A General Route to Enantiomerically Pure Sulfoxides from a Chiral Sulfite†

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Enantiomerically pure cyclic chiral sulfite (*S*)-7 (trans stereochemistry) has been easily obtained in two steps from (*S*)-ethyl lactate. This compound was found to react cleanly with many organometallics to give crystalline sulfinates with high regioselectivity (>90:10). Addition of a second organometallic transforms the purified sulfinate in excellent yield into a chiral sulfoxide (100% ee) of predictable absolute configuration. The mechanism and scope of this approach are discussed. This method completes the various other methods of preparation of chiral sulfoxides and is especially convenient for the preparation of *tert*-butyl sulfoxides. Examples for the synthesis of many chiral *tert*-butyl sulfoxides are given. The case of chiral sulfites derived from a C_2 diol or of a chiral monoalcohol is also proposed as a route to chiral sulfinates, and some promising preliminary results have been obtained. The general main routes to obtain chiral sulfoxides from sulfites are also discussed.

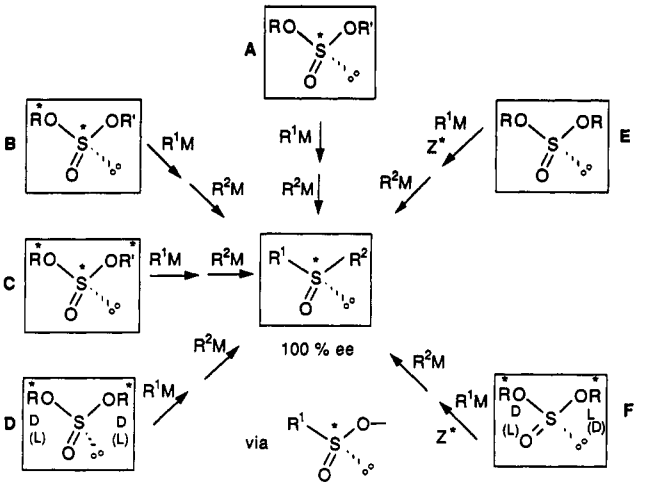
Introduction

Chiral sulfoxides are useful auxiliaries in asymmetric synthesis.[1-8] The preparation of chiral sulfoxides with high enantiomeric excess is still of great interest. They are potentially of interest in the field of biology and in material science, for example, in the synthesis of liquid crystals with ferroelectric properties.[9] The known methods for their preparation (excluding resolution) can be divided into two classes.

The first is the widely used *Andersen method*.[10] It is based on the conversion of chiral sulfinates into sulfoxides with various types of organometallics. The reaction occurs with full inversion of configuration at sulfur.[11] The starting sulfinate is usually obtained from a chiral alcohol as a mixture of epimers at sulfur which have to be separated. A convenient crystalline sulfinate to use is $(R)_S$-(1*R*)-menthyl *p*-tolyl sulfinate because crystallization can be combined with epimerization at sulfur (catalyzed by HCl).[2] Both enantiomers are now available (Aldrich), thus making very easy the synthesis of various *p*-tolyl sulfoxides. This method has also been applied to the synthesis of menthyl (4-chlorophenyl)sulfinate.[12] Although some other routes are described for the synthesis of diastereomerically pure alkylsulfinates,[13] yields are too low for large-scale preparations of chiral sulfoxides.

The second method is the *asymmetric oxidation of sulfides* and has been efficiently employed in some specific cases. *Chiral sulfides* can be prepared from *natural compounds* such as camphor. Oxidation of *m*-PCBA when controlled by the chiral backbone affords one diastereomer.[14,15] The chiral sulfoxide has a limitation in its structure; one group necessarily derives from the natural product. The sulfoxide structure can be rendered more flexible by asymmetric oxidation of *prochiral sulfides*, and enzymatic oxidation is sometimes highly enantioselective.[16] Also, the action of some oxidants in presence of various modifiers of the Sharpless reagent[19-21] is very efficient. We have developed a reagent ($Ti(OiPr)_4$/(+)-DET/H_2O = 1:2:1) that leads to asymmetric oxidation of sulfides such as aryl-S-CH_3 with ee up to 95-96%.[19,20,22-27] Unfortunately, the method is less spectacular for the synthesis of dialkyl sulfoxides (ee < 80%). Oxidation with hydroperoxides in the presence of BSA[28] (ee's up to 90%) or with some chiral oxaziridines[29] is efficient (ee's up to 96%) but not sufficiently general and not always easy to perform on a large scale.

Scheme I. Various Possibilities of Conversion of Sulfites into Chiral Sulfoxides



In what follows we propose a new approach for the synthesis of various classes of enantiomerically pure sul-

† This paper is dedicated to Professor J. K. Stille, who died in 1989.

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foxides, especially sulfoxides bearing two alkyl groups. This synthesis is based on the use of chiral sulfite 7 as a starting material.

Conversion of Sulfites into Chiral Sulfoxides

Sulfites are compounds that have been known for a long time (their chemistry has been reviewed in 1963 by Van Woerden[30] and more recent information is found in ref 31, for example). It was demonstrated in 1952 for the first time that sulfur in sulfites can be a stereogenic center due to its stable tetrahedral geometry allowing separation of epimeric steroidal cyclic sulfites.[32] Since then, many cyclic sulfites with a stereogenic sulfur have been prepared, especially with five- or six-membered rings; for example, see refs 33 and 34.

The usual starting material for sulfite chemistry is thionyl chloride, a low-cost sulfur compound. It can react with an alcohol to be converted into a chlorosulfite and then into a sulfite.

Conversion of sulfites to chiral sulfoxides R^1–S(O)–R^2 needs two consecutive substitution reactions at sulfur that introduce R^1 and R^2 groups. At some point, it is necessary also to make use of a source of chirality. In Scheme I are analyzed all the possibilities for the conversion of a sulfite into a chiral sulfoxide. This general classification will be briefly commented on. In our analysis, it will be assumed as usual that nucleophilic substitution at sulfur occurs with full inversion of configuration.[4,11] Different structural types of sulfites can be envisaged as starting material. The first substitution by organometallics R^1M provides a sulfinate R^1–S(O)–OR if one can avoid further transformation into symmetrical sulfoxides R^1–S(O)–R^1. In order that the synthetic method becomes useful, it is also necessary that at this stage an asymmetric sulfur is created with high stereoselectivity. The subsequent step, e.g., the action of organometallic R^2M on sulfinate R^1–S(O)–OR, should provide the final sulfoxide R^1–S(O)–R^2 as is the case with the Andersen method.[10] Scheme I shows the main reactions allowing the transformation of a sulfite into a chiral sulfoxide. Sulfite A is already chiral at sulfur. If the chemical reactivity of OR and OR' groups are sufficiently different, one expects a transfer of chirality leading to a chiral sulfinate. In sulfite C there is also already an asymmetric sulfur but the two different leaving groups are chiral, and in the intermediate situation B there is one chiral and one achiral leaving group. In sulfite D the two chiral leaving groups are chemically equivalent with the same absolute configuration; however, due to the tetrahedral geometry at sulfur they are not related by a symmetry operation (mirror or axis). They have diastereotopic relationships[35] and should have different reactivities in the presence of an achiral reagent such as R^1M. In E and F cases, one cannot expect any discrimination between the leaving groups since sulfites are achiral (symmetry plane). These compounds have two enantiotopic leaving groups. Stereoselective monosubstitution should occur in principle if one combines an organometallic reagent R^1M with a chiral auxiliary Z* (acting as a coreagent or as a catalyst).

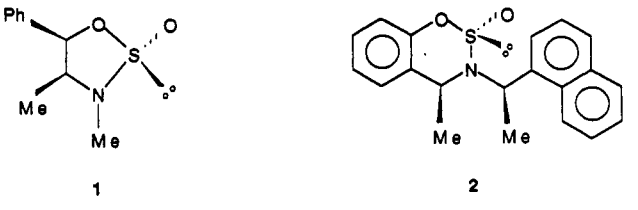

Figure 1. Aminosulfites.

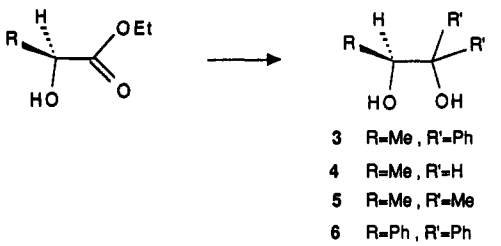

Figure 2. Preparation of various chiral diols from ethyl lactate.

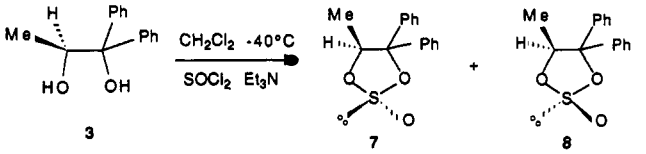

Figure 3. Synthesis of cyclic sulfites *trans*-7 + *cis*-8.

In conclusion, the various approaches (A–F) described in Scheme I need to fulfill four conditions: (i) easy synthesis of the starting sulfites having the right stereochemical features; (ii) high yield in sulfinates at the first nucleophilic substitution (avoiding competitive formation of R^1–S(O)–R^1); (iii) high regioselectivity, diastereoselectivity, or enantioselectivity during the first step leading to a sulfinate; and (iv) high stereospecificity for each substitution reaction.

We decided to explore the various possibilities offered by Scheme I, and we present here some of our results. First, we concentrated our efforts on case B, which represents a chiral sulfite with two different leaving groups (for a preliminary report see ref 36). We also started to investigate case D where the chiral leaving group is derived from the same chiral alcohol. This will be developed in the following sections, following a brief report of the relevant earlier literature.

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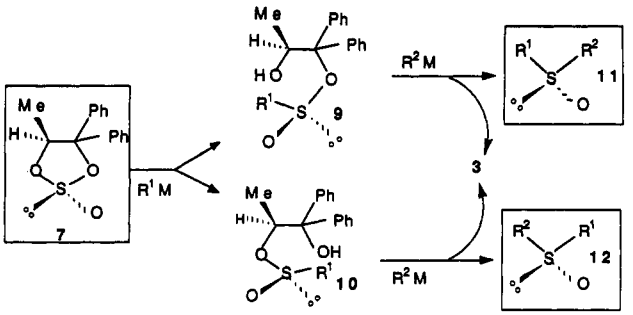

Figure 4. Pathways for obtention of sulfoxides from sulfite *trans*-7.

Early Reports on the Use of Sulfites and Related Compounds in Asymmetric Synthesis. Mikolaczyk and Drabowicz discovered that tertiary-alkylmagnesium halides are able to transform symmetrical sulfites into tertiary-alkylsulfinates.[37] In 1988, these authors modified the experimental conditions and obtained chiral sulfinates (ee's up to 70%) by addition of alkaloids.[38] This asymmetric synthesis corresponds to case E in Scheme I. Cases B or C are unknown in literature, but a related process has been described for aminosulfites 1 and 2 by Wudl and Lee[39] and by Hiroi et al.,[40] respectively. In these examples the S–O bond is cleaved rather than the S–N bond (Figure 1).

Preparation of a Chiral Sulfite. We decided to study class B or C of Scheme I by trying to create an asymmetric sulfur under the influence of a chiral auxiliary (alkoxy group OR*). We also planned to prepare a cyclic sulfite expecting an enhancement of stereoselectivity and regioselectivity at the various stages of the process leading ultimately to chiral sulfoxides. We envisaged to synthesize five-membered cyclic sulfites deriving from the most easily available chiral 1,2-diols such as **3**–**6**, lactic acid being one of the cheapest chiral compounds. Various chiral diols have been prepared from ethyl lactate by addition of a Grignard reagent (Figure 2).[41]

We selected the diol **3**[41,42] (prepared in 1 mol scale in 75% yield) for the synthesis of cyclic sulfite (Figure 3).

The traditional procedure was used to synthesize the chiral sulfite (thionyl chloride, triethylamine).[30] The reaction was not stereoselective and gave a 1:1 mixture of cis and trans sulfites (reaction performed at room temperature with slow addition of thionyl chloride to diol **3** and triethylamine dissolved in methylene chloride). It was satisfying to determine the experimental conditions giving a large preference (90:10) for one diastereomer **7** (trans stereochemistry, see below). This was obtained stereochemically pure in 70% yield after crystallization in hexane. The improved procedure involves an inverse addition of reactants, e.g., slow addition at −40 °C of triethylamine into a methylene chloride solution of diol **3** and thionyl chloride. Cyclic sulfite **7** is a stable compound that can be stored for a long time. It contains a stereogenic sulfur in a chiral molecule and represented a promising starting material for our project.

Reactivity of Cyclic Sulfite 7 toward Organometallics. In order to transfer efficiently the chirality from sulfur of **7** into a sulfoxide **11** or **12** (Figure 4), it was necessary to overcome several difficulties:

(i) The first organometallics R^1M should avoid overeaction on intermediate sulfinate (with formation of R^1–S(O)–R^1).

(ii) Sulfinate must be generated by a regioselective cleavage involving only one of the two potential leaving groups (formation of either **9** or **10**).

(iii) The substitution reactions at sulfur should occur with the highest possible stereospecificity (most probably inversion, as found in many sulfur compounds[4,11]).

We were encouraged by the report of Mikolaczyk and Drabowicz[37] to start our experiments by using *tert*-butylmagnesium halides. We expected a good yield of sulfinate. Indeed, we were delighted to get *tert*-butylsulfinate in high yield; moreover, the regioselectivity in the ring cleavage is excellent (90:10), affording mainly sulfinate **10** (R^1 = *tert*-Bu). This pure sulfinate has been obtained in 70% yield after crystallization. The structures of isomeric sulfinates **9** (R^1 = *t*-Bu) and **10** (R^1 = *t*-Bu) were established by ^{1}H NMR, H and Me at asymmetric center being significantly deshielded in **10** by respect to **9** (Table I).

The large difference in chemical shifts also allows one to evaluate by ^{1}H NMR the ratio **10**:**9** on the crude product (prior to crystallization). The *tert*-butylsulfinate **10** (R^1 = *t*-Bu) is obtained devoid of its epimer at sulfur. This epimeric compound **13** was prepared by the action of *t*-BuMgCl on cis sulfite **8** and was isolated as a pure material

Table I. ^{1}H NMR of Sulfinates 9, 10, 13, and 14

entry[a]	sulfinate	H on asymmetric center	Me on asymmetric center
1	**9** (R^1 = Me)	4.80	1.15
	10 (R^1 = Me)	5.15	1.40
2	**9** (R^1 = Et)	4.95	1.05
	10 (R^1 = Et)	5.35	1.35
3	**9** (R^1 = *n*-octyl)	4.85	1.05
	10 (R^1 = *n*-octyl)	5.45	1.35
4[b]	**9** (R^1 = benzyl)	4.70	1.05
	10 (R^1 = benzyl)	5.30	1.35
5[c]	**9** (R^1 = vinyl)	4.95	1.10
	10 (R^1 = vinyl)	5.20	1.45
6	**9** (R^1 = *t*-Bu)	4.70	1.20
	10 (R^1 = *t*-Bu)	5.40	1.35
7	**9** (R^1 = mesityl)	4.85	1.15
	10 (R^1 = mesityl)	5.45	1.40
8	**13** (R^1 = *t*-Bu)	5.25	1.25
	14 (R^1 = *t*-Bu)	4.70	1.20

[a] Spectra run in $CDCl_3$, unless otherwise stated. [b] In CD_3COCD_3. [c] In CD_3CN.

Table II. Synthesis of Chiral Sulfinates 9 or 10 from Sulfite 7 (Scheme III)

entry	R^1M[a]	9/10 ratio[b]	isolated yield[c] (%) of pure sulfinate
1	MeLi	75/25	55 **9** (R^1 = Me)
2	MeMgI	80/20	70 **9** (R^1 = Me)
3	EtMgBr	92/9	80 **9** (R^1 = Et)
4	*n*-OctMgBr	95/5	60 **9** (R^1 = *n*-octyl)
5	*t*-BuMgBr	5/95	60 **10** (R^1 = *t*-Bu)
6	*t*-BuMgCl	10/90	70 **10** (R^1 = *t*-Bu)
7	*t*-BuLi		*d*
8	BnMgCl	70/30	50 **9** (R^1 = CH_2Ph)
9	BnMgBr	55/45	*e*
10	HC≡CHMgCl	95/5	50 **9** (R^1 = vinyl)
11	MesMgBr	12/88	70 **10** (R^1 = mesityl)
12	PhMgBr	50/50	*e*

[a] Reaction performed in THF at −78 °C (except entry 5, 25 °C) with 1 equiv of R^1M. [b] Measured by ^{1}H NMR on the crude product. [c] Purification by crystallization. [d] Di-*tert*-butyl sulfoxide is obtained. [e] Separation of the two isomeric sulfinates by crystallization failed.

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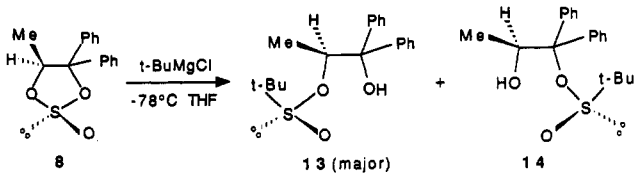


Figure 5. Obtention of sulfinates from sulfite *cis*-8.

after crystallization from the crude product (13:14 = 90:10). ^{1}H NMR of epimeric sulfinates **10** (R^1 = *t*-Bu) and **13** (R^1 = *t*-Bu) are different. However, we never detected **13** by ^{1}H NMR when preparing **10** (R^1 = *t*-Bu); similarly, **10** (R^1 = *t*-Bu) was absent in crude **13** (R^1 = *t*-Bu). These observations establish that the substitution reaction at sulfur in cyclic sulfites **7** or **8** occurs with a very high degree of stereoselectivity (>98%). This conclusion seems also to hold for reaction of **7** with all the organometallic reagents that were later used (Table II).

In order to keep the possibility of stopping the reaction at the sulfinate stage, we tried another bulky reagent, namely mesitylmagnesium bromide. Indeed, the yield is excellent (90%), with preferential formation of sulfinate **10** (R^1 = mesityl) (**10:9** = 88:12). Pure sulfinate **10** (R^1 = mesityl) is isolated in 65% overall yield after crystallization. The sulfinates **10** (R^1 = *t*-Bu or mesityl) are stable compounds, easy to store, and excellent precursors in asymmetric synthesis of many sulfoxides as it will be detailed in the next paragraph.

The next step in the investigation of the conversion of sulfite **7** into sulfinates was to consider the use of nonbulky organometallics, namely R^1M where R^1 is a linear alkyl. Large amounts of byproduct R^1–S(O)–R^1 should be expected if one refers to the behavior of acyclic sulfites.[37] We found that linear alkyl or vinyl Grignard reagents (R^1 = Et, *n*-octyl, or vinyl) give in excellent yields the corresponding sulfinates and no formation of symmetrical sulfoxides. Surprisingly, these Grignard reagents led with high selectivity (>90:10) to the alternate sulfinates **9** (R^1 = Et, *n*-octyl or vinyl). MeMgI is less regioselective (80:20). Structure **9** has been established by ^{1}H NMR (Table I). Up to now all the sulfinates **9** or **10** have been isolated as crystalline compounds that are easy to obtain chemically and stereochemically pure by crystallization in good yields (60–80%). Results concerning synthesis of sulfinates are listed in Table II. Sulfinates **9** cannot be stored at room temperature, by contrast with **10**, presumably because of some instability induced by the vicinity of a sulfite function and a benzylic carbon atom. Crystalline sulfinates **9** decomposed at room temperature (within 10 mins to a few days according to the structure), forming diphenylacetone. R^1–S(O)–O– group seems to play the role of a leaving group giving a stabilized carbocation precursor of diphenylacetone.[43] A typical procedure for avoiding the decomposition of sulfinates **9** is to store the recrystallized sulfinates at −20 °C. In those conditions the compounds can be kept for several weeks.

A mixture of sulfinates **9** and **10** (70:30 to 50:50) is produced by the reaction of some reagents such as $PhCH_2MgCl$, $PhCH_2MgBr$, or PhMgBr. The usual experimental conditions for the preparation of sulfinates **9** or **10** is to allow sulfite **7** to react with R^1MgX in THF at −78 °C. Organolithium reagents are less regioselective and sometimes afford symmetrical sulfoxides R^1–S(O)–R^1. By looking at the above data (see also Table II), one concludes that when R^1 is bulky the regioselective cleavage mainly gives sulfinate **10**, while when R^1 is small the sulfinate **9** is the major product. A gratifying behavior of cyclic sulfite **7** is its ability to react with all kinds of Grignard reagents giving sulfinates and not symmetrical sulfoxides, at the difference of acyclic sulfites.[37] This could be related to an increased reactivity of five-membered cyclic sulfites with respect to their open analogues.[44-46]

Table III. Synthesis of Enantiomerically Pure Sulfoxides 11 or 12 from Sulfinate 9 or 10 and Organometallic R^2M

entry	sulfinate[a]	R^2M[b]	temp (°C)	R^1–S(O)–R^2 ee[c] (%)	config
1	**10** (R^1 = *t*-Bu)	MeLi[d]	25	100	*R*
2	**10** (R^1 = *t*-Bu)	PhLi[d]	25	100	*S*
3	**10** (R^1 = *t*-Bu)	*n*-BuLi[d]	25	100	*R*
4	**10** (R^1 = *t*-Bu)	H_2C=$CHMgCl$[d]	25	100	*R*
5	**10** (R^1 = *t*-Bu)	1-[(2-CH_2)C_5H_4N]Li[e]	−72	100	*R*[f]
6	**10** (R^1 = *t*-Bu)	$PhCH_2MgBr$[e]	25	100	*R*
7	**10** (R^1 = *t*-Bu)	$Ph(CH_2)_2MgBr$[e]	25	100	*R*
8	**10** (R^1 = mesityl)	MeLi[d]	0	100	*R*
9	**10** (R^1 = mesityl)	PhMgBr[e]	0	100	*R*
10	**9** (R^1 = Me)	*n*-OctMgBr[e]	0	100	*R*
11	**9** (R^1 = Et)	PhLi[e]	0	100	*R*
12	**9** (R^1 = Et)	$PhCH_2MgBr$[e]	25	100	*R*
13	**9** (R^1 = *n*-octyl)	MeMgI[e]	25	100	*S*
14	**9** (R^1 = $PhCH_2$)	EtMgBr[e]	0	100	*S*

[a] Stereochemically pure **9** or **10** prepared from **7**. Sulfoxides **11** and **12** are derived from sulfinates **9** and **10**, respectively (see Figure 4). [b] Quantitative yield after isolation of product by flash chromatography. [c] Measured by ^{1}H NMR with Eu(hfc)$_3$ or (*R*)-(3,5-dinitrobenzoyl)-1-phenylethylamine[47] and by comparison with maximum specific rotation (see Table IV). [d] Procedure 1 (addition of R^2M on sulfinate), see Experimental Section. [e] Procedure 2 (addition of sulfinate on R^2M), see Experimental Section. [f] Reference 64.

Transformation of Sulfinates 9 or 10 into Chiral Sulfoxides 11 or 12. In principle, the path from sulfinates **9** and **10** to chiral sulfoxides should not present major difficulties since it corresponds to a conversion widely used in the Andersen method.[10] As in the Andersen method, one expects inversion of configuration during the substitution step.[11] One special feature of **9** or **10** is the presence of an hydroxyl group, which will be transformed into an alcoholate by reaction with 1 equiv of organometallic reagent. By using 2 molar equiv of various organometallics in THF at room temperature of 0 °C the expected sulfoxides **11** or **12** were produced and isolated *in quantitative yield* by flash chromatography (Table III). Grignard reagents or organolithiums are equally suitable for the reaction. In all the investigated cases it has been found that the recovered *sulfoxides are enantiomerically pure.* The ee's were measured by ^{1}H NMR using Eu(hfc)$_3$ as chiral shift reagent or (3,5-dinitrobenozyl)-1-phenylethylamine as chiral solvating reagent[47] and by specific rotation of a purified sample.[48] The absolute configuration of some of the final sulfoxides was known (e.g., Table IV), allowing us to assign absolute configuration at the sulfur of sulfinate (as indicated in **9** and **10**, Scheme II). These

(43) The ease of benzylsulfinates to generate a carbocation is known: Braverman, S.; Duar, Y. *Tetrahedron* **1990**, *46*, 2975.

(44) It has been established that cyclic sulfites with a five-membered ring hydrolyze in base faster than do acyclic analogues.[45]

(45) (a) Brestow, P. A.; Tillet, J. G.; Wiggins, D. E. *J. Chem. Soc. B* **1968**, 1360. (b) Kaiser, E. T.; Panar, M.; Westheimer, F. H. *J. Am. Chem. Soc.* **1963**, *85*, 602.

(46) We are currently checking the possibility to use the cyclic sulfite derived of achiral glycols for sulfinate preparation.

(47) Deshmukh, M. N.; Dunach, E.; Juge, S.; Kagan, H. B. *Tetrahedron Lett.* **1984**, *25*, 3467; Erratum: Ibid. **1985**, *26*, 402.

(48) We checked that there is not change in ee during the purification of sulfoxides by flash chromatography on silica gel. Chromatography on achiral phase of some partially resolved compounds can give fractions with different ee's.[49,50]

(49) Charles, R.; Gil-Av, E. *J. Chromatogr.* **1984**, *298*, 516.

(50) Tsai, W. L.; Hermann, K.; Hug, B.; Rohde; B.; Dreiding, A. *Helv. Chim. Acta* **1985**, *68*, 2238.

Table IV. Absolute Configuration of Sulfoxides Prepared in Table III

sulfinate	sulfoxide R^1-S(O)-R^2	conf[a]	$[\alpha]_D$	lit conf	lit $[\alpha]_D$	lit ref
10 (R^1 = *t*-Bu)	*t*-Bu-S(O)-Me	*R*	−10.5, $CHCl_3$	*R*	−10, $CHCl_3$	20
			−3.6, acetone	*R*	−4.2, acetone	62
10 (R^1 = *t*-Bu)	*t*-Bu-S(O)-Ph	*S*	−175, $CHCl_3$	*R*	175, $CHCl_3$	38
10 (R^1 = *t*-Bu)	*t*-Bu-S(O)-*n*-Bu	*R*	125, acetone	*S*[b]	125, acetone	63
10 (R^1 = *t*-Bu)	*t*-Bu-S(O)-CH=CH_2	*R*	283, acetone			
10 (R^1 = *t*-Bu)	*t*-Bu-S(O)-[(2-CH_2)C_5H_4N]	*R*	304, acetone			64
10 (R^1 = *t*-Bu)	*t*-Bu-S(O)-Bn	*R*	279, EtOH	*R*	280, EtOH	65
10 (R^1 = *t*-Bu)	*g*-Bu-S(O)-CH_2CH_2Ph	*R*	95, $CHCl_3$	*R*	26, $CHCl_3$	66
10 (R^1 = Mes)	Mes-S(O)-Me	*R*	45, EtOH	*R*	43, isooctane	11
9 (R^1 = Mes)	Mes-S(O)-Ph	*R*	256, acetone		203, acetone	67
9 (R^1 = Me)	Me-S(O)-*n*-Oct	*R*	−63, acetone	*R*	−62, acetone	20
9 (R^1 = Et)	Et-S(O)-Ph	*R*	176, EtOH	*R*	177, EtOH	61
9 (R^1 = Et)	Et-S(O)-Bn	*R*	105, $CHCl_3$	*R*	106, $CHCl_3$	61
9 (R^1 = *n*-oct)	*N*-Oct-S(O)-Me	*S*	62.5, acetone	*R*	−62, acetone	20
9 (R^1 = Bn)	Bn-S(O)-Et	*S*	−105, $CHCl_3$	*R*	106, $CHCl_3$	61

[a] Absolute configuration deduced from the synthetic scheme (Figure 4) involving two consecutive inversions of configuration. [b] It is the only discrepancy between absolute configuration deduced by our method and data of literature.

assignments are based assuming inversion of configuration during the substitution step. As expected from Figure 3, sulfinates **9** lead to enantiomerically pure (ep)[51] sulfoxides **11** (e.g., R = ethyl phenyl sulfoxide) while sulfinate **10** gives enantiomerically pure sulfoxides **12** enantiomers of **11** (e.g., (*S*)-*tert*-butyl phenyl sulfoxide). In all cases, the unchanged chiral auxiliary diol **3** is recovered in quantitative yield, allowing regeneration of chiral sulfite **7**.

Synthesis of Each Enantiomer of a Given Sulfoxide. (*S*)-Lactic acid (and its derivatives) is the enantiomer that is commercially available. It was therefore important to devise a process starting from cyclic sulfite (*S*)-**7** that will generate each enantiomer of a sulfoxide. A simple way is to permute R^1 and R^2 in organometallics involved in the two substitution steps. This has been realized in the synthesis of methyl *n*-octyl sulfoxide. The route involving the sequence MeMgI and *n*-octylMgBr gave enantiomerically pure *R* sulfoxide **11** (R^1 = Me, R^2 = *n*-octyl), while the alternate sequence *n*-octylMgBr and MeMgI afforded ep *S* sulfoxide **12** (R^1 = *n*-octyl, R^2 = Me). Similarly, (*S*)- or (*R*)-benzyl ethyl sulfoxide has been obtained from benzylsulfinate **9** (entry 8, Table II) or ethylsulfinate **9** (entry 3, Table II) by addition of EtMgBr (entry 14, Table III) or $PhCH_2MgBr$ (entry 12, Table III), respectively. The method should apply in all cases where R^1 and R^2 are both small groups (as in the previous example) or bulky groups (e.g., *t*-Bu or mesityl). Unfortunately, if one group is bulky and the other small (e.g., *t*-Bu and Me), the groups permutation will necessarily lead to the same *R* sulfoxide, since the inversion in the order of introduction of the groups is "on offset" by the change in the side cleavage of sulfite **7** during the sulfinate synthesis.

Fortunately, (*R*)-isobutyl lactate has been recently marketed (Fluka). *R* Diol is easily derived from that ester, giving access to the enantiomer of sulfite **7** and then to sulfoxides **11** or **12** (R^1 small and R^2 bulky).

In conclusion, we set up conditions for the synthesis of the desired enantiomer of a given sulfoxide. A wide variety of sulfoxides is now available by this approach, the only drawback being the low chemical yield observed where some organometallics (like PhMgBr) react with **7**, giving mixtures of sulfinates **9** and **10** in a ratio close to 1:1.

Stereochemistry of Sulfite 7 and Sulfinates 9 and 10. As shown above, all the substitution steps are highly stereospecific, allowing excellent transfer of chirality from sulfite **7** to sulfoxide **11** or **12**. The purification of intermediate sulfinate involves removal of the minor constitutional isomer, which also has opposite absolute configuration at sulfur (Figure 4). This is a key operation to get ep sulfoxides. A one-pot synthesis of ethyl phenyl sulfoxide has been performed without isolation of sulfinate. The sequential addition at −78 °C of EtMgBr followed by PhLi transformed sulfite **7** into (*R*)-ethyl phenyl sulfoxide **11** of 85% ee. The addition of EtMgBr produces sulfinates **9** and **10** (R = Et) in the ratio 92:8. Isolation of pure **9** (R = Et) (60% yield) and further reaction with PhLi gives (*R*)-ethyl phenyl sulfoxide **11** of 100% ee. Comparisons of the data are in excellent agreement with a full stereospecificity at each substitution step. If one retains the hypothesis of inversion of stereochemistry,[4,11] and taking into account the known absolute configuration of sulfoxides **11** or **12** generated from sulfinates **9** and **10**, respectively, one concludes that cyclic sulfite **7** (major epimer) has the trans stereochemistry (configuration R_S). Sulfinates **9** and **10** should have R_S and S_S configurations, respectively.

Since trans stereochemistry in sulfide **7** has been obtained by an indirect way it was necessary to confirm this assignment. ^1H NMR of epimeric sulfites **7** and **8** don't show significant differences allowing the assignment of their relative configuration. However, sulfite **7** gave monocrystals suitable for a X-ray crystallographic study (for a preliminary report see ref 54). Sulfite **7** has a trans stereochemistry. The structural information is available in the auxiliary material. The five-membered ring has a distorted twist conformation with the sulfinyl group having a pseudoaxial orientation. The S–O–S angle is 93°.

The X-ray structure of **7** confirms the assignment of configuration at sulfur in sulfinates **9** and **10** if one assumes that the two consecutive substitutions likely occur with inversion of stereochemistry.[55,56] It was interesting to establish directly at least in one case the stereochemistry at sulfur in a sulfinate. Single-crystal X-ray structure of *tert*-butyl sulfinate **10** (R^1 = *t*-Bu) could be realized (see auxiliary materials for details). The stereochemistry at

(51) We prefer to use the expression enantiomerically pure (ep) as previously proposed by Seebach[52] instead of homochiral, which can have several meanings.[53]

(52) Seebach, D.; Hungerbühler, E. *Mod. Synth. Methods* **1980**, 93.

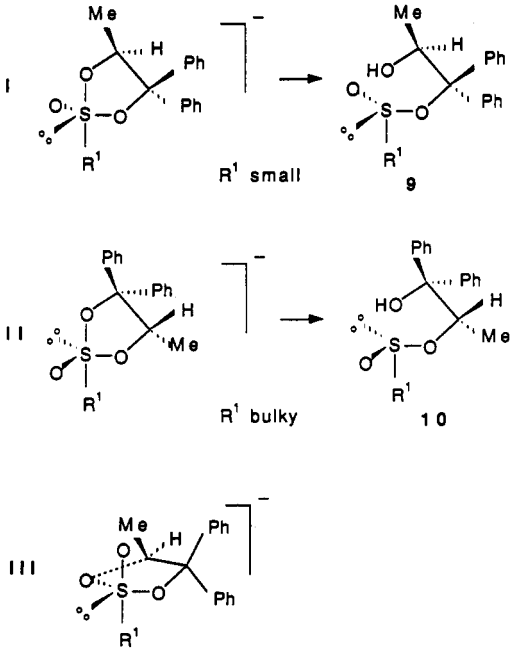
(53) Eliel, E.; Wilen, S. *Chem. Eng. News* **1990**, *10*, 2.

(54) Ricard, L.; Rebiere, F.; Kagan, H. B. *C. R. Acad. Sci. Paris*, Ser. II **1991**, *312*, 225.

(55) Two consecutive substitutions with retention will also correlate absolute configuration at sulfur in **7** and absolute configuration of sulfoxides **9** and **10**. This scenario could not be immediately rejected because of the presence of a five-membered ring in **7** and a γ-alcoholate moiety during the second substitution at sulfur.

(56) A tandem inversion–retention (or vice-versa) is very unlikely unless an additional step is introduced by transfer of sulfinyl from one oxygen to the other one in sulfinate during reaction with R^2M.

Scheme II. Trigonal Bipyramidal Transition States or Intermediates



sulfur is *S* in this compound in full agreement with the hypothesis of inversion of configuration at each substitution step.

Sulfinate **9** (R = *t*-Bu) (100% de) has also been treated by 1 equiv of *t*-BuMgCl at room temperature for 1 h (formation of alcoholate). The recovered material after hydrolysis was pure **9** (R = *t*-Bu) devoid of a trace of its diastereomer **10**. This shows that the diastereomer ratio 95:5 to 90:10 observed in the synthesis of **9** (R = *t*-Bu) (Table II) is not the result of an equilibration by sulfinyl transfer from one oxygen to the other. An equilibration is also unlikely when **9** is transformed into sulfoxides **11**, although in that case it becomes immaterial if the intramolecular migration occurs with retention of configuration.

Regioselectivity in the Cleavage of Cyclic Sulfite 7. We propose to interpret the selective synthesis of either sulfinate **9** or **10** by the formation of a trigonal bipyramidal transition state or intermediate (I or II, Scheme II). In I, the bulky group (O–CPh_2) placed itself in the equatorial position. In this species, the incoming and leaving groups are both in apical positions and the ring cleavage in sulfite **7** will occur giving a secondary alcohol and hence sulfinate **9**. When the incoming nucleophile is bulky it will severely interact with the O–CPh_2 moiety linked to equatorial oxygen. The alternate structure II where the O–CPh_2 is apical becomes favored, and as a consequence the alternate sulfinate **10** will be produced. There is a good qualitative agreement between experimental data and the above picture; however, it is difficult to define the borderline cases giving a mixture of sulfinates. Structures I and II are not the lone trigonal bipyramids, allowing the discussion of the regioselective cleavage of **7**. One can evisage structure III where there has been apical entrance of the R^1 group anti to oxygen of the S(O) group. Pseudorotation is then required in order to place one of the two oxygens of the alkoxy group in apical position (anti to S(O)) before opening of the five-membered ring. We do not favor structure III because the O–S–O angle in sulfite **7** (93°) is ideal to initiate the substitution reaction through I or II.

Origin of the Diastereoselective Formation of Trans Sulfite 7. It was very fortunate that sulfite **7** could

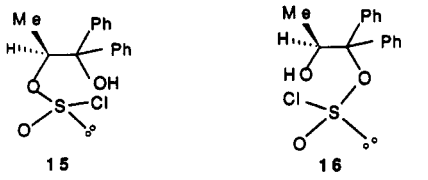
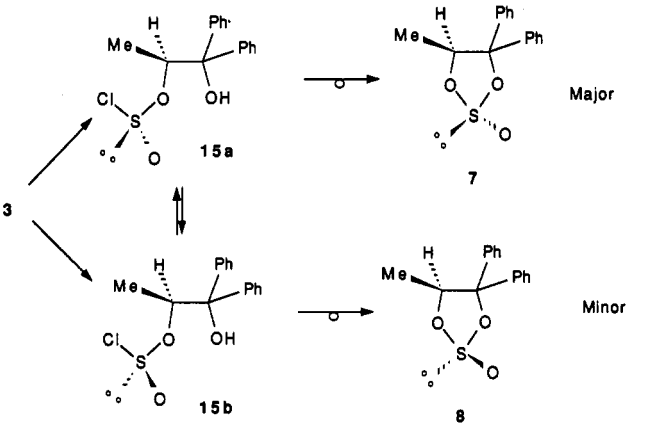


Figure 6. Chlorosulfite intermediates involved in sulfite formation.

Scheme III. Possible Mechanisms for the Formation of *trans*-7 Sulfite



be prepared in high yield from diol **3** (7:8 = 90:10). The diastereoselective formation of **7** has been achieved in very specific conditions, namely the slow addition of triethylamine into a CH_2Cl_2 solution of diol **3** and thionyl chloride (reaction performed at −40 °C). The reverse addition of thionyl chloride to a solution of **3** and triethylamine leads to a mixture of the two diastereomers (7:8 = 1:1). We checked that the reaction is not under thermodynamic control:pure **7** or **8** does not epimerize in the above conditions (or in presence of some HCl). The sulfite formation involves a chlorosulfite intermediate.[30] In the present case it is reasonable to assume that formation of chlorosulfite **15** is preferred over chlorosulfite **16** because of higher reactivity of the secondary alcohol (Figure 6). The sulfur in **15** is already an asymmetric center.

One can envisage two extreme mechanisms to explain preferred formation of trans sulfite **7**. In the first one, a slow and stereoselective esterification of **3** will provide **15** (as diastereomer **15a**), and then a fast cyclization with inversion of stereochemistry will lead to **7** (Scheme III). The other possibility is to consider that the stereoselective formation of **7** is controlled at the cyclization step by a slow closure of **15a** combined to a fast epimerization equilibrium between **15a** and **15b**. We presently favor this latter hypothesis. The addition of 1 equiv of $Cl^-NBu_4^+$ to the reaction medium prior to the slow addition of triethylamine improves slightly the trans/cis ratio (7:8 = 92:8). This is in agreement with an enhancement rate of the epimerization reaction at sulfur in **15** by nucleophilic attack of chloride ions.[57]

Cyclic Sulfites Derived from Various Chiral Alcohols. It is interesting to compare the ring cleavage of **3** with the ring cleavage of a set of chiral sulfites deriving from various diols. (*S*)-Propane-1,2-diol **4** was converted

(57) It is known that Cl^- catalyzes the interconversion between sulfites and chlorosulfites in presence of thionyl chloride.[58] The competitive formation of an acyclic sulfite of diol **3** (through the secondary hydroxyls) followed by reaction with thionyl chloride is also a route to return to chlorosulfites **15**.

(58) Bartlett, P. D.; Herdbrandson, H. F. *J. Am. Chem. Soc.* **1952**, *74*, 5971.

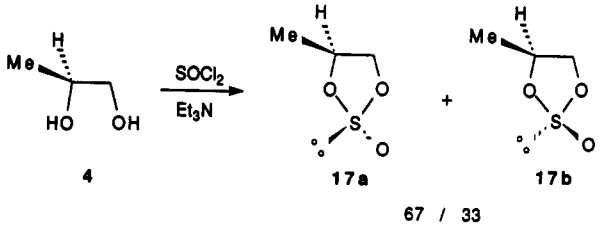


Figure 7. Obtention of cyclic sulfites 17 from (*S*)-propane-1,2-diol (4).

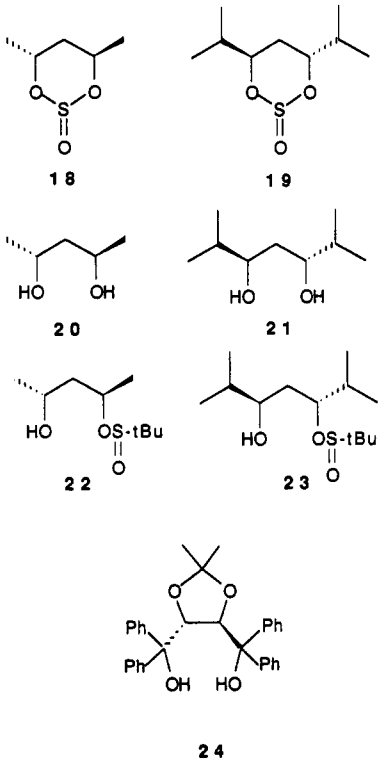


Figure 8. Preparation of sulfites 18 and 19 and sulfinates 22 and 23 from some C_2 symmetry diols.

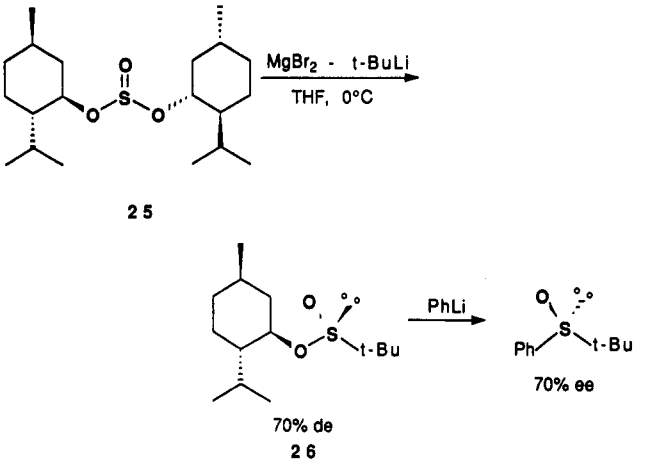
into an oily mixture of sulfites of **17a** and **17b** (67:33), which unfortunately could not be resolved into pure epimers (Figure 7).

Sulfites from diols **6** and **24** could not be prepared. We obtained the chlorohydrin from **24** and a mixture of products from **6**. Sulfites **18** and **19** were synthetized from diols **20** and **21**, respectively.[59] Cyclic sulfites **18** and **19** correspond to class D of Scheme I, where sulfur is not a stereogenic center. The compounds (noncrystalline) are easy to prepare since there is no need of separation of stereoisomers. Sulfites **18**, and **19** were treated by *t*-BuMgCl in THF at room temperature, and then by phenyllithium at the same temperature. *tert*-Butyl phenyl sulfoxide was obtained with 50% ee (*S* configuration) and 75% ee (*R* configuration), respectively. Clearly, cyclic sulfites **18** and **19**, which derive from simple C_2 diols, are not the best candidates for asymmetric synthesis of sulfoxides (Figure 8).

We then investigated acyclic sulfites of class D in Scheme I, e.g., sulfites of enantiomerically pure monoalcohols. Dimenthyl sulfite **25** was prepared from (−)-menthol and isolated as a crystalline and stable compound. We checked its reactivity toward *tert*-butyl organometallics. *t*-BuLi gives only di-*tert*-butyl sulfoxide, and *t*-BuMgBr reacts very slowly at 60 °C and furnishes

(59) We thank Pr A. Tai for a generous gift of chiral diols **23** and **24**.

Scheme IV. Obtention of Menthyl *tert*-Butyl Sulfinate and (*S*)-*tert*-Butyl Phenyl Sulfoxide from Dimenthyl Sulfite



menthyl *tert*-butylsulfinate (0% de). The diastereomeric excess could be measured by ^1H NMR on *t*-Bu signals. We checked then the behavior of a 2:1 mixture of *t*-BuLi and $MgBr_2$. This combination gives an excellent yield of menthyl *tert*-butylsulfinate, when it was prepared by the reaction of Mg and 1,2-dibromoethane in THF followed by addition of 2 equiv of *t*-BuLi. The clean solution transforms dimenthyl sulfite into menthyl *t*-butylsulfinate **26** in excellent yield and 70% de at 0 °C (Scheme IV). This sample was treated by phenyllithium and transformed into (*S*)-*tert*-butyl phenyl sulfoxide (70% ee) in quantitative yield. This is a very promising result for an acyclic chiral sulfite. *S* stereochemistry at sulfur in sulfinate **26** was assigned by assuming inversion of stereochemistry in the step leading to sulfoxide. With the same hypothesis for the conversion of **25** and **26** one concludes that it is the *pro-R* oxygen in sulfite **25** that preferentially departed. We are looking for other types of simple chiral alcohols in order to improve the diastereoselectivity of the reaction. This approach, however, will generate only tertiary-alkylsulfinates as already discussed for acyclic sulfites.[37,38] Indeed, dimenthyl sulfite and various *n*-butyl organometallics always led to di-*n*-butyl sulfoxide.

Conclusion

We investigated in detail the transformation of sulfites into chiral sulfinates and then into enantiomerically pure sulfoxides. The chiral sulfite **7** was selected as the best starting material since it combines several advantages:

(i) It is produced in good yield in two steps from ethyl lactate (50% overall yield in pure *trans*-**7**).

(ii) Organometallic reagents react smoothly with **7** and the reaction stops at the sulfinate stage.

(iii) Up to now, all the isolated sulfinates were crystalline compounds, allowing their easy purification.

(iv) Very often the ring cleavage of cyclic sulfite **7** occurs with a high regioselectivity (90:10) leading to the isolation of a chemically and stereochemically pure sulfinate in good yield.

(v) Transformation of sulfinates is almost quantitative, affording enantiomerically pure sulfoxides with a predictable absolute configuration. Chiral diol **3** can be recovered and reused.

(vi) Enantiomer of **7** is also easy to prepare from commerically available (*R*)-isobutyl lactate.

Many ep sulfoxides have been prepared by our method. We hope to see future applications of this approach in organic synthesis. For example, α-carbanions derived from *tert*-butyl sulfoxides (racemic mixture) were used in highly

stereoselective 1,4-additions on conjugated esters.[60] Enantiomerically pure t-Bu(SO)CH_2Ph and t-Bu(SO)-$(CH_2)_2$Ph were prepared by us (entries 6 and 7, Table III); this should extend the scope of the reactions described in ref 60. Various types of chiral sulfoxides that are not attainable by asymmetric oxidation of sulfides may now be synthetized as diaryl sulfoxides (e.g. mesityl phenyl sulfoxide, entry 9, Table III) or sulfoxides with similar chains (e.g., n-heptyl n-octyl sulfoxide). Dialkyl sulfoxides are not easy to synthesize by the Andersen method or by asymmetric oxidation; in contrast, sulfite 7 is an excellent starting material for that purpose.

Most of the stereochemical problems associated with the present work have been solved, namely stereochemistry of the chiral sulfite 7 and of the intermediate sulfinate (9 or 10). As discussed above, the method has some limitations in terms of structure of the sulfoxide; nevertheless, as it stands at the moment it already appears to be a useful complement to existing routes to chiral sulfoxides.[2-4,61] We are currently working on the extension of the scope of the reaction (e.g., synthesis of functionnalized sulfoxides, one-pot process on sulfite 7, ...) and on the exploration of the various facets of sulfite chemistry as a route to ep sulfinates, sulfoxides, and derivatives.

Experimental Section

Materials and General Methods. ^1H and ^{13}C NMR spectra (δ ppm) were recorded in $CDCl_3$, unless stated otherwise. THF was distilled with sodium benzophenone under argon. Silica gel 60 (230–400 mesh) supplied by Merck was used for flash chromatography. (S)-Ethyl lactate and (R)-isobutyl lactate were purchased from Fluka Co. Diol (S)-3 (mp = 91–93 °C, $[\alpha]_D$ = −101 (c = 1, MeOH)) was prepared as described in ref 41. Diol (R)-3 was prepared by the same procedure from (R)-isobutyl lactate. Diols (R,R)-20 and (R,R)-21 were given by Pr. A. Tai and are available at Wako Co. (Osaka). Diol 24 has been synthesized according to ref 69. (1R,2S,5R)-(−)-menthol was purchased from Janssen Co.; (S)-(+)-1,2-propanediol (4) and diol 6, t-BuMgCl, n-BuLi, and t-BuLi, were obtained from Aldrich Co.

Preparation of Chiral Cyclic Sulfites. The general procedure using chiral diol, $SOCl_2$, and NEt_3 is exemplified for the preparation of sulfite 7.[68]

Sulfite 7 ((2R,5S)-*trans*-4,4-Diphenyl-5-methyl-1,3,2-dioxathiolane 2-Oxide). To a solution of (S)-3 (46 g, 0.2 mol) in 300 mL of CH_2Cl_2 was added at one time a solution of $SOCl_2$ (0.3 mol, 21 mL) in 100 mL of CH_2Cl_2 at −40 °C. The flask was maintained at −40 °C, and then triethylamine (0.5 mol, 67 mL) in 600 mL of CH_2Cl_2 was added dropwise. At the end point a white precipitate appeared. The reaction was quenched by 250 mL of water. The product was recovered after extraction with CH_2Cl_2, washed with water, dried on $MgSO_4$, and evaporated. The crude solid product (55 g) was crystallized in 200 mL of solvent (cyclohexane/hexane = 1/1). Pure (−)-7 was isolated in 68% yield (38 g) mp 109–111 °C. $[\alpha]_D$: −246 (c = 1, $CHCl_3$). ^1H NMR: 7–7.5 (10 H, m); 5.7 (1 H, q); 1.3 (3 H, d). ^{13}C NMR: 140.3 (1 C); 138.3 (1 C); 128.7–128.5–128.3–128–127.5–126.7 (10 C); 96 (1 C); 80.4 (1 C); 16.5 (1 C). Anal. Calcd for: $C_{15}H_{14}O_3S$: C, 65.67; H, 5.14; O, 17.50; S, 11.69. Found: C, 65.72; H, 5.05; O, 17.49; S, 11.71.

X-ray structure: see supplementary material.

(+)-(2S,5R)-Sulfite 7 has been also prepared from (R)-3, with 60% yield in crystallized product (cyclohexane–hexane). $[\alpha]_D$: 244 (c = 1, $CHCl_3$). Same NMR data, mp, and centesimal analysis as above.

Sulfite 8 (epimer of 7) was obtained by crystallization of the above mother liquor (preparation of (−)-7), mp 80–83 °C. $[\alpha]_D$: −309 (c = 1.5, $CHCl_3$). ^1H NMR: 7.2–7.6 (10 H, m); 5.55 (1 H, q); 1.35 (3 H, d). ^{13}C NMR: 142 (1 C); 138.5 (1 C); 128.6–128.5–128.3–128–126.5–126 (10 C); 96.2 (1 C); 83.3 (1 C); 20.2 (1 C). Anal. Calcd for $C_{15}H_{14}O_3S$: C, 65.67; H, 5.14; O, 17.50; S, 11.69. Found: C, 65.75; H, 5.08; O, 17.45; S, 11.74.

Sulfites 17a–17b were obtained from (S)-diol 4 as an oil in 70% yield (trans:cis = 67:33). Epimers could not be separated. ^1H NMR of the mixture is similar to data in ref. 70. ^1H NMR: 1.4 (CH_3 trans, d); 1.6 (CH_3 cis, d); 3.86 (1 H trans, dd); 4.27 (1 H, cis, dd); 4.5 (1 H, cis, dd); 4.6 (1 H, cis, m); 4.7 (1 H, trans, dd); 5.1 (1 H, trans, m). Anal. Calcd for $C_3H_6O_3S$: C, 29.5; H, 4.9; O, 39.3; S, 26.2. Found: C, 29.5; H, 4.9; O, 39.4; S, 26.2.

Sulfite (R,R)-18 was prepared from (R,R)-20 in 80% yield as a colorless oil and used as such for the reaction with t-BuMgCl. ^1H NMR: 5.1 (1 H, m); 4.45 (1 H, m); 2.05 (2 H, m); 1.6 (3 H, d); 1.35 (3 H, d).

Sulfite (R,R)-19 was prepared from (R,R)-21 in 80% yield and used as such for the reaction with t-BuMgCl. ^1H NMR: 4.5 (1 H, q); 3.8 (1 H, q); 1.8–2.1 (4 H, m); 0.95 (12 H, m).

General Procedure for the Preparation of Sulfinates. Grignard reagent RMgCl (1 equiv) is added to sulfite (−)-7 in THF according to the procedure described below for synthesis of sulfinate 10 (R^1 = t-Bu). Ratio of sulfinates 9 and 10 in the crude product is given in Table II. ^1H NMR data of sulfinates 9 and 10 used for analysis of 9/10 ratio and assignment of structure are collected in Table I.

All sulfinates are crystalline compounds that could be recrystallized. Sulfinates 10 are stable and can be stored, while sulfinates 9 are prone to decomposition at rt and have to be used immediately (storage is, however, possible at −20 °C for some weeks).

Sulfinate 10 (R^1 = t-Bu) (2,2-Diphenyl-1,2-dihydroxypropyl 2-*O*-*tert*-Butylsulfinate). A solution of t-BuMgCl (50 mmol) in THF was added dropwise to a solution of (−)-7 (14 g, 50 mmol) in THF at −78 °C. Reaction is checked by TLC (eluent, cyclohexane/AcOEt (5:1)). When conversion was over, the solution was quenched by H_2O, extracted by ether, washed by H_2O, dried on $MgSO_4$, and evaporated. The crude product was crystallized in 100 mL of cyclohexane, and pure 10 (R^1 = t-Bu) was obtained in 70% yield (12.1 g), mp 135–137 °C. $[\alpha]_D$: −120 (c = 0.9, $CHCl_3$). ^1H NMR: 7.15–7.65 (10 H, m); 5.4 (1 H, q); 3.1 (1 H, s); 1.35 (3 H, d); 0.9 (9 H, s). ^{13}C NMR: 145.5 (1 C); 143.3 (1 C); 128.4–127–126.5–126 (10 C); 82.5 (1 C); 79.7 (1 C); 58 (1 C); 21.5 (3 C); 16.3 (1 C). Anal. Calcd for $C_{19}H_{24}O_3S$: C, 68.64; H, 7.28; O, 14.43; S, 9.64. Found: C, 68.67; H, 7.21; O, 14.14; S, 9.87.

X-ray structure: see supplementary material. Configuration S_cR_c.

Sulfinate 9 (R^1 = Me) (1,1-Diphenyl-2-hydroxypropyl 1-Methylsulfinate). Configuration, S_cR_s. 70% yield (after crystallization in cyclohexane). $[\alpha]_D$: 46 (c = 0.5, $CHCl_3$). $[\alpha]_D$: −49 (c = 0.5, acetone). Mp: 92–94 °C. ^1H NMR: 7.1–7.6 (10 H, m); 4.8 (1 H, q); 3.6 (1 H, s); 2.7 (3 H, s); 1.15 (3 H, d).

Sulfinate 9 (R^1 = Et). Configuration, S_cR_s. 80% yield (after crystallization in cyclohexane). $[\alpha]_D$: −31 (c = 0.5, acetone). Mp: 76–78 °C. ^1H NMR (acetone-d_6): 7.2–7.55 (10 H, m); 4.95 (1 H, q); 4.6 (1 H, s); 2.85 (2 H, q); 1.2 (3 H, t); 1.05 (3 H, d).

Sulfinate 9 (R^1 = n-Octyl). Configuration, S_cR_s. 60% yield (after crystallization in cyclohexane). $[\alpha]_D$: −46 (c = 0.5, acetone). Mp: 69–71 °C. ^1H NMR (acetone-d_6): 7.2–7.55 (10 H, m); 4.95 (1 H, q); 4.25 (1 H, m); 2.85 (2 H, m); 1.65 (2 H, m); 1.2–1.35 (10 H, m); 1.05 (3 H, d); 0.85 (3 H, t).

Sulfinate 9 (R^1 = Vinyl). Configuration, S_cR_s. 50% yield (after crystallization in cyclohexane). $[\alpha]_D$: −52 (c = 1, acetone).

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Mp: 53–55 °C. ^{1}H NMR (acetone-d_6): 7.3–7.6 (10 H, m); 7.1 (1 H, alkene); 6–6.1 (2 H, alkene); 4.95 (1 H, q); 3.3 (1 H, s); 1.05 (3 H, d).

Sulfinate 9 (R^1 = Benzyl). Configuration, S_cR_s. 55% yield (after crystallization in cyclohexane). $[\alpha]_D$: −31 (c = 1, acetone). Mp: 88–91 °C. ^{1}H NMR (acetone-d_6): 7–7.5 (15 H, m); 4.7 (1 H, q); 4.15 (2 H, q); 3.8 (1 H, s); 1.05 (3 H, d).

Sulfinate 10 (R^1 = Mesityl). Configuration, S_cS_s. 70% yield after crystallization in cyclohexane. $[\alpha]_D$: −113 (c = 0.8, $CHCl_3$). Mp: 110 °C. ^{1}H NMR: 7.1–7.6 (12 H, m); 5.45 (1 H, q); 2.25 (9, H, s); 1.4 (3 H, d). Anal. Calcd for $C_{24}H_{26}O_3S$: C, 73.06; H, 6.65; O, 12.17; S, 8.26. Found: C, 73.21; H, 6.55; O, 12.02; S, 8.26.

Sulfinate 10 (R^1 = Benzyl). Configuration, S_cS_s. 50% yield after recrystallizations from cyclohexane. $[\alpha]_D$: −72 (c = 0.5, $CHCl_3$). Mp: 112–115 °C. ^{1}H NMR (acetone-d_6): 6.95–7.55 (15 H, m); 5.3 (1 H, q); 3.65 (2 H, q); 1.6 (1 H, s); 1.35 (3 H, d). See NMR spectrum in supplementary material. Anal. Calcd for $C_{22}H_{22}O_3S$: C, 71.16; H, 6.25; O, 13.54; S, 9.05. Found: C, 72.04; H, 6.21; O, 13.00; S, 8.63.

Sulfinate 13. Configuration, S_cR_s. Epimeric at sulfur of **10** (R^1 = t-Bu). Was obtained from *cis*-sulfite **8** and t-BuMgCl in THF. Ratio **13**/**14** 92/8 in the crude product. 45% yield (after crystallization in cyclohexane). $[\alpha]_D$: +50 (c = 1, $CHCl_3$). Mp 162–165 °C. ^{1}H NMR: 7.15–7.60 (1 H, m); 5.25 (1 H, q); 2.75 (1 H, s); 1.25 (3 H, d); 1.1 (9 H, s). Anal. Calcd for $C_{19}H_{24}O_3S$: C, 68.64; H, 7.28; O, 14.43; S, 9.64. Found: C, 68.74; H, 7.19; O, 14.09; S, 9.91.

Sulfinate 22. 70% yield after flash chromatography into a mixture of two unseparable diastereoisomers: $R_cR_cR_s/R_cR_cS_s$ = 25/75 (calculated from further transformation into *tert*-butyl phenyl sulfoxide). Oil. $[\alpha]_D$: −137 (c = 0.4, $CHCl_3$). ^{1}H NMR: 4.55 (1 H, m); 4 (1 H, m); 3.95 (1 H, s); 1.65 (1 H, t); 1.6 (1 H, t); 1.30 (3 H, d); 1.2 (9 H, s); 1.18 (3 H, d). See NMR spectrum in supplementary material. Anal. Calcd for $C_9H_{20}O_3S$: C, 51.89; H, 9.68; O, 23.05. Found: C, 51.65; H, 9.48; O, 23.35.

Sulfinate 23. 65% yield after flash chromatography into a mixture of two unseparable diastereoisomers: $R_cR_cR_s/R_cR_cR_s$ = 88/12 (calculated from further transformation into *tert*-butyl phenyl sulfoxide). Oil. $[\alpha]_D$: 167 (c = 0.8, $CHCl_3$). ^{1}H NMR: 4.25 (1 H, m); 3.5 (1 H, m); 3.2 (1 H, s); 1.7 (1 H, m); 1.4–1.75 (3 H, m); 1.25 (9 H, s); 0.85–1 (12 H, m). See NMR spectrum in supplementary material. Anal. Calcd for $C_{13}H_{28}O_3S$: C, 59.27; H, 10.71; O, 18.22. Found: C, 59.96; H, 10.28; O, 18.43.

Preparation of Chiral Sulfoxides. Sulfoxides were obtained in quantitative yield by addition of 2 equiv of RMgCl or RLi reagents on sulfinate **9** or **10** (procedure 1) or addition of sulfinate on RMgBr (procedure 2) in THF at rt, according to the procedures described below. Yields, ee's, organometallics, and reaction temperatures are collected in Table III. Specific rotations, absolute configurations, and comparisons with literature data are in Table IV.

Procedure 1. Sulfoxide 12 (R^1 = t-Bu, R^2 = n-Bu). A solution of 2.2 equiv of n-BuLi (4.5 mL of a 1.6 M solution in hexane) was added slowly to 1 equiv of sulfinate **10** (R^1 = t-Bu) (1 g; 3 mmol) in 20 mL of THF at rt. The mixture was stirred 0.5 h, then quenched with H_2O, extracted by ether, washed with H_2O, dried on $MgSO_4$, and evaporated. 0.49 g (100% yield) of pure product was obtained. $[\alpha]_D$: 125 (c = 1, acetone). ee: 100%. This procedure was used for preparation of **sulfoxide 12** (R^1 = t-Bu, R^2 = Me), R configuration; **sulfoxide 12** (R^1 = t-Bu, R^2 = Ph), R configuration; **sulfoxide 12** (R^1 = mesityl, R^2 = Me) R configuration; **sulfoxide 12** (R^1 = t-Bu, R^2 = vinyl) R configuration. Yield: 90%. $[\alpha]$: 283 (c = 1, acetone). ^{1}H NMR: 6.6 (1 H, m); 6.1 (1 H, d); 6 (1 H, d); 1.35 (9 H, s). See NMR spectrum in supplementary material. Unstable compound, prone to polymerization.

Procedure 2. All the other sulfoxides of Table III were prepared by the following procedure here described for **sulfoxide 11** (R^1 = Et, R^2 = Bn). A solution of 13 mmol of sulfinate **9** (R^1 = Et) in ether (prepared by reaction between 3.5 g, (13 mmol) of sulfite (−)-**7** and 18 mL of a 1 M solution of EtMgBr in THF) was added slowly at rt to 30 mL of a 1 M solution of $PhCH_2MgBr$ (prepared by 0.72 g of Mg and 5.13 g of $PhCH_2Br$ in 30 mL of Et_2O). The mixture was then stirred for 0.5 h, quenched, and extracted. After a purification by flash chromatography (eluent AcOEt/cyclohexane (4:1), enantiomerically pure sulfoxide **11** (R^1 = Et, R^2 = Bn) was obtained in 90% yield. $[\alpha]$: 105 (c = 0.75, $CHCl_3$). In a few cases, sulfinates **9** (R^1 = n-octyl, Bn, or Me) were dissolved in toluene, as in preparation of sulfoxides **11**: R^1 = octyl, R^2 = Me, R^1 = $PhCH_2$, R^2 = Et, R^1 = Me, R^2 = octyl.

Preparation of (*S*)-*tert*-Butyl Phenyl Sulfoxide from Dimenthyl Sulfite. 1. Dimenthyl Sulfite 25. Reaction was performed at −60 °C (in order to eliminate the formation of a byproduct) using (−)-menthol and following the procedure for the synthesis of cyclic sulfite **7**. Yield: 95%. $[\alpha]_D$: −60 (c = 1, $CHCl_3$). Mp: 49 °C (crystallized from hexane after flash chromatography, eluent cyclohexane/AcOEt (9:1)). ^{1}H NMR: 0.8 (2d, 2 CH_3); 0.9 (2dd, 4 CH_3); 1–1.5 (10 H); 1.7 (2 CH_2); 2.1 (2 CH_2); 4.25 (dt, 1 H); 4.35 (dt, 1 H). Anal. Calcd for $C_{20}H_{38}O_3S$: C, 67.03; H, 10.61; O, 13.41; S, 8.94. Found: C, 66.63; H, 10.47; O, 13.34; S, 8.92.

2. Sulfinate 26. (a) Reagent, (2-*t*-BuLi, $MgBr_2$). 122 mg (5 mmol) of Mg turnings were stirred under argon 0.5 h, then 5 mL of THF was added and 0.44 mL (5 mmol) of 1,2-dibromoethane. The solution refluxed a few min (precipitation occurred) and was stirred vigorously until no more Mg was observed. Then, 6 mL of t-BuLi (1.7 M in pentane; 10.2 mmol) was added, and the resulting green solution was stirred during 1 h then cooled at 0 °C.

(b) Sulfinate. To the 2-t-BuLi, $MgBr_2$ reagent was added 1 g (2.8 mmol) of sulfite **25** in 5 mL of THF at 0 °C. The reaction was over (no more sulfite) after 4 h. After ususal workup, an oily product was recovered (100% yield) composed of two diastereomers (70% de). The diastereomeric ratio could be measured by ^{1}H NMR (on Me of t-Bu at 1.2 ppm). ^{1}H NMR: 0.8 (1 CH_3, d); 0.9 (2 CH_3, 2dd); 1.2 (3 CH_3, s); 1–1.3 (3 H, m); 1.4 (2 H, m); 1.6 (2 H, m); 2.1 (2 H, m); 3.95 (1 H, m). Anal. Calcd for $C_{14}H_{28}O_2S$: C, 64.9; H, 10.4; O, 12.3; S, 12.3. Found: C, 65.2; H, 11.2, O, 12.1; S, 11.5. The transformation of **26** (70% de) into (*S*)-*tert*-butyl phenyl sulfoxide (70% ee) was achieved in quantitative yield by addition of 2.1 equiv of PhLi in THF at rt to the crude above sulfinate.

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Supplementary Material Available: X-ray structures of cyclic sulfite *trans*-**7** and of sulfinate **10** (R^1 = t-Bu), ^{1}H NMR spectra of sulfinates **9** and **10** (R^1 = benzyl), of sulfinates **22** and **23**, of sulfoxide **12**, and of sulfinate **10** (R^1 = t-Bu) (25 pages). Ordering information is given on any current masthead page.