

Nucleophilic Reactions between Cyclic 1,2-Sulfites and Chloride Ions

Kirsten Nymann, Linda Jensen and John S. Svendsen*

University of Tromsø, Institute of Mathematical and Physical Sciences, Department of Chemistry, N-9037 Tromsø, Norway

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When cyclic 1,2-sulfites are ring opened by chloride ion, the chlorohydrins are formed with low regio- and stereo-selectivity. The mechanisms involved in the process were investigated by measuring the stereochemical outcome of the reactions. The results showed that reversible inversion pathways (S_N2 reactions) and a retention pathway (S_N2i reaction) gave rise to the loss in ee in both the chlorohydrins and in the cyclic 1,2-sulfites.

Over the last years cyclic sulfites and sulfates have entered the mainstream of organic synthesis as important supplements to epoxides.¹ The main reason for the increased popularity is the development of catalytic asymmetric dihydroxylation (ADH) of alkenes, where a wide array of alkenes, ranging from mono- to tetra-substituted, are smoothly converted into the corresponding diols with good to excellent enantioselectivity.^{2–9} These diols can subsequently be converted into cyclic sulfites and sulfates without any loss of enantiomeric purity. Similar to the epoxide, the cyclic sulfates and sulfites provide both high reactivity for nucleophilic attack as well as simultaneous protection of the neighbouring functionalised carbon atom.¹⁰ The cyclic sulfites have not been extensively used in organic synthesis, but several reports show that cyclic sulfites are capable of reacting with azide,^{11–14} cyanide,¹⁴ dimethyl malonate,¹⁴ bromide¹⁵ or chloride^{14,15} ion. With the exception of the reactions with chloride and bromide ion, the processes are stereospecific and take place with inversion of configuration.

The cyclic sulfites can react with a nucleophile either on carbon or on sulfur. The general trend is that harder Lewis bases add to sulfur, while softer nucleophiles have a larger tendency to react on carbon; e.g., methyl lithium adds to sulfur, while dimethyl malonate anion adds to carbon. A similar trend can also be envisioned for the halides, with fluoride adding to sulfur and bromide to carbon, while chloride ions displays intermediate selectivity.

When chloride ion, provided as triethylbenzylammonium chloride (TEBACl), was employed as nucleophile in DMF the stereoselectivity, as well as the regioselectivity, in the reaction with cyclic sulfites was low.¹⁴ This

* To whom correspondence should be addressed.

result was in contrast with a previous report where the cyclic sulfites of (\pm)- and *meso*-1,2-diphenyl-1,2-ethanediol were treated with dry hydrogen chloride in refluxing dioxane forming the *threo*- and *erythro*-1,2-diphenyl-2-chloroethanol respectively, showing that the reaction takes place with retention of configuration.¹⁶

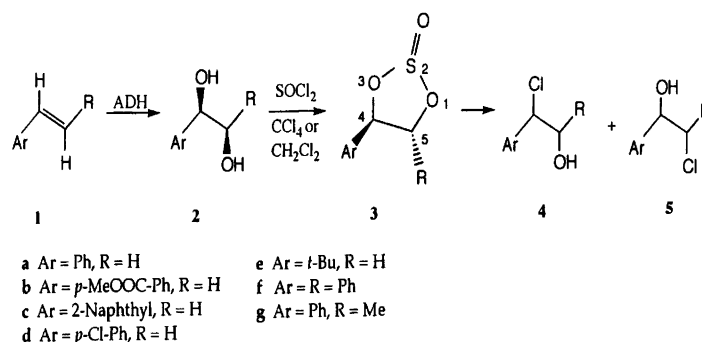
This anomalous stereoselectivity has been explained by a double displacement mechanism, where the cyclic sulfite is ring-opened by addition of dioxane, followed by a chloride addition to the resulting oxonium ion.¹⁷ An alternative explanation is an addition of chloride to the sulfur atom followed by ring opening to the chlorosulfite. This chlorosulfite decomposes to the chlorohydrin with retention of configuration.¹⁸

We have addressed the question of which mechanism operates in the reaction between chloride ion and cyclic sulfites in DMF by determining the stereochemical outcome of the reaction as a function of substrates with different steric and electronic properties.

Results and discussion

The diols **2a–g** were prepared in excellent enantiomeric excess by catalytic asymmetric dihydroxylation (ADH) of the corresponding alkenes **1a–g**. The diols were converted into the cyclic sulfites **3a–g** by treatment with thionyl chloride in carbon tetrachloride¹⁹ or dichloromethane (Scheme 1).

When (*S*)-1-phenyl-1,2-ethanediol cyclic sulfite (**3a**) was treated with TEBACl in hot DMF, two regioisomers, 2-chloro-2-phenylethanol (**4a**) and 2-chloro-1-phenylethanol (**5a**) were formed in a 35:65 ratio (Table 1). The enantiomeric purity of the benzylic substitution product **4a** was very low, only 6% ee, but more disturbing was the fact that the absolute configuration of the major



Scheme 1.

Table 1. Regioselectivity and enantioselectivity in the formation of chlorohydrins.

Cyclic sulfite	4:5 ^d	enantiomeric excess (absolute config.)	
		4	5
(<i>S</i>)-3a	35:65	6 (<i>S</i>)	70 (<i>S</i>)
(<i>S</i>)-3a ^a	21:79	9 (<i>S</i>)	4 (<i>R</i>)
(<i>S</i>)-3a ^c	56:44	10 (<i>S</i>)	96 (<i>S</i>)
(<i>S</i>)-3a	63:37	0.5 (<i>R</i>)	91 (<i>S</i>)
(<i>S</i>)-3b	44:56	9 (<i>R</i>) ^e	83 (<i>S</i>) ^e
(<i>S</i>)-3c	36:64	7 (<i>R</i>) ^e	51 (<i>S</i>) ^e
(<i>S</i>)-3d	24:76	12 (<i>R</i>) ^e	68 (<i>S</i>) ^e
(<i>R</i>)-3e	0:100		89 (<i>R</i>)

^a The reaction was performed under dry conditions. ^b The reaction was performed in the presence of 5 equiv. water. ^c The reaction was performed in the presence of BF₃. ^d Determined by NMR spectroscopy. ^e Tentatively assigned based on retention sequences.

enantiomer was *S*, corresponding to a retention of the stereochemistry in the substitution process. Even more puzzling was the loss of enantiomeric purity in regioisomer 5a, where the substitution had taken place at the primary carbon atom. The benzylic carbinol carbon, which was expected to be stereochemically silent during the reaction, had an enantiomeric purity of merely 70% ee (*S*). We were concerned about the stereochemical stability of the halohydrin products and treated each halohydrin with TEBACl in hot DMF. No interconversion between the regioisomeric chlorohydrins took place, and with the exception that the benzylic product 4a lost enantiomeric purity, the products were stable to the reaction conditions, and hence, product decomposition could not account for the formation of partially racemised 5a. The halohydrins, although formed under the normal conditions of the process, are not the primary products in the reaction. Chloride ion initiated ring opening of the cyclic sulfites were expected to take place by a nucleophilic substitution on either the benzylic or primary carbon with a sulfite monoester anion as leaving group. These sulfite monoesters are not easily characterised as they are very prone to hydrolysis, and we decided to use an indirect approach to study their stereochemical stability. The experiment was performed

by sampling the reaction mixture at regular intervals, and determining the product composition and enantiomeric purity of each component (after hydrolysis of the sulfite monoesters). The results from this experiment are compiled in Figs. 1 and 2. Fig. 1 shows the composition of the reaction mixture during the course of the reaction, and reveal that the two diastereomers of the cyclic sulfite are consumed at different rates; the major isomer, *trans*-cyclic sulfite, is absent from the reaction mixture after 8 h, while the minor isomer, *cis*-cyclic sulfite, reaches the 1% level within 2.5 h. It should, however, be noted that the *cis* isomer remains in the reaction mixture at an extent of <1% until the *trans* isomer is consumed. The primary substitution product 5a rises steadily and levels out at approximately 70% after 6–8 h. The benzylic substitution product 4a rises rapidly to 30% within 4 h, whereafter the formation levels out and even starts to decline. The rate of this decline is higher while cyclic sulfites are present in the reaction mixture.

Fig. 2 shows the enantiomeric purity of the reactants and products during the reaction. In the initial phases of the reaction the halohydrin products are formed with high enantioselectivity. The enantiomeric purity of the benzylic product is invariably lower than for the primary product. In the primary product 5a the loss of enantiomeric purity is fast until the majority of the cyclic sulfites are consumed, whereafter the enantiomeric purity remains almost constant. In the benzylic product 4a the enantiomeric purity declines monotonously until a racemic mixture is reached between 5–6 h. The enantiomeric purity then rises again, but now in the opposite sense until a level of 6% ee favouring the *S*-isomer is reached. The loss of enantiomeric purity with time is also seen in the cyclic sulfites, where the *trans* isomer had an ee of 74% and the *cis* isomer was 53% after 2.5 h.

Some conclusions can be drawn from this experiment. (1) The regioisomeric halohydrins are not interconverted. (2) The cyclic sulfites racemise during the course of reaction. (3) The formation of the benzylic product 4a must involve at least one mechanism that gives retention of stereochemistry.

The stereochemical lability of the cyclic sulfites was studied by separation of the *cis*- and *trans*-diastereomers of cyclic sulfite 3a by column chromatography and

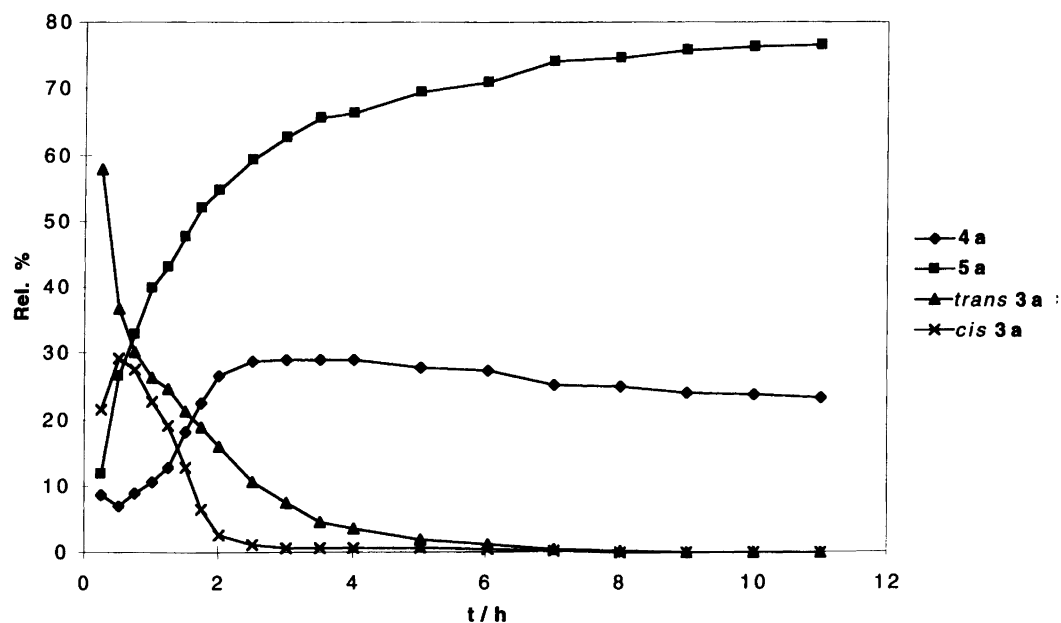


Fig. 1. Relative amounts determined by GC of cyclic sulfites **3a**, and chlorohydrins **4a** and **5a** as a function of reaction time.

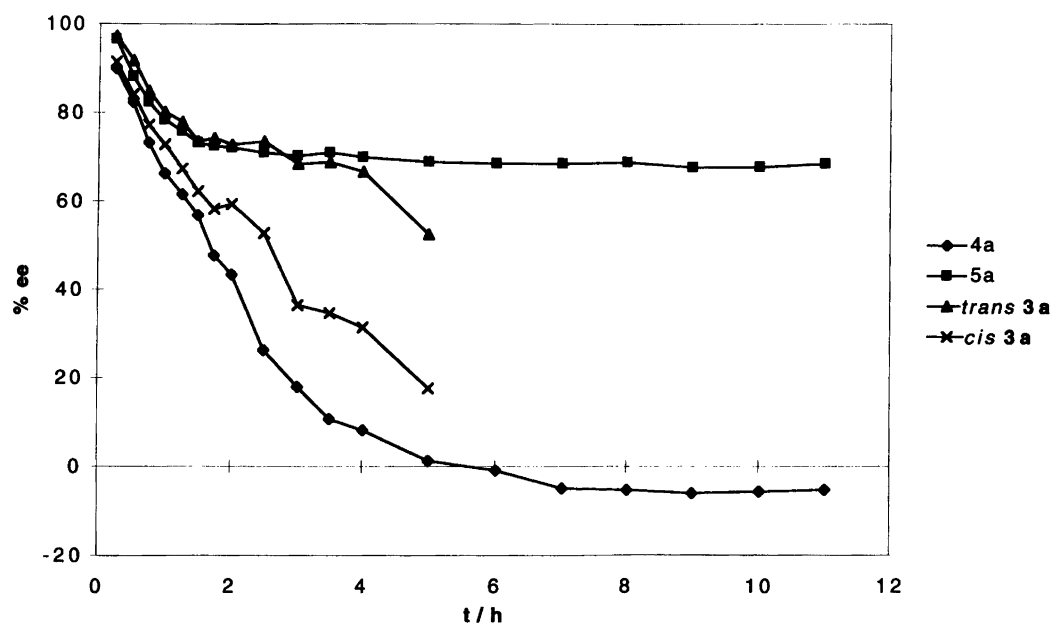
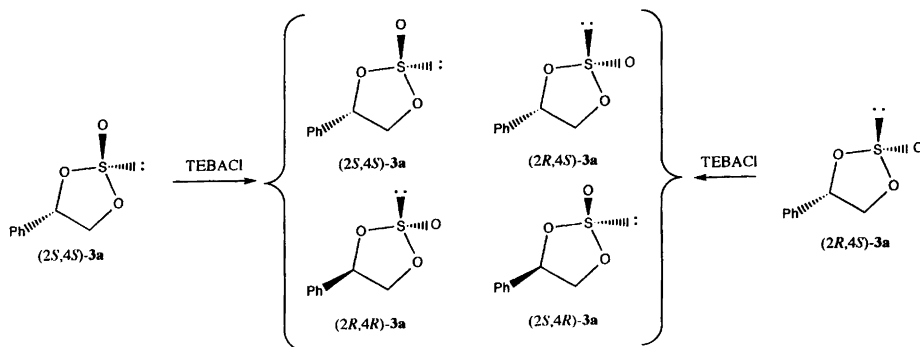


Fig. 2. Enantiomeric excess (ee) determined by chiral column GC of cyclic sulfites **3a**, and chlorohydrins **4a** and **5a** as a function of reaction time.

subsequent treatment with TEBACl in hot DMF. A portion of the reaction mixture was quenched after 2 h, the rest after 4 h. The product composition and enantiomeric purity of each product were determined and are compiled in Table 2. As shown in Scheme 2, a mixture of all possible stereoisomers of the cyclic sulfites are formed starting with either enantiomerically pure *trans*-**3a** [(2*S*,4*S*) 4-phenyl-1,3,2-dioxathiolan-2-one] or pure *cis*-**3a** [(2*R*,4*S*) 4-phenyl-1,3,2-dioxathiolan-2-one]. In addition chlorohydrins **4a** and **5a** are formed. The loss of stereochemical integrity of the cyclic sulfites can take place by epimerisation of the chiral benzylic carbon atom

Table 2. Product distribution and optical purity by treatment of cyclic sulfites with TEBACl in hot DMF.

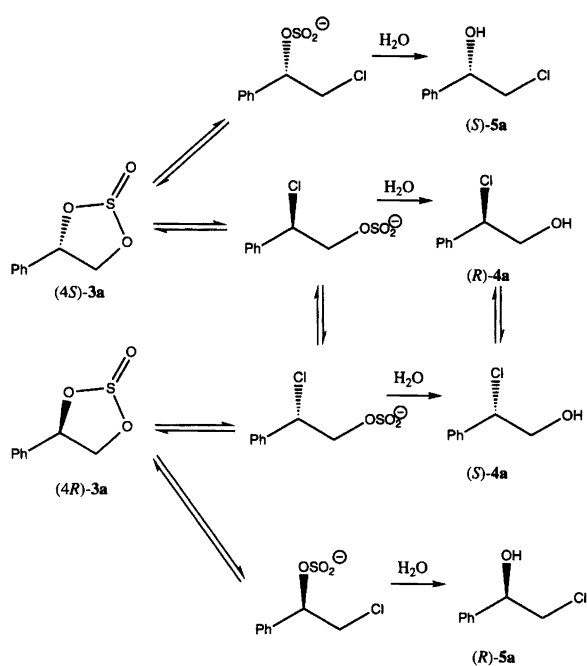
Cyclic sulfite	Reaction time/h	Ratio (ee)		Ratio (ee)	
		<i>trans</i> 3a	<i>cis</i> 3a	4a	5a
<i>trans</i> 3a	2	55 (57)	45 (44)	26 (36)	74 (59)
	4	56 (38)	44 (31)	25 (6)	75 (66)
<i>cis</i> 3a	2	50 (66)	50 (60)	21 (55)	79 (72)
	4	82 (52)	18 (~0)	30 (9)	70 (69)



Scheme 2.

or the sulfite sulfur atom or both. If only one of the mechanisms were operative, a true epimerisation will take place and two enantiomerically pure diastereoisomers would be formed, if both *S*- and *C*-epimerisation were operative both diastereoisomers would be formed, but the cyclic sulfites would be (partially) racemised. By treatment of the optically pure *trans* cyclic sulfite (2*S*,4*S*)-**3a** with TEBACl in hot DMF for 2 h, the four stereoisomers are formed in a 12 (2*R*,4*R*): 43(2*S*,4*S*): 13 (2*S*,4*R*): 32 (2*R*,4*S*) ratio. The first pair, the (2*S*,4*S*) and (2*R*,4*R*) enantiomers are *trans*, while the (2*R*,4*S*) and (2*S*,4*R*) enantiomers are *cis*. The enantiomeric purity of the sulfur center is determined by the ratio of the combined 2*S* enantiomers [(2*S*,4*R*)-**3a** and (2*S*,4*S*)-**3a**] and the combined 2*R* enantiomers [(2*R*,4*S*)-**3a** and (2*R*,4*R*)-**3a**], whereas the ratio between the combined 4*R* enantiomers and the combined 4*S* enantiomers determines the enantiomeric purity of the carbon center. This corresponds to a chiral sulfur center with 12% ee and a chiral carbon center with 50% ee. Starting with the enantiomerically pure *cis*-cyclic sulfite (2*R*,4*S*)-**3a** the corresponding figures are 0% and 63% ee for sulfur and carbon, respectively. These results show that the stereochemical integrity of the sulfur center is lost during the process while the stereochemistry of the carbon center still remains significantly unchanged.

In the light of these findings a mechanistic rationale can be proposed. The key point in this rationale (Scheme 3) is that the ring opening of the cyclic sulfite by chloride ions is a reversible process. As previously described, the ring opening reaction forms chloride substituted sulfite monoesters. The monoesters can subsequently close again to the cyclic sulfites, but the stereochemical information on sulfur is lost as the sulfur atom on the sulfite anion has no chirality. The significant loss of stereochemical integrity of the carbon center must be due to either racemisation during the ring opening process or stereochemical instability of the benzylic carbon atom in the resulting sulfite monoester. In this manner the loss of stereochemical integrity on the benzylic carbon is transferred via the interconverting cyclic sulfites to the primary isomer **5a**. This hypothesis requires that the rate of ring closure in the intermediates is greater than the rate of hydrolysis. The reactions are



Scheme 3.

generally performed in dry DMF, but not under strictly dry conditions. If water could be excluded from the reaction, the rate of hydrolysis should be negligible, and the loss of enantiomeric purity of the primary products should be even more pronounced. In an experiment performed under strictly dry conditions, the enantiomeric excess of the primary product **5a** was very close to zero, and the benzylic chlorohydrin was 9% favouring the *S*-enantiomer. The hypothesis also points out a way of avoiding the racemisation of the chlorohydrin formed by substitution of the primary carbon; facilitate the hydrolysis of the sulfite monoesters by the addition of water. Pleasingly, when the reaction is performed with 5 equiv. of water, the ee of **5a** is increased to 96%; however, less gratifyingly, the regioselectivity of the reaction is now reversed favouring the racemic isomer **4a**. Addition of a Lewis acid $\text{BF}_3 \cdot \text{OEt}_2$, likewise changed the outcome of the reaction; the benzylic substitution product **4a** again became predominant and racemic and the ee in chlorohydrin **5a** increased to 91%. The shift in product forma-

tion is again probably due to increased hydrolysis of the monosulfite ester intermediate.

While this hypothesis successfully accounts for the loss of stereochemical integrity in the products with substitution on the primary carbon, it does not address the question of why the ring opening of the cyclic sulfite in the benzylic position takes place with full or at least partial epimerisation. The mechanistic alternatives can be summarised as follows: by concurrent S_N2 and S_N2i or S_N1 processes, racemisation in the ring-opened sulfite monoesters by S_N2 or S_N1 processes or racemisation during ring closure by an S_N1 process.

The formation of chlorohydrin **4a** with retention of absolute configuration strongly suggests the participation of an S_N2i process. The cyclic sulfite moiety is formed by a nucleophilic addition of one of the hydroxy groups in the diol to thionyl chloride, forming an hydroxy chlorosulfite intermediate.²⁰ The next step is an intramolecular nucleophilic addition of the second hydroxy group to the chlorosulfite function forming the cyclic sulfite. If the ring-closure reaction in the formation of the cyclic sulfite can be envisioned to be reversed by the addition of chloride ions to the sulfur atom of the cyclic sulfite, an alkoxy chlorosulfite will be formed as shown in Scheme 4. This intermediate can then decompose with retention of stereochemistry in an S_N2i process, which would account for the formation of *S*-**4a** from *S*-**3a**.

The possible importance of S_N1 processes could be probed by the ring opening of cyclic sulfite **3b** with an electron-withdrawing substituent in the phenyl ring. This substrate gives marginally less racemisation than **3a**; regioisomer **5b** is formed in 83% ee, and the ee in **4b** is 9%. The absolute configuration of **4b** is tentatively assigned as *R*, based on the retention sequence on a β -cyclodextrin column. The meagre improvement in ee in the *p*-methoxycarbonylphenyl-substituted cyclic sulfite **3b**, where the S_N1 mechanism is discouraged, suggests that the participation of the unimolecular pathway in the racemisation process is small. A very similar result is also observed in the ring opening of the *p*-chloro-substituted cyclic sulfite **3d**. Elimination of enantiomeric excess can also be observed for the naphthyl-substituted cyclic sulfite **3c**.

For the *tert*-butyl-substituted cyclic sulfite **3e**, the substitution reaction is regio- and enantio-specific. As expected, addition of chloride ions to the neopentyl-like secondary carbon is strongly discouraged, and only chlorohydrin **5e** is formed with an enantiomeric excess identical with that of the starting diol **2e**. As no substitution

takes place on the chiral carbon no loss of stereochemical integrity should be expected. The reactivity of sulfite **3e** is very low, requiring 6 days to give 40% conversion.

When (1*R*,2*R*)-1,2-diphenyl-1,2-ethanediol cyclic sulfite (**3f**) is treated with TEBACl in hot DMF two compounds identified as (1*R*,2*S*)-2-chloro-1,2-diphenylethanol [(1*R*,2*S*)-**4f**] and (1*R*,2*R*)-2-chloro-1,2-diphenylethanol [(1*R*,2*R*)-**4f**] were formed in a 44:56 ratio. Both (1*R*,2*S*)-**4f** and (1*R*,2*R*)-**4f** were obtained enantiomerically pure (>99.5% ee). Similarly, when (1*R*,2*R*)-1-phenyl-1,2-propanediol cyclic sulfite (**3g**) is ring opened under identical conditions, a 47:53 ratio of (1*S*,2*R*)-1-chloro-1-phenyl-2-propanol [(1*S*,2*R*)-**4g**] and (1*R*,2*R*)-1-chloro-1-phenyl-2-propanol [(1*R*,2*R*)-**4g**] was formed. These chlorohydrins were also enantiomerically pure. Only 2% corresponding to chloride substitution on the secondary carbon was observed.

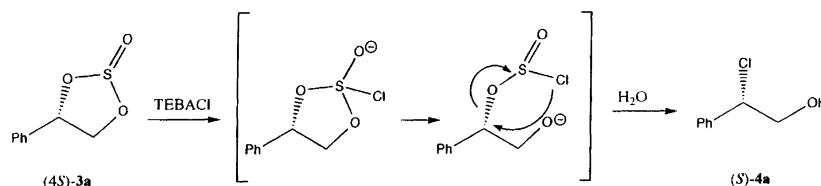
The formation of two enantiomerically pure diastereomeric chlorohydrins from the cyclic sulfite **3g** is compatible with the rationale presented above: the benzylic position is epimerised, and as long as very little substitution takes place on the non-benzylic secondary carbon, two enantiomerically pure diastereomeric chlorohydrins are formed. In cyclic sulfite **3f** the same reaction sequence may take place; however, at least for the retentive ring opening, the ring opening is not reversible because a reversible ring opening would lead to the *meso*-cyclic sulfite giving chlorohydrins devoid of enantiomeric purity.

Conclusions

Our investigation shows that cyclic sulfites are ring-opened by chloride ion via both retention and inversion pathways. In the majority of examples, the ring opening is reversible leading to loss of enantiomeric purity of the cyclic sulfite. In the monoaryl-substituted cyclic sulfites the racemisation of the products substituted in the primary position can be avoided by addition of water to the reaction medium.

Experimental

General. Proton NMR spectra were recorded on a Jeol EX 400 (399.65 MHz), Jeol FX 90 Q (89.55 MHz) or a PMX 60SI (60 MHz) spectrometer and CDCl₃ was used as the solvent unless otherwise stated. The chemical shifts are reported in ppm downfield from tetramethylsilane. Gas chromatography was performed on a Varian 3400



Scheme 4.

gas chromatograph equipped with a Supelco SPB 5 capillary column (30 m × 0.32 mm ID). Combined gas chromatography–mass spectrometry was carried out on a Hewlett-Packard 5890 Series II gas chromatograph equipped with either a Supelco SPB 5 (25 m × 0.25 mm ID) or a β -cyclodextrin (50 m × 0.25 mm ID) column connected to a VG Analytical Tribrid mass spectrometer. The mass spectra were recorded using EI ionisation (70 eV) and the ion source temperature was 180 °C. Optical rotations were determined on a Perkin-Elmer 241 polarimeter.

General procedure for the preparation of (R)-1-aryl-1,2-ethanediols. To a well stirred mixture of (DHQD)₂-PHAL (0.1 mmol), K₃Fe(CN)₆ (9.80 g, 30 mmol) and K₂CO₃ (4.1 g, 30 mmol) in *tert*-butyl alcohol–water (1:1, 100 ml) at 0 °C, were added K₂OsO₂(OH)₄ (7.4 mg, 0.02 mmol) and alkene (10 mmol) during which the stirring was maintained. The reaction was monitored by TLC. The reaction was quenched by addition of Na₂SO₃ (15 g, 120 mmol) and stirred for 30 min. The phases were separated and the aqueous phase extracted with ethyl acetate (3 × 50 ml). The combined organic extracts were washed with aqueous sodium hydrogencarbonate (3 × 50 ml) and brine (2 × 50 ml) before being dried (MgSO₄).

General procedure for the preparation of (S)-1-aryl-1,2-ethanediols. The title compounds were prepared as described above using (DHQ)₂-PHAL (0.1 mmol) as a chiral ligand.

Preparation of (R)-1-phenyl-1,2-ethanediol [(R)-2a]. The title compound was prepared from phenylethene (**1a**) according to the general procedure. (R)-1-phenyl-1,2-ethanediol [(R)-2a] was isolated in 77% yield after flash chromatography (SiO₂; EtOAc–heptane 3:1) and crystallisation from toluene.

2a: ¹H NMR (400 MHz): δ 3.10 (1 H, m), 3.50 (1 H, d), 3.61 (1 H, m), 3.70 (1 H, m), 4.75 (1 H, m), 7.32 (5 H, m). MS [*m/z* (% rel. int.)]: 138 (6, *M*), 120 (15), 107 (100). [α]₂₀^D –39.1° (*c* 1.07, EtOH). The enantiomeric purity of (R)-2a was better than 99.9% ee.

Preparation of (S)-1-phenyl-1,2-ethanediol [(S)-2a]. The title compound was prepared according to the general procedure in 83% yield. The spectroscopic properties were in accordance with (R)-2a, and the enantiomeric purity was better than 99.2% ee.

Preparation of methyl 4-[(1R)-1,2-dihydroxyethyl]-benzoate [(R)-2b]. The title compound was prepared from methyl 4-ethenylbenzoate (**1b**)²¹ according to the general procedure. The title compound was isolated in 51% yield after flash chromatography (SiO₂; EtOAc–heptane 2:1).

2b: ¹H NMR (400 MHz): δ 2.06 (1 H, m), 2.66 (1 H, d), 3.65 (1 H, m), 3.80 (1 H, m), 3.92 (3 H, s), 4.90 (1 H,

m), 7.45 (2 H, d), 8.03 (2 H, d). MS [*m/z* (% rel. int.)]: 178 (4), 165 (100). [α]₂₀^D –48.95° (*c* 0.19, CHCl₃). The enantiomeric purity of (R)-2b was better than 99.9% ee.

Preparation of methyl 4-[(1S)-1,2-dihydroxyethyl]-benzoate [(S)-2b]. The title compound was prepared in 69% yield in accordance with the general procedure. The spectroscopic properties were in accordance with (R)-2b and the enantiomeric purity was better than 99.9% ee.

Preparation of (R)-1-(2-naphthyl)-1,2-ethanediol [(R)-2c]. The title compound was prepared from 2-naphthylethene (**1c**) according to the general procedure. (R)-2c was isolated in 46% yield after flash chromatography (SiO₂; EtOAc–heptane 1:4) and crystallisation from ethyl acetate.

2c: ¹H NMR (400 MHz): δ 2.06 (1 H, br s), 2.61 (1 H, br s), 3.76 (1 H, m), 3.86 (1 H, m), 5.0 (1 H, m), 7.47 (3 H, m), 7.84 (4 H, m). MS [*m/z* (% rel. int.)]: 188 (9, *M*), 170 (31), 157 (35), 141 (100). [α]₂₀^D –31.8° (*c* 1.1, EtOH). The enantiomeric purity of (R)-2c was better than 99.9% ee.

Preparation of (S)-1-(2-naphthyl)-1,2-ethanediol [(S)-2c]. The title compound was prepared in 77% yield in accordance with the general procedure except that the solvent was *tert*-butyl alcohol–water–toluene 2:2:1. The spectroscopic properties were in accordance with (R)-2c. The enantiomeric purity of (S)-2c was better than 99.9% ee.

Preparation of (R)-1-(4-chlorophenyl)-1,2-ethanediol [(R)-2d]. The title compound was prepared from 4-chlorophenylethene (**1d**) according to the general procedure. (R)-1-(4-chlorophenyl)-1,2-ethanediol [(R)-2d] was isolated in 72% yield after flash chromatography (SiO₂; EtOAc–heptane 2:1) and crystallisation from MeOH–water.

2d: ¹H NMR (60 MHz, CDCl₃–CD₃OD): δ 3.4 (2 H, br s), 3.6 (2 H, m), 4.9 (1 H, dd), 7.4 (5 H, s). MS [*m/z* (% rel. int.)]: 174 (2), 172 (6, *M*), 156 (3.5), 154 (10), 143 (33), 141 (100), 127 (15), 125 (44), 115 (6), 113 (18). [α]₂₀^D –29.9° (*c* 1.02, EtOH) The enantiomeric purity of (R)-2d was better than 99.5% ee.

Preparation of (S)-1-(4-chlorophenyl)-1,2-ethanediol [(S)-2d]. The title compound was prepared according to the general procedure in 71% yield. The spectroscopic properties were in accordance with (R)-2d. (S)-2d: [α]₂₀^D +30.1° (*c* 1.01, EtOH); the enantiomeric purity was better than 99.9% ee.

Preparation of (R)-3,3-dimethyl-1,2-butanediol (2e). To a well stirred mixture of DHQD-MEQ (0.2 mmol), K₃Fe(CN)₆ (9.88 g, 30 mmol) and K₂CO₃ (4.15 g, 30 mmol) in *tert*-butyl alcohol–water (1:1, 100 ml) at 0 °C, were added K₂OsO₂(OH)₄ (7.4 mg, 0.02 mmol) and 3,3-dimethyl-1-butene (**1e**) (1.68 g, 20 mmol) during

which stirring was maintained. The reaction was monitored by TLC. The reaction was quenched by addition of Na_2SO_3 (7.5 g, 60 mmol) and stirred for 30 min. The phases were separated and the aqueous phase extracted with dichloromethane (2×50 ml). The combined organic extracts were evaporated under reduced pressure and the residue was taken up in ethyl acetate (200 ml) and washed with sulfuric acid (1 M, 3×50 ml), aqueous sodium hydrogencarbonate (3×50 ml) and brine (2×50 ml) before being dried (MgSO_4). The title compound was isolated by column chromatography (SiO_2 ; EtOAc-*n*-heptane 1:4) in 38% yield.

2e: ^1H NMR (90 MHz): δ 0.9 (9 H, s), 3.25–3.75 (5 H, m). ^{13}C NMR (22.5 MHz): δ 25.95, 33.62, 63.22, 79.80. MS [m/z (% rel. int.)]: 118 (1, *M*), 100 (4), 87 (91), 57 (100). $[\alpha]_{20}^{\text{D}}$ -18.4° (*c* 0.75, CHCl_3). The enantiomeric purity of (*R*)-**2e** was 89% ee.

Preparation of (1R, 2R)-1,2-diphenyl-1,2-ethanediol (1R, 2R)-2f. Solid $\text{K}_2\text{OsO}_2(\text{OH})_4$ (7.4 mg, 0.02 mmol) and (*E*)-1,2-diphenylethene (0.36 g, 2 mmol) (**1f**) were added to a well stirred mixture of DHQD-CLB (0.2 mmol), $\text{K}_3\text{Fe}(\text{CN})_6$ (1.97 g, 6 mmol) and K_2CO_3 (0.83 g, 6 mmol) in *tert*-butyl alcohol–water (1:1, 20 ml) at ambient temperature during which the stirring was maintained. The reaction was monitored by TLC. The reaction was quenched by addition of Na_2SO_3 (2.52 g, 20 mmol) and stirred for 30 min. The phases were separated and the aqueous phase extracted with dichloromethane (2×50 ml). The combined organic extracts were evaporated under reduced pressure and the residue was taken up in ethyl acetate (200 ml) and washed with sulfuric acid (1 M, 2×50 ml), aqueous sodium hydrogencarbonate (2×50 ml) and brine (2×50 ml) before being dried (MgSO_4). The title compound **2f** was isolated by crystallisation from ethyl acetate in 76% yield.

2f: ^1H NMR (90 MHz): δ 2.88 (2 H, s), 4.70 (2 H, s), 7.25 (10 H, m). $[\alpha]_{20}^{\text{D}}$ $+95.5^\circ$ (*c* 1.2, EtOH). The optical purity of (1*R*, 2*R*)-**2f** was better than 99.9% ee.

Preparation of (1S, 2S)-1,2-diphenyl-1,2-ethanediol [(1S, 2S)-2f]. The title compound was prepared in 70% yield as described above using (DHQD)₂-PHAL as a chiral ligand. The spectroscopic properties were in accordance with (1*R*, 2*R*)-1,2-diphenyl-1,2-ethanediol. $[\alpha]_{20}^{\text{D}}$ -97.4° (*c* 1.22, EtOH). The optical purity of (1*S*, 2*S*)-**2f** was better than 99.9% ee.

Preparation of (1R, 2R)-1-phenyl-1,2-propanediol (2g). To a well stirred mixture of (DHQD)₂-PHAL (0.2 mmol), $\text{K}_3\text{Fe}(\text{CN})_6$ (19.76 g, 60 mmol), K_2CO_3 (8.29 g, 60 mmol) and methanesulfonamide (1.90 g, 20 mmol) in *tert*-butyl alcohol–water (1:1 200 ml) at ambient temperature $\text{K}_2\text{OsO}_2(\text{OH})_4 \cdot 2\text{H}_2\text{O}$ (16.2 mg, 0.04 mmol) and (*E*)-1-phenylpropene (2.36 g, 20 mmol) (**1g**) was added during which the stirring was maintained. The reaction was monitored by TLC. The reaction was quenched by addition of Na_2SO_3 (30 g, 240 mmol) and

stirred for 30 min. The phases were separated and the aqueous phase extracted with ethyl acetate (3×50 ml). The combined organic extracts were washed with KOH (2 M, 2×30 ml) and brine (2×20 ml) before being dried (MgSO_4). The ligand was removed by flash chromatography (SiO_2 ; EtOAc–heptane 1:4). The title compound **2g** was crystallised from toluene–heptane 1:1 in 80% yield. **2g**: ^1H NMR (400 MHz): δ 1.06 (3 H, d), 2.50 (1 H, d), 2.63 (1 H, d), 3.87 (1 H, m), 4.4 (1 H, dd), 7.33 (5 H, m). MS [m/z (% rel. int.)]: 134 (15), 128 (12), 107 (100). $[\alpha]_{20}^{\text{D}}$ -27.6° (*c* 1.2, EtOH). The enantiomeric purity of (1*R*, 2*R*)-1-phenyl-1,2-propanediol (**2g**) was 99.1% ee.

General procedure for the preparation of cyclic sulfites. Thionyl chloride (1.2–1.5 equiv.) was added to a solution or mixture of the diol in tetrachloromethane or in dichloromethane (4 ml per mmol of diol) and the solution was refluxed for 1–2 h. After being cooled to ambient temperature, the reaction mixture was washed twice with saturated sodium hydrogencarbonate solution and brine. The organic phase was dried (MgSO_4) and evaporated under reduced pressure to give the cyclic sulfite.

Preparation of (R)-1-phenyl-1,2-ethanediol cyclic sulfite [(R)-4-phenyl-1,3,2-dioxathiolan-2-one] [(R)-3a]. The title compound was prepared in 79% yield from diol (*R*)-**2a**. The diastereomer ratio was 59:41 [*trans* (2*R*,4*R*): *cis* (2*S*,4*R*)] as determined by GC.²² The spectral data were in accordance with the literature.¹⁴

Preparation of (S)-1-phenyl-1,2-ethanediol cyclic sulfite [(S)-4-phenyl-1,3,2-dioxathiolan-2-one] [(S)-3a]. The title compound was prepared in 99% yield from diol (*S*)-**2a**. The diastereomer ratio was 59:41 [*trans* (2*S*,4*S*): *cis* (2*R*,4*S*)] as determined by GC. The spectral data were in accordance with the literature.¹⁴

Preparation of methyl 4-[(1R)-1,2-dihydroxyethyl]-benzoate cyclic sulfite [(R)-4-(4-methoxycarbonylphenyl)-1,3,2-dioxathiolan-2-one] [(R)-3b]. The title compound was prepared in 83% yield from diol (*R*)-**2b**. The diastereomer ratio was 70:30 as determined by ^1H NMR spectroscopy.

3b: ^1H NMR (400 MHz): δ 3.98 (3 H, s), 4.25 (1/3 H, dd), 4.51 (2/3 H, dd), 4.85 (2/3 H, dd), 5.05 (1/3 H, dd), 5.51 (2/3 H, dd), 6.02 (1/3 H, dd), 7.47 (2/3 H, d), 7.60 (1 1/3 H, d), 8.13 (2/3 H, d), 8.14 (1 1/3 H, d). MS [m/z (% rel. int.)]: 242 (6, *M*), 212 (77), 211 (22), 184 (8), 178 (6), 163 (27), 149 (25) 133 (100).

Preparation of methyl 4-[(1S)-1,2-dihydroxyethyl]-benzoate cyclic sulfite [(S)-4-(4-methoxycarbonylphenyl)-1,3,2-dioxathiolan-2-one] [(S)-3b]. The title compound was prepared in 94% yield from diol (*S*)-**2b**. The diastereomer ratio was 70:30 as determined by ^1H NMR spectroscopy. The spectroscopic properties were in accordance with (*R*)-**3b**.

Preparation of (R)-1-(2-naphthyl)-1,2-ethanediol cyclic sulfite [(R)-4-(2-naphthyl)-1,3,2-dioxathiolan-2-one] [(R)-3c]. The title compounds were prepared in 38% yield from diol (R)-2c after recrystallisation from MeOH–water. The diastereomer ratio was 74:26 as determined by ¹H NMR spectroscopy.

3c: ¹H NMR (400 MHz): δ 4.37 (1/4 H, dd), 4.65 (3/4 H, dd), 4.87 (3/4 H, dd), 5.10 (1/4 H, dd), 5.65 (3/4 H, dd), 6.17 (1/4 H, dd), 7.50 (3 H, m), 7.89 (4 H, m). MS [*m/z* (% rel. int.)]: 234 (26, *M*), 170 (24), 156 (35), 141 (100).

Preparation of (S)-1-(2-naphthyl)-1,2-ethanediol cyclic sulfite [(S)-4-(2-naphthyl)-1,3,2-dioxathiolan-2-one] [(S)-3c]. The title compound was prepared in 81% yield from diol (S)-2c after recrystallisation from MeOH–water. The diastereomer ratio was 74:26 as determined by ¹H NMR spectroscopy. The spectroscopic properties were in accordance with (R)-3c.

Preparation of (R)-1-(4-chlorophenyl)-1,2-ethanediol cyclic sulfite [(R)-4-(4-chlorophenyl)-1,3,2-dioxathiolan-2-one] [(R)-3d]. The title compound was prepared in 94% from diol (R)-2d. The diastereomer ratio was 69:31 as determined by ¹H NMR spectroscopy.

3d: ¹H NMR (400 MHz): δ 4.17 (1/3 H, dd), 4.44 (2/3 H, dd), 4.76 (2/3 H, dd), 4.95 (1/3 H, dd), 5.40 (2/3 H, dd), 5.90 (1/3 H, dd), 7.40 (4 H, m). MS [*m/z* (% rel. int.)]: 220 (3), 218 (9, *M*), 190 (18), 188 (46), 162 (6), 160 (18), 156 (5), 154 (17), 141 (35), 139 (95), 127 (35), 125 (100).

Preparation of (R)-3,3-dimethyl-1,2-butanediol cyclic sulfite [(R)-4-(1,1-dimethylethyl)-1,3,2-dioxathiolan-2-one] [(R)-3e]. The title compound was prepared in 88% yield from diol 2e. The diastereomer ratio was 67:33 as determined by ¹H NMR spectroscopy.

3e: ¹H NMR (400 MHz): δ 0.97 (2.97 H, s), 1.05 (6.03 H, s), 4.13 (0.33 H, m), 4.21 (0.67 H, m), 4.38 (1.34 H, m), 4.59 (0.18 H, m), 4.71 (0.15 H, m). MS [*m/z* (% rel. int.)]: 107 (7, *M*), 85 (29), 70 (33), 57 (100).

Preparation of (1R,2R)-1,2-diphenyl-1,2-ethanediol cyclic sulfite [(4R,5R)-4,5-diphenyl-1,3,2-dioxathiolan-2-one] [(1R, 2R)-3f]. The title compound was prepared in 74% yield from diol (1R, 2R)- 2f after recrystallisation from MeOH. The spectral data were in accordance with the literature.¹⁴

Preparation of (1R,2R)-1-phenyl-1,2-propanediol cyclic sulfite [(4R,5R)-5-methyl-4-phenyl-1,3,2-dioxathiolan-2-one] [(1R,2R)-3g]. The title compound was prepared in 82% yield from diol 2g. The spectral data were in accordance with the literature.¹⁴

General procedure for nucleophilic ring opening of cyclic sulfites by chloride ion. The cyclic sulfite (2 mmol) and nucleophilic reagent (4 mmol) were dissolved in DMF

(2.5–5 ml) and stirred with heating (70–80 °C). The reaction was quenched by addition of sulfuric acid (20%, 5 ml). The resulting mixture was extracted with EtOAc (2 × 10 ml), and the organic phase was washed with sulfuric acid (20%, 5 ml), saturated sodium hydrogencarbonate solution (2 × 2.5 ml) and brine (5 ml) before being dried (MgSO₄).

Preparation of 2-chloro-2-phenylethanol (4a) and 2-chloro-1-phenylethanol (5a). The title compounds were prepared by treating the cyclic sulfite (S)-3a with TEBACl and heating for 6 h. The combined yield was 95% and the regioisomer ratio was 35:65 as determined by NMR spectroscopy. The spectral data for compound 4a^{23,24} and 5a¹⁴ were in accordance with the literature. The absolute configuration of 4a was determined by the sign of the optical rotation.²⁵

Reaction of (S)-1-phenyl-1,2-ethanediol cyclic sulfite (3a) with TEBACl in the presence of H₂O. Cyclic sulfite (S)-3a (0.15 g, 0.81 mmol) and TEBACl (0.37 g, 1.62 mmol) were dissolved in DMF (6 ml) and H₂O (73 μl 4.05 mmol) was added before the reaction mixture was stirred with heating (70–80 °C) for 24 h. The combined yield was 92% and the regioisomer ratio was 56:44 as determined by NMR spectroscopy.

Reaction of (S)-1-phenyl-1,2-ethanediol cyclic sulfite (3a) with TEBACl in the presence of BF₃. Cyclic sulfite (S)-3a (0.08 g, 0.43 mmol) and TEBACl (0.20 g, 0.86 mmol) were dissolved in dry DMF (3 ml) and BF₃·(OEt₂) (54 μl, 0.43 mmol) was added before the reaction mixture, under strictly dry conditions, was stirred with heating (70–80 °C). After 28 h no starting material was left, and sulfuric acid (20%, 5 ml) was added. The resulting mixture was extracted with EtOAc (2 × 10 ml), and the organic phases were washed with sulfuric acid (20%, 5 ml), saturated sodium hydrogencarbonate solution (2 × 2.5 ml) and brine (5 ml) before being dried (MgSO₄). The crude product consisted of chlorohydrins 4a and 5a (93.5%) with the regioisomer ratio 63:37 as determined by ¹H NMR spectroscopy.

Preparation of methyl 4-(1-chloro-2-hydroxyethyl) benzoate (4b) and methyl 4-(2-chloro-1-hydroxyethyl) benzoate (5b). The title compounds were prepared by treating the cyclic sulfite (S)-3b with TEBACl and heating for 6 h. The combined yield was 100% and the regioisomer ratio was 44:56 as determined by ¹H NMR spectroscopy.

4b and 5b: ¹H NMR (400 MHz): δ 3.03 (0.6 H, br s), 3.10 (0.4 H, s), 3.65 (0.56 H, dd), 3.78 (0.56 H, dd), 3.92 (3H, s), 3.95 (0.44 H, m), 4.98 (0.56 H, dd), 5.03 (0.44 H, dd), 7.49 (2 H, m), 8.04 (2H, d).

4b: MS [*m/z* (% rel. int.)]: 216 (3), 214 (8, *M*), 186 (34), 184 (100), 185 (33), 183 (70), 178 (15), 157 (7), 155 (23), 149 (64), 121 (6).

5b: MS [*m/z* (% rel. int.)]: 216 (0.5), 214 (2, *M*), 185 (8), 183 (27), 178 (3), 165 (100), 147 (7), 134 (16), 121 (15).

Preparation of 2-chloro-2-(2-naphthyl) ethanol (4c) and 2-chloro-1-(2-naphthyl) ethanol (5c). The title compounds were prepared by treating the cyclic sulfite (*S*)-**3c** with TEBACl and heating for 6 h. The combined yield was 86% and the regioisomer ratio was 36:64 as determined by ¹H NMR spectroscopy.

4c and **5c**: ¹H NMR (400 MHz): δ 2.89 (1 H, br s), 3.73 (0.64 H, dd), 3.82 (0.64 H, dd), 4.02 (0.72 H, m), 5.06 (0.64 H, dd), 5.14 (0.36 H, dd), 7.48 (3 H, m), 7.85 (4 H, m).

4c: MS [*m/z* (% rel. int.)]: 208 (3.5), 206 (11, *M*), 177 (13), 175 (41), 170 (26), 154 (27), 141 (100), 127 (5), 115 (33).

5c: MS [*m/z* (% rel. int.)]: 208 (8), 206 (26, *M*), 190 (3), 88 (9), 170 (17), 157 (100), 141 (48), 129 (85), 115 (17).

Preparation of 2-chloro-2-(4-chlorophenyl) ethanol (4d) and 2-chloro-1-(4-chlorophenyl) ethanol (5d). The title compounds were prepared by treating the cyclic sulfite **3d** with TEBACl and heating for 23 h. The combined yield was 94% and the regioisomer ratio was 24:76 as determined by ¹H NMR spectroscopy.

4d and **5d**: ¹H NMR (400 MHz): δ 2.18 (0.24 H, br s), 2.77 (0.76 H, br s), 3.60 (0.76 H, dd), 3.71 (0.76 H, dd), 3.91 (0.48 H, m), 4.88 (0.76 H, dd), 4.96 (0.24 H, dd), 7.34 (4H, m).

4d: MS [*m/z* (% rel. int.)]: 194 (1.5), 192 (5), 190 (8, *M*), 163 (8), 161 (37), 159 (54), 140 (10), 138 (26), 127 (34), 125 (100).

5d: MS [*m/z* (% rel. int.)]: 194 (0.55), 192 (2.6), 190, (3.8, *M*), 176 (1.2), 174 (3.0), 172 (4.0), 156 (4.0), 154 (7.9), 143 (30), 141 (100), 127 (8.5), 125 (24.5).

Preparation of (2R)-1-chloro-3,3-dimethylbutan-2-ol (5e). The title compound was prepared by treating the cyclic sulfite **3e** with TEBACl and heating for 6 days. The conversion was 42%.

5e: ¹H NMR (400 MHz): δ 3.81 (1 H, m), 3.49 (2 H, m), 0.96 (9 H, s). MS [*m/z* (% rel. int.)]: 123 (3), 121 (1), 100 (0.6), 87 (48), 57 (100).

Preparation of (1R,2S)-2-chloro-1,2-diphenylethanol [(1R,2S)-4f] and (1R,2R)-2-chloro-1,2-diphenylethanol [(1R,2R)-4f]. The title compounds were prepared by treating the cyclic sulfite (1R,2R)-**3f** with TEBACl and heating for 2 days. The conversion was 52%. The diastereomer ratio was 44:56 as determined by ¹H NMR spectroscopy. The diastereomers were separated (SiO₂; 10% EtOAc in *n*-heptane).

(1R,2S)-**4f**: ²⁶¹H NMR (400 MHz); δ 7.24–7.08 (10 H, m), 4.99 (1 H, d, *J* 8.06 Hz), 4.93 (1 H, d, *J* 8.06 Hz), 3.07 (1 H, br s).

(1R,2R)-**4f**: ¹H NMR (400 MHz); δ 7.31–7.23 (10 H, m), 5.06 (1 H, d, *J* 6.35 Hz), 5.00 (1 H, d, *J* 6.35 Hz), 2.35 (1 H, br s).

Preparation of (1S,2R)-1-chloro-1-phenyl-2-propanol [(1S,2R)-4g] and (1R,2R)-1-chloro-1-phenyl-2-propanol

[(1R,2R)-4g]. The title compounds were prepared by treating the cyclic sulfite **3g** with TEBACl and heating for 2 days. The combined yield was 66% and the diastereomer ratio was 47:53 as determined by NMR spectroscopy. The diastereomers were separated (SiO₂; 10% EtOAc in *n*-heptane). The configuration was identified by converting each chlorohydrin into the corresponding epoxide by treatment with CH₃ONa in methanol. The first eluting chlorohydrin gave *cis*-2-methyl-3-phenyloxirane and is hence (1R, 2R)-**4g**. The second eluting chlorohydrin gave *trans*-2-methyl-3-phenyloxirane and is hence (1S, 2R)-**4g**.

(1R, 2R)-**4g**: ¹H NMR (400 MHz): δ 7.42–7.31 (5 H, m), 4.72 (1 H, d, *J* 7.0 Hz), 4.13 (1 H, m, *J* 7.0 and 6.2 Hz), 2.60 (1 H, br s), 1.10 (3 H, d, *J* 6.2 Hz). ¹³C NMR (22.5 MHz): δ 138.7, 128.7, 127.8, 72.0, 71.1, 19.5. MS [*m/z* (% rel. int.)]: 172 (4), 170 (12), 135 (23), 128 (93), 126 (54), 125 (88), 91 (54).

(1S, 2R)-**4g**: ¹H NMR (400 MHz): δ 7.50–7.31 (5 H, m), 4.81 (1 H, d, *J* 5.6 Hz), 4.18 (1 H, m, *J* 6.0 and 5.6 Hz), 1.96 (1 H, br s), 1.29 (3 H, d, *J* 6.0 Hz). ¹³C NMR (22.5 MHz): δ 138.1, 128.6, 128.1, 71.8, 68.3, 19.3. The mass spectrum was identical with that of (1R, 2R)-**4g**.

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