depleted fractions is usually low (~10% *ee*) precluding the discovery of the SDE via achiral chromatography until relatively recently.

As predicted by Charles and Gil-Av[2] and proved by experimental studies, which have been carried out in our groups and by others, SDE via achiral chromatography turns out to be a remarkably comprehensive phenomenon observed for virtually all types of chiral compounds containing central,[17,23,31-33,40] axial[5,7,41] or helical[42] chirality. It is worth mentioning that the results of experiments are supported by theoretical modelling of chromatographic behaviour of non-racemic compounds under various conditions of achiral chromatography.[43-50] The results of these experimental studies and theoretical calculations allow the formulation of the concept of the SDE-phoric groups as a structural element responsible for the occurrence of the SDE during achiral chromatography.[51-61] Considering the structure of the SDE-phoric moieties one can expect interesting properties for a chiral sulfinyl grouping or a chiral thioamide residue. This results from the ability that compounds containing these groups have to form homo- and heterochiral dimers or higher-order aggregates by dipole–dipole interactions and/or hydrogen bonds. Thus, a sulfinyl group is better represented as its resonance structure (Scheme 3) bearing a positive charge on the sulfur and a negative charge on the oxygen.[62-63] It is interesting to note that hydrogen bonding between the sulfur oxygens and the acidic α-hydrogens in sulfoxides was proposed as a supramolecular synthon in crystal engineering.[64]



Scheme 3. Resonance structures for a sulfinyl bond.

Similarly, a thioamide group is better represented as its resonance structure (Scheme 4) bearing a positive charge on the nitrogen and a negative charge on the sulfur. The higher charge transfer from nitrogen to sulfur atom, in comparison with the amide bond, results from the small difference in electronegativity between the S and C atoms and a larger atomic size of sulfur. Therefore, in thioamides the C-N bond has a greater double bond character[65] resulting in a higher rotation barrier.[66] When one is considering the ability to form hydrogen bonds, the thioamides are weaker hydrogen bond acceptors (as compared to the oxoamides), and they offer a more acidic NH proton as a hydrogen bond donor.[67,68]



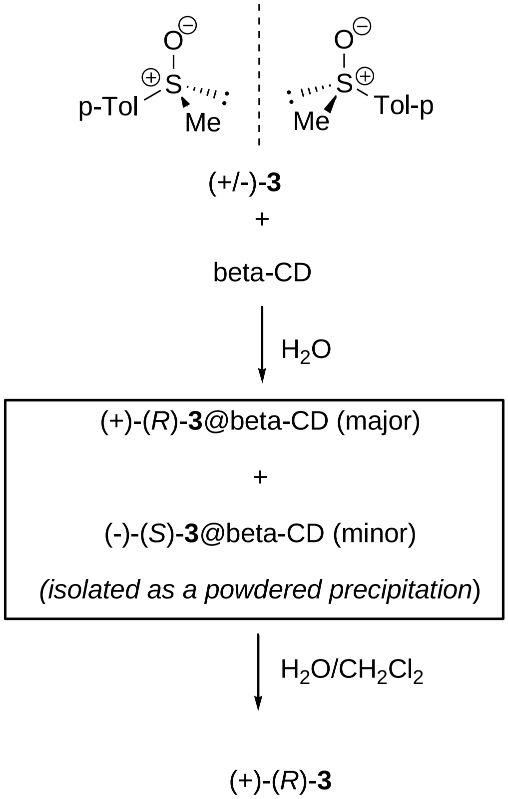
Scheme 4. Resonance structures for a thioamide bond.

The main goal of this paper is to review all relevant literature data dealing with the phenomenon of SDE-via achiral chromatography of chiral sulfur-containing compounds. We discuss the observed SDE magnitude as a function of the structure of the compounds, composition of eluent and stationary phase, also providing some mechanistic considerations.

2. Optically Active Sulfoxides

2.1 The SDE of chiral sulfoxides during their gravity-driven silica gel column chromatography

Great interest in the synthesis of optically active sulfoxides[69-73] results at least from two reasons. First of all they are recognized as valuable and efficient reagents in synthetic chemistry, particularly for asymmetric synthesis due to high asymmetric induction exerted by a sulfinyl fragment, and its configurational stability.[69,71,74-76] Several review articles are devoted to this topic.[77-84] Moreover, sulfoxides are present in many natural products and they play an important role in biology.[85] Moreover, a few sulfoxides have found application in medicinal chemistry.[86] Therefore, their availability as single enantiomers is of growing interest and importance. Generally, the most convenient way to obtain optically active sulfoxides is based on asymmetric oxidation of the corresponding sulfides. Despite the great advances in searching for more efficient procedures for asymmetric oxidation of sulfides, these protocols allow, as a rule, isolation of a mixture enriched in one enantiomer.[69-73,77,78] However, the optical purification of scalemic sulfoxides as an approach to enantiomerically pure products is still problematic, because results may not always be forthcoming. Therefore the studies devoted to the SDE phenomenon in the liquid phase in the family of optically active sulfoxides are very timely and their results should be very helpful in solving the limitations of this approach for the isolation of enantiomerically pure sulfoxides. With reference to this statement it is worth noting that since the first report on the occurrence of the SDE phenomenon during recrystallization (from light petroleum) of samples of scalemic (*R*)-methyl *p*-tolyl sulfoxide **3** which were isolated by the decomposition of a supramolecular complex formed between β-cyclodextrin (beta-CD) and a racemic mixture of this sulfoxide (Scheme 5)[87] the enrichment of the enantiomeric excess of scalemic sulfoxides by recrystallization has been reported frequently.[69-73,77-80]

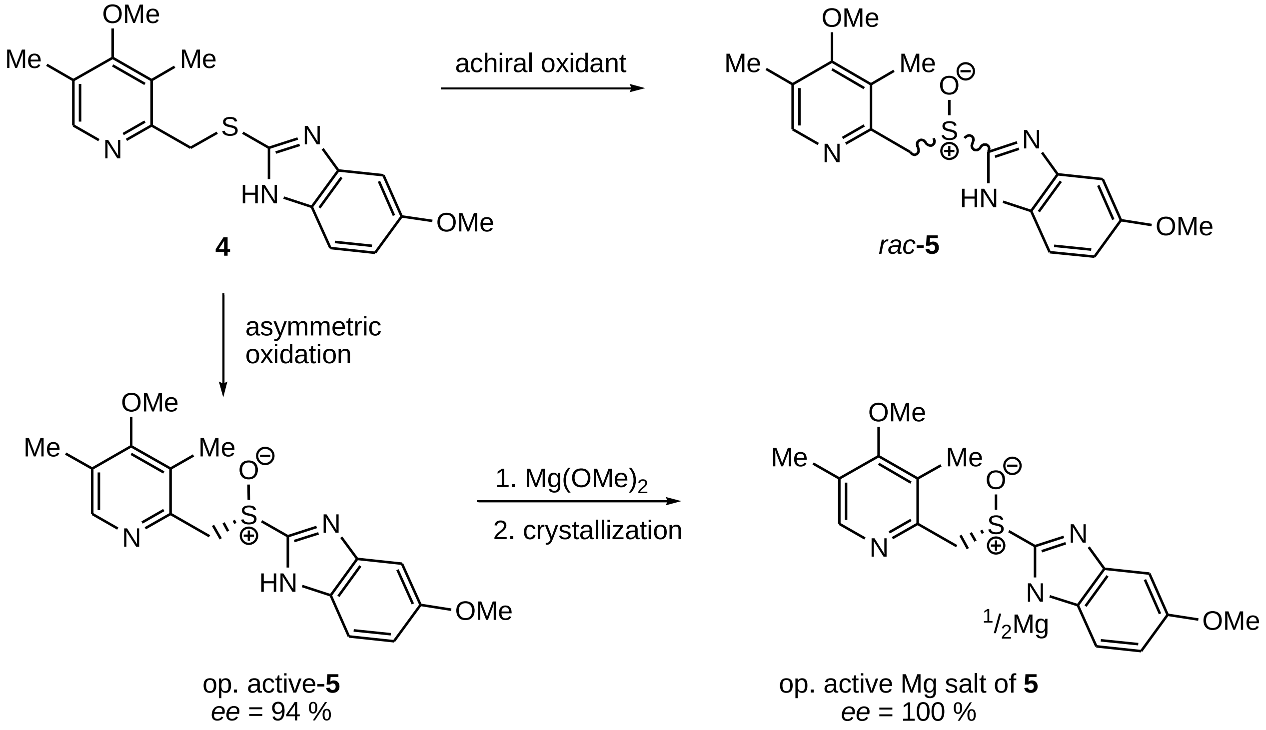


$[L]_{589} = 11.5$ (*ee* = 8.1%)

Crystallization	$[L]_{589}$	*ee* (%)
1	+ 21.0	14.9
2	+ 65.0	46.1
3	+ 91.3	64.8
4	+100.8	71.5

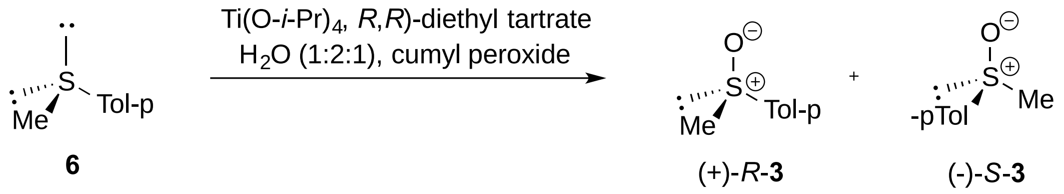
Scheme 5. The enrichment of the enantiomeric excess of scalemic (*R*)-methyl *p*-tolyl sulfoxide-**3** by recrystallization.

In our opinion, the most appealing example of the application of this phenomenon is the large scale production of enantiomerically pure esomeprazole **5** (5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole) based on asymmetric oxidation of the corresponding sulfide **4** which gives the requested sulfoxide having 94% *ee*. This is increased to 100% by a crystallization of a magnesium salt of esomeprazole **5** (Scheme 6).[88-89]



Scheme 6. The large scale synthesis of enantiomerically pure esomeprazole **5** (5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole).

On the other hand, the first systematic study of the SDE phenomenon of sulfoxides in solution, which accompanied achiral flash chromatography on silica gel, was performed[90] with the use of (*R*)-methyl *p*-tolyl sulfoxide-**3** obtained by the asymmetric oxidation of methyl *p*-tolyl sulfide **6** with the use of cumene hydroperoxide as an oxidant in the presence of the combination Ti(O-*i*-Pr)$_4$/diethyl tartrate/H$_2$O = 1:2:1 (Scheme 7).[91]



Scheme 7. Preparation of (*R*)-methyl *p*-tolyl sulfoxide-**3** by asymmetric oxidation of methyl *p*-tolyl sulfide **6**.

The sulfoxide (86% *ee*) obtained by this procedure was subjected to flash chromatography on a silica gel column. Elution by ethyl acetate allowed the recovery of pure methyl *p*-tolyl sulfoxide **3** in 14 fractions of 20 mL each. The enrichment of *ee* occurred in the first fraction (99.5% *ee*) while depletion (up to 77% *ee*) was observed in the last fraction (entries 7 and 8 in Table 1). A similar relationship was noted for samples of (-)-(*S*)-**3** with *ee* 82.0% (entries 9 and 10 in Table 1) and for a sample prepared by mixing the two enantiopure sulfoxides (entries 1-6 in Table 1). A similar effect, although less pronounced, was observed on alumina (entries 11-12 in Table 1) and on reverse-phase silica chromatography (entries 13-16 in Table 1). It was also observed that an increase of the amount of silica gel (three times) did not improve the efficiency of the enantiomeric enrichment and the fractionation of *ee* occurs in a similar way on reverse-phase flash chromatography (reverse-phase silica), using ethyl acetate as eluent. The enrichment of enantiomeric excess by flash chromatography on silica gel was also observed for methyl ferrocenyl sulfoxide **7a** (entries 17-21 in Table 1) and benzyl *tert*-butyl sulfoxide-**8** (entries 22 and 23 in Table 1). The authors claimed that in the case of ferrocenyl *p*-tolyl sulfoxide **7c** and ferrocenyl *tert*-butyl sulfoxide **7d**, no measurable magnitude of the SDE was recorded. In the case of ferrocenyl phenyl sulfoxide (-)-(*R*)-**7b** chromatography on silica gel and elution by ethyl acetate provided reproducibly 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*).

(*R*)-**7a-d**

(*S*)-**8**

a) R = Me
b) R = Ph
c) R = *t*-Bu
d) R = *p*-Tol

Fc = ferrocenyl

Figure 1. The chemical structures of sulfoxides **7**, **8** studied by flash chromatography.

Table 1. Flash chromatography of sulfoxides **3**, **7a** and **8**

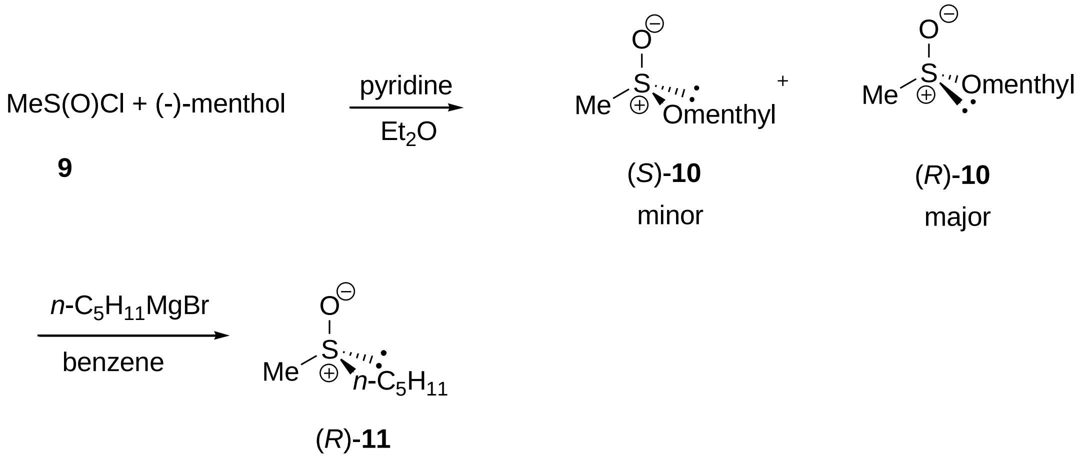
Entry	Sulfoxide/% *ee*	Fraction	*ee* (%)
	(+)-(*R*)-**3**/86.0 *ee*[a]		
1		1	99.5
2		2	99.0
3		3	92.5
4		9	80.2
5		12	76.5
6		14	73.5
	(+)-(*R*)-**3**/85.0 *ee*		
7		1	99.5
8		14	77.0
	(-)-(*S*)-**3**/82.0 *ee*		
9		1	89.0
10		14	70.0
	(+)-(*R*)-**3**/86.0 *ee*,[a,b]		
11		1	91.0
12		14	80.5
	(+)-(*R*)-**3**/91.0 *ee*,[a,c]		
13		1	99.5
14		4	94.8
15		17	81.0

Table 1. Continued

Entry	Sulfoxide/% ee	Fraction	ee (%)
	(+)-(R)-3/86.0 eea		
16		19	73.0
	(+)-(*R*)-**7a**/90.0 *ee*		
17		1	99.5
18		4	97.0
19		8	94.0
20		16	86.5
21		23	82.0
	(+)-(*S*)-**8**/44.5 *ee*		
22		1	53.0
23		14	42.0

[a]Prepared by mixing the two enantiopure sulfoxides; diameter of the column - 4 cm; amount of silica gel (230-400 mesh) - 50 g; volume of the collected fractions - 20 mL each. [b]Flash chromatography on Al_2O_3.
[c]Reverse-phase silica.

Very recently this initial study of the SDE phenomenon for sulfoxides by gravity-driven column chromatography over achiral silica gel was performed in our group[39] by more detailed experiments with the use of methyl *n*-pentyl sulfoxide **11** (MPS **11**) as the analyte. The samples needed of this sulfoxide, enriched in the *R* enantiomer, were prepared according to a literature modification[92] of the Andersen methodology[93] by a Grignard reaction between *n*-pentylmagnesium bromide and *O*-menthyl methanesulfinate **10**, which in turn was produced as a pair of diastereomers by the reaction of methylsulfinyl chloride **9** and (−)-menthol (Scheme 8).



Scheme 8. Preparation of methyl *n*-pentyl sulfoxide **11** (MPS **11**) enriched in the *R* enantiomer with the use of O-menthyl methanesulfinate **10** as a chiral precursor.

We decided to use for our study MPS **11** having a relatively modest enantiomeric purity (34.62% *ee* enriched in the R enantiomer) in order to determine if it is indeed possible to obtain a sample with high optical purity, e.g. > 99% *ee*. The results of the executed experiments listed in Table 2 are fully in line with this assumption.

Table 2. SDE of MPS **11** with a starting 34.62% during achiral, gravity-driven column chromatography

Run	Eluent (ratio)	First fraction (% *ee*)	Last fraction (% *ee*)	Δ*ee*
1	CH_2Cl_2 /EtOAc (5/1)[a]	74.32	28.64	45.68
2	EtOAc[a]	97.42	3.90	93.52
3	EtOAc/*c*-hexane (5/1)[a]	>99.99	13.00	86.99
4	CH_2Cl_2/MeCN (5/1)[a]	57.26	28.64	28.62
5	MeCN/toluene (1/1)[a]	61.70	31.12	30.58
6	Acetone/*c*-hexane (1/3)[a]	48.98	33.78	15.20
7	EtOAc/*c*-hexane/MeOH (5/1/0.5)[a]	50.08	29.30	20.78
8	EtOAc/*c*-hexane (5/1)[b]	85.50	15.92	69.58
9	EtOAc/*c*-hexane (5/1)[c]	>99.99	13.98	86.01
10	EtOAc/*c*-hexane (5/1)[d]	74.28	21.22	53.06
11	EtOAc/*c*-hexane (5/1)[e]	>99.99	31.08	68.91

[a] Ratio of MPS-11 to silica gel, ca. 1 mmol:30 g.

[b] Ratio of MPS-11 to silica gel, ca. 1 mmol:15 g.

[c] Ratio of MPS-11 to silica gel, ca. 1 mmol:60 g.

[d] Silica gel of 70-230 mesh was used.

[e] MPS-11 of 55.24% *ee* was used.

Analysis by GC using a chiral column of the collected fractions showed that the early eluting fractions were enantiomerically enriched in comparison to the starting sample while the later eluting fractions were enantiomerically depleted. Moreover, the basic features of the presented results constitute the following relationships:

(a) the magnitude of the SDE was far greater (more than doubled in fact) in EtOAc (run 2, Table 2) in comparison to the run using CH_2Cl_2–EtOAc eluent (run 1, Table 2)

(b) chromatography using EtOAc–*c*-hexane (5:1) as eluent (run 3, Table 2) yielded an even better result– the *ee* value for the first eluting fraction was > 99.99%, though the Δ*ee* value at 86.99% was actually relatively diminished slightly

(c) the incorporation of 7.7% of MeOH to the EtOAc–*c*-hexane eluent (run 7, Table 2) failed to fully suppress the SDE phenomenon whereby the reduction was comparable to the acetone–*c*-hexane (1:3) run.

(d) increasing the ratio of MPS to silica gel, thereby effectively reducing the length of the constant diameter column, resulted, unsurprisingly, in a decrease of Δ*ee* (run 8, Table 2).

(e) reducing the ratio of MPS to silica gel did not improve the magnitude of the SDE (run 9, Table 2).

(f) the use of silica gel with a larger grain size, 70–230 mesh, as the stationary phase resulted in a decrease in the magnitude of the SDE (run 10, Table 1).

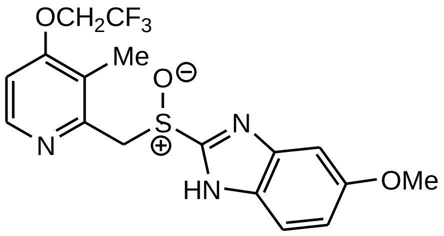
(g) chromatography for the sample of MPS starting with 55.24% *ee* (run 2) provided fractions of high *ee* in much greater yield than for the sample starting with 34.62% *ee* (run 2) (Table 3).

Table 3. Effect of the starting *ee* on the SDE of MPS **11**

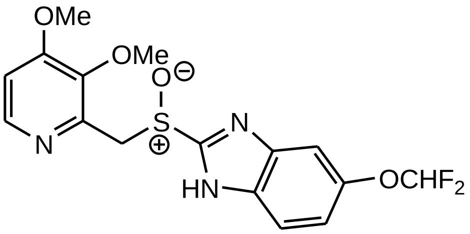
Percentile band for *ee* (%)	Weight (%)	
	Starting *ee* 34.6%	Starting *ee* 55.2%
> 99.9	0.16	1.05
90–99.9	1.98	4.93
80–90	1.65	7.64
70–80	2.04	8.56
60–70	2.18	8.10
50–60	5.03	29.31
40–50	8.75	18.70
30–40	38.20	21.72
20–30	28.25	–
< 20	11.75	–

The results discussed above constitute the first example of SDE predictability. Moreover, they allow us to say that SDE can be considered as a practical and useful method to obtain a sulfoxide with extremely high enantiomeric excess starting from a sample of only modest *ee*. This can be explained by the strong tendency of the sulfoxide moiety to form homo- and heterochiral dimers or higher-order aggregates by dipole–dipole interactions with the differing chromatographic behaviour of the entities, the underlying mechanism responsible for the SDE phenomenon. This is exceptional in that in the majority of cases the appearance of the SDE phenomenon is based on hydrogen bonding interactions. This opinion is nicely supported by the SDE behaviour of a non-racemic mixture of esomeprazole **5**, lansoprazole **12**, pantoprazole **13**, and rabeprazole **14** on regular gravity-driven silica gel column chromatography using different eluents.[89] It should be added here that a growing interest in the chemistry of these prazole–containig sulfoxides results from the fact that they are commonly used as drugs for peptic ulcers.[88,94-95] Racemic omeprazole **5** (losec, prilosec) launched in 1988, was the first gastric proton-pump inhibitor (PPI) used for treatment of this type of gastric problems and quickly became the world's best selling drug in the late 1990s.[88,94-95] Esomeprazole, the (*S*)-form of omeprazole **5**, was introduced to the pharmaceutical market in 2001 as the first single-optical-isomer PPI, under name Nexium. It has the better acid control and a favourable pharmacokinetic profile relative to omeprazole.[95] In 2003 was the 7th most sold drug (with 3.8 billion US dollars sales) and its sales still reached 3.9 billion US dollars in 2012. The large-scale production of the (*S*)-enantiomer of esomeprazole is achieved by asymmetric oxidation of the same sulfide intermediate as is used in the production of omeprazole **5**, which gives a 94% enantiomeric excess (*ee*). This is increased to >99.99% by preparing a magnesium salt of esomeprazole and then performing a crystallization.

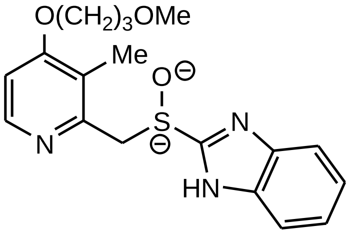
The results that are listed in Table 4 show that the SDE phenomenon occurs for all samples of prazole-containing sulfoxides **5**, **12-14** (with high to low enantiomeric purity) during their gravity–driven chromatographic purification. The pure enantiomer of each prazole was isolated from non-racemic starting materials by this chromatography (entries 1, 4, 8, and 11).[89] Therefore, we suggest that further research on the SDE of these compounds could make their enantiomeric purification by achiral chromatography affordable and competitive to crystallization.



12



13



14

Figure 2. Prazole–containing sulfoxides **12**-**14**.

Table 4. SDE of prazole-containg sulfoxides **5** and **12**-**14** with different *ee* values on achiral silica gel chromatography[a]

Entry	Sulfoxide (% *ee*)	First fraction (% *ee*)[b]	Last fraction (% *ee*)[b]	Δ*ee*
1	Esomeprazole-**5** (88.2)	>99.9	80.0	20.0
2	Esomeprazole-**5** (60.0)	69.6	51.2	18.4
3	Esomeprazole-**5** (20.1)	31.0	12.0	19.0
4	(*R*)-Lansoprazole-**12** (87.0)	>99.9	75.6	24.4
5	(*R*)-Lansoprazole-**12** (82.0)	99.2	73.8	25.4
6	(*R*)-Lansoprazole-**12** (60.0)	72.0	58.0	20.0
7	(*R*)-Lansoprazole-**12** (17.2)	20.0	14.4	5.6
8	(*S*)-Pantoprazole-**13** (84.0)	>99.9	70.1	29.9
9	(*S*)-Pantoprazole-**13** (59.3)	69.5	50.2	19.3
10	(*S*)-Pantoprazole-**13** (18.4)	26.8	11.2	15.6
11	(*R*)-Rabeprazole-**14** (89.4)	>99.9	80.0	20.0
12	(*R*)-Rabeprazole-**14** (87.2)	96.3	78.8	17.5
13	(*R*)-Rabeprazole-**14** (64.0)	73.0	57.4	15.6
14	(*R*)-Rabeprazole-**14** (22.2)	29.4	15.0	14.4

[a] 2.9 mmol of sulfoxide, 87 g of silica gel (300-400 mesh; 30 g silica gel/mmol sulfoxide), 40 × 600 mm glass column, 30 mL fractions were collected per bottle.

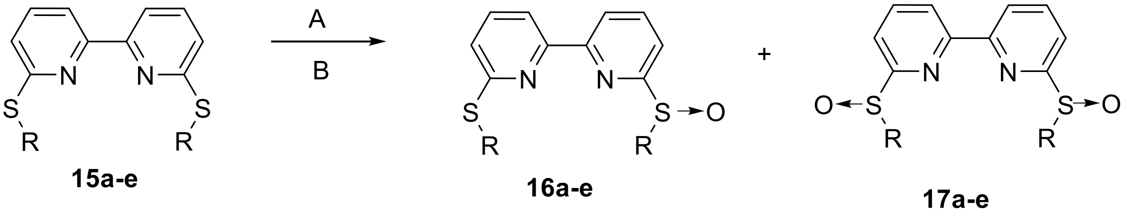
[b] Measured by HPLC on Chiralcel AD-H (Daicel).

The formation of heterochiral dimers based on H-bonds between the sulfoxide (proton acceptor) and the benzimidazole (proton donor) moieties was proposed as the reason for the SDE of the prazole-containing sulfoxides **5** and **12**-**14** during their gravity-driven silica gel column chromatography.[89] This proposal stems from both the X-ray crystallographic structure analysis of omeprazole **5**, which showed the existence of a cyclic dimer of two enantiomers,[96-97] and a great extent of dimerization observed for a chloroform solution.[98]

2.2 Comments related to problems with the accurate determination of the enantiomeric excess of chiral sulfoxides isolated via any type of asymmetric synthesis

It is obvious that the accurate determination of optical purities and/or enantiomeric excesses of optically active sulfoxides prepared by any type of asymmetric synthesis is possible only if the purification procedures do not change the ratio of enantiomers which are present in a crude product. For a number of decades gravity driven chromatography under achiral conditions has been considered as such a safe, "enantiomeric excess maintaining", procedure. Due to the above mentioned cases of SDE, this assumption must be treated with caution and cannot be considered any longer as an empirical rule. Consequently, there is a need to examine very carefully the stereochemical outcome of reactions leading to the generation of a new stereogenic sulfinyl sulfur atom in which the isolation of pure products is based on a chromatographic purification of crude reaction mixtures. First of all the accurate determination of the optical purities and/or enantiomeric excess values for sulfoxides requires total washing-out of a sample introduced on a chromatographic column. Not always can this be easily done due to the strong interaction of a sulfoxide molecule and the surface of a solid chromatographic loading, especially in the cases of sulfoxides which contain additional functional groups able to participate in hydrogen bonding. Moreover, such a determination cannot be based on a sample isolated from a particular set of fractions but should be done using an averaged sample prepared from the whole of the product obtained during the given purification procedure.

Bearing in mind these requirements and the fact that the SDE phenomenon for the family of sulfoxides has been known since 1994, we have checked a number of publications from the last 10 years devoted to the catalytic asymmetric oxidation of sulfides to sulfoxides, hoping to assess whether the possibility of an erroneous determination of the enantiomeric excesses of the isolated products due to the SDE phenomenon was considered by the authors at all. Among the analyzed publications we have not been able to identify a single work in which this possibility was recognized. Simultaneously, among the analyzed papers we noted a few papers for which the opinion, that the enantiomeric excesse values reported can be burdened with an error, has some substantive grounds. This is based on the fact that the reported enantiomeric excess values differ very much for derivatives having very similar structures. Among them there are papers co-authored by one of us[99-100] devoted to the asymmetric oxidation of 2,2'-bipyridine alkyl sulfides **15a-e** to non-racemic 2,2'-bipyridine alkyl sulfoxides **16a-e** and bis-sulfoxides **17a-e** using either (+)-(8,8-dichlorocamphorylsulfonyl) oxaziridine (method A)[101] or the Kagan reagent (method B)[91] (Scheme 9).



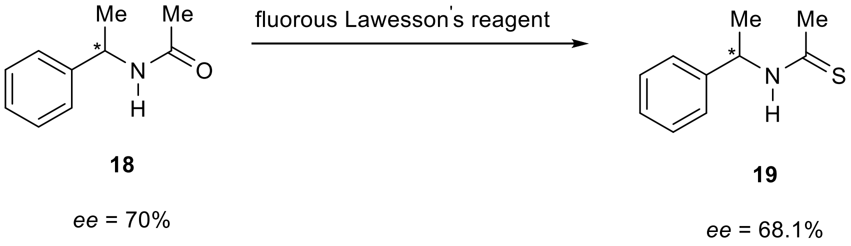
a) R = Me; b) R = Et; c) R = *i*-Pr; d) R = CH_2OEt; e) R = CH_2Ph

Scheme 9. Asymmetric oxidation of 2,2'-bipyridine alkyl sulfides **15a-e** to non-racemic 2,2'-bipyridine alkyl sulfoxides **16 a-e** and bis-sulfoxides **17a-e.**

It was found that the enantiomeric excesses of the final products, isolated by flash chromatography of the crude product (SiO_2, methylene chloride), differ substantially for the pure mono sulfoxides **16a-e** (values from 5 to 82%) and for the bis sulfoxides **17-a-e** (values from 5.4 to 99%). Therefore, it is strongly recommended that these and many other data on determination of the stereochemical outcome should be revisited and, most likely, corrected. As it is obvious that a very exhaustive and detailed report on this topic should be considered as a very timely we are planning to prepare independently such a manuscript.

3. Optically Active Thioamides

To compare the SDE phenomenon in amides and thioamides, we synthesised[102] *N*-(1-phenylethyl) thioacetamide, **19**,[103] the sulfur analogue of *N*-(1-phenylethyl) acetamide **18**,[104] using the literature procedure (Scheme 10).[106]



Scheme 10. Preparation of *N*-(1-phenylethyl)thioacetamide **19** by thionation of *N*-(1-phenylethyl)acetamide **18**.

It was found that the isolated thioamide **19** shows the expected SDE phenomenon, although its magnitude (Δ*ee* 3.6) is substantially lower in comparison with the corresponding amide **18** (Δ*ee* 40.8). This relationship clearly indicates that replacement of oxygen with sulfur has evident consequences for the formation of associates under chromatographic conditions, as the hydrogen bonding ability of the thioamide **19** is strongly reduced. This result has a very powerful mechanistic implication suggesting that thioamide derivatives can be used to probe the importance of H-bonding interactions in SDE research and in non-linear effects in general.

4. Conclusions

The data discussed above, which are based on a limited number of examples of the SDE phenomenon for sulfoxides (since the first paper by Kagan at al.[90]), clearly indicate that the relatively strong SDE phenomenon should be observed as a rule when a chiral sulfoxide is subjected to achiral gravity–driven chromatography. This means that the sulfinyl moiety should be considered as a SDE-phoric group[18,103] along with chiral amides[31,51-55,102] and fluorine-containing compounds.[33,56-61] Thus, it may now be a suitable time to consider addition, in papers dealing with asymmetric synthesis of sulfoxides, information regarding the magnitude of the SDE phenomenon during a gravity-derived chromatographic purification. The discussed examples of the SDE phenomenon of chiral sulfoxides constitute an additional support for an opinion that this chromatographic method can be considered as advantageous in comparison with fractional crystallization as:

a) it works for both liquid and crystalline compounds, b) enantiomeric enrichment does not so heavily depend on an initial enantiomeric ratio of a sample, c) it can be applied for compounds of low % *ee*, while crystallization cannot. A model experiment using *N*-(1-phenylethyl)thioacetamide **19** indicates that the substitution of the sulfur atom for the oxygen in the acyl group, strongly reduces the observed magnitude of the SDE phenomenon.

5. Acknowledgements

The authors gratefully acknowledge financial support from IKERBASQUE, Basque Foundation for Science (VAS), the Ministry of Science and Higher Education–Grant No. 612 561 (AW) and from the National Science Center (Kraków, Poland)–grant UMO 2014/15/B/ST5/05329 (JD). We gratefully acknowledge valuable comments and suggestions from referees as well as a discussion with Prof. P. Kiełbasiński which allowed us to improve the quality of our review.

6. References

1. Cundy, K. C.; Crooks, P. A. *J. Chromatogr*. **1983**, *281*, 17.
   http://dx.doi.org/10.1016/S0021-9673(01)87863-8
2. Charles, R.; Gil-Av, E. *J. Chromatogr.* **1984**, *298*, 516.
   http://dx.doi.org/10.1016/S0021-9673(01)92750-5
3. Soloshonok, V. A.; Ueki, H.; Yasumoto, M.; Mekala, S.; Hirschi, J. S.; Singleton, D. A. *J. Am. Chem. Soc.* **2007**, *129*, 12112.
   http://dx.doi.org/10.1021/ja065603a
4. Tsai, T.-L.; Herman, K.; Hug, E.; Rohde, B.; Dreiding, A. S. *Helv. Chim. Acta* **1985**, *68*, 2238.
   http://dx.doi.org/10.1002/hlca.19850680818
5. Dobashi, A.; Motoyama, Y.; Kinoshita, K.; Hara, S.; Fukasaku, N. *Anal. Chem*. **1987**, *59*, 2209.
   http://dx.doi.org/10.1021/ac00144a043
6. Carman, R. M.; Klika, K. D. *Aust . J. Chem*. **1991**, *44*, 895.
   http://dx.doi.org/10.1071/CH9910895
7. Matusch, R.; Coors, C. *Angew. Chem., Int. Ed. Engl*. **1989**, *28*, 626.
   http://dx.doi.org/10.1002/anie.198906261
8. Loza, E.; Lola, D.; Kemme, A.; Freimanis, J. *J. Chromatogr. A* **1995**, *708*, 231.
   http://dx.doi.org/10.1016/0021-9673(95)00385-Z
9. Nicoud, R.-M.; Jaubert, J.-N.; Rupprecht, I.; Kinkel, J. *Chirality* **1996**, *8*, 234.
   http://dx.doi.org/10.1002/(SICI)1520-636X(1996)8:3<234::AID-CHIR2>3.0.CO;2-H
10. Monde, K.; Harada, N.; Takasugi, M.; Kutschy, P.; Suchy, M.; Dzurilla, M. *J. Nat. Prod.* **2000**, *63*, 1312.
    http://dx.doi.org/10.1021/np000043t
11. Suchy, M.; Kutschy, P.; Monde, K.; Goto, H.; Harada, N.; Takasugi, M.; Dzurilla, M.; Balentova, E. *J. Org. Chem.* **2001**, *66*, 3940.
    http://dx.doi.org/10.1021/jo0155052
12. Kosugi, H.; Abe, M.; Hatsuda, R.; Uda, H.; Kato, M. *Chem. Commun.* **1997**, 1857.

13. Diter, P.; Taudien, S.; Samuel, O.; Kagan, H. B. *J. Org. Chem.* 1994, 59, 370.
http://dx.doi.org/10.1021/jo00081a015
14. Takahata, H. *Yuki Gosei Kagaku Kyokaishi* **1996**, *54*, 708.
http://dx.doi.org/10.5059/yukigoseikyokaishi.54.708
15. Tanaka, K.; Osuga, H.; Suzuki, H.; Shogase, Y.; Kitahara, Y. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 935.
http://dx.doi.org/10.1039/a707196e
16. Ernholt, B. V.; Thomsen, I. B.; Lohse, A.; Plesner, I. W.; Jensen, K. B.; Hazell, R. G.; Liang, X.; Jacobsen, A.; Bols, M. *Chem. Eur. J.* **2000**, *6*, 278.
http://dx.doi.org/10.1002/(SICI)1521-3765(20000117)6:2<278::AID-CHEM278>3.0.CO;2-6
17. Soloshonok, V. A. *Angew. Chem. Int. Ed.* **2006**, *45*, 766.
http://dx.doi.org/10.1002/anie.200503373
18. Soloshonok, V. A.; Klika K. *Helv. Chim. Acta* **2014**, *97*, 1583.
http://dx.doi.org/10.1002/hlca.201400122
19. Faigl, F.; Fogassy, E.; Nógrádi, M.; Pálovics, M.; Schindler, E. *Org. Biomol. Chem.* **2010**, *8*, 947.
http://dx.doi.org/10.1039/b917564d
20. Wallach, O. *Liebigs Ann. Chem.* **1895**, *286*, 90.
http://dx.doi.org/10.1002/jlac.18952860105
21. Pratt Brock, C.; Schweizer, W. B.; Dunitz, J. D. *J. Am. Chem. Soc.* **1991**, *113*, 9811.
http://dx.doi.org/10.1021/ja00026a015
22. Mastai, Y.; Volkel, A.; Colfen, H. *J. Am. Chem. Soc.* **2008**, *130*, 2426.
http://dx.doi.org/10.1021/ja067905i
23. Han, J.; Nelson, D. J.; Sorochinsky, A. E.; Soloshonok, V. A. *Curr. Org. Synth*. **2011**, *8*, 310.
http://dx.doi.org/10.2174/157017911794697303
24. Yasumoto, M.; Ueki, H.; Soloshonok, V. A. *J. Fluorine Chem.* **2010**, *131*, 540.
http://dx.doi.org/10.1016/j.jfluchem.2009.11.010
25. Yasumoto, M.; Ueki, H.; Soloshonok, V. A. *J. Fluorine Chem.* **2010**, *131*, 266.
http://dx.doi.org/10.1016/j.jfluchem.2009.10.002
26. Ueki, H.; Yasumoto, M.; Soloshonok, V. A. *Tetrahedron: Asymmetry* **2010**, *21*, 1396.
http://dx.doi.org/10.1016/j.tetasy.2010.04.040
27. Avalos, M.; Babiano, R.; Cintas, P.; Jimenez, J. L. Palacios, J. C. *Tetrahedron: Asymmetry* **1997**, *8*, 2997.
http://dx.doi.org/10.1016/S0957-4166(97)00375-3
28. Girard, C.; Kagan, H. B. *Angew. Chem. Int. Ed.* **1998**, *37*, 2922.
http://dx.doi.org/10.1002/(SICI)1521-3773(19981116)37:21<2922::AID-ANIE2922>3.0.CO;2-1
29. Kagan, H. B. *Synlett* **2001**, 888.
http://dx.doi.org/10.1055/s-2001-14660
30. Inanaga, J.; Furuno, H.; Hayano, T. *Chem. Rev.* **2002**, *102*, 2211.
http://dx.doi.org/10.1021/cr010444t
31. Soloshonok, V. A.; Roussel, C.; Kitagawa, O.; Sorochinsky, A. E. *Chem. Soc. Rev.* **2012**, *41*, 4180.
http://dx.doi.org/10.1039/c2cs35006h
32. Soloshonok, V. A.; Berbasov, D. O. *Chim. Oggi/Chem. Today* **2006**, *24*, 44.
33. Sorochinsky, A. E.; Aceña, J. L.; Soloshonok, V. A. *Synthesis* **2013**, *45*, 141.
34. Soloshonok, V. A.; Berbasov, D. O. *J. Fluorine Chem.* **2006**, *127*, 597.
http://dx.doi.org/10.1016/j.jfluchem.2005.11.004
35. Sorochinsky, A. E.; Katagiri, T.; Ono, T.; Wzorek, A.; Aceña, J. L.; Soloshonok, V. A. *Chirality* **2013**, *25*, 365.

http://dx.doi.org/10.1002/chir.22180

36. Martens, J.; Bhushan, R. *Helv. Chim. Acta* **2014**, 97, 161.
http://dx.doi.org/10.1002/hlca.201300392
37. Nieminen, V.; Murzin, D. Y.; Klika, K. D. *Org. Biomol. Chem.* **2009**, *7*, 537.
http://dx.doi.org/10.1039/B814905D
38. Mayani, V. J.;. Abdi, S. H. R; Kureshy, R. I.; Khan, N. H.; Agrawal, S.; Jasra, R. V. *Chirality* **2009**, *21*, 255.
http://dx.doi.org/10.1002/chir.20525
39. Wzorek, A.; Klika, K. D.; Drabowicz, J.; Sato, A.; Aceña, J. L.; Soloshonok, V. A. *Org. Biomol. Chem.* **2014**, *12*, 4738.
http://dx.doi.org/10.1039/c4ob00831f
40. Takahata, H.; Takahashi, S.; Kouno S.; Momose, T. *J. Org. Chem.* **1998**, *63*, 2224.
http://dx.doi.org/10.1021/jo971995f
41. Takahashi, H.; Tanabe, T.; Nakamura, D.; Kuribara, T.; Yamazaki O.; Kitagawa, O. *Tetrahedron* **2010**, *66*, 288.
http://dx.doi.org/10.1016/j.tet.2009.10.095
42. Tanaka, K.; Osuga, H.; Suzuki, H.; Shogase Y.; Kitahara, Y. *J. Chem. Soc., Perkin Trans. 1* **1998**, 935.
http://dx.doi.org/10.1039/a707196e
43. Nicoud, R.-M.; Jaubert, J.-N.; Rupprecht I.; Kinkel, J. *Chirality* **1996**, *8*, 234.
http://dx.doi.org/10.1002/(SICI)1520-636X(1996)8:3<234::AID-CHIR2>3.0.CO;2-H
44. Baciocchi, R.; Zenoni, G.; Mazzotti M.; Morbidelli, M. *J. Chromatogr. A* **2002**, *944*, 225.
http://dx.doi.org/10.1016/S0021-9673(01)01366-8
45. Baciocchi, R.; Mazzotti M.; Morbidelli, M. *J. Chromatogr. A* **2004**, *1024*, 15.
http://dx.doi.org/10.1016/j.chroma.2003.10.071
46. Gil-Av E.; Schurig, V. *J. Chromatogr. A* **1994**, *666*, 519.
http://dx.doi.org/10.1016/0021-9673(94)80413-3
47. Trapp O.; Schurig, V. *Tetrahedron: Asymmetry* **2010**, *21*, 1334.
http://dx.doi.org/10.1016/j.tetasy.2010.04.027
48. Jung M.; Schurig, V. *J. Chromatogr.* **1992**, *605*, 161.
http://dx.doi.org/10.1016/0021-9673(92)85233-J
49. Roussel, C.; Bonnet, B.; De Riggi I.; Suteu, C. *Biomed. Chromatogr.* **2001**, *15*, 173.
http://dx.doi.org/10.1002/bmc.58
50. Roussel, C.; Rafii, E.; Del Rio A.; Vanthuyne, N. *Biomed. Chromatogr.* **2005**, *19*, 434.
http://dx.doi.org/10.1002/bmc.502
51. Wzorek, A.; Sato, A.; Drabowicz, J.; Soloshonok, V. A.; Klika, K. D. *Amino Acids* **2016**, *48*, 605.
http://dx.doi.org/10.1007/s00726-015-2152-5
52. Wzorek, A.; Sato, A.; Drabowicz, J.; Soloshonok, V. A.; Klika, K. D. *Helv. Chim. Acta* **2015**, *98*, 1147.
http://dx.doi.org/10.1002/hlca.201500041
53. Wzorek, A.; Kamizela, A.; Sato, A.; Soloshonok, V. A. *J. Fluorine Chem.* **2016**
http://dx.doi.org/10.1016/j.jfluchem.2016.07.016
54. Wzorek, A.; Sato, A.; Drabowicz, J.; Soloshonok, V. A. *Isr. J. Chem.* **2016**.
http://dx.doi.org/10.1002/ijch.201600077
55. Suzuki, Y.; Han, J.; Kitagawa, O.; Aceña, J. L.; Klika, K. D.; Soloshonok, V. A. *RSC Adv.* **2015**, *5*, 2988.
http://dx.doi.org/10.1039/C4RA13928C

56. Maeno, M.; Tokunaga, E.; Yamamoto, T.; Suzuki, T.; Ogino, Y.; Ito, E.; Shiro, M.; Asahi, T. ; Shibata, N. *Chem. Sci.* **2015**, *6*, 1043. http://dx.doi.org/10.1039/C4SC03047H
57. Xie, C.; Wu, L.; Han, J.; Soloshonok, V. A.; Pan, Y. *Angew. Chem. Int. Ed*. **2015**, *54*, 6019. http://dx.doi.org/10.1002/anie.201500908
58. Zhang, L.; Xie, C.; Dai, Y.; Mei, H.; Soloshonok, V. A.; Pan, Y. Han, J. *J. Fluorine Chem.* **2016**, *184*, 28. http://dx.doi.org/10.1016/j.jfluchem.2016.01.008
59. Okusu, S.; Okazaki, H.; Tokunaga, E.; Soloshonok, V. A.; Shibata, N. *Angew. Chem. Int. Ed.* **2016**, *55*, 6744. http://dx.doi.org/10.1002/anie.201601928
60. Sha, W.; Zhang, L.; Wu, X.; Mei, H.; Han, J.; Soloshonok, V. A.; Pan, Y. *J. Fluorine Chem.* **2016**. http://dx.doi.org/10.1016/j.jfluchem.2016.06.008
61. Aceña, J. L.; Sorochinsky, A. E.; Katagiri, T.; Soloshonok, V. A. *Chem. Commun.* **2013**, *49*, 373. http://dx.doi.org/10.1039/C2CC37491A
62. Price C. C.; Oae S. *Sulfur Bonding*, Ronald, New York, 1962.
63. Basch H. in *The Chemistry of Sulfinic Acids, Esters and their Derivatives*, Patai S., Ed. John Wiley and sons, Chichester, 1990.
64. Brondel N.; Moynihan, E. J. A.; Lehane, K. N.; Eccles, K. S.; Elcoate, C. J.; Coles S. J.; Lawrence, S. E. Maguire, A. R. *CrystEngComm.* **2010**,12, 2910.
65. Wiberg, K. B.; Rush, D. J. *J. Am. Chem. Soc.* **2001**, *123*, 2038. http://dx.doi.org/10.1021/ja003586y
66. Wiberg, K. B. *Acc. Chem. Res*. **1999**, *32*, 922. http://dx.doi.org/10.1021/ar990008h
67. Newberry, R. W.; VanVeller, B.; Raines, R. T. *Chem. Commun.* **2015**, *51*, 9624. http://dx.doi.org/10.1039/C5CC02685G
68. Lee, H.-J.; Choi, Y.-S.; Lee, K.-B.; Park, J.; Yoon, C.-J. *J. Phys. Chem. A* **2002**, *106*, 7010. http://dx.doi.org/10.1021/jp025516e
69. Mikołajczyk, M.; Drabowicz, J. *Top. Stereochem.* **1982**, *13*, 333.
70. Drabowicz, J.; Kiełbasiński, P.; Mikołajczyk M. In *Syntheses of Sulfones, Sulfoxides and Cyclic Sulfides*, Patai, S.; Rappaport, Z. Eds.; Wiley: Chichester, 1994, pp 109–254.
71. Mikołajczyk, M.; Drabowicz, J.; Kiełbasinski, P. *Chiral Sulfur Reagents. Applications in Asymmetric and Stereoselective Synthesis*; CRC Press: Boca Raton, FL, 1997.
72. Wojaczynska, E.; Wojaczynski, J. *Chem. Rev.* **2010**, *110*, 4303.
73. Drabowicz, J.; Kiełbasinski, P.; Zając, A.; Wach-Panfiłow, P. In *Comprehensive Organic Synthesis*, Molander, G. A.; Knochel P. Eds.; 2nd Edn.; Elsevier: Oxford, 2014. Vol.6, pp 131-174.
74. Sorochinsky, A. E.; Soloshonok, V. A. *J. Fluorine Chem*. **2010**, *131*, 127. http://dx.doi.org/10.1016/j.jfluchem.2009.09.015
75. Mei, H.; Xie, C.; Han, J.; Soloshonok, V. A. *Eur. J. Org. Chem.* **2016**. http://dx.doi.org/10.1002/ejoc.201600578
76. Kukhar, V. P.; Sorochinsky, A. E.; Soloshonok, V. A. *Future Med. Chem.* **2009**, *1*, 793. http://dx.doi.org/10.4155/fmc.09.70
77. Fernandez, I.; Khiar, N. *Chem. Rev.* **2003**, *103*, 3651. http://dx.doi.org/10.1021/cr990372u
78. Hanquet, G.; Colobert, F.; Lanners, S.; Solladie´, G. *Arkivoc* **2003**, (vii), 328.
79. Pellissier, H. *Tetrahedron* **2006**, *62*, 5559.

http://dx.doi.org/10.1016/j.tet.2006.03.093

80. Carreño, M. C.; Hernández-Torres, G.; Ribagorda, M.; Urbano, A. *Chem. Commun.* **2009**, 6129.
81. Trost, B. M.; Rao M. *Angew. Chem. Int. Ed.* **2015**, *54*, 5026. http://dx.doi.org/10.1002/anie.201411073
82. Sipos, G.; Drinkel, E. E.; Dorta, R. *RSC Adv.* **2015**, *44*, 3834.
83. Mellah, M.; Voituriez, A.; Schulz, E. *Chem. Rev.* **2007**, *107*, 5133. http://dx.doi.org/10.1021/cr068440h
84. Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2004**, *43*, 5138. http://dx.doi.org/10.1002/anie.200400650
85. Bentley, R. *Chem. Soc. Rev.* **2005**, *34*, 609. http://dx.doi.org/10.1039/b418284g
86. Federsel, H.-J. *Chirality* **2003**, *15*, S128. http://dx.doi.org/10.1002/chir.10274
87. Mikolajczyk, M.; Drabowicz, J. *J. Am. Chem. Soc.* **1978**, *100*, 2510. http://dx.doi.org/10.1021/ja00476a040
88. Lindberg; P.;, Weidolf; L. U.S. Patent 5 877 192, 1997.
89. Song, W.; Zhou, Y.; Fu, Y.; Xu, W. *Tetrahedron: Asymmetry* **2013**, *24*, 909. http://dx.doi.org/10.1016/j.tetasy.2013.06.008
90. Diter, P.; Taudien, S.; Samuel, O.; Kagan, H. B. *J. Org. Chem.* **1994**, *59*, 370. http://dx.doi.org/10.1021/jo00081a015
91. Zhao, S. H.; Samuel, 0.; Kagan, H. B. *Tetrahedron* **1987**, *43*, 5135. http://dx.doi.org/10.1016/S0040-4020(01)87689-4
92. Drabowicz, J.; Bujnicki, B.; Mikolajczyk, M. *J. Org. Chem.* **1982**, *47*, 3325. http://dx.doi.org/10.1021/jo00138a026
93. Andersen K.K. *Tetrahedron Lett.* **1962**, 93. http://dx.doi.org/10.1016/S0040-4039(00)71106-3
94. Edwards S. J; Lind T.; Lundell L. Aliment. *Pharmacol. Ther*. **2006**, *24*, 743. http://dx.doi.org/10.1111/j.1365-2036.2006.03074.x
95. Olbe, L.; Carlsson, E.; Lindberg, P. *Nat. Rev. Drug Disc.* **2003**, *2*, 132. http://dx.doi.org/10.1038/nrd1010
96. Ohishi, H.; In, Y.; Ishida, T.; Inque, M. *Acta Crystallogr.* **1989**, *C45*, 1921.
97. Deng, J.; Chi, Y.; Fu, F.; Cui, X.; Yu, K.; Zhu, J.; Jiang, Y. *Tetrahedron:Asymmetry* **2000**, *11*, 1729. http://dx.doi.org/10.1038/nrd1010
98. Baciocchi, R.; Juza, M.; Classen, J.; Mazzotti, M.; Morbidelli, M. *Helv. Chim. Acta* **2004**, *87*, 1917. http://dx.doi.org/10.1002/hlca.200490172
99. Ławecka, J.; Bujnicki B.; Drabowicz, J.; Rykowski, A. *Tetrahedron Lett.* **2008**, *49*, 719. http://dx.doi.org/10.1016/j.tetlet.2007.11.104
100. Ławecka, J.; Bujnicki B.; Drabowicz, J.; Rykowski, A. *Phosphorus, Sulfur Silicon Relat. Elements,* **2009**, *184*, 1247. http://dx.doi.org/10.1080/10426500902856347
101. Davis, F. A.; Reddy, T. R.; Weismiller, M. C. *J. Am. Chem. Soc.* **1989**, *111,* 5964 http://dx.doi.org/10.1021/ja00197a080
102. Wzorek, A.; Sato, A.; Drabowicz. J.; Soloshonok, V. A. *J. Chrom. A,* **2016**. http://dx.doi.org/10.1016/j.chroma.2016.05.044

103. Pace, V.; Castoldi, L.; Monticelli, S.; Safranek, S.; Roller, A.; Langer, T.; Holzer, W.; Robust, A. *Chem. Eur. J.* **2015**, *21*, 18966.
http://dx.doi.org/10.1002/chem.201504247
104. Leathen, M. L.; Peterson, E. A. *Tetrahedron Lett.* **2010**, *51*, 2888.
http://dx.doi.org/10.1016/j.tetlet.2010.03.101
105. Kaleta, Z.; Makowski, B. T.; Soos, T.; Dembinski, R. *Org. Lett.* **2006**, *8* 1625.
http://dx.doi.org/10.1021/ol060208a

Authors' Biographies

Prof. Jozef Drabowicz born in 1946, studied at the University of Lodz (M.Sc. in 1969). Since then he has been employed at the Centre of Molecular and Macromolecular Studies (CMMS), Polish Academy of Sciences in Lodz. He got PhD under the supervision of Professor M. Mikolajczyk in 1975 and DSc (habilitation) (Lodz University- 1987). Since 1998 he has been Professor at the Centre of Molecular and Macromolecular Studies. Since 2002 he has been teaching simultaneously at the Jan Dlugosz University in Czestochowa, where since 2008 he has been Vice-Rector for Science and Research. He spent his postdoctoral stay at the University of Tsukuba, [with S. Oae (1976-1977)] and worked as a Research Associate with Professor J. C. Martin at Vanderbilt University, Nashville (1989-1990). He was a Visiting Professor at Universities in Bologna, Halle and Caen. He is co-author of more than 220 publications (154 research papers, 25 reviews and more than 40 monographic chapters including 16 chapters in "Science of Synthesis" – vol. 33, 39, 42 and 48). At present he is the Editor for "Science of Synthesis- Knowledge updates" Vol. 39. and Vol. 33 and member of the Editorial Board of ISRN Organic Chemistry and Phoshorus, Sulfur and Silicon and the Related Elements. He has been a member of the International Advisory Board of the International Conference on the Organic Chemistry of Sulfur (ISOCS- since 2012) and the International Symposium on Halogen Chemistry (HALCHEM- since 2010). He was Chairman of the ISOCS-25 and HALCHEM 7 held in Czestochowa (Poland) in 2012 and 2015. He was invited lecturer at more than 20 international scientific conferences and delivered more than 90 academic lectures at foreign Universities and Research Institutes. He has supervised more than 25 research trainees (PhD, Master and undergraduate students). He has been a coordinator of several national grants, and a partner of 2 EU grants. His research interests are concentrated on chemistry and stereochemistry of heteroorganic compounds, especially sulfur derivatives, synthetic methodologies, asymmetric synthesis and very recently on organic materials.

Aleksandra Jasiak studied at the Jan Dlugosz University in Czestochowa (M.Sc., May 2016). She is currently a PhD student in the group of Prof. Drabowicz at the Center of Molecular and Macromolecular Studies, Polish Academy of Sciences in Lodz. Her research interests are focused on sterochemistry of heteroorganic compounds and flow processes.

Alicja Wzorek studied at the Jan Kochanowski University in Kielce (M.Sc in 2001). From 2003 has been employed at Jan Kochanowski University as Assistant Professor. She received Ph.D. from Warsaw University in Chemistry in 2009. In 2005 she worked in Professor Johen Mattay's group at the Univeristy in Bielefel (Germany). In 2013 she started the cooperation with Professor Soloshonok's group (University of the Basque Country, Spain). Her research interests are focused on self-disproportionation of enantiomers (SDE), supramolecular chemistry, biocatalysis and synthesis of biologically active compounds.

Azusa Sato is Assistant Professor at Tokyo Women's Medical University. He received B.S. in Pharmacy at Tokyo University of Pharmacy and Life Sciences, then earned his Ph.D. in Pharmacy at Tokyo University of Pharmacy and Life Sciences, JP (with Professor Takeo Taguchi) in 2001. He joined Soloshonok group at University of the Basque Country, ES (2013) and Röschenthaler group at Jacobs University Bremen, DE (2015) as Visiting Research Scientist. His research involves studying the synthesis of organofluorine compounds as well as the elucidation of self-disproportionation of enantiomers of various organofluorine compounds.

Vadim A. Soloshonok graduated from Kiev State University in 1983 and received his Ph.D. in 1987 from the Ukrainian Academy of Sciences. In 1987 he joined the Institute of Bioorganic Chemistry, Kiev, Ukraine, where he has been working until 1995. From 1995 through 1999 he was Senior Researcher at the National Industrial Research Institute, Nagoya, Japan and from 2001 to 2010 Professor of Chemistry at the University of Oklahoma, USA. Currently he is the Ikerbasque Research Professor at the University of Basque Country, San Sebastian, Spain, EU. He is currently serving as a member of the international advisory editorial board of the Journal of Fluorine Chemistry, Synthesis Field Editor of Amino Acids, Past-Chair of the ACS Fluorine Division; author of over 270 research papers. His publications have generated over 10,300 citations with h-index of 63. His major current research interests are: fluorine chemistry, asymmetric synthesis and self-disproportionation of enantiomers.