Catalytic Asymmetric Epoxidation of Aldehydes. Optimization, Mechanism, and Discovery of Stereoelectronic Control Involving a Combination of Anomeric and Cieplak Effects in Sulfur Ylide Epoxidations with Chiral 1,3-Oxathianes

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Abstract: A range of 1,3-oxathianes based on camphorsulfonic acid have been prepared and tested in the catalytic asymmetric epoxidation of carbonyl compounds. It was found that the 1,3-oxathiane derived from acetaldehyde **5b** gave the highest yield and enantioselectivity in the epoxidation process. The enantioselectivity was independent of the solvent and metal catalyst used (although yields were dependent on both). The optimum conditions were applied to a range of aldehydes, and good enantioselectivities and diastereoselectivities were observed. The origin of the enantioselectivity was probed, and in particular the role of the oxygen of the 1,3-oxathiane was investigated. Thus, the sulfur and carbon analogues of the camphorsulfonic acid based 1,3-oxathiane (derived from formaldehyde) were prepared (i.e., 1,3-dithiane and thiane analogues). With this series of analogues the steric effects are minimized so that the electronic effects can be investigated. The series of compounds was reacted in the catalytic cycle with benzaldehyde and gave stilbene oxides with 44% ee (sulfur analogue), 41% ee (1,3-oxathiane), and 20% ee (carbon analogue). Thus, it was concluded that the oxygen of the 1,3-oxathiane exerted a significant electronic effect in controlling the face selectivity of the ylide reactions. This electronic effect was a result of combined anomeric (higher with the sulfur analogue, not present with the carbon analogue) and Cieplak effects. A strong anomeric effect was observed in the X-ray structures of one of the 1,3-oxathianes, and an even greater one was observed in the corresponding sulfoxide (this was used as an electronic analogue of the ylide). The face selectivity of the ylide was believed to be complete in reactions with **5b**. The minor enantiomer resulted from reaction of the minor conformer of the ylide, reacting again with high face selectivity. This was proven by using a more substituted diazo compound, which was expected to give much less of the minor conformer. Indeed, reaction with mesityldiazomethane gave the corresponding epoxide in essentially enantiomerically pure form.

Introduction

The search for efficient methods for the preparation of enantiomerically pure epoxides continues unabated, particularly as chiral epoxides are important intermediates in the synthesis of pharmaceuticals and agrochemicals. Most attention has focused on asymmetric oxidations of alkenes, and the methods developed by Sharpless and Jacobsen/Katsuki have stood the test of time and emerged as the best. Indeed, these methods represent landmark achievements in asymmetric synthesis.[1−8] However, although highly efficient and elegant, these methods have limitations. The Sharpless epoxidation requires an allylic alcohol, and the Jacobsen/Katsuki epoxidation generally requires cis-substituted alkenes bearing a π-stabilizing substituent. Very recently Shi has made a major breakthrough and found that simple sugar-based ketones can epoxidize a wide range of alkenes with high enantioselectivity.[9−11]

An alternative to oxidative processes for the synthesis of epoxides is the reaction of sulfur ylides with aldehydes and ketones.[12−14] Sulfur ylide epoxidation is a carbon−carbon bond forming reaction and as such offers a complementary method to the oxidative processes described above.

The first attempts at carrying out asymmetric epoxidations using chiral sulfur ylides were performed by Trost in 1973, using

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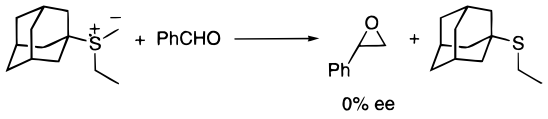
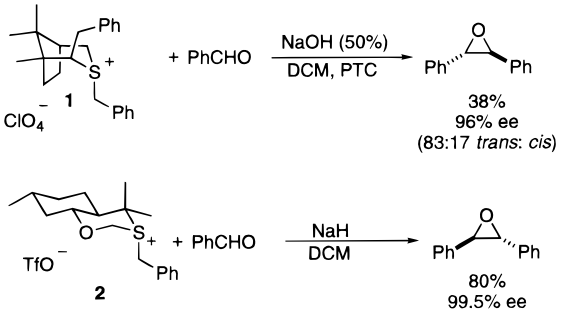
Scheme 1



Scheme 2



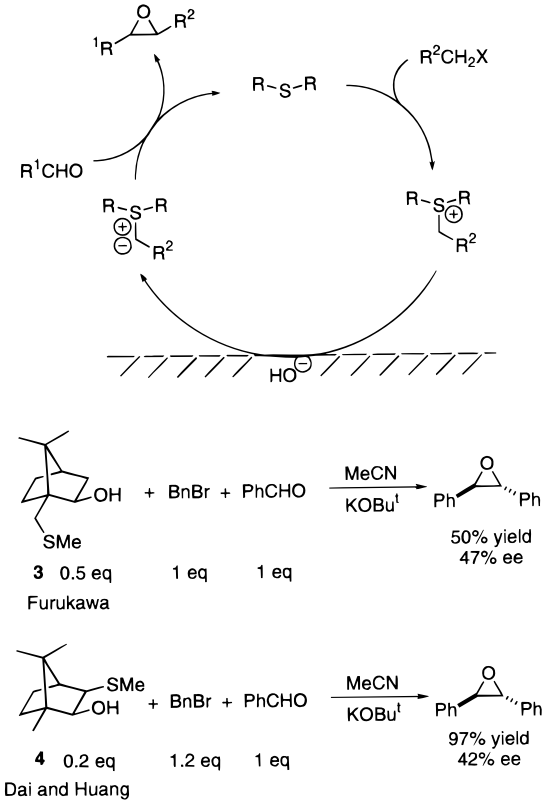
an adamantyl-based chiral sulfur ylide (Scheme 1).[15] Despite the large difference in size between the groups attached to sulfur, no asymmetric induction was obtained. This negative result presumably discouraged further work in asymmetric carbonyl epoxidation for many years, especially as it must have been difficult to conceive how the groups attached to sulfur could be further differentiated in order to improve the levels of enantioselectivity.

More recently a number of chiral sulfides have been developed and those of Durst[16,17](**1**) and Solladié-Cavallo[18] (**2**) provide very impressive levels of enantioselectivity in benzylidine ylide epoxidation (Scheme 2). In contrast to benzylidine ylide epoxidation, methylene ylide epoxidation using **1** (methyl instead of benzyl attached to S) was much less effective (less than 4% ee).[16] No doubt if Trost had attempted to carry out benzylidine rather than methylene ylide epoxidation, higher levels of enantioselectivity would have been achieved and asymmetric sulfur ylide epoxidations would have been born much earlier.

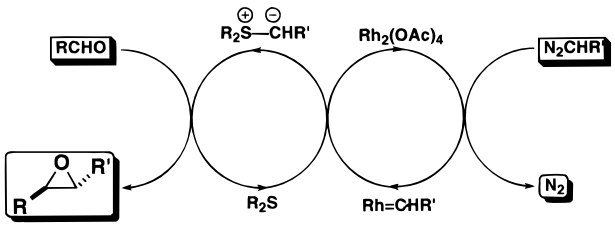
The asymmetric ylide epoxidations developed by Durst and Solladié-Cavallo, while giving high levels of asymmetric induction, suffer from requiring stoichiometric amounts of sulfide, and attempts have been made to make the process catalytic. The reaction of a sulfur ylide with an aldehyde gives epoxide and returns sulfide. Thus, to render the epoxidation process catalytic in sulfide, it is necessary to form the sulfur ylide in situ. This was achieved, originally by Furukawa[19] and more recently by Dai,[20] by sulfide alkylation and deprotonation in the presence of an aldehyde (Scheme 3). Using chiral sulfides, epoxides were obtained in variable yields but also with only moderate enantioselectivity. This process is, however, limited to simple, non-enolizable aldehydes.

An alternative method for ylide formation involves the reaction of a sulfide with a carbene or metal carbenoid.[21,22]

Scheme 3



Scheme 4



Indeed, we recently reported the successful application of this strategy to carbonyl epoxidation using catalytic quantities of sulfide (Scheme 4).[23] As these reaction conditions do not require the use of strong base, this method can be applied to readily enolizable and even base-sensitive aldehydes.[24,25] In this paper we describe the design and optimization of chiral sulfides for use in the catalytic cycle (Scheme 4) to produce nonracemic epoxides[26] and our studies into the mechanism of the enantioselectivity.

Results and Discussion

Optimization of Reaction Conditions. In the design of the chiral sulfides two factors were deemed important. First, a single sulfur ylide should be produced from the reaction of the sulfide with the metal carbenoid. If diastereomeric sulfur ylides were formed, they would certainly react with different and possibly opposite selectivities thereby eroding the enantio-

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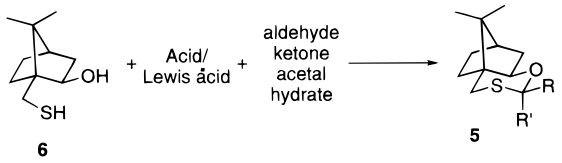
Scheme 5



6 **5**

5a R = H, R' = H
5b R = Me, R' = H
5c R = Pr^i, R' = H
5d R = Bu^t, R' = Me
5e R = Ph, R' = H
5f R = Bn, R' = H
5g R = CH_2OPh, R' = H
5h R = CH_2OMe, R' = H
5i R = CH_2O Bn, R' = H
5j R = R' = Me
5k R = R' = C_3H_6
5l R = CH_2OH, R' = H
5m R = CCl_3, R' = H
5n R = CH_2OAc, R' = H [a]
5p R = CH_2OPNB, R' = H [a]
5q R = TMS, R' = H [b]
5r R = CF_3, R' = H
5s R = H, R' = OMe

[a] Prepared from **5l** [b] Prepared from **5a**

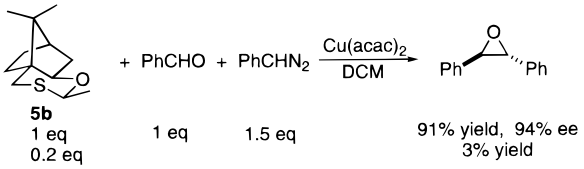
Table 1. Preparation of Sulfides **5a-5l** from Mercaptoisoborneol

entry	precursor	thioacetal	yield/%
1	acetaldehyde	**5b**	99
2	isobutyraldehyde	**5c**	100
3	pivaldehyde	**5d**	95
4	benzaldehyde	**5e**	84
5	phenylacetaldehyde	**5f**	98
6	phenoxyacetaldehyde dimethyl acetal	**5 g**	85
7	methoxyacetaldehyde dimethyl acetal	**5h**	81
8	benzyloxyacetaldehyde dimethyl acetal	**5i**	83
9	2,2-dimethoxypropane	**5j**	97
10	cyclobutanone	**5k**	94
11	glycolaldehyde diethyl acetal	**5l**	81
12	chloral hydrate	**5m**	93
13	trifluoroacetaldehyde dimethyl acetal	**5r**	0
14	trimethyl orthoformate	**5s**	0

selectivity obtained.[27] This could best be achieved by incorporating the sulfide within a rigid cyclic structure and making one of the lone pairs more accessible than the other. Indeed, the best chiral sulfides all have the sulfide moiety in a cyclic structure, and single diastereomeric sulfonium salts are formed upon alkylation. Second, we wanted to design chiral sulfides that could be easily modified, to explore both electronic and steric effects in the epoxidation process. Cyclic thioacetals of general structure **5** fulfill these requirements. A single sulfur ylide should be formed in the reaction of the sulfide with the metal carbenoid as the equatorial lone pair is much more accessible than the axial lone pair, which is hindered by the bridging geminal dimethyl group. The presence of the thioacetal moiety enables the R and R′ groups to be easily varied in order to probe steric and electronic effects by the use of different carbonyl compounds.

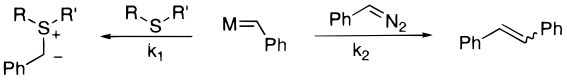
A range of thioacetals were easily prepared from camphorsulfonyl chloride via the known hydroxy thiol (Scheme 5, Table 1).[28−30] Thioacetal **5b** was initially tested in the epoxidation process using benzaldehyde and slow addition of phenyldiazomethane. Using stoichiometric amounts of **5b**, *trans*-stilbene oxide was obtained in good yield and in very high enantiomeric excess. With catalytic amounts of the sulfide, however, we were

Scheme 6



5b 1 eq, 0.2 eq — 1 eq — 1.5 eq — 91% yield, 94% ee, 3% yield

Scheme 7



surprised to obtain greatly reduced yields of the epoxide, with concomitant increased amounts of stilbenes (Scheme 6).

Stilbenes arise from the reaction of the metal carbenoid with phenyldiazomethane,[31,32] a reaction that competes with the formation of the intermediate sulfur ylide (Scheme 7). Increased amounts of stilbene and reduced yields of epoxide indicate that the former reaction is dominating over the latter. As we had previously shown that 0.2 equiv of sulfide were sufficient to obtain good yields of epoxides in the catalytic process,[25] the much reduced yields obtained with thioacetal **5b** suggested that the thioacetal was undergoing decomposition, perhaps catalyzed by $Cu(acac)_2$, thereby reducing the amount available for epoxidation. This was tested by subjecting thioacetal **5b** to $Cu(acac)_2$ in reagent grade CH_2Cl_2, and complete hydrolysis was observed after a few seconds. Under strictly anhydrous conditions the rate of hydrolysis could be reduced, but the desired improvement in yield was not obtained.

The solution to the problem was eventually found by using $Cu(acac)_2$ that was prepared ourselves from copper oxide and acetylacetone and purified by sublimation[33] instead of the commercial material. When this batch of $Cu(acac)_2$ was used, little hydrolysis was observed in our test experiments, indicating that the commercial material contained small quantities of impurities that showed high levels of catalytic activity in thioacetal hydrolysis. When the purified $Cu(acac)_2$[34] was used in the catalytic cycle with 0.2 equiv of thioacetal **5b**, stilbene oxide was obtained in good yield and with the same enantioselectivity. Upon discovery of suitable conditions for the catalytic epoxidation process, the other thioacetals were tested (Scheme 8), and the results are summarized in Table 2.

Sulfide **5b** (R = Me, entry 2) proved to be the most effective catalyst both in terms of enantioselectivity and yield. Increasing the size of the R group did not give an increase in enantioselectivity but instead lowered the yield (entries 2−4). For R = Bu^t (**5d**, entry 4), no epoxide was obtained; stilbenes were formed instead. Evidently the rate at which the sulfide reacts with the metal carbenoid (k_1) is dependent upon the size of R and R′ (Scheme 7), and if either is too hindered, as in the case of sulfide **5d**, k_1 slows down to such an extent that k_2 dominates.[25]

For R = Ph (**5e**, entry 5), no epoxide was formed but only limited amounts of stilbenes were obtained. In this case, ring expanded thioacetals **7** were believed to have been formed via

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(33) $Cu(acac)_2$ was prepared by adding saturated sodium carbonate to a solution of copper oxide and acetylacetone. See: Bryant, B. E.; Fernelius, W. C. *Inorg. Synth.* **1957**, *5*, 115.
(34) Commercial copper acetylacetonate that had been purified by sublimation was equally effective.

Scheme 8

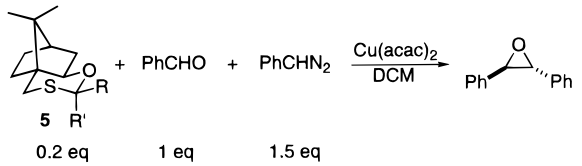
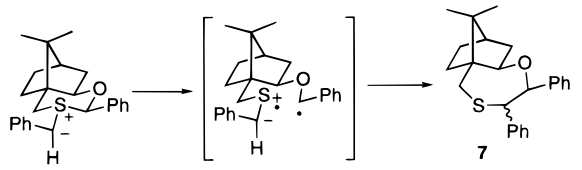


Table 2. Reactions of Sulfides **5** in the Catalytic Cycle with Benzaldehyde

entry	sulfide	R	R′	yield/%[a]	ee/%[b]
1	**5a**	H	H	83	41
2	**5b**	Me	H	71	93
3	**5c**	Pr^i	H	57	93
4	**5d**	Bu^t	H	0	
5	**5e**	Ph	H	0	
6	**5f**	CH_2Ph	H	56	88
7	**5m**	CCl_3	H	0	
8	**5g**	CH_2OPh	H	43	83
9	**5h**	CH_2OMe	H	70	92
10	**5i**	CH_2OBn	H	71	90
11	**5n**	CH_2OAc	H	68	93
12	**5q**	TMS	H	9	62
13	**5j**	Me	Me	11	70
14	**5k**	*spiro*-cyclobutyl		18	89

[a] Only *trans*-stilbene oxide was obtained (>98:2 trans/cis). [b] Ee values were measured by HPLC using a Chiralcel OD column. The (*R*,*R*) enantiomer was the major product in each case.

Scheme 9



a Stevens rearrangement.[35] The Stevens rearrangement of the ylide competes with carbonyl epoxidation and in this case is facilitated by the stability of the intermediate phenyl-substituted radical (Scheme 9). A single heteroatom in the side chain can be tolerated (entries 8−11), and the similar enantioselectivities obtained compared to R = Me showed that there was no substantial electronic effect. The trichloro derivative **5m** (entry 7) gave no epoxide, only stilbenes. This sulfide is either sterically too hindered or electronically too deactivated by the chlorines to react with the metal carbenoid, and so diazo dimerization is observed instead ($k_2 > k_1$). We expected the TMS derivative (sulfide **5q**, entry 12) to be less sterically hindered than sulfide **5d** and to be electronically activated to react with the metal carbenoid, and indeed it was, although only marginally so; epoxide was obtained but in low yield and with reduced enantioselectivity. The presence of two alkyl groups adjacent to sulfur gave much reduced yields of epoxide, again because of increased steric hindrance, but the enantioselectivity was also low (entries 13, 14).

We next decided to investigate whether the choice of metal salt would have any effect on the yield or diastereo- or enantioselectivity of the epoxidation process. Reactions were carried out in dichloromethane using 0.2 equiv of our optimum sulfide **5b** with benzaldehyde and a range of metal catalysts (Scheme 10, Table 3). All the metal salts used gave essentially the same enantioselectivity. These results showed that the choice of metal salt used for the diazo decomposition had little effect on the enantioselectivity of the process. It also showed

(35) It was not possible to isolate a pure sample of **7** to categorically prove its structure. The data are consistent with this product though.

Scheme 10

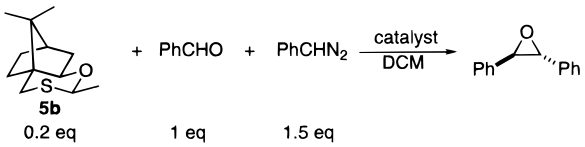


Table 3. Reactions of Sulfide **5b** with Benzaldehyde in the Catalytic Cycle Using Different Metal Salts

entry	catalyst[a]	yield/%[b]	ee/%[c]
1	copper acetylacetonate	73	93
2	copper tetramethylheptanedionate	64	92
3	copper hexafluoropentanedionate	0	
4	copper bronze	35	91
5	rhodium acetate[c]	61	92

[a] 5 mol% copper salts or 1 mol% $Rh_2(OAc)_4$. [b] Only *trans*-stilbene oxide was obtained (>98:2 trans/cis). [c] Ee values were measured by HPLC using a Chiralcel OD column. The (*R*,*R*) enantiomer was the major product in each case.

Scheme 11

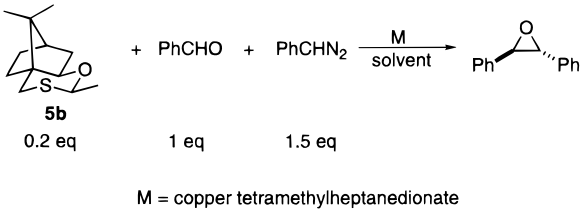


Table 4. Reactions of Sulfide **5b** with Benzaldehyde in the Catalytic Cycle in Different Solvents

entry	solvent	yield/%[a]	ee/%[b]
1	CH_2Cl_2	64	92
2	Bu^tOMe	35	94
3	EtOAc	39	94
4	toluene	42	93
5	MeCN	31	92
6	THF	43	89

[a] Only *trans*-stilbene oxide was obtained (>98:2 trans/cis). [b] Ee values were measured by HPLC using a Chiralcel OD column. The (*R*,*R*) enantiomer was the major product in each case.

that the metal did not participate in any way in the reaction of the sulfur ylide with the aldehyde. The optimum metal salt was copper acetonylacetonate.

The effect of solvent on the epoxidation process was also investigated. Reactions were carried out using copper tetramethylheptanedionate as the metal catalyst because we had found that this salt was soluble in all of the solvents we wished to investigate, unlike copper acetylacetonate (Scheme 11, Table 4), which was not completely soluble in toluene, tBuOMe, THF, or EtOAc. The table shows that all the solvents gave essentially the same enantioselectivity and that the highest yields were obtained using CH_2Cl_2.

Having optimized both the epoxidation conditions and sulfide catalyst choice (**5b**), we then performed epoxidation reactions with a range of aldehydes (Scheme 12, Table 5). It was found that good yields and high diastereo- and enantioselectivities were obtained for other aromatic and unsaturated aldehydes. However, lower yields and diastereoselectivities were observed with aliphatic aldehydes, but the level of enantioselectivity was essentially maintained. Reaction of valeraldehyde gave considerably lower enantioselectivity (see below).

Origin of Diastereoselectivity. To account for the origin of the enantioselectivity/diastereoselectivity, we needed to know whether the sulfur ylide reactions were under kinetic or

Scheme 12

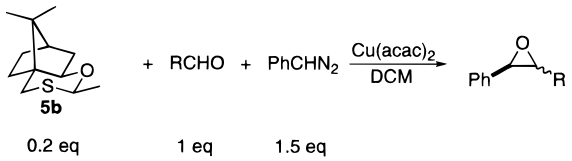
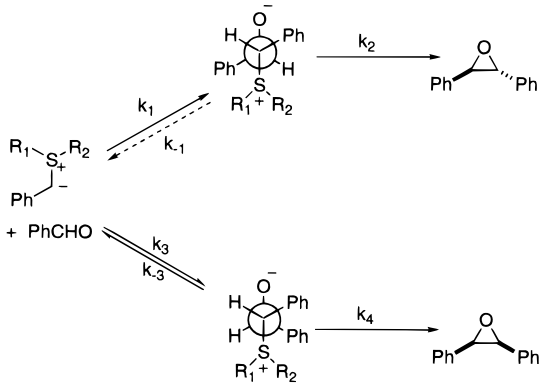


Table 5. Yields, Enantioselectivities and Ratios of Epoxides Formed from Aldehydes Using 0.2 equiv of Sulfide **5b**

entry	aldehyde	yield/%	ee/%[a]	trans/cis
1	benzaldehyde	73	94 (*R*,*R*)[b]	>98:2
2	*p*-chlorobenzaldehyde	72	92(*R*,*R*)[b]	>98:2
3	*p*-tolualdehyde	64	92(*R*,*R*)[b]	>98:2
4	cinnamaldehyde	55[c]	89[d]	>98:2
5	valeraldehyde	35	68[d]	92:8
6	cyclohexanecarbaldehyde	32	90[d]	70:30

[a] Enantiomeric excesses were determined by chiral HPLC using a Chiralcel OD column. [b] Absolute configurations were determined by comparison of $[\alpha]_D$ values with literature values.[36] [c] We originally reported a 73% yield, but this was incorrect. [d] By analogy we have assumed that the same absolute configuration (*R*,*R*) was obtained.

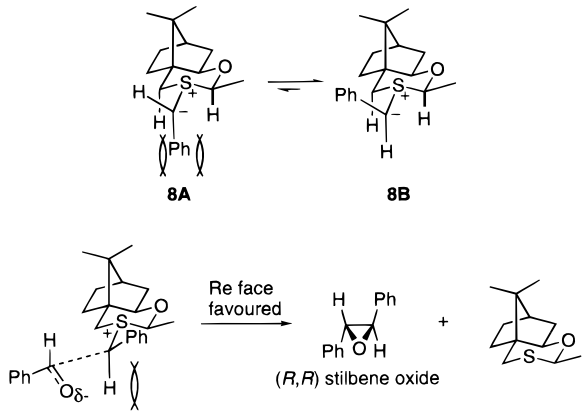
Scheme 13



thermodynamic control. From crossover experiments we had found that the addition of benzylsulfonium ylide to aldehydes was remarkably finely balanced.[37] The trans epoxide was derived directly from *irreversible* formation of the anti betaine or indirectly from *reversible* formation of the syn betaine. The cis epoxide was derived from partial reversible formation of the syn betaine. The higher trans selectivity observed in reactions with aromatic aldehydes compared to that with aliphatic aldehydes was due to greater reversibility in the formation of the syn betaine (Scheme 13).

Reactions of simple sulfides (Me_2S, tetrahydrothiophene) in the catalytic cycle with benzaldehyde give stilbene oxide as an 84:16 ratio of trans/cis epoxides.[25] However, epoxidation using our camphor-derived 1,3-oxathiane **5b** gave only trans epoxides with a range of aromatic and unsaturated aldehydes. This higher selectivity must be due to an increase in k_{-3} relative to k_4. An increase in k_{-3} relative to k_4 would be expected for sulfides of increasing steric hindrance or where the ylide had increased stability. In the case of the 1,3-oxathiane, we believe that the corresponding ylide shows increased stability relative to simple benzyl sulfonium ylides as a result of the anomeric effect (vide infra). The positive charge on sulfur can be delocalized over the oxygen, and this will lead to increased stability and therefore greater reversibility and thus greater trans selectivity. The moderate increase in stability of the ylide is evidently not sufficient to promote reversibility in syn betaine formation with aliphatic aldehydes however.

Scheme 14

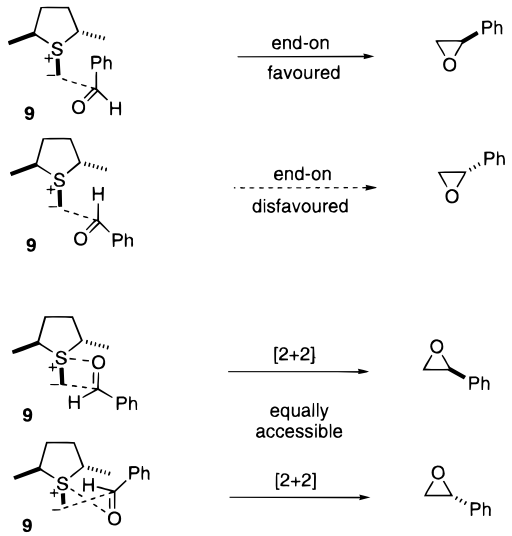


Origin of Enantioselectivity. Having established that trans epoxides are derived from irreversible formation of anti betaines, we needed information on the transition state leading to their formation in order to understand the origin of the enantioselectivity. As this was not possible, we focused on gaining information on the structure of the ylide. We believe a single sulfonium ylide is formed, as we have previously shown that alkylation of the related oxathiane **5a** only gave the equatorial sulfonium salt.[38] Ylide conformation has been studied by X-ray diffraction,[39,40] NMR,[41−46] and computation.[47,48] All of these studies indicate that the preferred conformation of sulfur ylides is one in which the filled orbital on the ylide carbon is orthogonal to the lone pair on sulfur. The barrier to rotation around the C−S bond of the semistabilized ylide, dimethyl sulfonium fluorenide, has been found to be 42 ± 1.0 kJ mol^{-1}.[46] This information implies that the ylide derived from **5b** will adopt conformations **8A** and **8B** and that these will be in rapid equilibrium at room temperature. Of these two, conformation **8B** will be favored, as **8A** suffers from 1,3-diaxial interactions between the phenyl ring and the axial groups. The aldehyde can then approach either face of the ylide, but the *re* face is more accessible as the *si* face is hindered by the equatorial methyl group (Scheme 14).

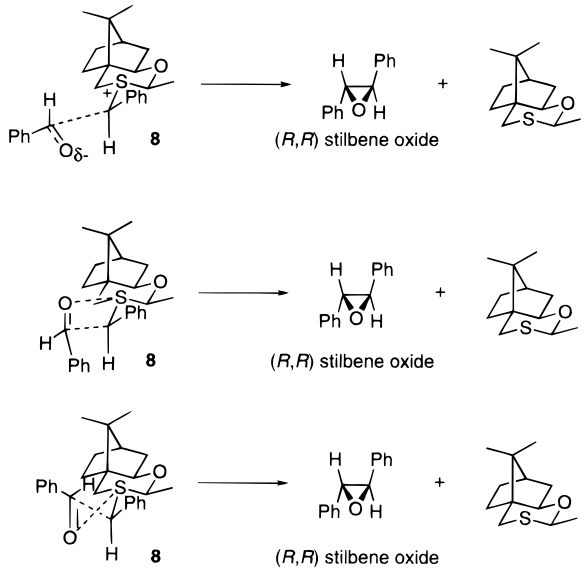
The aldehyde can react in an end-on or [2 + 2] mode, but there is no evidence, experimental or theoretical, to indicate which is preferred. While most examples invoke the end-on mode, there is circumstantial evidence that the [2 + 2] mode may be favored. This circumstantial evidence comes from a study of the asymmetric induction observed in methylene transfer from the C_2 symmetric sulfur ylide **9** to benzaldehyde.

(36) Imuta, M.; Ziffer, H. *J. Org. Chem.* **1979**, *44*, 2505.
(37) Aggarwal, V. K.; Calamai, S.; Ford, J. G. *J. Chem. Soc., Perkin Trans. 1* **1997**, 593−599.
(38) Aggarwal, V. K.; Thompson, A.; Jones, R. V. H.; Standen, M. *Tetrahedron: Asymmetry* **1995**, *6*, 2557−2564.
(39) Christensen, A. T.; Witmore, W. G. *Acta Crystallogr. B* **1969**, *25*, 73−78.
(40) Christensen, A. T.; Thom, E. *Acta Crystallogr. B* **1971**, *27*, 581−586.
(41) Ratts, K. W. *Tetrahedron Lett.* **1966**, 4707−4712.
(42) Cook, A. F.; Moffatt, J. G. *J. Am. Chem. Soc.* **1968**, *90*, 740−747.
(43) Matsuyama, H.; Minato, H.; Kobayashi, M. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 3393−3396.
(44) Galloy, J.; Watson, W. H.; Craig, D.; Guidry, C.; Morgan, M.; McKellar, R.; Ternay, A. L.; Martin, G. *J. Heterocycl. Chem.* **1983**, *20*, 399−405.
(45) Johnson, A. W.; Amel, R. T. *J. Org. Chem.* **1969**, *34*, 1240−1247.
(46) Aggarwal, V. K.; Schade, S.; Taylor, B. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2811−2813.
(47) Bernardi, F.; Schlegel, H. B.; Whangbo, M.-Y.; Wolfe, S. *J. Am. Chem. Soc.* **1977**, *99*, 5633−5636.
(48) Eades, R. A.; Gassman, P. G.; Dixon, D. A. *J. Am. Chem. Soc.* **1981**, *103*, 1066−1068.

Scheme 15



Scheme 16



In this process styrene oxide was obtained with essentially no enantioselectivity (Scheme 15).[49] Analysis of the two possible modes shows that an end-on approach would be expected to furnish styrene oxide with high enantioselectivity, as only one of the two approaches would be expected to be favored. In contrast, both approaches in the [2 + 2] addition mode are equally accessible and so this would give styrene oxide with low enantioselectivity, as observed. Thus both end-on and [2 + 2] modes should be considered.

End-on and [2 + 2] transition states in the reaction of ylide **8** with benzaldehyde, leading to trans epoxides, are shown in Scheme 16. From analysis of molecular models of these transition states it is clear that they can all be accommodated. Thus, our own results do not provide any further evidence as to which mode (end-on versus [2 + 2]) is favored. The transition states shown in Scheme 16 account for the high enantioselectivities observed.

We were curious as to the origin of the minor enantiomer and considered the possibility that it arose from *si*-face attack.

(49) This work was carried out by J. K. Whitesell and discussed in the following review: Durst, T.; Breau, L.; Ben, R. N. *Phosphorous Sulfur Relat. Elem.* **1993**, *74*, 215−232.

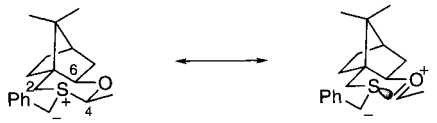


Figure 1.

If this was the case, enantioselectivity should be highly dependent upon the size of the equatorial substituent. However, increasing the size of this substituent from Me to Pr^i did not result in a concomitant increase in selectivity (Table 2, entries 2 and 3). Indeed, the enantioselectivity was essentially the same for a range of substituents suggesting that the facial selectivity was essentially complete.[50] Even in the absence of a substituent, good *re*-face selectivity was still observed (**5a** gave 41% ee: Table 2, entry 1). This latter result in particular suggested that the oxygen of the oxathiane was affecting the facial selectivity of the ylide, and we believe it is exerting this effect through a combination of the anomeric[51] and Cieplak effects.[52−54]

A resonance form of the ylide is shown in Figure 1. If there is a contribution from this resonance form to the ground-state structure of the ylide, then the C_4−S bond should be more electron rich than the C_2−S bond and this should affect the face selectivity of the ylide. The resonance form shown in Figure 1 is a result of the anomeric effect and should manifest itself in shortening of the C_4−O bond relative to the C_6−O bond and lengthening of the C_4−S bond relative to the C_2−S bond. Indeed, this was observed in the X-ray structure of oxathiane **5p** (Table 6, Figure 2).[55] The anomeric effect should be even greater in the ylide, but it was not possible to prepare and isolate this reactive intermediate. We therefore prepared the corresponding sulfoxide, an electronic analogue of the ylide, and were able to grow crystals of **10** (Figure 2).[55] The sulfoxide did indeed show even greater differences in bond lengths, demonstrating an even greater anomeric effect (Table 6).[56] As a control, an X-ray of the thiane sulfoxide **17**[55] (see later for synthesis) was also obtained and showed essentially no differences in bond lengths (Table 6).[56] This proved that the differences in bond lengths observed with oxathiane **10** were due to a significant anomeric effect. The X-ray data provide strong evidence for a significant contribution of the resonance form depicted in Figure 2 to the structure of the ylide. This

(50) Lower selectivities were observed in cases containing an aromatic ring in the side chain of the equatorial substituent. It is possible that aromatic groups offer π-stacking opportunities to an incoming aromatic aldehyde and result in some *si*-face attack.

(51) For a comprehensive review on the anomeric effect, including a discussion on second row elements, see (a) Juaristi, E.; Cuevas, G. *Tetrahedron* **1992**, *48*, 5019−5087 and also (b) Kirby, A. J. *The Anomeric Effect and Related Stereoelctronic Effects at Oxygen*, 1st ed.; Springer-Verlag: Berlin, 1983.

(52) Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540−4552.

(53) Cieplak, A. S.; Tait, B. D.; Johnson, C. R. *J. Am. Chem. Soc.* **1989**, *111*, 8447−8462.

(54) Gung, B. W. *Tetrahedron* **1996**, *52*, 5263−5301.

(55) The author has deposited atomic coordinates for **5p, 10**, and **17** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained on request from the director at Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.

(56) Second row elements show a substantial anomeric effect, often greater than first row elements.[51a] Indeed, n_S are better donors than n_O, and σ^*_{C-S} is a more effective acceptor orbital than σ^*_{C-O}.[51a] In oxathianes **5** two anomeric effects will be in operation ($n_S \rightarrow \sigma^*_{C-O}$ and $n_O \rightarrow \sigma^*_{C-S}$) and differences in bond length will result if one of the two anomeric effects is more powerful, and evidently one is ($n_O \rightarrow \sigma^*_{C-S}$). In the sulfoxide, only one anomeric effect is in operation ($n_O \rightarrow \sigma^*_{C-S}$). As this overlap of orbitals is likely to be even more effective than in the 1,3-oxathiane and because the anomeric effect in the reverse direction is essentially zero, very significant differences in bond lengths result. Indeed, the observed differences in bond lengths of oxathiane **10** are some of the largest differences recorded.

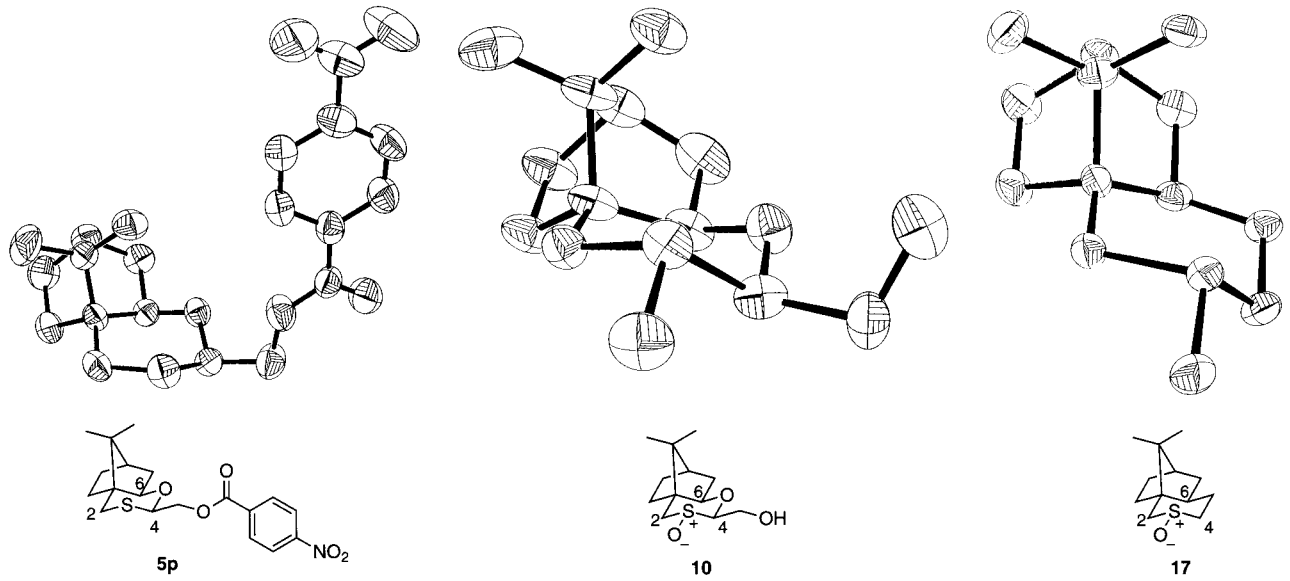


Figure 2.

Table 6. Bond Lengths from X-ray Structures of **5p**, **10**, and **17**

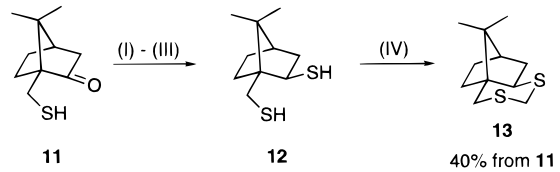
entry	compound	C_2-S/Å	$S-C_4$/Å	C_4-O/Å	$O-C_6$/Å	C_4-C_5/Å	C_6-C_5/Å
1	**5p**	1.798	1.814	1.406	1.439		
2	**10**	1.815	1.854	1.402	1.447		
3	**17**	1.809	1.801			1.537	1.524

resonance form will result in the C_4-S bond being more electron rich than the C_2-S bond. According to Cieplak, nucleophilic reactions on π systems occur on the face opposite the better donor.[57] Thus, the ylide derived from **5a** should preferentially react on the face opposite to the C_4-S bond, that is, the *re* face, and this is observed.

To gain further evidence of this combined anomeric and Cieplak effect, sulfur and carbon analogues (**13** and **16** respectively) of oxathiane **5a** were studied. These substrates were chosen to minimize steric effects in the epoxidation process and to allow us to focus on the above electronic effects.

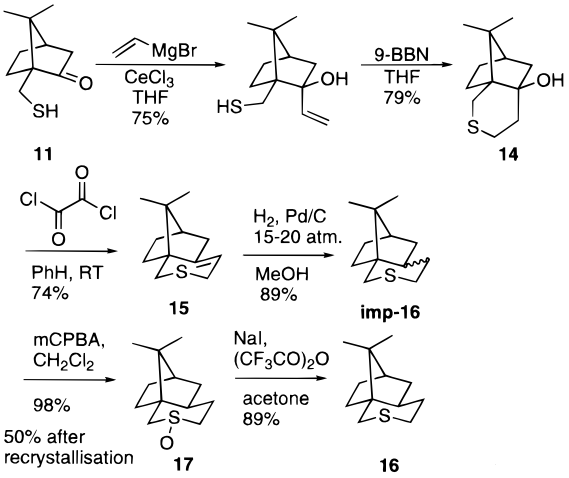
The sulfur analogue **13** was prepared as shown in Scheme 17. Dithiol **12**[58,59] was treated with paraformaldehyde and tosic acid under Dean−Stark conditions to give the desired 1,3-dithiane **13**. The carbon analogue **16** was prepared as shown in Scheme 18. Addition of vinylcerium[60,61] to **11** gave the exo alcohol, which upon treatment with 9-BBN gave the corresponding 4-hydroxythiane.[62] The six-membered ring is obtained, as the addition of thiyl radicals to olefins is reversible and the thiane results from formation of the more stable secondary radical.[63−67] Attempts to prepare the half oxalate chloride of **14** for subsequent radical deoxygenation[68,69] were unsuccessful as treatment with oxalyl chloride resulted in

Scheme 17

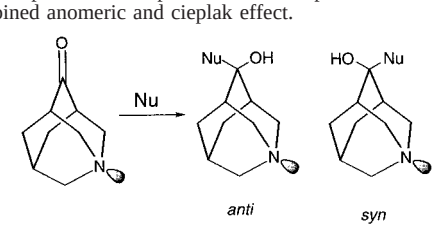


(I) PhCOCl, DMAP, DCM, 0 °C
(II) Lawesson's reagent, PhMe, 110 °C
(III) $LiAlH_4$, Et_2O
(IV) $(CH_2O)_n$, *p*-TSA, PhMe, 110 °C

Scheme 18



(57) The only other example in which an anomeric or anomeric-type effect controlled the outcome of a reaction in a manner similar to that described above is provided by Le Noble (Hahn, J. M.; le Noble, W. J. *J. Am. Chem. Soc.* **1992**, *114*, 1916−1917). He studied the addition of nucleophiles to 5-azaadamantone and found a slight preference for addition of MeLi anti to nitrogen. BH_4 reduction in MeOH gave addition syn to nitrogen possibly because of hydrogen bonding or metal chelation with the nitrogen lone pair. These experiments do not provide clear-cut evidence for a combined anomeric and cieplak effect.



(58) Montenegro, E.; Echarri, R.; Claver, C.; Castillon, S.; Moyano, A.; Pericas, M. A.; Riera, A. *Tetrahedron: Asymmetry* **1996**, *7*, 3553−3558.
(59) Oae, S.; Togo, H. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 3802−3812.
(60) Imamoto, T.; Takiyama, N.; Nakamura, K. *Tetrahedron Lett.* **1985**, *26*, 4763−4766.
(61) Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392−4398.
(62) Masuda, Y.; Hoshi, M.; Nunokawa, Y.; Arase, A. *J. Chem. Soc., Chem. Commun.* **1991**, 1444−1445.
(63) Henrick, C. A.; Willy, E.; Baum, J. W.; Baer, T. A.; Garcia, B. A.; Mastre, T. A.; Chang, S. M. *J. Org. Chem.* **1975**, *40*, 1−7.
(64) Schulte-Elte, K. H.; Ohloff, G. *Helv. Chim. Acta* **1968**, *51*, 548−553.

Table 7. Yields and Enantioselectivities of Epoxides Formed from Benzaldehyde Using 0.2 equiv of Sulfide

entry	sulfide[a]		yield/%	ee/%[d]
1	**16**	C	96[b]	20
2	**5b**	O	83[c]	41
3	**13**	S	19[c]	44

[a] The element in the 5 position of the thiane is indicated (thiane **16**, oxathiane **5b**, and dithiane **13**). [b] 96:4 trans/cis ratio was observed.[c] Only *trans*-stilbene oxide was observed (>98:2 trans/cis). [d] Ee values were measured by HPLC using a Chiralcel OD column. The (*R*,*R*) enantiomer was the major product in each case.

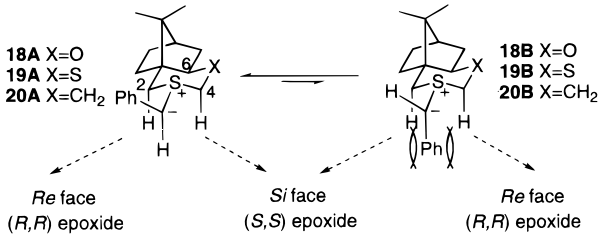


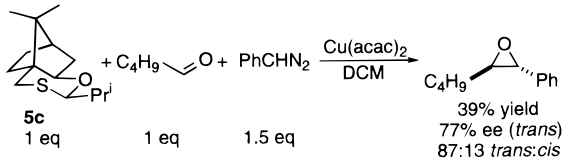
Figure 3.

elimination to give **15** instead. The unsaturated thiane was reduced to the thiane **16** by hydrogenation,[70] but a mixture of inseparable products were obtained. Attempts to purify this mixture by formation of the $HgCl_2$ salt[71] and subsequent recrystallization were unsuccessful. Oxidation to the sulfoxide **17** led to a substrate that we were able to recrystallize, and subsequent reduction gave pure **16**.

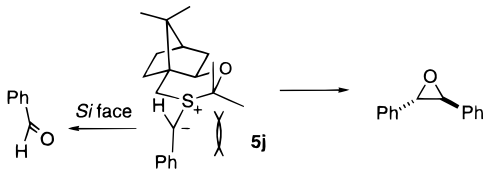
In the epoxidation process, the sulfur analogue **13** should show enhanced selectivity (greater anomeric effect), and the carbon analogue **16** should show reduced selectivity (no anomeric effect). In the event, the sulfur analogue **13** gave only slightly higher selectivity (and only moderate yield[72]), while the carbon analogue **16** gave much reduced selectivity (Table 7).

The stereochemical outcome of the ylide reaction is determined by two factors: the face selectivity of the ylide and the conformation of the ylide (Figure 3). The sulfur analogue **13** of the oxathiane was expected to give an increase in selectivity due to an increase in the anomeric effect,[73] which should result in an increase in face selectivity. However, replacement of oxygen by sulfur results in a more distorted chair and therefore reduced 1,3-diaxial interactions, which will result in an increase in the population of conformer **19B** (Figure 3). Thus, the ylide conformations may react with increased face selectivity, but a greater proportion of conformer **19B** will result in a reduction in enantioselectivity. The observed enantioselectivity results from a balance between these two effects. The carbon analogue **16** gave reduced selectivity. As the thiane adopts a very similar

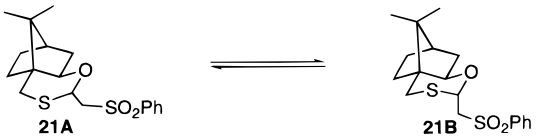
Scheme 19



Scheme 20



Scheme 21



conformation to the 1,3-oxathiane (C−O and C−C have similar bond lengths), the ratio of conformers **18A/18B** and **20A/20B** will be similar, and the difference in enantioselectivity must result from a difference in face selectivity of the ylide. The oxygen of the 1,3-oxathiane therefore exerts a significant stereoelectronic effect in promoting reaction on the face opposite to this group.

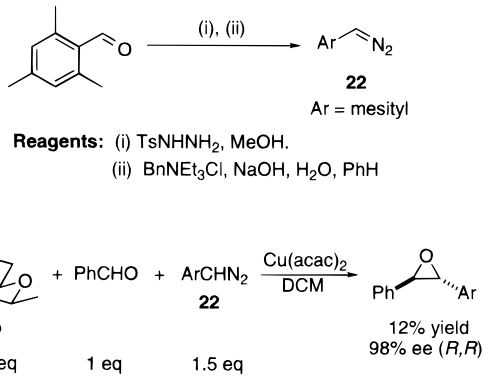
We therefore believe that there is a very high preference for *re*-face attack as a result of combined steric and electronic effects, which both act in concert and reinforce each other. The lower enantioselectivity observed with valeraldehyde compared to the other aldehydes could be due to its smaller size, which in turn may allow some *si*-face attack on the ylide. To test this, the size of the equatorial substituent on the sulfide was increased. Using sulfide **5c** higher enantioselectivity was indeed obtained (Scheme 19). This confirmed that facial selectivity in the reaction of sulfide **5b** is dependent on the size of the aldehyde; α-branched, aromatic, and unsaturated aldehydes react with essentially complete facial selectivity, while unbranched aldehydes react with moderate facial selectivity.

As facial selectivity appears to be complete, the source of the minor enantiomer could be reaction of the minor conformation of the ylide **8A** (Scheme 14). To reduce the amount of this minor conformation, we prepared thioacetals bearing axial substituents **5j** (R = Me) and **5l** (R = R^1 = *spiro*-cyclobutyl) to increase the 1,3-diaxial interactions. However, instead of increased selectivity, a decrease in enantioselectivity was observed. A study of the conformation of these thioacetals revealed the origin of this reduction in selectivity. NOE experiments carried out on **5b** and **5j** revealed that **5j** existed in both chair and boat forms, while **5b** adopted the chair form only. Reaction of the corresponding ylide from the boat conformer of **5j** should give the opposite enantiomer to that from the chair form (Scheme 20). The boat conformation may be favored because of severe 1,3-diaxial interactions in the chair form. The related thioacetal **21** has also been shown to exist in both chair (**21A**) and boat (**21B**) forms (Scheme 21).[74]

An alternative way to increase the 1,3-diaxial interactions and favor ylide conformer **8B** over **8A** would be to increase the bulk of the aromatic ring. Thus mesityldiazomethane **22**

(65) Thalmann, A.; Oertle, K.; Gerlach, H. *Org. Synth.* **1984**, *63*, 192−197.
(66) Walling, C.; Helmreich, W. *J. Chem. Soc. B* **1959**, *81*, 1144−1148.
(67) Claus, P. K.; Vierhapper, F. W.; Willer, R. L. *J. Org. Chem.* **1977**, *42*, 4016−4023.
(68) Barton, D. H. R.; Crich, D. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1603−1611.
(69) Barton, D. H. R.; Crich, D. *J. Chem. Soc., Chem. Commun.* **1984**, 774−775.
(70) Attempts to carry out ionic reduction of **15** failed due to competing rearrangements of the camphor skeleton. Hydrogenation using diimide and hydroboration of **15** were also unsuccessful.
(71) Whitehead, E. V.; Dean, R. A.; Fidler, F. A. *J. Am. Chem. Soc.* **1951**, *73*, 3632−3635.
(72) The low yield obtained with **13** is typical of 1,3-dithianes. 1,3-Dithiane itself gave 30% yield of stilbene oxide in the catalytic cycle. Also, ylide formation is quite sensitive to the steric hindrance of the sulfide, and only the more accessible sulfur should react.
(73) Juaristi, E.; Cuevas, G. *Tetrahedron* **1992**, *48*, 5019−5087.
(74) De Lucchi, O.; Lucchini, V.; Marchioro, C.; Modena, G. *Tetrahedron Lett.* **1985**, *26*, 4539−4542.

Scheme 22



was prepared and used in the catalytic cycle with thioacetal **5b** and benzaldehyde (Scheme 22). Greatly increased enantioselectivity was observed (but in only low yield). It therefore seems likely that the minor enantiomer formed in the reactions involving phenyldiazomethane arises from reaction of the minor conformer **8A**. Attempts to reduce the proportion of the minor conformer **8A** by lowering the temperature were unsuccessful. Reaction of *trans*-cinnamaldehyde[75] with thioacetal **5b**, phenyldiazomethane, and $Rh_2(OAc)_4$[76] at 0 °C furnished the epoxide with similar enantioselectivity. Evidently, the small difference in temperature was not sufficient to make a significant difference in enantioselectivity. At even lower temperatures the diazo compound did not decompose.

Conclusion

Oxathiane **5b** has been found to be a highly efficient sulfide for carbonyl epoxidation. It is easily prepared in two steps from camphorsulfonyl chloride (which is available in both enantiomeric forms) and can be used in substoichiometric amounts in our catalytic cycle. In reactions with aromatic and unsaturated aldehydes only trans epoxides are obtained, and this high selectivity is due to irreversible formation of the anti betaine and greater reversibility in the formation of the syn betaine. This is believed to result from the enhanced stabilization of the ylide due to an anomeric effect from the ring oxygen. Indeed, replacement of the ring oxygen by carbon results in reduced diastereoselectivity (96:4 compared to >98% de).

Two factors control the enantioselectivity of the epoxidation process: ylide conformation and face selectivity of the ylide. The sulfur ylide derived from oxathiane **5b** can exist in two conformations **8A** and **8B**. Conformer **8A** suffers from 1,3-diaxial interactions, and so conformation **8B** is favored. The ylide can potentially react on either face, but it is believed that there is very high selectivity for *re*-face attack with aromatic, unsaturated, and α-branched aldehydes. The high face selectivity is a result of steric effects (the equatorial methyl group) and electronic effects (a combination of anomeric and Cieplak effects), which both favor *re*-face attack, and they therefore reinforce each other. The minor enantiomer is believed to come from the reaction of the less favored ylide conformation **8A**. When more hindered diazo compounds (mesityldiazomethane) are used, the proportion of the minor conformation **8A** is reduced further as a result of increased 1,3-diaxial interactions and the enantiomeric excess is essentially complete. The lower selectivity observed with valeraldehyde is a result of reduced facial selectivity of the ylide due to reduced steric effects.

(75) This aldehyde was chosen as it gave a slightly lower enantioselectivity compared to other aldehydes, thereby allowing us to monitor changes more easily.

(76) Use of $Cu(acac)_2$ was unsuccessful. No epoxides, only stilbenes, were formed.

Experimental Section

Proton chemical shifts were recorded on the δ scale and were measured relative to the residual signal of chloroform at δ 7.25. All coupling constants are measured in hertz. The deuterated solvents used were as specified in the Experimental Section. ^{13}C chemical shifts were measured from the central peak of chloroform at δ 77.0. $[\alpha]^{20}_D$ values are given in 10^{-1} deg cm^2 g^{-1}. Enantiomeric excesses (ee) were determined by chiral HPLC using a Chiralcel OD column.

Typical Procedure for the Preparation of 1,3-Oxathianes. (a) Preparation of (1*R*,4*R*,6*R*,8*R*)-4,11,11-Trimethyl-5-oxa-3-thia-tricyclo-[6.2.1.0^{1,6}]undecane (5b). To a cooled solution (ice bath) of (+)-(10)-mercaptoisoborneol[30] (270 mg, 1.45 mmol) and acetaldehyde (0.24 mL, 4.29 mmol) in dichloromethane (2 mL) under argon was added boron trifluoride etherate (0.20 mL, 1.63 mmol). After a few minutes, the reaction mixture was loaded directly onto a silica gel column and eluted with 50% dichloromethane in petroleum ether (40−65 °C) to give the desired sulfide **5b** as a clear oil (305 mg, 99%) (Found: C, 67.71; H, 9.26; S, 15.30. $C_{12}H_{20}OS$ requires C, 67.87; H, 9.49, S, 15.10): $[\alpha]^{20}_D$ −140.4 (*c* 1.14 in $CHCl_3$); υ_{max} (thin film)/cm^{-1} 2940, 2872, 1097, 1072; δ_H (250 MHz, $CDCl_3$) 0.77−1.91 (16H, m), 2.68 (1H, d, J = 14.5), 3.08 (1H, d, J = 14.5), 3.58 (1H, dd, J = 3.5, 8.0), 4.73 (1H, q, J = 6.5); δ_C (63 MHz, $CDCl_3$) 20.48, 21.75, 23.28, 27.29, 28.67, 34.51, 37.85, 41.73, 45.57, 46.60, 77.62, 85.25; *m*/*e* (EI) 212 (M$^+$, 86%), 135 (95), 93 (100) (Found: M$^+$, 212.1238. $C_{12}H_{20}OS$ requires 212.1235).

(b) Preparation of (1*R*,4*R*,6*R*,8*R*)-4-(Acetoxymethyl)-11,11-dimethyl-5-oxa-3-thia-tricyclo[6.2.1.0^{1,6}]undecane (5n). To a solution of sulfide **5l** (118 mg, 0.52 mmol) and acetic anhydride (60 μL, 0.64 mmol) in ether (1 mL) under nitrogen was added pyridine (46 μL, 0.57 mmol). The stirred solution was left overnight before loading directly onto a silica gel column and eluting with 10% ethyl acetate in petroleum ether (40−65 °C) to give the desired *sulfide* **5n** as a clear oil (129 mg, 93%): $[\alpha]^{20}_D$ −120.6 (*c* 6.47 in $CHCl_3$); υ_{max} (thin film)/cm^{-1} 2953, 2879, 1746, 1220, 1071; δ_H (250 MHz, $CDCl_3$) 0.79−1.09 (5H, m), 1.28 (3H, s), 1.38−1.54 (3H, m), 1.61−1.75 (3H, m), 1.84−1.95 (1H, m), 2.07 (3H, s), 2.76 (1H, d, J = 14.0), 3.07 (1H, d, J = 14.0), 3.60 (1H, dd, J = 3.0, 8.0), 4.17−4.23 (2H, m), 4.91 (1H, dd, J = 4.5, 6.0); δ_C (63 MHz, $CDCl_3$) 20.41, 20.88, 23.09, 27.23, 28.25, 34.23, 37.72, 42.47, 45.49, 46.70, 65.82, 79.35, 85.17, 170.66; *m*/*e* (EI) 210 (M$^+$ − AcOH, 100%), 168 (47), 135 (76), 121 (37) (Found: M$^+$ − AcOH, 210.1078. $C_{12}H_{18}OS$ requires 210.1078).

(c) Preparation of (1*R*,4*R*,6*R*,8*R*)-4-(*p*-Nitrobenzoylmethyl)-11,11-dimethyl-5-oxa-3-thia-tricyclo[6.2.1.0^{1,6}]undecane (5p). To a slurry of *p*-nitrobenzoyl chloride (100 mg, 0.54 mmol) in pyridine (1 mL) was added a solution of sulfide **5l** (94 mg, 0.41 mmol) in pyridine (0.3 mL) at 0 °C under nitrogen. After 1.5 h the reaction mixture was allowed to warm to room temperature and was left for 5 h. The reaction mixture was poured into water, the resulting mixture was extracted with dichloromethane (3 times), and the combined organic extracts were dried ($MgSO_4$). After filtration and removal of the solvent under reduced pressure, the residue was purified by flash chromatography, eluting with 10% dichloromethane in petroleum ether (40−65 °C) to give the desired *sulfide* **5p** as a yellow crystalline solid (114 mg, 73%), mp 67−69 °C (Found: C, 60.22; H, 6.15; N, 3.51; S, 8.24. $C_{19}H_{23}NO_3S$ requires C, 60.46; H, 6.14; N, 3.71; S, 8.49): $[\alpha]^{20}_D$ −83.9 (*c* 5.96 in $CHCl_3$); υ_{max} (KBr disk)/cm^{-1} 2962, 1724, 1522, 1274; δ_H (250 MHz, $CDCl_3$) 0.77−1.19 (5H, m), 1.32 (3H, s), 1.41−1.56 (1H, m), 1.63−1.79 (3H, m), 1.83−1.96 (1H, m), 2.80 (1H, d, J = 14.0), 3.12 (1H, d, J = 14.0), 3.65 (1H, dd, J = 3.0, 8.0), 4.51 (2H, d J = 5.0) 5.07 (1H, d, J = 5.0), 8.15−8.33 (4H, m); δ_C (63 MHz, $CDCl_3$) 20.4, 23.2, 27.2, 28.3, 34.2 37.7, 42.5, 45.5, 46.8, 66.9, 79.2, 85.4, 123.6, 131.0, 135.3, 150.6, 164.3; *m*/*e* (CI) 378 (M$^+$, 8%), 395 (M$^+$ + NH_3, 100), 211 (40), 169 (12) (Found: M$^+$, 378.1359. $C_{19}H_{23}NO_3S$ requires 378.1375).

(d) Preparation of (1*R*,4*R*,6*R*,8*R*)-4-(Trimethylsilyl)-11,11-dimethyl-5-oxa-3-thia-tricyclo[6.2.1.0^{1,6}]undecane (5q). To a solution of sulfide **5a** (285 mg, 1.44 mmol) in tetrahydrofuran (3 mL) at −78 °C under nitrogen was added sec-BuLi (1.1 mL of a 1.3 M solution in

cyclohexane). After a few minutes, chlorotrimethylsilane (0.3 mL, 2.36 mmol) was added to the yellow solution. After 2.5 h the reaction was quenched at −78 °C with water before allowing the mixture to warm to room temperetaure and pouring it onto brine. The resulting mixture was extracted with dichloromethane (3 times), and the combined organic extracts were dried ($MgSO_4$). After filtration and removal of the solvent under reduced pressure, the residue was purified by flash chromatography, eluting with 50% dichloromethane in petroleum ether (40−65 °C) to give the desired *sulfide* **5q** as a white crystalline solid (314 mg, 81%), mp 36−39 °C (Found: C, 62.02; H, 9.49; S, 11.62. $C_{14}H_{26}OSSi$ requires C, 62.16; H, 9.69; S, 11.85): $[\alpha]^{20}_D$ −140.1 (*c* 11.49 in $CHCl_3$); υ_{max} (KBr disk)/cm^{-1} 2960, 2790, 1244, 1069; δ_H (250 MHz, $CDCl_3$) 0.07 (9H, s), 0.78−1.06 (5H, m), 1.22−1.47 (4H, m), 1.54−1.87 (4H, m), 2.69 (1H, d, J = 14.0), 3.00 (1H, d, J = 14.0), 3.38 (1H, dd, J = 3.0, 8.0), 4.44 (1H, s); δ_C (63 MHz, $CDCl_3$) −3.64, 20.51, 23.37, 27.49, 29.02, 35.19, 38.02, 42.64, 45.60, 46.58, 74.86, 85.42; *m*/*e* (EI) 270 (M^+, 11%), 197 (7), 165 (69), 121 (100) (Found: M^+, 270.1469. $C_{14}H_{26}OSSi$ requires 270.1474).

General Procedure for the Epoxidation of Benzaldehyde Using Sulfides 5, 13, and 16. By use of a syringe pump, phenyldiazomethane (0.75 mmol in 0.25 mL of dichloromethane) was added to a stirred solution of the desired sulfide (0.1 mmol), $Cu(acac)_2$ (0.025 mmol), and benzaldehyde (0.5 mmol) in dichloromethane (0.25 mL) under nitrogen at room temperature over a period of 3 h. After being stirred for an additional 1 h, the solvent was removed under reduced pressure and the residue was chromatographed on silica gel to give *trans*-stilbene oxide: δ_H (250 MHz, $CDCl_3$) 3.85 (2H, s), 7.35 (10 H, m) (lit. 25).

Epoxidation of Benzaldehyde Using Sulfide 5b in Dichloromethane with Different Metal Catalysts. By use of a syringe pump, phenyldiazomethane (0.75 mmol in 0.25 mL of dichloromethane) was added to a stirred solution of sulfide **5b** (0.1 mmol), the desired copper salt (0.025 mmol) or rhodium acetate (0.01 mmol), and benzaldehyde (50 μL, 0.5 mmol) in dichloromethane (0.25 mL) under nitrogen at room temperature over a period of 3 h. After being stirred for an additional 1 h, the solvent was removed under reduced pressure and the residue was chromatographed on silica gel to give *trans*-stilbene oxide: δ_H (250 MHz, $CDCl_3$) 3.85 (2H, s), 7.35 (10 H, m) (lit. 25).

Epoxidation of Benzaldehyde Using Sulfide 5b in Different Solvents. By use of a syringe pump, phenyldiazomethane (0.75 mmol in 0.25 mL of the desired solvent) was added to a stirred solution of sulfide **5b** (0.1 mmol), $Cu(Me_3COCHCOMe_3)_2$ (0.025 mmol), and benzaldehyde (0.5 mmol) in the same solvent (0.25 mL) under nitrogen at room temperature over a period of 3 h. After being stirred for an additional 1 h, the solvent was removed under reduced pressure and the residue was chromatographed on silica gel to give *trans*-stilbene oxide: δ_H (250 MHz, $CDCl_3$) 3.85 (2H, s), 7.35 (10 H, m) (lit. 25).

Typical Procedure for the Epoxidation of Aldehydes Using Sulfide 5b. By use of a syringe pump, phenyldiazomethane (1.5 mmol in 0.5 mL of dichloromethane) was added to a stirred solution of sulfide **5b** (0.2 mmol), $Cu(acac)_2$ (0.05 mmol), and the aldehyde (1 mmol) in dichloromethane (0.5 mL) under nitrogen at room temperature over a period of 3 h. After being stirred for an additional 1 h, the solvent was removed in vacuo and the residue was chromatographed on silica gel to give the desired epoxide. ***trans*-Stilbene oxide**: δ_H (250 MHz, $CDCl_3$) 3.85 (2H, s), 7.35 (10 H, m) (lit. 25). ***trans*-2-(4-Chlorobezeneyl)-3-phenyloxirane**: δ_H (250 MHz, $CDCl_3$) 3.82 (1H, d, J = 2.0), 3.85[t] (1H, d, J = 2.0), 7.04−7.50 (9H, m) (lit. 25). ***trans*-2-(4-Tolyl)-3-phenyloxirane**: δ_H (250 MHz, $CDCl_3$) 2.37 (3H, s), 3.83 (1H, d, J = 1.5), 3.86 (1H, d, J = 1.5), 7.16−7.44 (9H, m) (lit. 19 and 36). ***trans*-2-(*trans*-2-Phenylethylene)-3-Phenyloxirane**: δ_H(250 MHz, $CDCl_3$) 3.52 (1H, dd, J = 2.0,8.0), 3.88 (1H, d, J = 2.0), 6.06 (1H, dd, J = 8.0,16.0), 6.72 (1H, d, J = 16.0), 7.10−7.60 (10H, m) (lit. 77). **2-Cyclohexyl-3-phenyloxirane**: δ_H (250 MHz, $CDCl_3$) 0.76−2.09 (10H, m), 2.76[t] (1H, dd, J = 7.0, 2.0), 2.91[c] (1H, dd, J = 9.0, 4.0), 3.68[t] (1H, d, J = 2.0), 4.08[c] (1H, d, J = 4.0), 7.20 (5H, m) (lit. 25). **2-*n*-Butyl-3-phenyloxirane**: δ_H (250 MHz, $CDCl_3$) 0.90−1.90 (7H, m), 2.95[t] (1H, dt, J = 2.0, 5.5), 3.15[c] (1H, m), 3.61[t] (1H, d, J = 2.0), 4.08[c] (1H, d, J = 4.5), 7.35 (5H, m) (lit. 25).

(77) Padwa, A.; Gasdaska, J. R. *Tetrahedron* **1988**, *44*, 4147−4156.

Preparation of (1*S*,4*R*,6*R*,8*R*)-(11,11-Dimethyl-5-oxa-3-thia-tricyclo[6.2.1.0^{1,6}]undec-4-yl)-methanol-3-oxide (10). A solution of 3-chloroperoxybenzoic acid (125 mg, 0.73 mmol) in dichloromethane (0.5 mL) was added to a solution of sulfide **5l** (141 mg, 0.62 mmol) in dichloromethane (1 mL) under nitrogen. After 15 h, the solvent was removed under reduced pressure and the residue was loaded onto a silica gel column eluting with ethyl acetate. The second fraction, eluted with acetone, gave *sulfoxide* **10** as a white crystalline solid (136 mg, 96%), mp 145−146 °C: $[\alpha]^{20}_D$ −151.5 (*c* 1.65 in $CHCl_3$); υ_{max} (KBr disk)/cm^{-1} 3377 (OH), 3275 (OH), 2955, 1022, 998; δ_H (250 MHz, $(D_3C)_2SO$) 0.91 (3H, s), 1.01 (3H, s), 0.97−1.12 (1H, m), 1.12−1.25 (1H, m), 1.44−1.83 (5H, m), 2.72 (1H, d, J = 12.5), 3.50 (1H, d, J = 12.5), 3.66−3.81 (2H, m), 3.81−3.90 (1H, m), 4.14 (1H, dd, J = 5.0, 2.0), 5.18 (1H, dd, J = 6.0, 5.5); δ_C (63 MHz, $(D_3C)_2SO$) 20.49, 22.85, 27.19, 33.00, 36.98, 45.47, 46.81, 51.62, 52.49, 59.00, 85.02, 96.61.

Preparation of (1*S*,4*R*)-10-Mercaptomethyl-7,7-dimethyl-bicyclo-[2.2.1]heptan-2-one (11). Camphorsulfonyl chloride (12.0 g, 48 mmol) and triphenylphosphine (50.1 g, 191 mmol) were refluxed in a mixture of water (40 mL) and 1,4-dioxane (160 mL) for 1 h under nitrogen. After the reaction mixture had cooled it was extracted with petroleum ether (200 mL and 3 × 100 mL). The combined organic extracts were washed with water (2 × 100 mL) and brine (100 mL) before being dried over $MgSO_4$. After filtration and removal of the solvents under reduced pressure were complete, the resulting oil was loaded directly onto a silica gel column and eluted with 5% ethyl acetate in petroleum ether to give thiol **11** as a white crystalline solid (7.3 g, 82%), mp 62−65 °C [lit. 59, 65−66 °C]: δ_H (250 MHz, $CDCl_3$) 0.89 (3 H, s), 1.00 (3 H, s), 1.21−2.01 (6H, m), 2.07 (1H, t, J = 4.6), 2.26−2.43 (2H, m), 2.85 (1H, dd, J = 13.7, 6.7) [lit. 59, δ_H (CCl_4) 0.93 (3 H, s), 1.05 (3 H, s), 1.2−2.6 (8H, m), 2.73 (1H, d, J = 6), 2.95 (1H, d, J = 6)]; δ_C (63 MHz, $CDCl_3$) 19.83, 20.31, 21.40, 26.63, 27.06, 29.92, 43.29, 43.67, 47.85, 60.65.

Preparation of (1*R*,2*R*,4*R*)-1-Mercaptomethyl-7,7-dimethyl-bicyclo[2.2.1]heptane-2-thiol (12). A solution of (1*R*,4*R*)-dithiobenzoic acid 7,7-dimethyl-2-thioxo-bicyclo[2.2.1]hept-1-ylmethyl ester[58] (0.52 g, 1.6 mmol) in ether (9 mL) was added dropwise to a suspension of lithium aluminum hydride (62 mg, 1.6 mmol) in ether (9 mL) at room temperature under nitrogen. After a few seconds, the red color of the starting material had been quenched. After 30 min, the reaction was quenched with ethyl acetate (0.5 mL) before hydrochloric acid (1 mL of a 3% solution) was added and the suspension was filtered. The solids were washed with ether, and the combined organics were dried over $MgSO_4$. After filtration of the mixture and removal of the solvents under reduced pressure, the residue was loaded onto a silca gel column and eluted with 5% ethyl acetate in petroleum ether to give a 10:1 mixture of exo/endo dithiols (0.24 g, 72% of **12**) together with benzylmercaptan (0.14 g, 67%): δ_H (250 MHz, $CDCl_3$) 0.85 (3H, s), 1.02 (3H, s), 1.12−2.06 (10H, m), 2.55 (1H, dd, J = 13.0, 7.0), 2.98 (1H, dd, J = 13.7, 9.0).

Preparation of (1*R*,6*R*,8*R*)-11,11-Dimethyl-3,5-dithia-tricyclo-[6.2.1.0^{1,6}]undecane (13). The 52:48 mixture of sulfide **12** and benzyl mercaptan (145 mg, total mass), paraformaldehyde (145 mg, 2.0 mmol), and *p*-toluenesulfonic acid (6.3 mg, 0.03 mmol) were refluxed in toluene (1 mL) in a Dean−Stark trap under nitrogen. Water was added after a few hours, and after separation, the organic layer was washed with sodium hydroxide (2 M) and water before being dried over $MgSO_4$. After filtration of the mixture and removal of the solvents under reduced pressure were complete, chromatography with 10% dichloromethane in petroleum ether gave *dithiane* **13** (57 mg, 72% based on **12**) and a mixture of **13** and its C_6 epimer: $[\alpha]^{20}_D$ −39.41 (*c* 2.03 in $CHCl_3$); υ_{max} (thin film)/cm^{-1} 2952, 2879; δ_H (250 MHz, $CDCl_3$) 0.91 (3H, s), 1.12−1.47 (2H, m), 1.31 (3H, s), 1.52−1.88 (5H, m), 2.59 (1H, d, J = 14.5), 3.01 (1H, d, J = 14.5), 2.98−3.18 (1H, m), 3.61 (1H, d, J = 12.5), 3.87 (1H, d, J = 12.5); δ_C (63 MHz, $CDCl_3$) 20.81, 21.77, 27.17, 29.86, 30.69, 35.88, 37.36, 44.92, 45.59, 46.27, 48.26; *m*/*e* (EI) 214 (M^+, 100%), 168 (27), 93 (26) (Found: M^+, 214.0843. $C_{11}H_{18}S_2$ requires 214.0850).

Preparation of (1*S*,2*S*,4*R*)-1-Mercaptomethyl-7,7-dimethyl-2-vinyl-bicyclo[2.2.1]heptan-2-ol. Cerium chloride heptahydrate (6.08 g, 16.3 mmol) was dried under vacuum at 150 °C for 2.5 h before being suspended in tetrahydrofuran (20 mL) under nitrogen. This

suspension was submitted to sonication for 1 h and then stirred at room temperature for 1 h. After cooling at −78 °C, vinylmagnesium bromide (16.5 mL of a 1 M solution in tertrahydrofuran) was added. After 2 h, ketone **11** (1 g, 5.35 mmol) was added portionwise to the rapidly stirred suspension (over 7 min). The reaction mixture was allowed to warm to room temperature overnight before being quenched with water; hydrochloric acid (3 M aqueous) was added to the mixture to dissolve the solids. The resulting mixture was extracted with petroleum ether (100 mL and 3 × 50 mL), and the combined extracts were dried over $MgSO_4$. After filtration of the mixture and removal of the solvents under reduced pressure were complete, chromatography with 50% dichloromethane in petroleum ether gave the desired *thioalcohol* (864 mg, 75%): υ_{max} (thin film)/cm^{-1} 3478, 2951, 2582, 1732; δ_H (250 MHz, $CDCl_3$) 0.91 (3H, s),1.02−1.21 (1H, m), 1.16 (3H, s), 1.35 (1H, t, J = 7.5), 1.51−1.84 (6H, m), 1.99 (1H, ddd, J = 13.0, 3.5, 3.5), 2.55 (1H, dd, J = 13.5, 7.5), 2.99 (1H, dd, J = 13.5, 7.5), 5.08 (1H, dd, J = 10.5, 1.0), 5.26 (1H, dd, J = 17.5, 1.0), 6.36 (1H, dd, J = 17.5, 10.5); δ_C (63 MHz, $CDCl_3$) 21.35, 21.66, 22.78, 26.38, 27.89, 45.49, 45.90, 50.74, 55.74, 81.82, 112.00, 145.10; *m*/*e* (EI) 212 (M^+, 35%), 194 (34), 108 (100) (Found: M^+, 212.1242. $C_{12}H_{20}OS$ requires 212.1235).

Preparation of (1*S*,6*R*,8*R*)-11,11-dimethyl-3-thia-tricyclo[6.2.1.0^{1,6}]-undecan-6-ol (14). 9-Borabicyclo[3.3.1]nonane (0.61 mL of a 0.5 M solution in tetrahydrofuran, 0.31 mmol) was added to an ice-cooled solution of (1*S*,2*S*,4*R*)-1-mercaptomethyl-7,7-dimethyl-2-vinyl-bicyclo-[2.2.1]heptan-2-ol (0.643 g, 3.03 mmol) in tetrahydrofuran (5.5 mL) under nitrogen. After 4 h, the solution was allowed to warm to room temperature and was left overnight. The reaction mixture was diluted with petroleum ether and filtered through a short silica plug, which was then washed with dichloromethane. After removal of the solvents under reduced pressure, the residue was loaded onto a silica gel column and eluted with 5% ethyl acetate in petroleum ether to give *sulfide* **14** (506 mg, 79%) as a white solid, mp 34−35 °C: $[\alpha]^{20}_D$ +57.0 (*c* 10.00 in $CHCl_3$); υ_{max} (solution, $CHCl_3$)/cm^{-1} 3473, 2934, 1066, 911; δ_H (400 MHz, $CDCl_3$) 0.88 (3H, s), 0.99 (1H, ddd, J = 11.5, 9.5, 4.5), 1.13 (3H, s), 1.29 (1H, d, J = 13.5), 1.43 (1H, br s), 1.53 (1H, ddd, J = 14.0, 12.0, 4.5), 1.64 (1H, m), 1.76 (1H, dddd, J = 14.0, 4.5, 2.5, 1.0), 1.78 (1H, dd, J = 4.5, 4.0), 2.03 (1H, ddd, J = 13.5, 5.0, 3.0), 2.06 (1H, dd, J = 12.0, 1.0), 2.19 (1H, ddd, J = 14.0, 13.5, 5.0), 2.25 (1H, ddd, J = 14.0, 9.5, 3.5), 2.33 (1H, dddd, J = 12.0, 5.0, 2.5, 1.0), 3.14 (1H, ddd, J = 13.5, 12.0, 4.5), 3.19 (1H, d, J = 12.0); δ_C (101 MHz, $CDCl_3$) 20.91, 22.45, 23.18, 26.55, 27.09, 30.57, 34.93, 45.14, 46.96, 48.63, 50.78, 76.91; *m*/*e* (EI) 212 (M^+, 52%), 194 (21), 108 (100) (Found: M^+, 212.1230. $C_{12}H_{20}OS$ requires 212.1235).

Preparation of (1*S*,8*R*)-11,11-Dimethyl-3-thia-tricyclo[6.2.1.0^{1,6}]-undec-5-ene (15). (1*S*,6*R*,8*R*)-11,11-Dimethyl-3-thia-tricyclo[6.2.1.0^{1,6}]-undecan-6-ol (**14**) (578 mg, 2.73 mmol) was added to a solution of oxalyl chloride (1.16 mL, 13.53 mmol) in benzene (2.5 mL) under nitrogen. After 5 h, the solvents and excess reagent were removed under high vacuum, and the residue was eluted through a short silica gel column with 10% ethyl acetate in petroleum ether to give *sulfide* **15** (392 mg, 74%) as a colorless oil: $[\alpha]^{20}_D$ −44.6 (*c* 1.57 in $CHCl_3$); υ_{max} (thin film)/cm^{-1} 2943, 2874, 1686, 1448; δ_H (400 MHz, $CDCl_3$) 0.76 (3H, s, H_{13}), 0.93 (3H, s), 1.20 (1H, ddd, J = 12.0, 9.5, 4.5), 1.61 (1H, ddd, J = 12.0, 12.0, 4.5), 1.73 (1H, dd, J = 4.5, 4.5), 1.76−1.94 (3H, m), 2.33−2.41 (1H, m), 2.41 (1H, dd, J = 13.0, 1.0), 2.68 (1H, d, J = 13.0), 2.81 (1H, dm, J = 17.0), 3.28 (1H, dm, J = 17.0), 5.50 (1H, dm, J = 5.5); δ_C (101 MHz, $CDCl_3$) 18.52, 19.49, 25.57, 27.37, 28.46, 32.92, 36.43, 43.82, 47.95, 48.94, 113.77, 146.87; *m*/*e* (EI) 194 (M^+, 100%), 179 (37), 151 (47) (Found: M^+, 194.1128. $C_{12}H_{18}S$ requires 194.1129).

Preparation of (1*R*,6*S*,8*R*)-11,11-Dimethyl-3-thia-tricyclo[6.2.1.0^{1,6}]-undecane (16). Palladium on 10% activated carbon (3.44 g) was added to a solution of (1*S*,8*R*)-11,11-dimethyl-3-thia-tricyclo[6.2.1.0^{1,6}]undec-5-ene (**15**) (344 mg, 1.77 mmol) in anhydrous methanol (80 mL). This mixture was submitted to hydrogenation at 15−20 atm at room temperature for 22 h. After the mixture was filtered through Celite and the solvent removed, the residue was loaded onto a silica gel column and eluted with petroleum ether to give *sulfide* **16** (291 mg, 89%) as a mixture of diastereomers (3:1). To a solution of the diastereomeric mixture of *sulfide* **16** (229 mg, 1.17 mmol) in dichloromethane (1.5 mL) was added a solution of 3-chloroperoxybenzoic acid (258 mg, 1.40 mmol) in dichloromethane (1.5 mL) at 0 °C under nitrogen. After 1 h the mixture was diluted with dichloromethane (15 mL) and washed with aqueous sodium hydrogencarbonate solution (1 × 15 mL) and brine (1 × 15 mL) before drying over $MgSO_4$. After filtration and removal of the solvent were complete, the residue (244 mg, 98%) was recrystallized in petrol/dichloromethane to give *sulfoxide* **17** (124 mg, 50%): $[\alpha]^{20}_D$ −97.5 (*c* 0.4 in $CHCl_3$); υ_{max} (thin film)/cm^{-1} 2839, 2872, 1464, 1016; δ_H (400 MHz, $CDCl_3$) 0.96 (3H, s), 1.18−1.24 (3H, m), 1.47−1.75 (8H, m), 2.06−2.09 (1H, m), 2.47−2.53 (1H, m), 2.55−2.59 (1H, d, J = 12.9), 3.26−3.32 (1H, m), 3.32−3.36 (1H, dd, J = 12.9, 2.3); δ_C (101 MHz, $CDCl_3$) 20.9, 23.1, 27.4, 29.6, 35.8, 40.5, 42.4, 46.4, 47.3, 51.0, 54.9; *m*/*e* (EI) 212 (M^+, 38%), 195 (24), 163 (100). A solution of trifluoroacetic anhydride (0.06 mL, 0.40 mmol) in acetone (0.5 mL) was added slowly to a mixture of *sulfoxide* **17** (50 mg, 0.24 mmol) and dried sodium iodide (85 mg, 0.57 mmol) in acetone (1 mL) at 0 °C under nitrogen. After 20 min the mixture was diluted with ethyl acetate (20 mL) and washed with sodium thiosulfate solution (1 × 20 mL) and brine (1 × 20 mL). After being dried over $MgSO_4$ and having the solvents removed, the residue was eluted through a short silica gel column with petroleum ether to give *sulfide* **16** (41 mg, 89%): $[\alpha]^{20}_D$ −92.9 (*c* 0.7 in $CHCl_3$); υ_{max} (thin film)/cm^{-1} 2949, 2877, 1463, 1385, 1251, 1150, 953; δ_H (400 MHz, $CDCl_3$) 0.89 (3H, s), 1.04−1.21 (2H, m), 1.21 (3H, s), 1.46−1.70 (6H, m), 1.97−2.10 (1H, m), 2.44−2.59 (4H, m), 2.69−2.75 (d, J = 14.4, 1H); δ_C (63 MHz, $CDCl_3$) 21.1, 23.4, 27.4, 28.4, 29.5, 34.4, 36.8, 40.4, 43.5, 44.3, 46.2, 47.4; *m*/*e* (EI) 196 (M^+, 100%).

Preparation of Mesitaldehyde Tosylhydrazone.[78] To a slurry of *p*-toluenesulfonhydrazide (5.0 g, 27 mmol) in methanol (12 mL) was added mesitaldehyde (4 mL, 27 mmol). Crystallization of the resultant white cake from methanol gave the desired hydrazone as a white crytalline solid, mp 159−161 °C (lit. 79, 158−160 °C) (Found: C, 64.47; H, 6.38; N, 8.89; S, 10.06. $C_{17}H_{20}N_2O_2S$ requires C, 64.53; H, 6.37; N, 8.85; S, 10.13): υ_{max} (KBr disk)/cm^{-1} 3203, 1608, 1557, 1326, 1165; δ_H (250 MHz, $CDCl_3$) 1.95 (3H, s), 2.25 (6H, m), 2.41 (3H, m), 6.84 (2H, m), 7.25−7.35 (2H, m), 7.55 (1H, br d, CH), 7.80 (2H, m); δ_C (63 MHz, $CDCl_3$) 21.1, 21.3, 21.6, 127.1, 128.1, 129.6, 135.3, 137.9, 139.3, 144.2, 148.0; *m*/*e* (EI) 316 (M^+, 37%) 161 (100), 132 (96), 91 (77).

Preparation of Mesityldiazomethane 22.[80] A suspension of mesitaldehyde tosylhydrazone (2.41 g, 7.62 mmol) in benzene (12 mL) was heated with sodium hydroxide (12 mL of a 14% solution) and benzyl triethylammonium chloride (0.32 g, 1.39 mmol) at 60−70 °C for 1 h. After cooling, the organic layer was separated and washed with sodium hydroxide (14%, 2 × 15 mL) and water (15 mL) before being dried over sodium sulfate. Filtration and removal of the solvent in vacuo gave the desired diazo compound as an orange oil. The diazo compound was dissolved in dichloromethane and used without further purification. The concentration of the solution was determined by titration of 50 μL of the solution with *p*-toluic acid (0.25 mmol) in dichloromethane and comparison of the peaks at 5.38 (ester CH_2) and 2.43 (*p*-toluic acid CH_3) ppm.

Epoxidation of Benzaldehyde Using Sulfide 5b and Mesityldiazomethane. To a stirred solution of sulfide **5b** (19.0 mg, 0.09 mmol), $Cu(acac)_2$ (6.1 mg, 0.023 mmol), and benzaldehyde (50 μL, 0.49 mmol) in dichloromethane (0.25 mL) under nitrogen was added a solution of mesityldiazomethane **22** (0.75 mmol in 0.25 mL of dichloromethane) at room temperature over a period of 3 h using a syringe pump. After being stirred for an additional 1 h, the solvent was removed in vacuo and the residue was chromatographed on silica gel to give the desired epoxide as a white solid (13.8 mg, 12%), mp 66−68 °C (lit. 81, 67−68 °C) (Found: C, 85.45; H, 7.58. $C_{17}H_{18}O$ requires C, 85.67; H, 7.61): υ_{max} (thin film)/cm^{-1} 2971, 2918, 1607, 890, 792; δ_H (250 MHz, $CDCl_3$) 2.28 (3H, s), 2.41 (9H, s), 3.82 (1H, d, J = 2.0), 3.90 (1H, br d), 6.86 (2H, s), 7.26−7.54 (5H, m); δ_C (63 MHz, $CDCl_3$) 19.88, 20.95,

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60.00, 62.11, 125.50, 128.26, 128.61, 128.72, 130.96, 137.05, 137.51; *m*/*e* (EI) 238 (M^+, 26%), 223 (48), 132 (100), 117 (97%) (Found: M^+, 238.1357. $C_{17}H_{18}O$ requires 238.1358).

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Supporting Information Available: Experimental procedures, including data for the preparation of compounds not given below, tables of crystallographic data for **5p**, **10**, and **17**, and methods for the enantiomeric excess determination of epoxides (35 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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