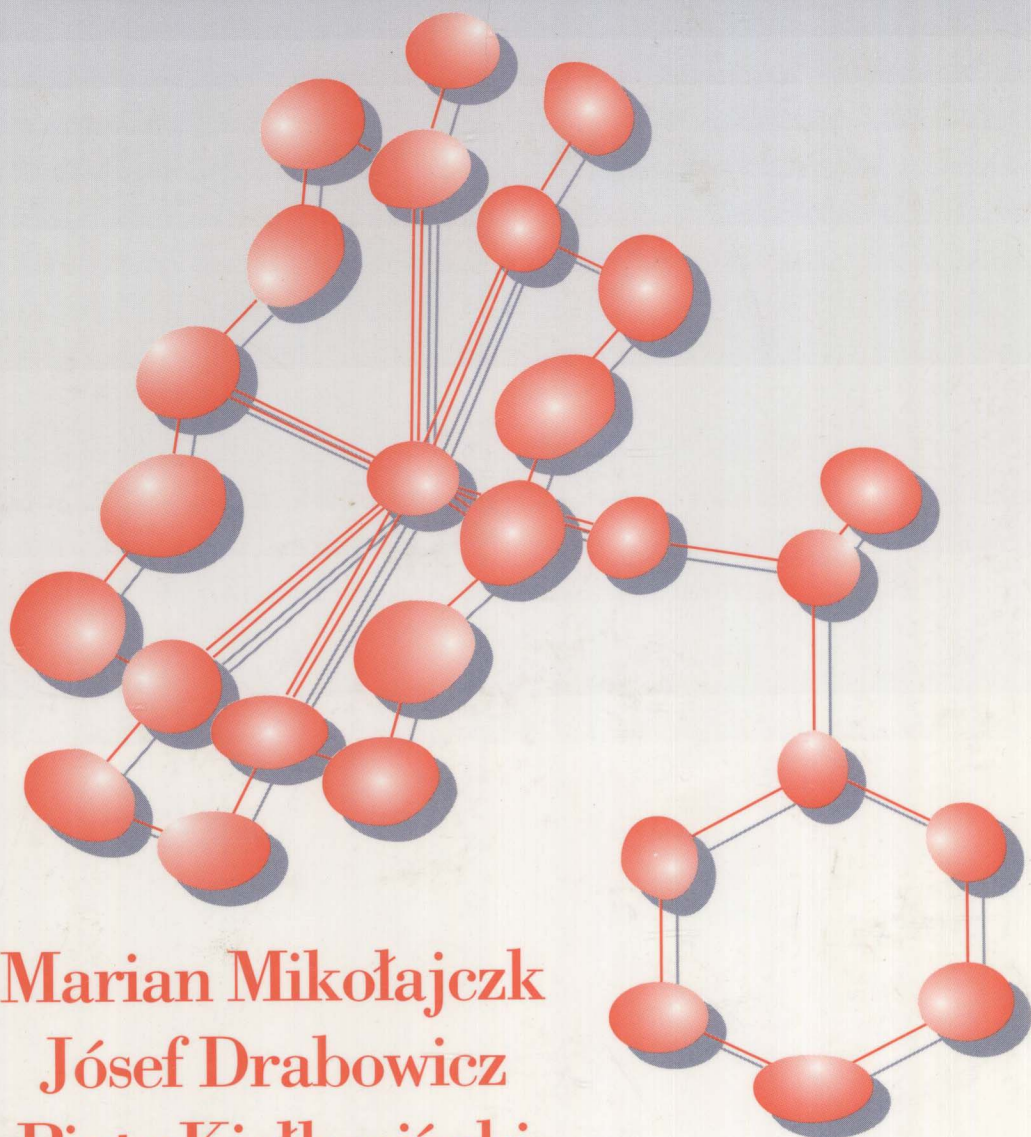


CHIRAL SULFUR REAGENTS

Applications in Asymmetric
and Stereoselective Synthesis



Marian Mikołajczk
Józef Drabowicz
Piotr Kielbasiński

062
1636

CHIRAL SULFUR REAGENTS

Applications in Asymmetric
and Stereoselective Synthesis

Marian Mikołajczk

Józef Drabowicz

Piotr Kielbasiński

*Center of Molecular and
Macromolecular Studies*

Polish Academy of Sciences

Łódź, Poland



E9960054



CRC Press

Boca Raton New York

Library of Congress Cataloging-in-Publication Data

Mikołajczyk, Marian.

Chiral sulfur reagents : applications in asymmetric and stereoselective synthesis / Marian Mikołajczyk, Józef Drabowicz, and Piotr Kiełbasiński.

p. cm. -- (New directions in organic and biological chemistry)

Includes bibliographical references (p. --) and index.

ISBN 0-8493-9120-2 (alk. paper)

1. Organosulphur compounds. 2. Chirality. 3. Asymmetric synthesis. 4. Stereochemistry. I. Drabowicz, Józef.

II. Kiełbasiński, Piotr. III. Title. IV. Series.

[DNLM: 1. Hepatitis B virus. QW 710 G289h]

QD305.S3M5 1996

547'.060459--dc20

96-6162

CIP

This book contains information obtained from authentic and highly regarded sources. Reprinted material is quoted with permission, and sources are indicated. A wide variety of references are listed. Reasonable efforts have been made to publish reliable data and information, but the author and the publisher cannot assume responsibility for the validity of all materials or for the consequences of their use.

Neither this book nor any part may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, microfilming, and recording, or by any information storage or retrieval system, without prior permission in writing from the publisher.

The consent of CRC Press LLC does not extend to copying for general distribution, for promotion, for creating new works, or for resale. Specific permission must be obtained in writing from CRC Press LLC for such copying.

Direct all inquiries to CRC Press LLC, 2000 Corporate Blvd., N.W., Boca Raton, Florida 33431.

© 1997 by CRC Press LLC

No claim to original U.S. Government works

International Standard Book Number 0-8493-9120-2

Library of Congress Card Number 96-6162

Printed in the United States of America 1 2 3 4 5 6 7 8 9 0

Printed on acid-free paper

CHIRAL SULFUR REAGENTS

Applications in Asymmetric
and Stereoselective Synthesis

Preface

Although the first chiral organosulfur compounds were obtained at the beginning of this century, they have received more attention since the early 1960s. Initially, chiral sulfur compounds served as model compounds in studies on the mechanism and stereochemistry of nucleophilic substitution at sulfur's center. Quite soon, however, it was recognized that chiral sulfur compounds are of great value in asymmetric synthesis, since many reactions may be efficiently stereocontrolled by chiral sulfur auxiliaries which later are easily removable under mild conditions by reductive or eliminative methods. As a result, there has been a literature explosion in this field. On the one hand, over the last three decades more than 40 different classes of chiral sulfur compounds have been described in the chemical literature and a large number of useful procedures for the synthesis of enantiomerically pure sulfur compounds have been developed, especially of tri- and tetracoordinated sulfur structures. On the other hand, every year literature records dozens and dozens of diverse sulfur-mediated asymmetric syntheses applied in both academic and industrial laboratories for obtaining desirable chiral materials like natural products, drugs, or agrochemicals.

Many of these developments have received treatment in recent books and monographs on sulfur chemistry and organic synthesis, but no comprehensive text covering the whole area is available. The aim of this book, therefore, is to take a somewhat broader view, encompassing as many as possible of the chiral sulfur reagents, their preparation, and application in asymmetric and stereoselective synthesis. It does not seek to be totally comprehensive because compilation of such a text would entail a task of daunting proportions. Therefore, we apologize that many interesting contributions to this field which have been published could not be cited in this book.

As this is a practical book, the greater emphasis has been usually placed on describing the modern methodologies and procedures furnishing compounds with full or high enantiomeric purity. For the same reasons, some selected experimental data and examples of experimental procedures have been included which we felt were liable to be of greatest use both to students working for their first degree as well as to research chemists. However, some space has also been devoted to mechanistic aspects of the discussed asymmetric reactions.

Though the main purpose of this book is to demonstrate the great potential of enantiomerically pure sulfur reagents in transmitting chirality to other centers, the results obtained with racemic compounds are also discussed, particularly in cases where a high diastereoselectivity was observed. Such results can be easily transferred to enantiopure sulfur compounds, the only problem being the effective synthesis of the latter. Furthermore, several rather unsuccessful results (low extent of asymmetric induction, unsatisfactory yields) have also been mentioned to warn and prevent the reader from undertaking efforts which had already been made by others.

Finally, we believe that the scientific technological importance of chiral sulfur compounds justifies the conclusion that the subject of this book will be of interest to many chemists in many countries. We can only hope that our treatment of it has been adequate.

M. Mikołajczyk
J. Drabowicz
P. Kiełbasiński

Contents

Preface	iii
1 Structure-Chirality Relationship in Organic Sulfur Compounds	1
References	5
2 Chiral Sulfinic Acid Derivatives	7
2.1 Sulfinic Esters.....	7
2.1.1 Diastereomeric Sulfinic Esters.....	7
2.1.2 Enantiomeric Sulfinic Esters.....	13
2.1.3 Synthetic Application of Optically Active Sulfinic Esters	16
2.1.4 Examples of Experimental Procedures	26
2.2 Chiral Sulfinamides and N-Alkylidenesulfinamides.....	28
2.2.1 Diastereomeric Sulfinamides	28
2.2.2 Enantiomeric Sulfinamides	30
2.2.3 Enantiomeric N-Alkylidenesulfinamides	31
2.2.4 Synthetic Application of Chiral Sulfinamides and N-Alkylidenesulfinamides.....	33
2.2.5 Examples of Experimental Procedures.....	42
References	44
3 Chiral Sulfoxides	47
3.1 α -Sulfinyl Carbanions	47
References (3.1)	56
3.2 Dialkyl and Alkyl Aryl Sulfoxides	57
3.2.1 Alkylation.....	57
3.2.1.1 Synthetic Applications	59
3.2.2 Michael Addition to α,β -Unsaturated Carbonyl Compounds.....	60
3.2.3 Hydroxyalkylation.....	61
3.2.3.1 Synthetic Applications	64
3.2.4 Aminoalkylation.....	70
3.2.5 Acylation	73
3.2.6 Examples of Experimental Procedures.....	74
References (3.2)	77
3.3 Allyl Sulfoxides.....	78
3.3.1 Asymmetric Allylic Sulfoxide-Sulfenate Rearrangements.....	78
3.3.1.1 Chirality Transfer from Carbon to Sulfur	78
3.3.1.2 Chirality Transfer from Sulfur to Carbon: Asymmetric Synthesis of Chiral Allyl Alcohols.....	80
3.3.2 Reactions of Allyl Sulfoxide Carbanions	82
3.3.2.1 Conjugate Addition of Chiral Allyl Sulfoxide Anions.....	83

3.3.2.2	Asymmetric Synthesis of (+)-Hirsutene.....	87
3.3.2.3	Asymmetric Synthesis of Enantiomers of 12,13-Epoxytrichothec-9-ene.....	88
3.3.2.4	Asymmetric Synthesis of (+)-Pentalene.....	89
3.3.3	Examples of Experimental Procedures.....	89
References (3.3)		90
3.4	Alkyl and Arylsulfinylmethyl Sulfoxides	91
3.4.1	Synthesis.....	91
3.4.2	Michael Addition.....	92
3.4.3	Hydroxyalkylation.....	93
3.4.4	Acylation	94
3.4.5	Examples of Experimental Procedures.....	95
References (3.4)		96
3.5	α -Sulfinyl-, α -Sulfonyl-, and α -Sulfoximino Sulfoxides.....	98
3.5.1	α -Sulfinyl Sulfoxides	98
3.5.2	α -Sulfonyl Sulfoxides	101
3.5.3	α -Sulfoximino Sulfoxides.....	104
3.5.4	Examples of Experimental Procedures.....	104
References (3.5)		105
3.6	α -Halogeno Sulfoxides	106
3.6.1	Examples of Experimental Procedures.....	114
References (3.6)		115
3.7	α -Phosphoryl Sulfoxides and α -Sulfinyl Phosphonium Salts.....	116
3.7.1	Synthesis of Chiral α -Phosphoryl Sulfoxides	116
3.7.2	Synthesis of Chiral α -Sulfinyl Phosphonium Salts and Ylides	119
3.7.3	α -Phosphoryl Sulfoxides and α -Sulfinyl Phosphonium Ylides as Key Reagents in the Synthesis of Chiral α,β -Unsaturated Sulfoxides.....	120
3.7.4	Asymmetric Reactions of α -Phosphoryl Sulfoxides.....	124
3.7.5	Examples of Experimental Procedures.....	127
References (3.7)		128
3.8	β -Oxosulfoxides and Related Derivatives	129
3.8.1	α -Sulfinylcarboxylates	129
3.8.1.1	Synthesis	129
3.8.1.2	Reactions of the Carbanion of α -Sulfinylcarboxylates with Electrophiles	131
3.8.2	β -Oxosulfoxides.....	135
3.8.2.1	Asymmetric Synthesis of Both Enantiomers of 4-Hydroxy-2-Cyclohexanone.....	137
3.8.2.2	Synthesis of Optically Active Epoxides	137
3.8.2.3	Asymmetric Synthesis of Protected α -Hydroxyaldehydes.....	138
3.8.2.4	Stereoselective Synthesis of (R)-3-Benzoyloxy- 2-Butanone	138

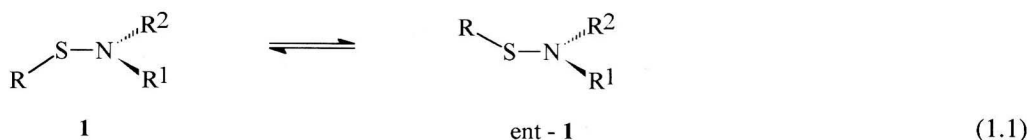
	3.8.2.5	Synthesis of Chiral 1,3-Diols	138
	3.8.2.6	Reduction of Fluoroalkyl-Oxosulfoxides	139
3.8.3		β -Thioxosulfoxides	139
3.8.4		β -Iminosulfoxides and Analogs	140
3.8.5		Examples of Experimental Procedures	141
References (3.8)			143
3.9		Acyclic α,β -Unsaturated Sulfoxides	144
3.9.1		Electrophilic Addition	144
3.9.2		Michael Addition of Carbon Nucleophiles	145
3.9.3		Michael Addition of Oxygen Nucleophiles	148
	3.9.3.1	Enantioselective Synthesis of Each Enantiomer of a Sex-Pheromone of an Olive Fly	148
	3.9.3.2	Synthesis of the Chroman Ring of α -Tocopherol (Vitamin E)	150
	3.9.3.3	Synthesis of (+) and (-)-(cis-6-Methyltetrahydropyran-2-yl)acetic Acids	152
3.9.4		Conjugate Addition of Nitrogen Nucleophiles	152
	3.9.4.1	Total Synthesis of (+)-(R)-Carnegine and (+)- and (-)-Sedamine	154
	3.9.4.2	Total Synthesis of (+)-(R)-Canadine	156
3.9.5		Conjugate Addition of Silicon Nucleophiles	157
3.9.6		Diels-Alder Cycloaddition	158
	3.9.6.1	Enantiodivergent Synthesis of Fused Bicyclo [2.2.1] Heptane Lactones; Enantioselective Synthesis of (-)-Boschnialactone	166
	3.9.6.2	Synthesis of the Ohno's Intermediate for the Preparation of Carbocyclic Nucleosides	168
	3.9.6.3	Stereoselective Syntheses of Some Bicyclic Alkaloids	168
	3.9.6.4	Reactions of Sulfinyl Dienophiles with Dane's Diene; Synthesis of Steroid Precursors	169
3.9.7		Miscellaneous Reactions of α,β -Unsaturated Sulfoxides	170
	3.9.7.1	Additive Pummerer Rearrangement	169
	3.9.7.2	Asymmetric Cyclopropanation	170
	3.9.7.3	Asymmetric Radical Cyclizations	173
3.9.8		Cycloadditions of Sulfinyl Dienes	174
3.9.9		Examples of Experimental Procedures	175
References (3.9)			178
3.10		Cycloalkenone Sulfoxides	180
3.10.1		Synthesis of 2-Sulfinyl-2-Cycloalkenones	180
3.10.2		Synthesis of 2-Sulfinyl-2-Alkenolides	180
3.10.3		Conjugate Addition of Nucleophiles to Sulfinyl Cycloalkenones	182
3.10.4		Conjugate Addition of Nucleophiles to Sulfinyl Alkenolides	185
3.10.5		Applications of the Conjugate Addition of Nucleophiles to 2-Sulfinyl-2-Cycloalkenones and 2-Sulfinyl-2-Alkenolides in the Synthesis of Natural Products: Selected Examples	186
	3.10.5.1	Formal Total Synthesis of 11-Oxoequilenin	186
	3.10.5.2	Synthesis of (+)- α -Cuparenone	186
	3.10.5.3	Synthesis of Natural (-)-Methyl Jasmonate	187

3.10.5.4	Synthesis of (+)-Estrone Methyl Ether	187
3.10.5.5	Synthesis of (+)-A Factor	188
3.10.5.6	Synthesis of Aphidicolin	188
3.10.5.7	Preparation of Chiral 2-Substituted Chroman-4-Ones	189
3.10.6	Asymmetric Radical Reaction	190
3.10.7	Examples of Experimental Procedures	191
References (3.10)		193
4	Chiral Sulfilimines and Sulfoximines	195
4.1	Synthesis of Chiral Sulfilimines	195
4.2	Synthesis of Chiral Sulfoximines	198
4.3	Chiral Sulfilimines and Sulfoximines in Asymmetric Synthesis	206
4.4	Examples of Experimental Procedures	233
References		239
5	Chiral "Onium" Derivatives of Sulfur and Chiral Sulfur Ylides	241
5.1	Preparation of Chiral Sulfur Onium Salts and Ylides	242
5.2	Synthetic Application of Chiral Sulfur "Onium" Salts and Ylides	251
5.3	Examples of Experimental Procedures	264
References		266
Index		267

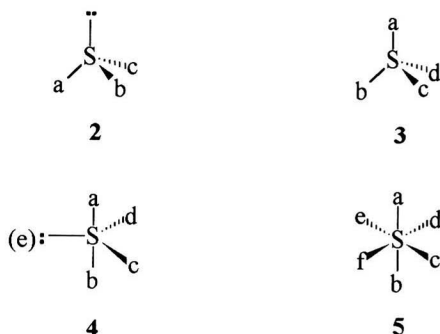
Chapter 1

Structure-Chirality Relationship in Organic Sulfur Compounds

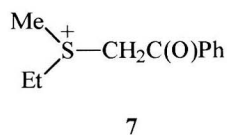
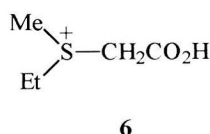
Sulfur forms a variety of organic compounds showing different structural and stereochemical properties. A very useful criterion to classify all the organosulfur compounds is the number (N) of ligands on sulfur.¹⁻³ Based on this criterion sulfur compounds are divided into six classes with ligand numbers N = 1 to 6. A limited number of monocoordinate (N = 1) sulfur compounds of linear structure are not interesting from the point of view of chirality at sulfur, since they are achiral compounds. Similarly, sulfur in dicoordinate (N = 2) compounds having angular structures cannot be a center of chirality. The only exception is the sulfenamide **1** which, due to the partial double bond character of the sulfur-nitrogen bond, shows, like allenes and carbodiimides, an axial chirality and may exist in two enantiomeric forms. This stereochemical feature of sulfenamides was first demonstrated by Kost and Raban⁴ and then widely investigated.



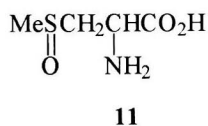
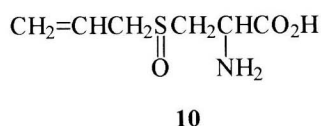
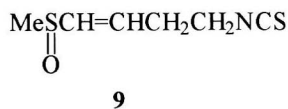
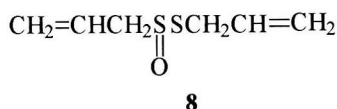
Sulfur compounds with the ligand number N = 3 may adopt a trigonal planar or trigonal pyramidal structure. However, planar arrangement of three different substituents around sulfur is not a sufficient condition for chirality at sulfur. On the contrary, pyramidal sulfur compounds, of the general structure **2**, containing three different ligands and the lone electron pair occupying the fourth position of a distorted tetrahedron are chiral and configurationally stable. This is in contrast to isoelectronic amines and carbonium ions. A higher, configurational stability of this class of sulfur compounds is due to the higher amount of s-character and the longer bond lengths about the central sulfur atom.



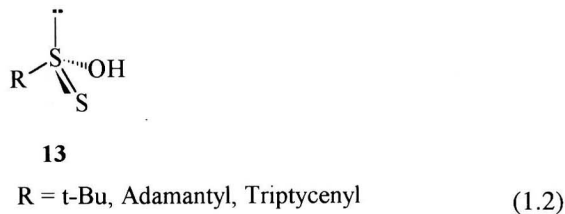
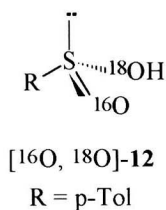
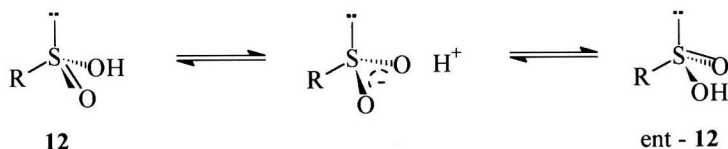
To the class of chiral tricoordinate sulfur compounds belong various sulfonium salts, $R^1R^2R^3S^+A^-$, sulfinyl compounds, $R^1R^2S=O$, and iminosulfinyl compounds, $R^1R^2S=NR$, which, in the majority of cases, are configurationally stable and have been obtained in optically active states. It is interesting to note that the first resolution of chiral sulfur compounds was reported in 1900 by Pope and Peachey⁵ and by Smiles,⁶ who resolved the sulfonium salts **6** and **7** via diastereomeric salts with chiral acids.



The isolation, around 1950, of many chiral sulfinyl compounds such as **8**, **9**, **10**, and **11** from natural sources resulted in intense activity in the preparation and study of new chiral tricoordinate sulfur structures.^{7,8}

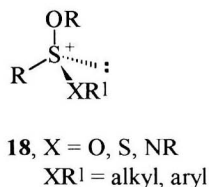
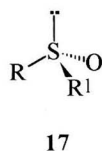
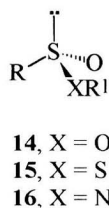


A great number of chiral tricoordinate sulfur compounds may be derived from sulfinic acids **12** which, however, are themselves effectively achiral. This is due to a fast proton exchange between two enantiomeric forms of **12** via the achiral sulfinic acid anion (Equation 1.2).

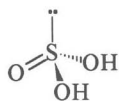
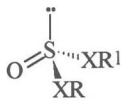


Replacement of one of the two ¹⁶O oxygen atoms in **12** by ¹⁸O or by sulfur leads to chiral structures of sulfinic acid [¹⁶O, ¹⁸O]-**12** and thiosulfinic acid **13**, respectively.⁹ The former was recently obtained in optically active form by stereoselective synthesis.¹⁰

Other sulfinic acid derivatives such as sulfinates **14**, thiosulfinates **15**, sulfinamides **16**, sulfoxides **17**, and sulfoxonium salts **18** as well as their imino-analogs are chiral and have been obtained in enantiomeric forms.²

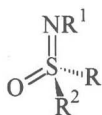
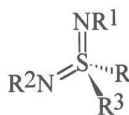
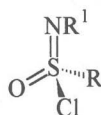
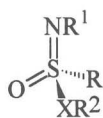


Another series of chiral tricoordinate sulfur compounds may be derived from achiral sulfurous acid **19** by replacement of the hydroxy groups by suitable substituents. Thus, sulfites, amidosulfites, and amidothiosulfites of the general structure **20** belong to this class of compounds. Although these chiral compounds have been obtained in enantiomeric or diastereomeric forms, they are not in common use.

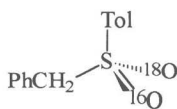
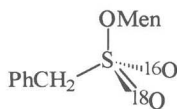
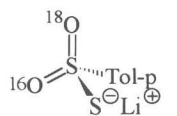
**19****20**, X = O, S, NR

The structure of sulfur compounds with four ligands (N = 4) and without a "stereochemically active" nonbonding electron pair is tetrahedral. If the four ligands are different as in **3**, such tetrahedral, tetracoordinate sulfur compounds are chiral and can be resolved or prepared in enantiomeric forms. Here, the situation is quite similar to the tetrahedral, sp³-carbon compounds if one neglects the different bond order between some substituents and sulfur.

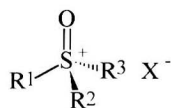
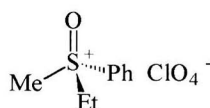
The most common chiral, tetracoordinate sulfur compounds are sulfoximines **21** which formally arise from achiral, unsymmetrical sulfones by replacement of one of the two oxygen atoms by the imino nitrogen. Consequently, replacement of both oxygen atoms in unsymmetrical sulfones by different imino groups leads to other chiral, tetracoordinate structures, namely sulfodiimides **22**. Of interest is that chiral, optically active sulfonimidoyl chlorides **23** have also been obtained. Due to the presence of a good leaving group, these chlorides are excellent substrates for nucleophilic substitution reaction and afford in a highly stereoselective way the corresponding esters and amides **24**.^{2,11}

**21****22****23****24**, X = O, NH

As in the case of sulfinic acids, the chirality at sulfur in unsymmetrical sulfones may be generated by isotopic substitution. The first example of such a chiral sulfone, i.e., (–)-benzyl p-tolyl [¹⁶O, ¹⁸O]-sulfone **25** was described by Stirling¹² as early as 1963. A few years later, Sabol and Andersen¹³ prepared diastereomerically pure (–)-menthyl [¹⁶O, ¹⁸O]-phenylmethanesulfonate **26**. The list of the tetracoordinate sulfur compounds chiral by virtue of isotopic oxygen substitution was recently extended by the synthesis of the lithium salt of chiral [¹⁶O, ¹⁸O]-p-toluenethiosulfonic acid **27**.¹⁰

**25****26****27**

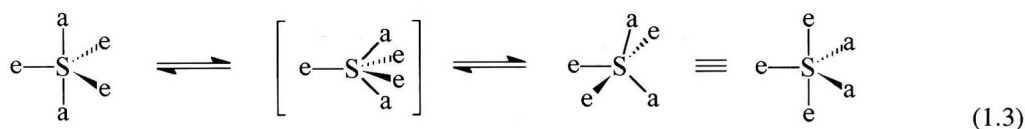
Oxosulfonium salts of the general formula **28** belong to the group of tetrahedral tetracoordinate sulfur compounds with four different ligands ($N = 4$). Therefore, they are chiral at sulfur and can exist in enantiomeric forms. Thus far, however, methylethylphenyloxosulfonium perchlorate **29** is the only compound of this type whose enantiomers have been isolated.¹⁴

**28****29**

Tetracoordinate sulfur compounds ($N = 4$), which contain the lone electron pair as a phantom ligand, as well as pentacoordinate sulfur compounds ($N = 5$) possess a trigonal bipyramidal structure exemplified by **4**. A common name, sulfurane, is generally accepted for this type of high-coordinated compounds.¹⁵

In the present brief account at least three significant features of sulfuranes should be mentioned. The first concerns the positions of substituents in a trigonal bipyramidal structure. In such a structure two substituents occupy apical positions while the remaining three are placed in a basal plane in equatorial positions. This nonequivalence of ligand positions is preserved even in the case of the same substituents connected with the central sulfur atom. The tendency of a substituent to occupy an apical position is defined as apicophilicity. In the first approximation apicophilicity is related to electronegativity, i.e., the more electronegative the ligand the greater its apicophilicity. Ring strain, steric bulk, and electronic effects are the other factors affecting the apicophilicity order in sulfuranes.

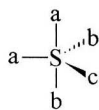
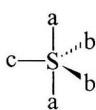
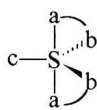
Secondly, the most interesting phenomenon observed in sulfuranes as well as in other valency-shell expanded compounds is the internal ligand reorganization changing the relative positions of ligands in a trigonal bipyramidal structure. This process is commonly called pseudorotation. A single process of pseudorotation according to the Berry mechanism is visualized below (Equation 1.3).



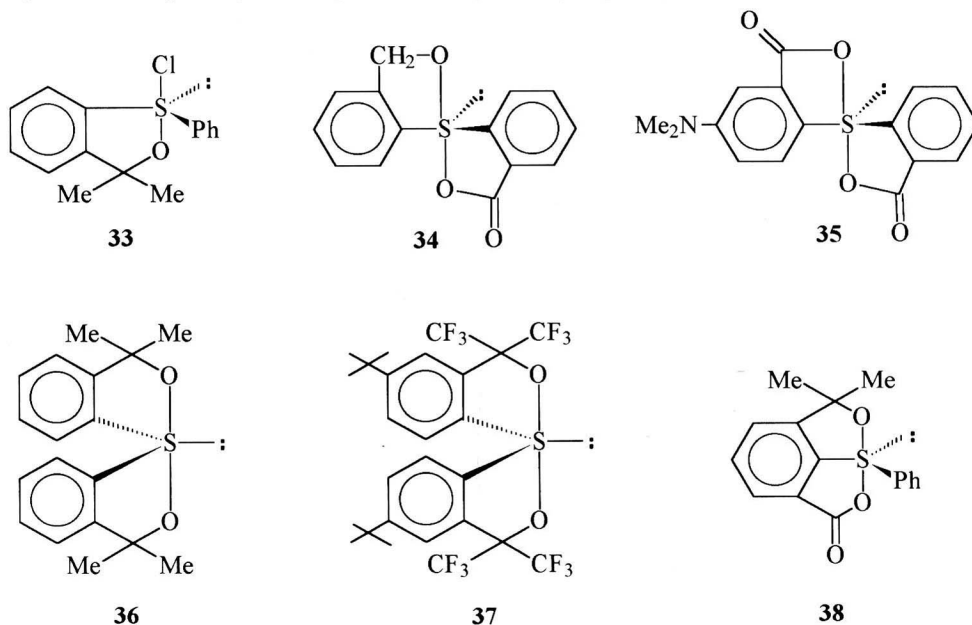
(1.3)

Since the energy required for pseudorotation is usually very low, this process may have an important influence on the stereochemical properties of sulfuranes.

Finally, it should be emphasized that sulfuranes may be chiral. However, the number of optically active isomers is dependent on the nature of substituents connected with sulfur, their apicophilicity, and the energy for pseudorotation. In this context, it is interesting to note that acyclic sulfuranes with five different ligands like **4** should exist in twenty isomeric chiral forms. However, in the case of sulfuranes, all structures containing at least three different ligands can be chiral. Thus, the sulfurane structure **30** is chiral in contrast to the more symmetrical **31**, which is achiral. Moreover, considering the topological properties of such trigonal bipyramidal molecules, it should be pointed out that, after incorporation of cyclic ligands into this structure, chirality may still appear in the more symmetrical spiro system **32**.

**30****31****32**

The first example of an optically active sulfurane was the dextrorotatory chlorosulfurane **33** prepared by Martin and Balthazor.¹⁶ All other sulfuranes **34–38**, which have been till now prepared^{17,18} as optically active species, belong to the group of spiro derivatives and are shown below.



For hexacoordinate sulfur compounds ($N = 6$) the octahedral arrangement of ligands is characteristic as pictured in **5**. In spite of the fact that such compounds are known their stereochemistry has yet to begin. Till now, no optically active compounds of this type have been described in the literature.

REFERENCES

1. Laur, P.H., in *Sulfur in Organic and Inorganic Chemistry*, Vol. 3, Senning, A., Ed., Marcel Dekker, New York, 1972.
2. Mikołajczyk, M., Drabowicz, J., *Top. Stereochem.*, **13**, 333, 1982.
3. Oae, S., *Organic Sulfur Chemistry: Structure and Mechanism*, CRC Press, Boca Raton, FL, 1991, chap. 3, p.67.
4. Kost, D., Raban, M., in *The Chemistry of Sulfinic Acids and Their Derivatives*, Patai, S., Ed., John Wiley & Sons, Chichester, 1990, pp 23–82.
5. Pope, W.J., Peachey, S.J., *J. Chem. Soc.*, **77**, 1072, 1900.
6. Smiles, S., *J. Chem. Soc.*, **77**, 1174, 1900.
7. Challenger, F., *Aspects of the Organic Chemistry of Sulfur*, Butterworths, London, 1959.
8. Kjaer, A., *Pure Appl. Chem.*, **49**, 137, 1977.
9. Mikołajczyk, M., Łyżwa, P., Drabowicz, J., *Angew. Chem., Int. Ed. Engl.*, **28**, 97, 1989.
10. Drabowicz, J., Łyżwa, P., Bujnicki, B., Mikołajczyk, M., *Phosphorus, Sulfur and Silicon*, **95–96**, 293, 1994.
11. Nudelman, A., *The Chemistry of Optically Active Sulfur Compounds*, Gordon and Breach, New York, 1984.
12. Stirling, C.J.M., *J. Chem. Soc.*, 5741, 1963.
13. Sabol, M., Andersen, K.K., *J. Am. Chem. Soc.*, **91**, 3603, 1969.
14. Kobayashi, M., Kamiyama, K., Minato, H., Oishi, Y., Takada, Y., Hattori, Y., *J. Chem. Soc. D.*, 1577, 1971; Kamiyama, K., Minato, H., Kobayashi, M., *Bull. Chem. Soc. Jpn.*, **46**, 3895, 1973.
15. Drabowicz, J., Łyżwa, P., Mikołajczyk, M., in *Supplement S: the Chemistry of Sulfur-Containing Functional Groups*, Patai, S. and Rappoport, Z., Eds., John Wiley & Sons, Chichester, 1993, pp. 799–956.
16. Martin, J. C., Balthazor, T. M., *J. Am. Chem. Soc.*, **99**, 152, 1977.
17. Kapovits, I., *Phosphorus, Sulfur and Silicon*, **58**, 39, 1991.
18. Drabowicz, J., Martin, J. C., *Tetrahedron: Asymmetry*, **4**, 297, 1993.

Chapter 2

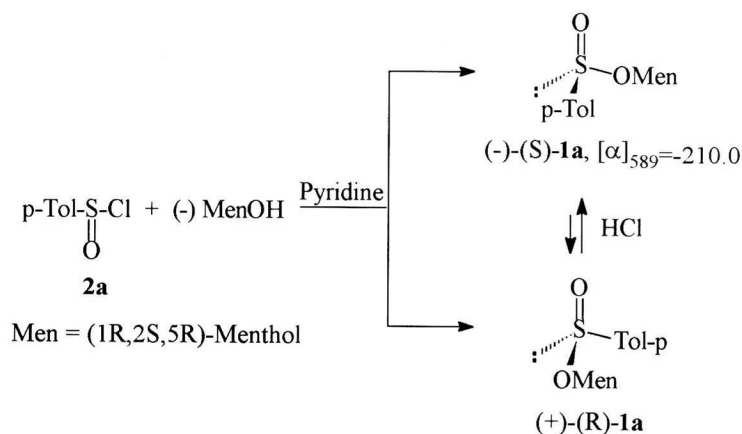
Chiral Sulfinic Acid Derivatives

2.1 SULFINIC ESTERS

Sulfinic esters of the general structure $R-S(O)OR^1$ belong to the oldest group of chiral organosulfur derivatives prepared as optically active species.¹ Depending on the nature of a substituent R^1 , they can be obtained as enantiomers (if R^1 is achiral) or as diastereomeric mixtures (if R^1 contains at least one chiral center). A high stability of the pyramidal structure around the central sulfur atom^{1,2} allows the synthesis of a rich family of stable, optically active sulfinic esters. Their importance as substrates in the synthesis of optically active sulfinyl derivatives and in establishing the absolute configuration of three- and tetracoordinated sulfur compounds is well recognized.^{1,3} A presentation of synthetic routes reported for the preparation of the most important diastereomeric and enantiomeric sulfinic esters as well as their synthetic applications will follow these introductory remarks. A comprehensive review on the synthesis of sulfinates can be found in Reference 3.

2.1.1 Diastereomeric Sulfinic Esters

The oldest and up to now the most common procedure for the preparation of diastereomeric sulfinic esters involves condensation of sulfinyl chlorides with the appropriately selected enantiomerically or diastereomerically pure alcohols carried out in the presence of an organic or inorganic base. This method was for the first time used by Phillips⁴ for obtaining O-menthyl p-toluenesulfinate **1a**. Thus, in the reaction between p-toluenesulfinyl chloride **2a** and (–)-(1R,2S,5R)-menthol in the presence of pyridine a mixture of the diastereomeric O-menthyl p-toluenesulfinate **1a** was formed (Scheme 2.1.1), from which Phillips was able to isolate a pure, solid, diastereomer (–)-(S)-O-menthyl p-toluenesulfinate **1a** by crystallization from acetone.

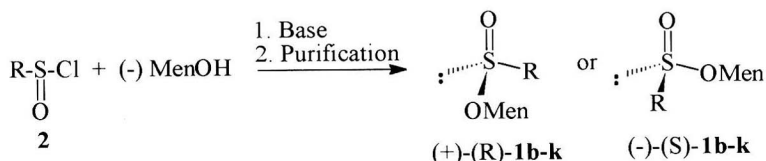


Scheme 2.1.1

Because of the importance of (–)-(S)-**1a** as a substrate in the synthesis of other optically active sulfinyl derivatives, a considerable effort has been devoted to improve its synthesis. The most important improvement is based on the observation reported by Herbrandson and Dickerson⁵ as early as 1959 that the addition of hydrogen chloride gas to a mixture of diastereomeric **1a** causes epimerization of the liquid diastereomer (+)-(R)-**1a** to its crystalline epimer (–)-(S)-**1a**. Mioskowski and Solladie⁶, by modifying the conditions of Herbrandson and Dickerson under which diastereomeric sulfinates **1a** undergo epimerization in favor of the less soluble (–)-(S)-**1a** isomer, were able to isolate it in 90% yield. In our laboratory,^{7a} the above-discussed isomerization procedures did not always give fully reproducible results. It has been found that the more consistent results of epimerization of the sulfinates **1a** are observed when the solid diastereomer, once formed, is dissolved in the mother liquid and the crystallization process is repeated. Another modification of the reaction between p-toluenesulfinyl chloride and (–)-menthol, which allows the isolation of the solid (–)-(S)-**1a** diastereomer in a high yield, involves a very rapid addition of the reaction components.⁸

It is obvious that the use of (+)-(1S,2R,5S)-menthol leads to the formation of (+)-(R)-O-menthyl p-toluenesulfinate. Both sulfinates **1a** with the opposite configuration at the sulfinyl sulfur atom are now commercially available.

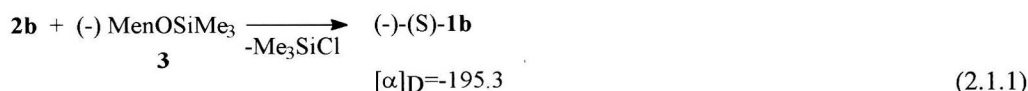
The Phillips approach to the synthesis of diastereomeric O-menthyl sulfinates is general in scope and a great number of other diastereomeric sulfinates **1b–k** were prepared in a similar way starting from the appropriate sulfinyl chlorides **2b–2k** (Scheme 2.1.2).



Sulfinyl chloride 2		Sulfinic ester 1			
No	R	No	$[\alpha]_{589}$	Abs.conf.	de
b	Ph	b	–206.1	S	100
c	p-MeOC ₆ H ₄	c	–189.1	S	100
d	p-ClC ₆ H ₄	d	–181.1	S	100
e	p-IC ₆ H ₄	e	–145.8	S	100
f	1-C ₁₀ H ₇	f	–433.2	S	100
g	PhCH ₂	g	+105.0	R	90.5
g	PhCH ₂	g	+123.0	R	100
h	Me	h	–99.1	R	13
i	n-Bu	i	+50.0	R	47
k	2-MeO-C ₁₀ H ₆	k	–183.0	S	100

Scheme 2.1.2

It should be noted that (–)-(S)-O-menthyl benzenesulfinate-**1b** was also prepared from benzene-sulfinyl chloride **2b** and 1-menthoxytrimethylsilane **3** in 91% yield (Equation 2.1.1).¹⁵



The *in situ* reduction of commonly available sulfonyl chlorides **4** with trimethyl phosphite in the presence of (–)-menthol was found to be a simple method for the preparation of diastereomeric O-menthyl sulfinates **1**, especially those for which there are no readily available sulfinyl chloride