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Practical and Highly Selective Sulfur Ylide-Mediated Asymmetric Epoxidations and Aziridinations Using a Cheap and Readily Available Chiral Sulfide: Extensive Studies To Map Out Scope, Limitations, and Rationalization of Diastereo- and Enantioselectivities

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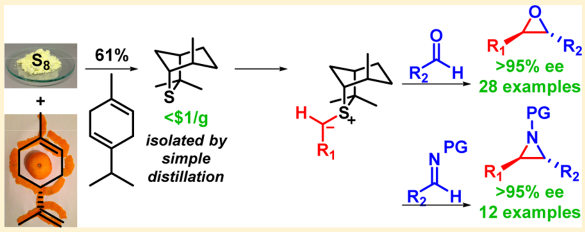
Supporting Information

ABSTRACT: The chiral sulfide, isothiocineole, has been synthesized in one step from elemental sulfur, γ-terpinene, and limonene in 61% yield. A mechanism involving radical intermediates for this reaction is proposed based on experimental evidence. The application of isothiocineole to the asymmetric epoxidation of aldehydes and the aziridination of imines is described. Excellent enantioselectivities and diastereoselectivities have been obtained over a wide range of aromatic, aliphatic, and α,β-unsaturated aldehydes using simple protocols. In aziridinations, excellent enantioselectivities and good diastereoselectivities were obtained for a wide range of imines. Mechanistic models have been put forward to rationalize the high selectivities observed, which should enable the sulfide to be used with confidence in synthesis. In epoxidations, the degree of reversibility in betaine formation dominates both the diastereoselectivity and the enantioselectivity. Appropriate tuning of reaction conditions based on understanding the reaction mechanism enables high selectivities to be obtained in most cases. In aziridinations, betaine formation is nonreversible with semistabilized ylides and diastereoselectivities are determined in the betaine forming step and are more variable as a result.



INTRODUCTION

The direct asymmetric transformation of carbonyl compounds into epoxides using chiral sulfur ylides offers a complementary and potentially advantageous method over the two-step protocol of Wittig olefination followed by asymmetric epoxidation.[1−5] However, despite its appeal and over 30 years of research, the methodology has rarely been used. Herein, we detail results that make the sulfur ylide disconnection a genuine alternative to alkene epoxidation for practical asymmetric epoxidation, which can be incorporated into a synthetic plan with confidence.

The previous lack of use of the sulfur ylide disconnection can be attributed to two main factors:

(i) Limited demonstrated substrate scope. The majority of asymmetric, sulfur ylide-mediated epoxidations have been used to prepare 1,2-diaryl epoxides, which have limited synthetic utility. A survey of more than 80 publications with reports of sulfur ylide asymmetric epoxidations found that just 22 chiral sulfides (Chart 1, Supporting Information) show enantioselectivities of >90% enantiomeric excess (ee) in the preparation of 1,2-diaryl epoxides. However, in aldehyde epoxidations, only 11 sulfides have been shown to give >90% ee for epoxides that are not 1,2-diaryl epoxides (Figure 1).[6−8] Table 1 shows the demonstrated ability of these 11 sulfides to deliver epoxides in >90% ee from different ylide/aldehyde combinations.[6,7] Being able to also control diastereoselectivity is critical to the practical usage of the technology. To the best of our knowledge, only 3 sulfides (**1**, **2**, and **10**) have been shown to give >90:10 diastereoselectivity with >90% ee in epoxidations of aliphatic aldehydes.

(ii) Sulfide availability. The sulfides that deliver high enantioselectivity usually require multistep synthesis.[1] The number of steps required for each sulfide synthesis is shown in Figure 1. Furthermore, in a number of cases, the chiral pool starting material is only readily available in one enantiomeric form, which clearly limits the application of such sulfides. The examples of **1** and **7** are illustrative. Solladié-Cavallo has reported many examples of asymmetric epoxidations using **7**,[7i,j] giving very high ee's (>95%) over a range of substrates, but the sulfide was derived in three steps[9] from pulegone, which is only readily available in one enantiomeric form. We are only aware

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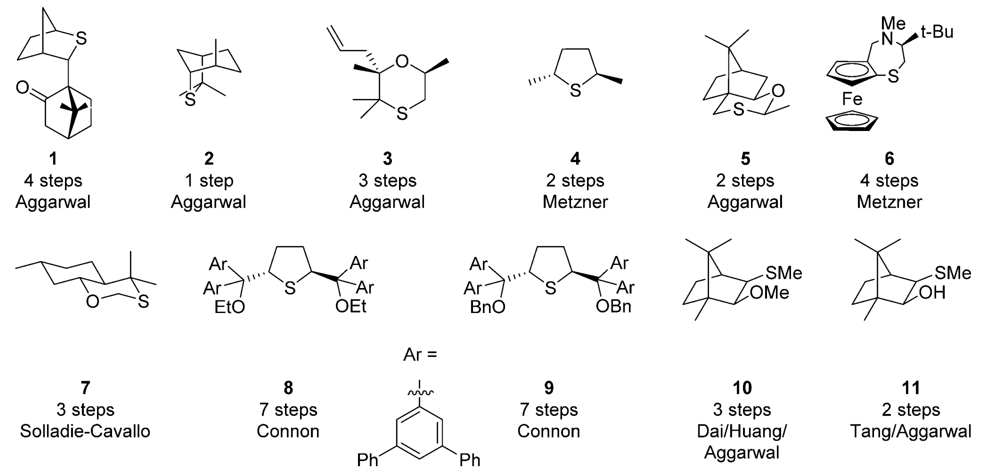


Figure 1. Sulfides that mediated asymmetric epoxidations of aldehydes giving >90% ee for epoxides other than 1,2-diarylepoxides.[6,7] The number of steps to synthesize the sulfides from commercially available precursors is given (sulfide **2** is now commercially available).[17]

Table 1. Scope of Sulfur Ylide-Mediated Asymmetric Epoxidation of Aldehydes—Sulfides with >90% ee in the Synthesis of Epoxides Other than 1,2-Diaryl Epoxides[6,7,a]

ylide	aldehyde	sulfide	1	2	3	4	5	6	7	8	9	10	11
benzyl	aliphatic		Y*	Y*	Y	Y	Y						
	aromatic		Y*	Y*	Y*	Y*	Y*	Y	Y*				
	heteroaromatic		Y*	Y*		Y*		Y	Y*				
	vinyl		Y*	Y*	Y*			Y	Y*				
	alkynyl		Y	Y	Y								
	formaldehyde								Y				
allyl	aliphatic		Y[b]	Y*									
	aromatic		Y*	Y*		Y							Y
alkyl (intramol)	aliphatic		Y[c]										
methyl	aromatic									Y	Y		
	heteroaromatic									Y			
amido	aliphatic											Y*	
	aromatic											Y*	Y*
	heteroaromatic											Y*	

[a]An asterisk indicates a diastereomeric ratio (dr) >90:10 (favoring *trans*-epoxide). Some of the entries for sulfide **2** are reported in this paper. [b]dr not reported.[6i] [c]dr n/a.

of two reports of its use in asymmetric epoxidation by a group other than the Solladié-Cavallo group.[10] Similarly, we reported a sulfide, **1**, which gave high ee's (>95%) over a range of substrates and reported its application to a range of synthetic targets.[6,11,12] However, it requires four synthetic steps from camphorsulfonyl chloride (available in both enantiomeric forms),[13] and although we have reported its synthesis on multigram-scale,[14] we are only aware of two reports by groups other than our own using this sulfide in asymmetric epoxidations.[6h,i,11,15,16]

We recently reported a chiral sulfide, isothiocineole **2**, which simultaneously addressed both of these limitations.[7a] The sulfide was easily prepared in one step from limonene and elemental sulfur and delivered the highest combined outcome in terms of enantioselectivity and diastereoselectivity in epoxidations and aziridinations of any sulfide to date. In this paper, we describe (i) substantial improvements in the synthesis of the sulfide, (ii) enhanced scope of ylide reactions in terms of the ylide substituents (aryl, alkenyl) and the aldehyde (aromatic, heteroaromatic, α,β-unsaturated, and aliphatic) and imine components, and (iii) models to account for the diastereo- and enantioselectivity of the reactions. We believe these significant improvements, underpinned by the models to account for selectivity, now provide a genuine, practical methodology that can be applied in synthesis.

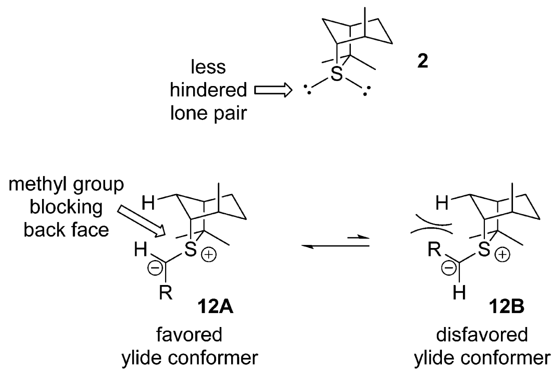
■ RESULTS AND DISCUSSION

Sulfide Synthesis. In the search for a suitable chiral sulfide, we were attracted to the little-known bicyclic compound isothiocineole **2**, as it seemed to fulfill many of the criteria established as desirable.[1,2] In terms of enantioselectivity (Scheme 1):

(i) Its rigid bicyclic structure would dictate the position of the ylide substituent in relation to the sulfide scaffold (lone pair selectivity);
(ii) Its rigid bicyclic structure would control the conformation of the ylide through nonbonded steric interactions;
(iii) One of the two *gem*-dimethyl groups should block one face of the ylide leading to high enantioselectivity.

In terms of preparation, Weitkamp had reported a one-step synthesis of isothiocineole from the simplest and cheapest of reagents, elemental sulfur and limonene.[18] Heating the two components followed by distillation and separation of isothiocineole **2** from dehydroisothiocineole **13** by thiourea co-crystallization gave the target molecule in 20% yield and

Scheme 1. Design Features of Isothiocineole for Enantioselectivity in Asymmetric Epoxidation



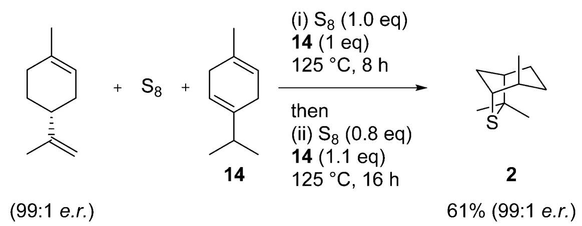
94:6 enantiomeric ratio (er), a reaction we were able to reproduce (Scheme 2). Despite being known for over 50 years, isothiocineole's potential utility in synthesis was not recognized.

The reaction had been conducted on scales from 0.2 to 2300 mol limonene. Although the reaction had been operated on >100 gal scale,[18b,19] further improvements were required to improve the yield and to avoid partial racemization and formation of the side product **13**, which was difficult to remove. This was challenging because of the lack of mechanistic information and because substantial optimization would have been conducted prior to conducting the reaction on such a vast scale. In our initial analysis, we noted that the conversion of limonene into isothiocineole **2** requires the overall addition of sulfur and two hydrogens (Scheme 2). Although sulfur is clearly added, the source of the two hydrogens is actually limonene itself, which, in the process of liberating the hydrogens, becomes converted to various aromatic byproducts (e.g., *p*-cymene). The generation of the two hydrogens from limonene is evidently not very efficient because it requires high temperatures and thus results in significant formation of the unsaturated sulfide **13**, which requires the addition of sulfur only. Therefore, a more efficient source of the two hydrogens was required to allow the reaction to run at lower temperatures and to limit the formation of **13**.

We believed that limonene undergoes a series of 1,3-hydrogen shifts at high temperature leading to a key intermediate, γ-terpinene **14** (Scheme 2). Because it is a 1,4-cyclohexadiene, γ-terpinene should be a good hydrogen donor and thus be able to contribute to the formation of isothiocineole, itself being converted into *p*-cymene as a byproduct. Therefore, we decided to add γ-terpinene[20] directly to the reaction mixture because we expected that this would allow us to avoid the high temperatures required for 1,3-hydrogen shifts, which would avoid losing limonene to various aromatic byproducts.

It was found that by adding 1.0 equiv of γ-terpinene **14**, the reaction between elemental sulfur and limonene could indeed be conducted at 125 °C and the formation of **13** was completely suppressed. Furthermore, simple distillation of the crude reaction mixture furnished essentially pure isothiocineole in much improved yield (36%), but more importantly, now without racemization (99:1 er).[7a] Further optimization of stoichiometry, time, and temperature has led to further significant improvements including conducting the reaction at 125 °C and adding the sulfur (1.0 and 0.8 equiv) and γ-terpinene (1.0 and 1.1 equiv) in two portions (the second after 8 h) gave >95% conversion of limonene after 24 h (Scheme 3).

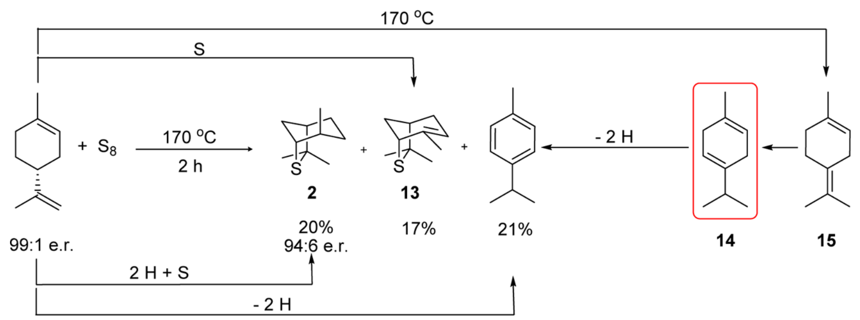
Scheme 3. Improved Synthesis of Isothiocineole 2 with Added Equivalents of Reagents after 8 h



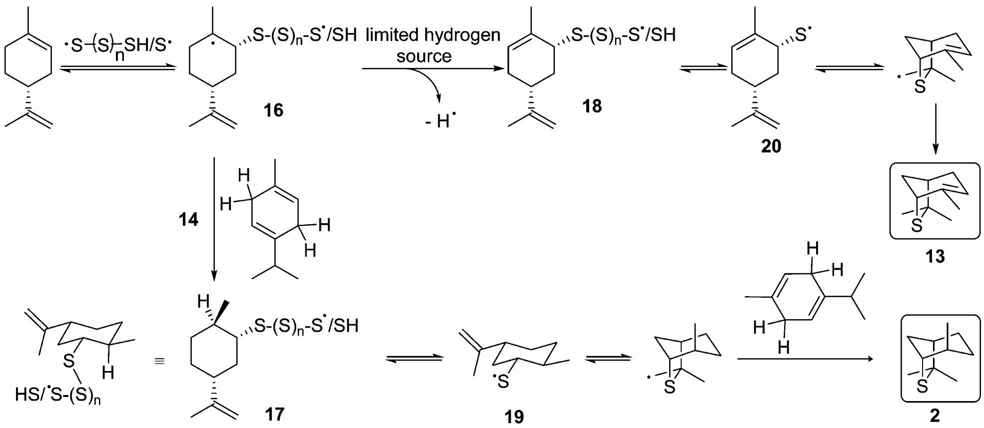
This ultimately gave isothiocineole **2** in an improved 61% yield, even on a mole scale. With such inexpensive reagents, a simple protocol and facile isolation, (+)-isothiocineole is now easily obtained. The (−)-isomer can also be accessed with equal ease by the same method but with lower er (90:10) because (−)-limonene is only available commercially as a 90:10 mixture of enantiomers. Nevertheless, low temperature recrystallization (−50 °C) from pentane (twice) can be used to upgrade this material to >98:2 er, if required.[17,21]

Mechanism for Formation. We propose the mechanism shown in Scheme 4 for the formation of isothiocineole **2** from limonene.[22] First, elemental sulfur and γ-terpinene **14** interact at elevated temperature and form a thiol radical.[23] Then, the sulfur-centered radical adds to the cyclic alkene of limonene to give the more stable tertiary radical **16**,[24] which reacts with the hydrogen atom donor, γ-terpinene, leading to the all-equatorial, thermodynamic intermediate **17**. Addition to the exocyclic alkene may occur but does not lead to the desired product. In the absence of a good hydrogen source (γ-terpinene), **16** loses a hydrogen atom to give alkene **18**. Both **17** and **18** suffer reversible loss of sulfur to generate radicals **19** and **20**, respectively, which cyclize to give the products isothiocineole **2** and dehydroisothiocineole **13**.

Scheme 2. Weitkamp's Synthesis of Isothiocineole[18]



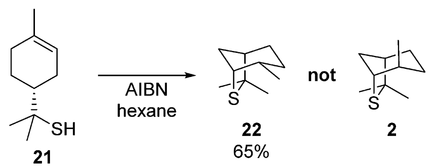
Scheme 4. Plausible Mechanism for Isothiocineole 2 Formation



Evidence for this proposal comes from the following observations and literature examples:

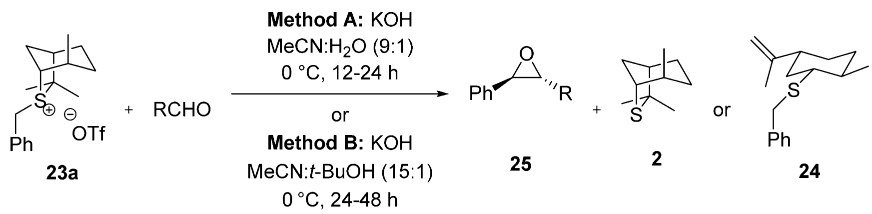
(i) Radical cyclization of 1-*p*-menthene-8-thiol **21** (reportedly the most powerful flavor compound ever found in nature,[25]) gave sulfide **22** exclusively in which the methyl group is oriented in an equatorial rather than an axial position (Scheme 5).[25] This indicates that in the formation of isothiocineole, the order of events must be addition of the thiol radical to the endocyclic alkene first, followed by intramolecular cyclization, not initial addition to the exocyclic alkene. Furthermore, it is hard to see how the thiol radical could add to the exocyclic alkene of limonene to generate thiol **21** because it would be expected to add *anti*-Markovnikov instead.[26]

Scheme 5. Formation of Thiocineole 22 from Thiol 21 under Radical Conditions[25]



(ii) In the presence of the hydrogen donor γ-terpinene, no racemization occurred. We believe that the source of racemization in the absence of γ-terpinene is thermal isomerization of the alkenes in limonene. After the first 1,3-hydrogen shift to give **15**, a subsequent 1,3-hydrogen shift will lead to γ-terpinene (Scheme 2). However, **15**, which is achiral, could undergo the reverse of the first 1,3-hydrogen shift and give racemic limonene. This is the likely source of the small amount of racemization observed at elevated temperature and in the absence of γ-terpinene.

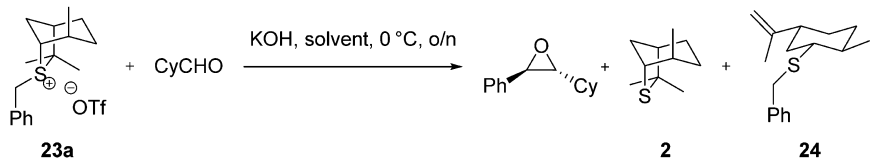
Table 2. Reactions of Benzyl Sulfonium Salt 23a with Aldehydes



entry	aldehyde	method	yield (%)	dr[a]	er[b]
1	benzaldehyde	A	86	>95:5	99:1
2	*p*-methoxybenzaldehyde	A	89	>95:5	98:2
3	*p*-cyanobenzaldehyde	A	86	>95:5	99:1
4	(*E*)-cinnamaldehyde	A	88[c]	>95:5	99:1
5	(*E*)-crotonaldehyde	A	86[c]	>95:5	97:3
6	(*E*)-PhCH=C(Me)CHO	A	84[c]	>95:5	98:2
7	2-pyridinecarboxaldehyde	A	85	>95:5	98:2
8	3-pyridinecarboxaldehyde	A	80	>95:5	98:2
9	furan-3-carbaldehyde	A	71	>95:5	99:1
10	cyclohexanecarboxaldehyde (Cy)	B	62[d]	93:7	99:1
11	valeraldehyde (Val, *n*-BuCHO)	B	56[d]	91:9	99:1
12	pivaldehyde (*t*-BuCHO)	B	0[e]		
13	TIPS-propargyl aldehyde	Neat MeCN[f]	51[d]	68:32	97:3
14	TIPS-propargyl aldehyde	A[g]	76[d]	60:40	

[a]*trans*:*cis*. [b]Determined by chiral HPLC. [c]Determined by ^{1}H NMR with an internal standard. [d]Mixture of diastereomers. [e]Formation of **24** was observed. [f]KOH, rt, 3 h. [g]rt, 3 h.

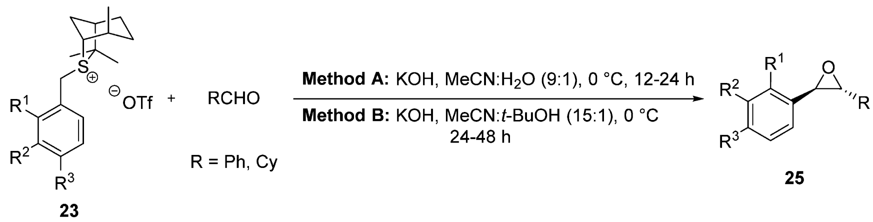
Table 3. Effect of Protic Solvent on Reactions of Benzyl Sulfonium Salt 23a with Cyclohexanecarboxaldehyde



entry	solvent	yield (%)	dr[a]	er[b]	2:24
1	MeCN	44	>95:5	99:1	56:44
2	MeCN/*t*-BuOH (50:1)	50	94:6	99:1	63:37
3	MeCN/*t*-BuOH (25:1)	55	94:6	99:1	67:33
4	MeCN/*t*-BuOH (15:1)	62	93:7	99:1	70:30
5	MeCN/*t*-BuOH (9:1)	75	91:9	99:1	87:13
6	MeCN/H_2O (9:1)	57	73:27	99:1	100:0

[a]*trans:cis*. [b]Determined by chiral HPLC.

Table 4. Reactions of Electron-Rich Benzyl Sulfonium Salts with Aldehydes



a: R^1,R^2,R^3 = H
b: R^1 = OMe, R^2,R^3 = H
c: R^3 = OMe, R^1,R^2 = H
d: R^1 = Me, R^2,R^3 = H
e: R^1,R^2 = -$(CH)_4$-, R^3 = H

entry	salt	R^1	R^2	R^3	R	method	yield (%)	dr[b]	er[c]
1	**23a**	H	H	H	Ph	A	86	>95:5	>99:1
2	**23a**	H	H	H	Cy	B	62	93:7	99:1
3	**23b**	OMe	H	H	Ph	A	66[a]	>95:5	99:1
4	**23b**	OMe	H	H	Cy	B	63[a]	84:16	98:2
5	**23c**	H	H	OMe	Ph	A	65	90:10	94:6
6	**23c**	H	H	OMe	Ph	A (MeCN)[d]	69	97:3	96:4
7	**23c**	H	H	OMe	Cy	B	56	67:33	98:2
8	**23d**	Me	H	H	Ph	A	45	>95:5	98:2
9	**23d**	Me	H	H	Cy	B	62[a](43)	72:28	99:1
10	**23e**	-$(CH)_4$-		H	Ph	A	97	>95:5	98:2
11	**23e**	-$(CH)_4$-		H	Cy	B	62	71:29	92:8

[a]Determined by ^{1}H NMR with an internal standard (isolated yield is given in parentheses for entry 9). [b]*trans:cis*. [c]Determined by chiral HPLC. [d]Method A except MeCN was used in place of MeCN/H_2O.

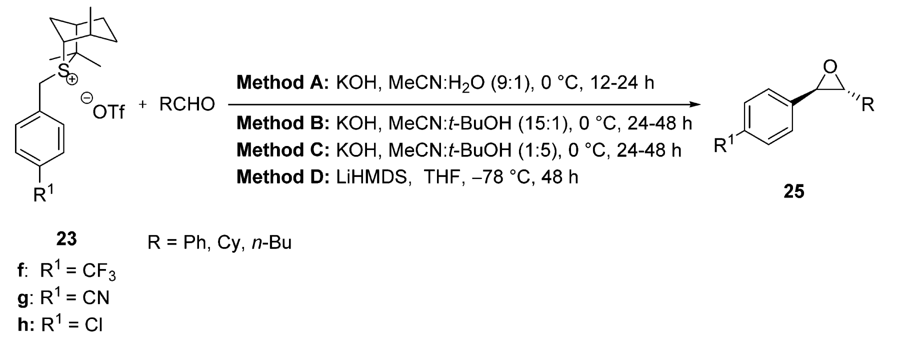
(iii) The mechanism for formation. The mechanism of the side product, dehydroisothiocineole **13**, and in particular its absolute stereochemistry, is consistent with the series of events shown in Scheme 4 and does not require the occurrence of some form of allylic shift when sulfur is added to the double bond as previously suggested.[18c]

Epoxide Synthesis. Because both (+)- and (−)-isothiocineole can be easily prepared on large scale and have now become commercially available, we explored the stoichiometric epoxidation reactions of sulfur ylides as these show considerably greater scope than the catalytic process.[6b,27] For example, the catalytic process usually leads to low yields, low dr's, or low er's with aliphatic, *α*,*β*-unsaturated, heteroaromatic, and acetylenic aldehydes.[6c] Further limitations of the catalytic process were the low yields and limited substrate scope with *α*,*β*-unsaturated hydrazones.[6b] Therefore, we set out to map the scope and limitations of the stoichiometric epoxidation reactions involving isothiocineole **2**. We were especially mindful of going beyond simple 1,2-diaryl epoxides that are commonly evaluated, to the synthetically much more useful 1,2-alkylaryl and *α*,*β*-unsaturated epoxides.

Several benzyl sulfonium salts were prepared by the reaction of benzyl bromide with isothiocineole in a two-phase mixture of CH_2Cl_2 and aqueous solution of LiOTf or $NaBF_4$. The tetrafluoroborate salt was found to be rather insoluble in most organic solvents and so subsequent studies focused on the triflate salt **23a**. The alkylations occurred exclusively on the exo lone pair, which is presumably less hindered. X-ray analysis of sulfonium salts **23a–d**, **f**, and **g** confirmed their structure (see the Supporting Information for crystal structure data).

We established two sets of conditions, Method **A** (MeCN:H_2O (9:1)) and Method **B** (MeCN:*t*BuOH (15:1)) for reactions with aromatic and aliphatic aldehydes, respectively, which gave moderate-to-high yields and high diastereo-

Table 5. Reaction of Electron-Deficient Benzyl Sulfonium Salts with Aldehydes



entry	salt	R^1	R	method	yield (%)	dr[b]	er[c]
1	**23f**	CF_3	Ph	A	94	>99:1	64:36
2	**23f**	CF_3	Cy	B	36[a]	97:3	87:13
3	**23f**	CF_3	Cy	C	42[a]	92:8	92:8
4	**23f**	CF_3	Cy	D	45	90:10	99:1
5	**23f**	CF_3	*n*-Bu	C	63[a]	97:3	94:6
6	**23f**	CF_3	*n*-Bu	D	58	99:1	98:2
7	**23g**	CN	Ph	A	77	>99:1	67:33
8	**23g**	CN	Cy	B	35[a]	>99:1	58:42
9	**23g**	CN	Cy	C	40[a]	95:5	73:27
10	**23g**	CN	Cy	D	43	92:8	78:22
11	**23g**	CN	*n*-Bu	C	54	97:3	85:15
12	**23g**	CN	*n*-Bu	D	69	99:1	90:10
13	**23h**	Cl	Ph	A	76[a]	98:2	95:5
14	**23h**	Cl	Cy	B	49[a]	92:8	95:5

[a]Determined by ^{1}H NMR with an internal standard. [b]*trans:cis*. [c]Determined by chiral HPLC.

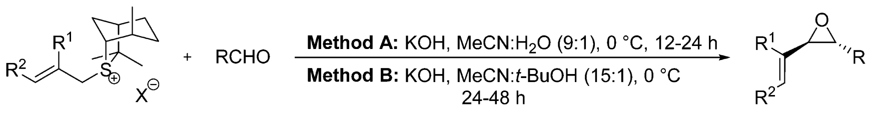
and enantioselectivities (Table 2). Method **A** was successfully applied to electron-rich and electron-deficient aromatics (entries 2 and 3), *α,β*-unsaturated aldehydes (entries 4–6), and heteroaromatics (entries 7–9) all leading to high yields, and very high diastereomeric ratio (dr) and er. Method **B** was successfully applied to *α*-branched and unbranched aliphatic aldehydes, again with moderate-to-high dr and very high er (entries 10 and 11). However, the more hindered pivaldehyde (*t*-BuCHO, entry 12) was not successful in epoxidation. In general, we found that, with slower reacting electrophiles, a competing elimination reaction of the ylide occurred leading to sulfide **24**. In fact, we were unable to extend this chemistry to cyclopropanation reactions with Michael acceptors (e.g., chalcone),[28] which are inherently less electrophilic, again because of competing elimination. Acetylenic aldehydes could also be employed and led to high enantioselectivity but low diastereoselectivity (entries 13 and 14). In this case we found that neat MeCN gave the best selectivities. To maximize diastereoselectivity with unhindered aldehydes, conditions are required that maximize the extent of reversibility in betaine formation, which requires aprotic conditions (see later for a discussion).

In our optimization studies for aliphatic aldehydes, we found that higher dr was obtained in less protic media, but higher yield was obtained in more protic media. A representative set of results, illustrating the effect of protic solvent on the reaction with cyclohexanecarboxaldehyde, is shown in Table 3. Particularly instructive is the ratio of sulfides **2**:**24** formed in the reaction, which is a measure of the ratio of two competing processes, epoxidation and elimination, which occurred under the reaction conditions. With increasing protic solvent, the yield of epoxide increased (increase in ratio of epoxidation/elimination **2**:**24**), but the diastereoselectivity decreased. The use of MeCN:*t*-BuOH (15:1) offered the optimum balance of yield and dr (entry 4). In fact, the dr obtained for the aliphatic aldehydes (Table 2) represent the highest to date.

Extension of the methodology to a range of electron-rich benzyl sulfonium salts **23a–e** was evaluated and the results are summarized in Table 4. Once again, all reactions were tested with a representative aromatic (PhCHO) and aliphatic (CyCHO) aldehyde. In all cases, essentially perfect enantioselectivity was observed but the dr was more variable. The dr was dependent on the electronic and steric properties of the benzyl group and the aldehyde. In all reactions with PhCHO, high dr was observed although the electron-rich and unhindered aryl substrate **23c** required aprotic conditions to achieve this (entries 5 and 6). Reactions with aliphatic aldehydes led to lower dr. This aspect is discussed in detail later.

Electron-deficient benzyl sulfonium salts **23f–h** were also explored (Table 5) and, in contrast to the results with electron-rich salts, this time high dr but variable levels of er were observed. To maximize enantioselectivity, reversibility in betaine formation had to be minimized and so more protic conditions (Method **C**) and low temperature with a coordinating metal counterion (Method **D**) were also explored with certain substrates. Reactions with the *highly* stabilized sulfur ylides derived from **23f** and **g** were expected to give low er with all aldehydes, especially aromatic ones. Therefore, we explored aliphatic aldehydes in more detail and extended our study to include valeraldehyde (*n*-BuCHO), which, being the least hindered of aldehydes, was expected to show the lowest degree of betaine reversibility and, thus, maximum enantioselectivity. In practice, reactions with aromatic aldehydes gave low er with the highly electron-deficient benzyl sulfonium salts **23f**

Table 6. Reaction of α,β-Unsaturated Sulfonium Salts with Aldehydes



26 27

a: R^1 = H, R^2 = H, X = OTf
b: R^1 = H, R^2 = Ph, X = BF_4
c: R^1 = Me, R^2 = Ph, X = BF_4
d: R^1 = Me, R^2 = H, X = OTf

entry	salt	R^1	R^2	R	method	yield (%)[a]	dr[b]	er
1	**26a**	H[c]	H	Ph	A	57	75:25	70:30[d]
2	**26b**	H[e]	Ph	Ph	A	65	80:20	85:15[d]
3	**26c**	Me[e]	Ph	Ph	A	97	>95:5	99:1[d]
4	**26d**	Me[c]	H	Ph	A	80	>95:5	99:1[d]
5	**26c**	Me[e]	Ph	Cy	B	77	>95:5	98:2[d]
6	**26d**	Me[c]	H	Cy	B	77	>95:5	97:3[f]

[a]Determined by ^1H NMR with an internal standard. [b]*trans:cis*. [c]X = OTf. [d]Determined by chiral HPLC. [e]X = BF_4 [f]Determined by chiral GC.

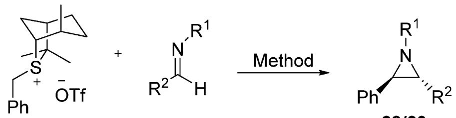
and **g** as expected, but high er was observed with the less electron-deficient benzyl sulfonium salt **23h** (compare entries 1 and 7 vs 13). In contrast, even with the highly stabilized ylides **23f** and **g** we were able to obtain *both* high diastereoselectivity and high enantioselectivity with both valeraldehyde (entries 6 and 12) and cyclohexanecarboxaldehyde (entries 4 and 10) using method **D**. Again, the factors that affect both dr and er are discussed later.

The process was also extended to α,β-unsaturated sulfonium salts **26a−d**, which were prepared either by the reaction of the sulfide with the corresponding allylic alcohol and HBF_4 or by alkylation with the appropriate allylic bromide. Although the α-unsubstituted allylic sulfonium salts **26a** and **b** only gave moderate dr and er (Table 6, entries 1 and 2), the α-substituted allylic sulfonium salts **26c** and **d** gave very high dr and er even with cyclohexanecarboxaldehyde (entries 3−6). The preparation of synthetically useful vinyl epoxides in high ee and high dr by this simple sulfur ylide disconnection is especially noteworthy.

Aziridination.[29,30] The benzyl sulfur ylide reaction was initially tested with a range of imines bearing different substituents and different activating groups on nitrogen (*p*-toluenesulfonyl (Ts) and *tert*-butyloxycarbonyl (BOC)) (Table 7). In all cases essentially complete enantioselectivity was observed although diastereoselectivity was, as expected,[1,2l] more variable. With *N*-Ts imines derived from aromatic aldehydes, moderate diastereoselectivity was obtained (entries 1−4), whereas the *N*-BOC imine gave very high dr (entry 7). Extension to unsaturated imines was also explored and this time both very high er and high dr (from 83:17 to >95:5) were observed (entries 5 and 6). The imine derived from pivaldehyde (*t*-BuCH═NTs) also worked (entry 8) and gave the aziridine with high *trans* selectivity and again perfect er. Interestingly, Hameršak obtained the *cis*-aziridine exclusively with this imine using the benzyl sulfonium ylide derived from Eliel's oxathiane **7**,[31] opposite to what we observed with isothiocineole **2**. It should be noted that pivaldehyde itself could not be employed in epoxidations because it was too unreactive and led to competing elimination of the sulfonium salt, indicating the higher reactivity of the *N*-Ts imines relative to aldehydes.

Allylic sulfonium salts were also explored with benzaldehyde-derived imines bearing a range of activating groups on nitrogen

Table 7. Reaction of Benzyl Sulfonium Salt with *N*-Ts and *N*-BOC Imines



28/29

Method A: K_2CO_3 (2.0 eq), MeCN, 0 °C to rt, 24 h
Method B: NaH (1.7 eq), CH_2Cl_2, 0 °C to rt, 24 h
Method C: NaH (1.3 eq), THF, −40 °C to rt, 16 h

entry	R^1	R^2	condition	dr[a]	er[b]	yield (%)
1	Ts	Ph	A	85:15	99:1	72
2	Ts	*p*-MeC_6H_4	A	86:14	99:1	63
3	Ts	*p*-ClC_6H_4	A	75:25	99:1	65
4	Ts	*p*-$MeOC_6H_4$	A	83:17	99:1	80
5	Ts	(*E*)-PhCH═CH	A	>99:1	98:2	78
6	Ts	(*E*)-TMSCH═CH	A	87:13	99:1	78
7	BOC	Ph	B	97:3	98:2	52
8	Ts	*t*-Bu	C	89:11	99:1	68

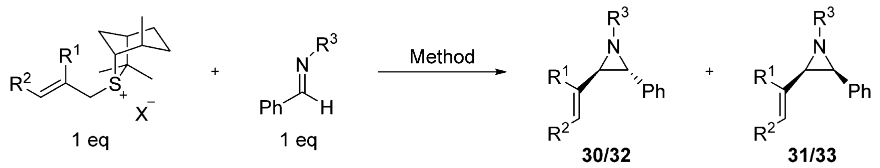
[a]*trans:cis* [b]Determined by chiral HPLC.

(Ts, $P(O)Ph_2$; note that BOC-imines were not successful) (Table 8). Essentially perfect er was obtained with α-substituted allyl sulfonium salts (entries 1, 2, and 5), but surprisingly, very high er was also observed with the α-unsubstituted allyl sulfonium salts, in contrast to epoxidation (entries 3, 4, and 6). Both *N*-Ts and *N*-$P(O)Ph_2$ imines showed similar levels of dr.

Origin of Diastereoselectivity in Epoxidation. Sulfur ylides react with carbonyl compounds via betaine intermediates to give epoxides. We have previously reported that the reaction of a benzyl sulfonium ylide with an aldehyde or ketone was remarkably finely balanced.[6b,32] In reactions with benzaldehyde, the *trans*-epoxide was derived from nonreversible formation of the *anti*-betaine, followed by bond rotation and ring closure (Scheme 6).[33]

In contrast, crossover experiments showed that the *syn*-betaine, which would lead to the *cis*-epoxide, was formed reversibly.[33] This indicated that bond rotation and ring closure had a higher activation barrier than that for reversion to starting materials (relative rates: $k_5 < k_{-4}$). DFT calculations under-

Table 8. Reaction of Allyl Sulfonium Salts with Benzaldehyde-Derived Imines

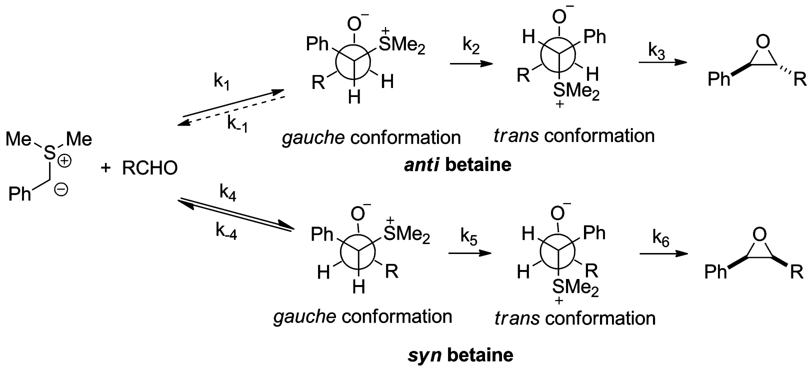


Method D: K_2CO_3 (1.2 eq), THF, 0 °C to rt, 48 h
Method E: NaH (1.2 eq), CH_2Cl_2, 0 °C to rt, 24 h

entry	R^1	R^2	R^3	method	dr[a]	er of *trans*[b]	er of *cis*[b]	yield (%)[d]
1	Me	Ph	Ts	D	78:22	99:1	97:3	76
2	Me	H	Ts	D	83:17	99:1	>99:1	72
3	H	H	Ts	D	85:15	94:6	85:15	73
4	H	Ph	Ts	D	80:20	95:5[c]	nd[e]	81
5	Me	H	Ph_2PO	E	84:16	99:1	>99:1	84
6	H	H	Ph_2PO	E	86:14	91:9	90:10	83

[a] *trans*/*cis* [b] Determined by chiral HPLC on the crude mixture. [c] Determined by chiral HPLC on the pure product. [d] Yield of combined *cis* and *trans* isomers. Determined by ^{1}H NMR with an internal standard. [e] Not determined.

Scheme 6. Rationalization of Diastereoselectivity in Epoxidations



pinned these experimental observations, producing the same relative activation barriers (relative rates: $k_2 > k_{-1}$; $k_{-4} > k_5$).[32] It was found that the highest activation barrier along the two reaction pathways was for the torsional rotation step from the *gauche* to the *trans* conformation of the *syn*-betaine. Thus, the formation of the *syn*-betaine is nonproductive under appropriate conditions; it is formed but reverts back to the aldehyde and ylide, as subsequent rotation from the *gauche* to the *trans* conformation has a higher activation barrier than that for reversion to starting materials. Hence, the high *trans* selectivity observed with benzaldehyde is a result of nonproductive formation of the *syn*-betaine and productive formation of the *anti*-betaine, not as a result of which betaine is preferentially formed. In general, providing *syn*-betaine formation is reversible and is nonproductive, high diastereoselectivity should result. The degree of reversibility in *syn*-betaine formation therefore determines the dr of the reaction and is thus critical. The degree of reversibility is influenced in the following ways: (i) an increase in the thermodynamic stability of the starting materials (ylide and aldehyde) will lead to greater reversibility in betaine formation (increase in k_{-4}) and thus higher diastereoselectivity, (ii) increasing the steric bulk of the ylide or aldehyde will give rise to an increase in the torsional rotation barrier (increase in k_5) and thus render betaine formation more reversible, resulting in increased diastereoselectivity, (iii) increased solvation of the alkoxide by metals or a protic solvent will result in the lowering of the torsional rotation barrier (decrease in k_5) and thus reduced reversibility leading to lower diastereoselectivity.

Of course, the factors that increase the reversibility in the *syn*-betaine formation also impact on the *anti*-betaine formation, and this process can, therefore, also be partially reversible. Although this tends not to have any effect on the diastereoselectivity, it does have important consequences for the enantioselectivity (vide infra).

These factors can now be used to account for the selectivity observed in the many examples provided and are discussed below.

1. Stability of the Carbonyl Group. Aromatic aldehydes give high *trans* selectivity because reversion of the *syn*-betaine yields a carbonyl group that is in conjugation with an aromatic ring. Such conjugation is not available to aliphatic aldehydes, thus, resulting in reduced reversibility, and therefore lower dr. On the basis of this analysis, the results in Table 2 can be broadly understood. Aromatic (entries 1−3), heteroaromatic (entries 7−9), and unsaturated aldehydes (entries 4−6) gave high diastereocontrol, whereas aliphatic aldehydes (entries 10 and 11) gave lower diastereoselectivities.

2. Steric Hindrance of the Ylide/Aldehyde. Reduced steric bulk of the ylide/aldehyde allows more facile bond rotation from the *gauche* to the *trans* conformation of the betaine, leading to reduced reversibility in betaine formation thereby resulting in a decrease in diastereoselectivity. Conversely, an increase in steric hindrance of the ylide/aldehyde leads to an

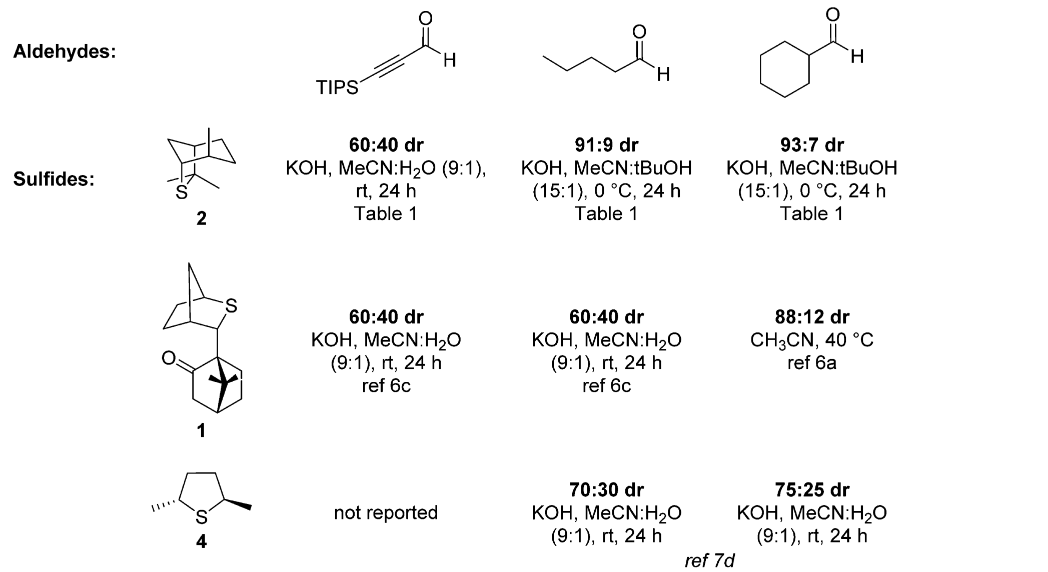


Figure 2. Influence of steric properties of sulfide and aldehyde on dr (*trans*:*cis*) of epoxidation reaction with benzyl sulfur ylides.[6a,c,7a,d]

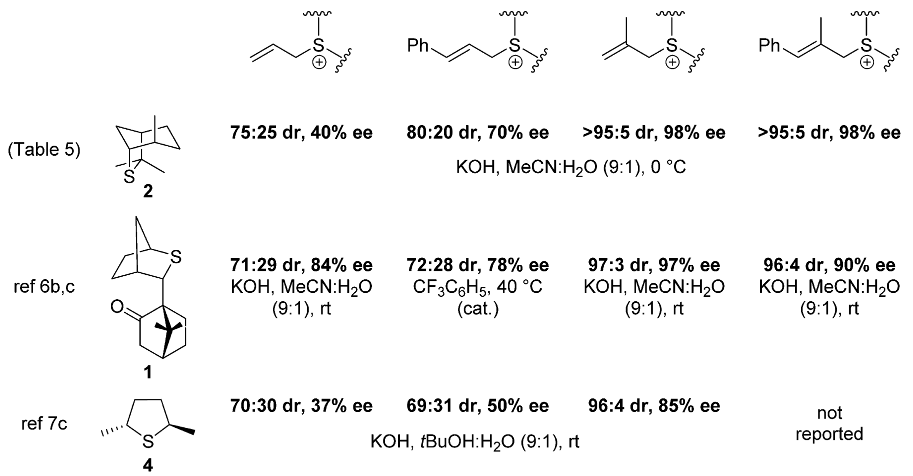


Figure 3. Influence of steric properties of sulfide and substitution of allyl moiety on dr (*trans*:*cis*) and er of epoxidation of benzaldehyde.[6b,c,7a,c]

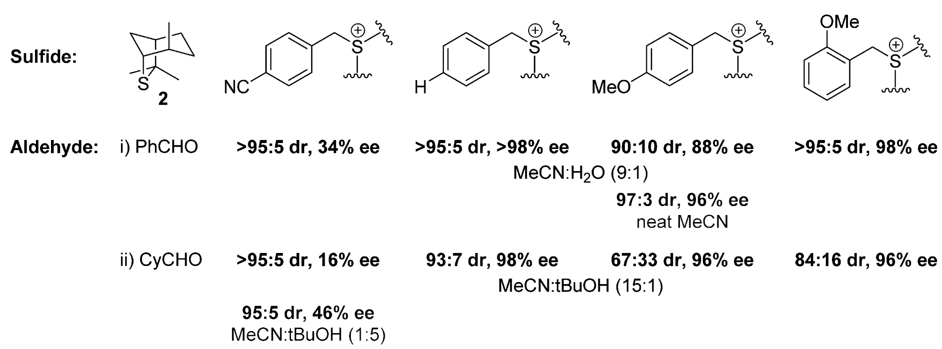


Figure 4. Comparison of different aryl stabilized ylides on dr of reactions with aromatic and aliphatic aldehydes (all results obtained with KOH as base at 0 °C).

increase in diastereoselectivity. Thus, propargylic aldehydes give low dr, whereas aliphatic aldehydes of increasing steric bulk showed increasing levels of diastereocontrol (Figure 2).

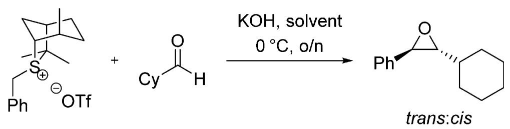
A comparison of different sulfides of increasing steric hindrance, employed in epoxidations with CyCHO is also shown in Figure 2. Isothiocineole **2** is clearly a hindered sulfide. Its steric bulk leads to an increase in the barrier to bond rotation of the intermediate betaines and a decrease in the barrier to reversion to its constituents. Figure 2 illustrates the record levels of dr obtained with isothiocineole **2**.

The α-substituted allylic sulfonium ylides also gave very high diastereoselectivity, presumably because they show similar steric properties to an aromatic group. In the absence of the α-substituent, lower dr was observed. Once again, in comparison to other sulfides, isothiocineole provides record levels of combined diastereo- and enantiocontrol, most likely because of its steric bulk (Figure 3).

3. Reduced Stability of the Ylide. On the basis of the principles described above, the selectivity with different benzyl sulfonium salts can also be rationalized. Clearly, *syn*-betaine formation will be more reversible with more stable ylides, resulting in increased *trans* selectivity. Indeed, electron-deficient benzyl substrates all gave very high diastereoselectivities, even with aliphatic aldehydes (Table 5). Conversely, betaine formation is less reversible with less stable ylides (electron-rich benzyl sulfonium salts) and so lower dr was obtained (Table 4; compare the dr observed for *p*-CN, *p*-H, *p*-MeO-substituted salts; Figure 4).

Interestingly, electron-rich substrates bearing an *ortho*-methoxy substituent also showed higher stereocontrol than that of the *para*-methoxy isomer (Figure 4) reflecting increased reversibility due to increased steric hindrance. Clearly, the selectivity will be dependent upon the nature and position of the substituents attached to the aromatic ring.

4. Solvation of Charge. The charges on the betaine are separated during the bond rotation step (Scheme 6), and so solvents that can solvate the charges (e.g., protic solvents) will lower the barrier to bond-rotation making *syn*-betaine formation less reversible, which in turn will lower diastereoselectivity. As illustrated in Figure 5, increased amounts of



MeCN	>95:5
MeCN-*t*BuOH (9:1)	91:9
MeCN-H_2O (9:1)	73:27

Figure 5. Influence of protic solvent on dr of reaction.

protic solvents lowered the dr of the reaction (see also Table 3). This ultimately led to the use of method **B** for reaction with aliphatic aldehydes and to the use of neat MeCN as solvent for the reaction of *p*-methoxy substituted benzyl ylide with benzaldehyde (Figure 4 and Table 4).

Diastereoselectivity in Aziridinations. In contrast to reactions with aldehydes, the addition of benzyl-stabilized sulfur ylides to *N*-Ts imines is nonreversible, and therefore, the selectivity is determined by the relative rates of formation of the *anti* and *syn*-betaines.[34] From computational studies, Robiette found that the lowest energy pathway to the *trans*-aziridine occurred via cisoid addition of the ylide to the imine to give the *anti*-betaine intermediate, followed by bond rotation and subsequent ring closure (Scheme 7).[35]

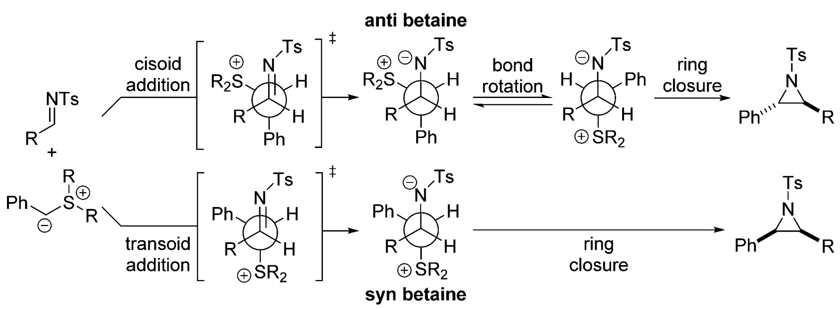
In contrast, the *cis*-aziridine was formed from a transoid addition of the ylide to the imine to give the *syn*-betaine intermediate, followed by direct ring closure. However, the differences between the energies of the barriers of the key TSs leading to the *syn* and *anti*-betaines and therefore the *cis*- and *trans*-aziridines in the model systems used in the calculations were relatively small, reflecting the low diastereoselectivity generally observed. Clearly, these systems are finely balanced, and it is difficult to predict what the outcome will be for a given substrate. The moderate *trans* selectivity observed with *N*-Ts imines derived from aryl aldehydes and the unsaturated imine is a reflection of the energy differences between the two addition TSs for formation of the *anti* and *syn*-betaines (Table 7, entries 1−4 and 6). It is difficult to explain why the unsaturated imine derived from cinnamaldehyde gave such high diastereoselectivity (Table 7, entry 5). The stark contrast between the high *trans* selectivity obtained with pivaldehyde-derived imine (*t*-BuCH=NTs) compared to the high *cis* selectivity obtained by Hameršak[31] is not something we can rationalize either at the present time.

The high *trans* selectivity observed for the *N*-BOC imine compared to *N*-Ts imines may be associated with its reduced steric properties coupled with its lower anion-stabilizing ability. The latter will result in a later addition TS. In turn this will increase the importance of steric factors but, maybe more importantly, of Coulombic interactions. The addition TS leading to the *trans*-aziridine has a cisoid TS where the anion and cation are *gauche* to each other and so will be favored. In contrast, the addition TS leading to the *cis*-aziridine has a transoid TS where the anion and cation are *anti* to each other and so will be disfavored.

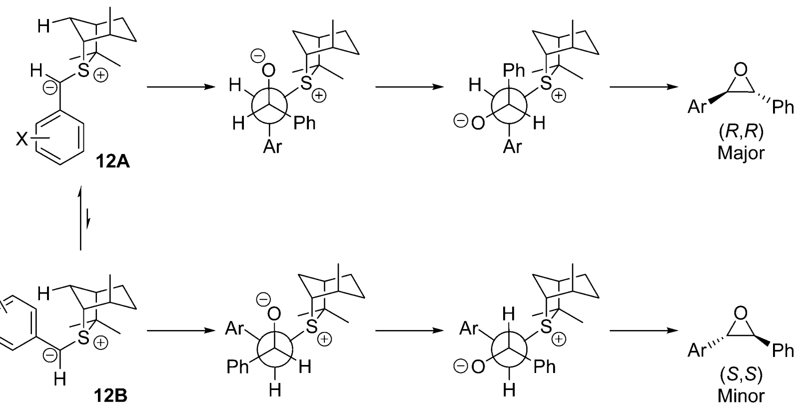
Origin of Enantioselectivity in Epoxidation and Aziridination Reactions. The model for the origin of enantioselectivity is shown in Scheme 8. Enantioselectivity is governed by three main factors: (i) ylide conformation, (ii) facial selectivity of the ylide reaction, and (iii) the degree of reversibility in betaine formation.

Analysis of space-filling models for sulfonium ylides derived from **2** shows that complete facial selectivity can be expected as a result of the Me group blocking reaction from one face. X-ray structures of several of the corresponding salts have been obtained (see Supporting Information) and one is illustrated below (Figure 6). The salt is closely related to the ylide intermediate and shows that one face is essentially completely blocked, whereas the other face is open and therefore accessible to substrates.

Scheme 7. Proposed Reaction Pathways in Aziridinations with Semistabilized Sulfur Ylides



Scheme 8. Origin of Enantioselectivity for Epoxidation with Sulfur Ylide 12



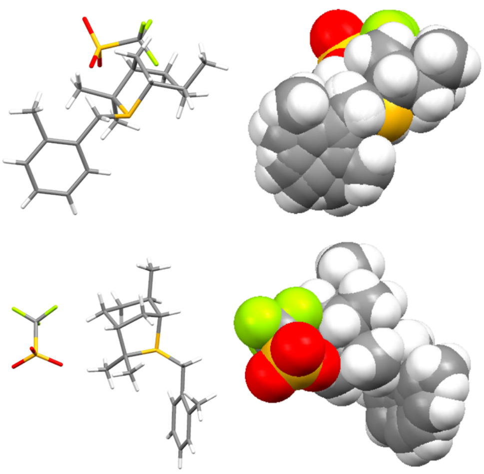


Figure 6. Two space-filling representations of crystal structure of **23d**.

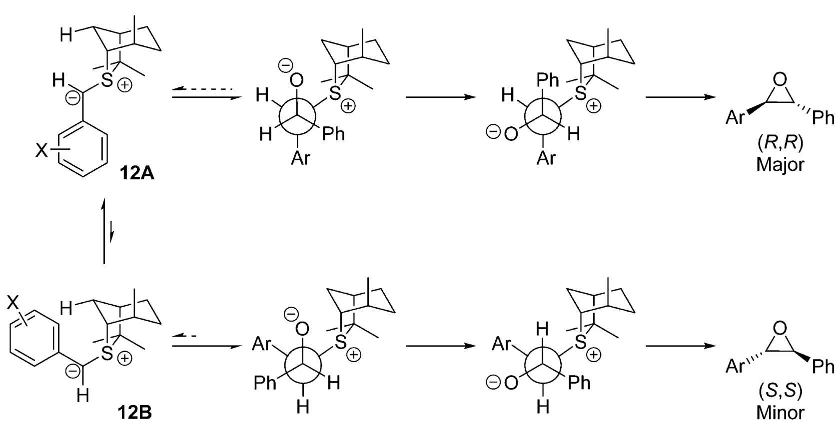
The enantioselectivity observed with different ylides is therefore influenced by factors (i) and (iii) and these are discussed, according to ylide type, in more detail below.

1. Electron Rich/Neutral Aryl-Stabilized and Alkenyl-Stabilized Ylides. Phenyl-stabilized sulfonium ylide gave high and uniform enantioselectivity, not only with different aldehydes (Table 2, 94–98% ee) but also in the aziridination of imines (96–98% ee; vide infra). Indeed, all electron-rich and neutral, aryl-stabilized ylides gave very high enantioselectivities with all of the aldehydes and imines studied (Tables 4 and 7). This suggests that the dominant factor responsible for enantioselectivity with all of these substrates is ylide conformation (**12A**:**12B** ratio), rather than the difference in reactivity of the two ylide conformers.[36] As stated above (Scheme 1), the ylide can adopt conformations **12A** or **12B**, but **12A** should be strongly favored as **12B** suffers from nonbonded 1,4 steric interactions (Scheme 8).

The α-substituted allylic sulfonium ylides also gave very high enantioselectivity, presumably because they show similar steric properties to an aromatic group. In the absence of the α-substituent, lower er was observed in epoxidation presumably because conformer **12B** was now less disfavored (reduced steric hindrance in conformer **12B**). The higher er observed in aziridination with α-unsubstituted allylic sulfonium ylides is intriguing and suggests that in this case the reactivity of the two ylide conformers is markedly different in reactions with imines compared to aldehydes (Curtin-Hammet).[36]

2. Hindered, Electron-Deficient, Aryl-Stabilized Ylides. Lower enantioselectivity was generally observed with electron deficient, aryl-stabilized ylides and particularly in their reactions with aromatic aldehydes (Table 5). As with the neutral/electron-rich substrates, ylide conformation should also be well controlled in favor of conformer **12A**. In these cases, formation of the *syn*-betaine is reversible and nonproductive, but formation of the *anti*-betaine is also likely to be partially reversible (see section on diastereoselectivity). This has consequences for enantioselectivity because the degree of reversibility in *anti*-betaine formation is likely to be different for the different conformers **12A** and **12B** (Scheme 9). Because ylide conformer **12B** is less stable (higher in energy) than

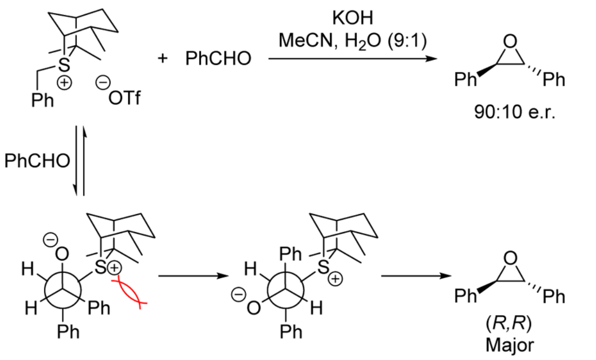
Scheme 9. Effect of *anti*-Betaine Reversibility on Enantioselectivity



conformer **12A**, it will react less reversibly (ylides of increasing stability react with increasing reversibility in betaine formation) with aldehydes resulting in an increased proportion of the product being derived from conformer **12B**, leading to low ee (Scheme 9) (Curtin-Hammett). Conditions that reduce reversibility in *anti*-betaine formation by promoting the bond rotation step (e.g., increased protic solvent, method **C**), or by inhibiting the breakdown of the betaine to its constituents (reduced entropic driving force for converting one molecule back to two molecules at low temperature, method **D**) increase the enantioselectivity (Table 5, entries 8–10).

*3. Alternative Diastereomeric Sulfide **22**.* The benzyl sulfonium salt of **22**, differing only in the stereochemistry of the methyl substituent, was also tested in epoxidation with benzaldehyde. This gave lower er than isothiocineole (90:10 vs 99:1), most likely because the methyl group points into the space occupied by the aldehyde and it inhibits bond rotation from the *gauche* to the *trans*-betaine (Scheme 10). The methyl group behaves like a stick inserted into the spokes of a wheel, inhibiting bond rotation, resulting in increased reversibility. This sulfide is effectively more hindered than **2**. Fortuitously, the easier-to-access isothiocineole gave considerably higher enantioselectivity. Once again, this highlights the importance of understanding the factors responsible for selectivity, because the stereochemistry of the remote methyl group would not have been expected to influence enantioselectivity at the outset based on a more simplistic model.

Scheme 10. Asymmetric Epoxidation of Benzaldehyde with Sulfide 22



CONCLUSIONS

We have described a simple protocol for the large-scale, one-step preparation of isothiocineole **2** from the simplest of reagents, limonene, elemental sulfur and γ-terpinene. This sulfide gives the highest selectivity (combined enantioselectivity and diastereoselectivity) to date in asymmetric epoxidations and aziridinations because of its rigidity, position of appropriate substituents, and its steric properties.

Interestingly, one issue dominates the selectivity observed in epoxidations with this sulfide and that is the degree of reversibility in betaine formation. If betaine formation is highly reversible, then high diastereoselectivity but low enantioselectivity will result. If betaine formation is essentially nonreversible, then low diastereoselectivity but high enantioselectivity will result. To achieve both high diastereoselectivity and high enantioselectivity, reversible formation of the *syn*-betaine and nonreversible formation of the *anti*-betaine are required. Although this scenario may seem on the surface to limit this reaction to a narrow set of substrates, from an understanding of the factors that influence reversibility (temperature, protic solvent, and metal counterion), we have in fact been able to find conditions that lead to high diastereo- and enantioselectivity for a broad range of epoxides and aziridines. Figure 7 shows the different classes of epoxides that can be made in good yield and with synthetically useful levels of stereocontrol. This analysis shows that diaryl, heteroaryl–aryl, aryl–alkyl and α,β-unsaturated epoxides can all be prepared with good levels of selectivity (>90:10 dr, >95:5 er).

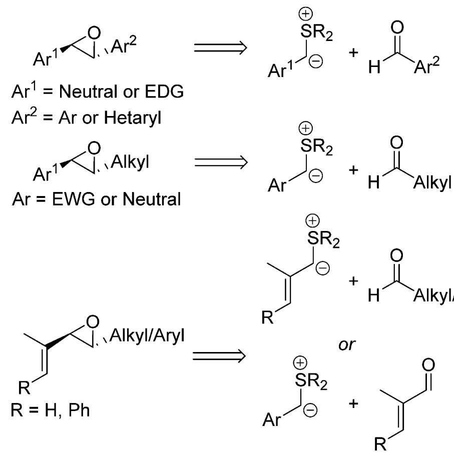


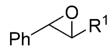
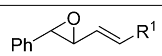
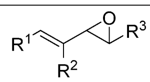
Figure 7. Epoxides available with >90:10 dr and >95:5 er using the sulfur-ylide disconnection.

The methodology is now a viable alternative to alkene epoxidation and offers a strategically different disconnection. Table 9 shows selected comparative data on results for the synthesis of epoxides using asymmetric alkene epoxidation versus the method described herein. To the best of our knowledge for aryl–alkyl-substituted *trans*-epoxides, Shi dioxirane epoxidations,[37] Mn(salen),[38] Ru(salen)[39] epoxidations, and biotransformations[40] are other leading alternatives. For vinyl epoxides, alternatives are alkene epoxidation by Mn(salen)[41] or dioxirane[42] catalysts. Of course the final decision on which methodology to use will come down to the individual requirements in a particular case.

In aziridination, betaine formation is largely nonreversible for the reactions of semistabilized ylides. The diastereoselectivity is therefore determined by the relative energies of the TSs involved in their formation, which in turn is influenced largely by the nature of the substituents on the imine and ylide. Although lower diastereoselectivity is often observed, the levels achieved are still synthetically useful. Figure 8 shows the different classes of aziridines that can be made in good yield and with >80:20 dr and >95:5 er. For the synthesis of vinyl–alkyl substituted aziridines, this sulfur ylide methodology is a viable alternative to the use of nitrido Mn(salen) complexes (Table 10 shows comparative data).[43] To the best of our knowledge, the enantioselectivities reported here for the synthesis of the types of unfunctionalized *trans*-disubstituted aryl/aryl and aryl/vinyl aziridines have not been matched by enantioselective alkene aziridinations to date.[29] It should be noted that other classes of alkenes such as α,β-unsaturated, *cis* and terminal alkenes can be aziridinated with high enantioselectivity.[29]

We have already applied sulfide **2** in the context of total synthesis: the asymmetric epoxidation methodology was

Table 9. Synthesis of *trans*-Epoxides by Asymmetric Alkene Epoxidation versus Aldehyde Epoxidation with Sulfide 2

R^1	R^2	R^3	Method	e.r.	Yield (%)	d.r.	r.r.[a]	Ref.
Aryl-Alkyl substituted								
Cy			Sulfide **2**	99:1	62	93:7		
n-Bu			Sulfide **2**	99:1	56	91:9		
			Mn(salen)	97.5:2.5	48			38
Me			Mn(salen)	95.5:4.5	77			38
			Ru(salen)	95.5:4.5	82			39
			Dioxirane	98:2	94			37b
			biotransformation	99.9:0.1	87			40a
Aryl-Vinyl substituted								
Ph			Sulfide **2**	99:1	88	>95:5		
			Dioxirane	98.5:1.5	77			42a
H			biotransformation	98:2	58			40d
Vinyl-Alkyl substituted								
Ph	Me	Cy	Sulfide **2**	98:2	77	>95:5		
n-C_6H_{13}	H	Me	Mn(salen)	96:4	50	52:48		41
CH_2OTBS	H	Me	Dioxirane	98:2	68		4.6:1	42a

[a] r.r. = regioisomeric ratio.

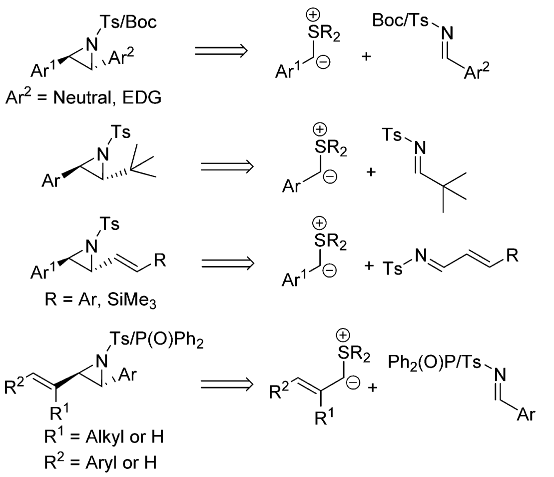
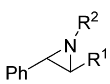


Figure 8. Aziridines available with >80:20 dr and >95:5 er using the sulfur-ylide disconnection.

Table 10. Synthesis of Aryl,Alkyl-Substituted *trans*-Aziridines by Asymmetric Alkene Aziridination vs Imine Aziridination with Sulfide 2



R^1	R^2	method	er	yield (%)	dr	ref.
t-Bu	Ts	Sulfide **2**	99:1	68	89:11	
Cy	SES	Mn(salen)≡N	96.5:3.5	62		43b
n-Pr	Ts	Mn(salen)≡N	95:5	66		43a
i-Pr	Ts	Mn(salen)≡N	97:3	53		43a
Me	H	Mn(salen)≡N	95.5:4.5	20		43c

utilized in the synthesis of quinine and quinidine,[7a,44,45] and the asymmetric aziridination methodology was utilized in the synthesis of kainic acid.[46] In these incidences, we demonstrated that the methodology could be applied on a multigram scale and that after the reaction the sulfide could be recovered in good yield by distillation or chromatography for reuse. Further applications in total synthesis are ongoing as they provide the ultimate litmus test for the methodology. We envisage that the ready availability of isothiocineole **2** combined with the mechanistic picture presented here will enable widespread use of the sulfur ylide disconnection in asymmetric epoxidations and aziridinations.

■ ASSOCIATED CONTENT

Supporting Information

Full experimental details and characterization of compounds including NMR spectra, HPLC/GC chromatograms, and X-ray text files are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(20) 1,4-Cyclohexadiene can also be used, but it is much more expensive than γ-terpinene and generates carcinogenic benzene as a byproduct.

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