Catalytic, Asymmetric Sulfur Ylide-Mediated Epoxidation of Carbonyl Compounds: Scope, Selectivity, and Applications in Synthesis

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ABSTRACT

The reaction of sulfur ylides with carbonyl compounds to give epoxides is an important synthetic method. This Account charts the recent advances in rendering this process both asymmetric and catalytic. Two catalytic methods have been developed: the first involving the reaction of a sulfide with an alkyl halide in the presence of a base and aldehyde and the second involving the reaction of a sulfide with a diazo compound or diazo precursor in the presence of a metal catalyst and aldehyde. These catalytic methods coupled with suitable chiral sulfides provide a new catalytic asymmetric epoxidation process for the preparation of epoxides. The scope of the two catalytic processes is discussed together with the factors that influence both relative and absolute stereochemistry. The application of these methods in target-orientated synthesis is also reviewed.

Introduction

Epoxides are important functional groups in synthesis because they undergo stereospecific nucleophilic ring opening to yield bifunctional compounds. There are two main ways of preparing an epoxide enantioselectively from a carbonyl compound: either by Wittig olefination (which controls relative stereochemistry) followed by enantioselective oxidation of the prochiral double bond[1−3] or by enantioselective alkylidenation using either an ylide, a carbene, or Darzens reagent (Figure 1).[4,5]

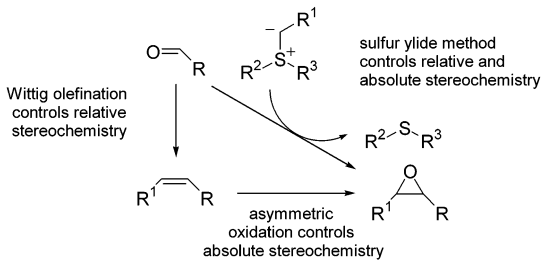

FIGURE 1.

While there are many examples of the two-step process involving a Wittig reaction followed by asymmetric oxidation, the one-step sulfur ylide route had not been widely used. We felt that if we could render the process both catalytic and asymmetric, the advantages of the new one-step route could begin to compete with the more traditional oxidative approach.

Introduction to Sulfur Ylide-Mediated Epoxidation

Johnson reported the first literature example of a sulfur ylide-mediated epoxidation reaction in 1958.[6] Reaction of the stable and isolable 9-dimethylsulfonium fluorenylide **1** (Figure 2) with 4-nitrobenzaldehyde did not afford an alkene, which had been expected on the basis of the related reactions of phosphorus ylides, but an epoxide instead. Several years later, Corey and Chaykovsky developed alternative ylides[7] (dimethyl sulfonium ylide **2** and dimethyloxosulfonium ylide **3**, Figure 2), which have since found widespread use in synthesis.[8]

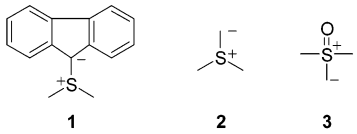

FIGURE 2.

The reaction of a sulfonium ylide with an aldehyde initially forms betaine intermediates that undergo subsequent ring closure to furnish an epoxide with regeneration of the sulfide. To render the process catalytic (with respect to the sulfide), the sulfide must be converted back into the ylide under suitably mild conditions. This is particularly important when chiral sulfides are employed. Two general methods exist for converting a sulfide into a sulfur ylide: alkylation with a suitable electrophile followed by deprotonation of the resulting sulfonium salt or reaction with a diazo compound in the presence of a metal catalyst. Both of these methods are discussed.

I. Catalytic Sulfur Ylide Epoxidation—Use of a Halide and Base. The first example of a catalytic, asymmetric epoxidation reaction was reported by Furukawa in 1989.[9] This process involved the reaction of a sulfide with an alkyl halide to give a sulfonium salt, which underwent deprotonation by KOH to furnish the corresponding ylide, which finally reacted with an aldehyde to afford the epoxide

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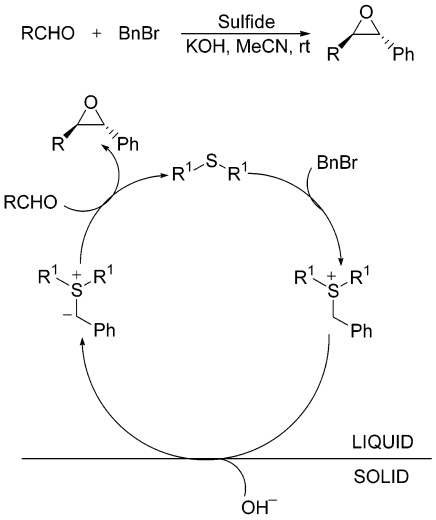
Scheme 1



(Scheme 1). In this catalytic cycle, substoichiometric amounts of sulfide could be employed (usually 50 mol %), and enantioselectivities of up to 47% ee were achieved using the camphor-derived sulfide **4** (Figure 3).

Based on this catalytic cycle, modified conditions and sulfide structures have been explored by a number of research groups (Figure 3).[9−15] Of these sulfides, the C_2-symmetric ones, **5** and **6**, gave the highest enantioselectivity. The lower yield but considerably higher enantioselectivity of the Goodman sulfide **6** is undoubtedly due to its increased steric hindrance, while the low catalyst loading achieved by Metzner through addition of substoichiometric quantities of Bu_4NI is particularly noteworthy. This additive speeds up the (slow) alkylation process thus providing acceptable reaction times with low sulfide loading.

Although modest to high levels of enantio- and diastereoselectivity have been reported, the substrate scope for this reaction remains somewhat limited. This is particularly true with respect to the alkyl halide component. While benzyl bromide has been the most popular choice, a smaller number of 4-substituted benzyl halides have also been tested. The only other class of substrates employed were a range of substituted allyl halides.[16] These were used in conjunction with a full equivalent of sulfide **5** in each case, and good levels of selectivity were achieved with methallyl halides and benzaldehyde.

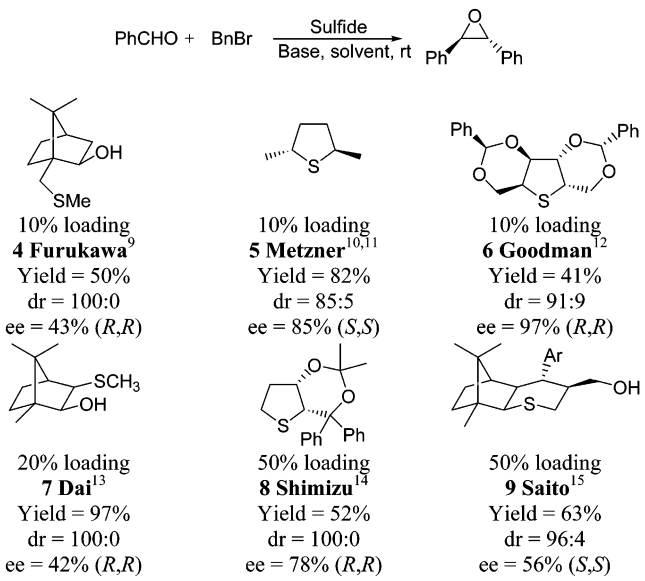


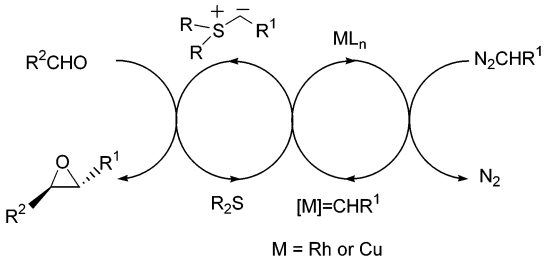
FIGURE 3. Literature chiral sulfides and results in epoxidation studies.

In terms of the carbonyl-coupling partner, aromatic and heteroaromatic aldehydes have mostly been employed;[9−15] aliphatic aldehydes are more problematic. *trans*-Cinnamaldehyde has also been employed with sulfide **5** and gave a 70% yield of the vinyl epoxide in 80% de with an enantiomeric excess of 86% after 6 days of reaction at room temperature.[11]

Although in a number of cases good enantiomeric excesses and diastereomeric ratios had been observed for substituted stilbene oxides, the process was still very limited in terms of substrate scope: the basic reaction conditions necessary to form the ylide prohibit the use of enolizable aldehydes, and the best results were always obtained with aromatic aldehydes.[4] Unfortunately however, the stilbene oxides that could be prepared are of limited synthetic value. Alkylation of the sulfide was also problematic in some cases, due to the low nucleophilicity of the sulfide.[17]

II. Catalytic Sulfur Ylide Epoxidation—Use of Metal Carbenes. As indicated above, an alternative method for the generation of sulfur ylides is by reaction of a sulfide with a diazo compound in the presence of a metal catalyst.[18] One of the principle advantages of this method is that the reaction is conducted under neutral conditions. Hence, under these conditions, it is possible to use base-sensitive substrates. Furthermore, the intermediate metal carbenes should be more reactive than the alkyl halides and should therefore facilitate ylide formation with less reactive sulfides.

Scheme 2



A catalytic cycle (Scheme 2) was developed involving decomposition of the diazo compound in the presence of a transition metal complex to yield a metallocarbene. This is then transferred to a sulfide, forming a sulfur ylide, which undergoes reaction with an aldehyde to give the desired epoxide, returning the sulfide to the cycle to make it available for further catalysis.

During our early studies, it became clear that several factors were important in minimizing the formation of side products, such as stilbene, which resulted from the reaction of the metal carbene with phenyl diazomethane.[19]

This could be minimized by the use of more nucleophilic sulfides (to enhance the rate of ylide formation), and maintaining low concentrations of the diazo compound by slow addition using a syringe pump.

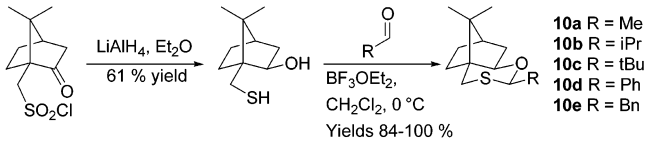
Under optimal conditions, we were able to show that the process could be applied to a range of aromatic,[20] aliphatic, and base-sensitive aldehydes.[21] Having developed a catalytic process with good substrate scope, the next goal was to make it asymmetric.

Designing Chiral Sulfides

In the design of chiral sulfides, several factors were deemed important, but most importantly, alkylation should lead to a single diastereoisomer of the sulfonium salt. This could be achieved by either (a) having a C_2-symmetric sulfide that could only give one diastereomer upon alkylation or (b) incorporating the sulfide in a rigid structure in which one of the two possible lone pairs was significantly more reactive.

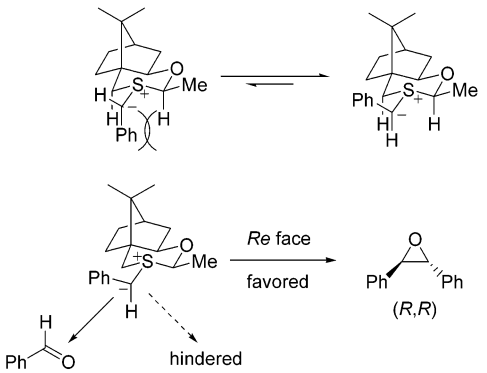
Additional practical issues include the ready availability of the sulfide, (via a short synthetic sequence) in both enantiomeric forms. These factors led to the design of sulfide **10**, which was readily available in two steps from camphor sulfonyl chloride (Scheme 3).[22]

Scheme 3



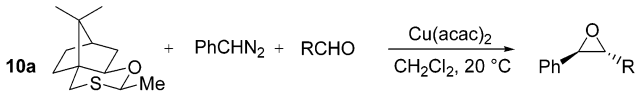
This sulfide could be easily modified through the appropriate choice of the carbonyl group used to form the thioacetal, and thus electronic and steric effects could be easily probed. More importantly, we thought that both the ylide conformation and the face selectivity of the ylide addition to the aldehyde would be controlled through nonbonded interactions and might therefore lead to high selectivity (Scheme 4).

Scheme 4



A series of sulfides was prepared, and the optimum was found (**10a**, R = Me): using 20 mol % of sulfide, epoxides were obtained in good yields with high enantioselectivities (Scheme 5).[23,24]

Scheme 5



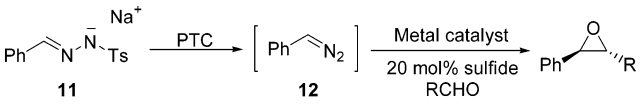
R = Ph, 4-ClC$_6$H$_4$, 4-MeC$_6$H$_4$, PhCH=CH, CH$_3$(CH$_2$)$_3$, (CH$_2$)$_6$
Yields = 32-73%, dr = 70:30 - 98:2, ee = 68-93%

If the acetal substituent R was sterically bulky or an electron-withdrawing group, reduced yields without improvement in selectivity were observed in the epoxidation process. This highlighted the importance of having a strongly nucleophilic sulfide to capture the metal carbene, thereby avoiding competing side reactions.

Development of an in Situ Process

A major limitation of the carbene methodology that we had developed was the need to synthesize and handle diazo compounds, which, since they are potentially explosive, severely limits the practicality of the process. We therefore considered the possibility of generating the diazo compound in situ and coupling this reaction to our established epoxidation process.

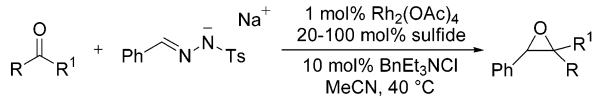
Scheme 6



After much experimentation, we found that warming a suspension of tosylhydrazone salt **11** in the presence of a phase transfer catalyst (PTC), allowed generation of the diazo compound (**12**) at moderate temperature (Scheme 6). This process was compatible with our established epoxidation process, and furthermore, the necessity for slow addition of the diazo compound that had previously required syringe pumps, now needed nothing more sophisticated than a thermostat. For very slow addition, reactions were performed at 25 °C and required 2 days to go to completion, while faster additions occurred at 45 °C and took 3 h to reach completion. An additional advantage of this in situ process is that it is much more efficient than that with the preformed diazo compound: less diazo precursor is required and higher yields and higher trans selectivities are obtained. Indeed, considering the number of steps and the potential for unwanted side reactions[25] in the cascade process, the efficiency is remarkable. At this stage, we decided to make a full investigation into the scope and limitations of our in situ process.[26]

These new conditions were tested with a range of carbonyl compounds using achiral sulfides, and the results are summarized in Table 1. All aromatic (entries 1−4), heteroaromatic (entries 5−7), and unsaturated aldehydes (entries 8 and 9) furnished the corresponding epoxide in high yield and high trans selectivity. Aliphatic aldehydes also worked well, although they generally gave lower yields and selectivities (entries 10−13). However, complete control over diastereoselectivity could be achieved by using arsines in place of sulfides (entry 14).[27]

Table 1. Scope of Carbonyl Coupling Partner

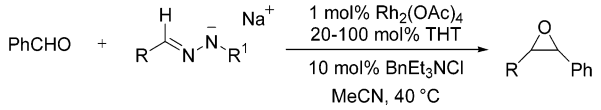


entry	carbonyl compound	sulfide/mol %[a]	% yield	trans/cis
1	PhCHO	THT/20	95	>98:2
2	4-$NO_2C_6H_4CHO$	THT/20	94	>98:2
3	4-$MeOC_6H_4CHO$	THT/20	98	>98:2
4	2,4,6-MeC_6H_2CHO	THT/20	87	>98:2
5	2-thiophenecarboxaldehyde	THT/20	90	>98:2
6	2-furaldehyde	THT/20	80	>98:2
7	2-pyridinecarboxaldehyde	THT/20	62	87:13
8	methacrolein	THT/100	39	>98:2
9	(*E*)-cinnamaldehyde	THT/20	97	>98:2
10	valeraldehyde	THT/20	53	70:30
11	cyclohexanecarboxaldehyde	THT/20	70	65:35
12	pivaldehyde	THT/100	49	>98:2
13	phenylacetaldehyde	THT/20	60	>98:2
14	cyclohexanecarboxaldehyde	Ph_3As/100	77	>98:2
15	TIPS-propargylaldehyde	THT/20	60	50:50
16	cyclohexanone	PMS/20	54	NA
17	acetophenone	PMS/20	15	<2:98

[a] THT = tetrahydrothiophene; PMS = pentamethylene sulfide.

The application of ketones as the carbonyl-coupling partner to afford trisubstituted epoxides was less successful when tetrahydrothiophene was used because of competitive Stevens and Sommelet−Hauser rearrangements[28,29] of the sulfur ylide with these less reactive substrates. However, these rearrangements could be minimized using pentamethylene sulfide as the catalyst (entries 16 and 17), and modest to high yields were achieved. It is interesting in this case to note that the cis product appeared to be favored over the trans: diastereomeric ratios of >98:2 were observed, although at this stage we are unable to explain this result.

Table 2. Scope of Hydrazone Coupling Partner



entry	R	R^1	% yield	trans/cis
1	C_6H_5	Ts	95	>98:2
2	4-$MeOC_6H_4$	Ts	73	71:29
3	2-$MeOC_6H_4$	Ts	92	>98:2
4	4-CNC_6H_4	Ts	90	>98:2
5	2,4,6-$Me_3C_6H_2$	Ts	17	>98:2
6	2-furyl	Ts	96	80:20
7	$CHC(Me)_2$	Ts	24	58:42
8	$CHC(Me)_2$	2,4,6-(^{i}Pr)$_3C_6H_2SO_2$	70	50:50
9	(*E*)-C(Me)CHPh	Ts	76	>98:2

We next turned our attention to the use of a more diverse range of tosylhydrazone reagents in the epoxidation reaction. Initially, we utilized a variety of substituted aryl tosylhydrazone salts, (Table 2, entries 1−5), which were readily prepared, stable compounds capable of being stored for prolonged periods of time. Yields of epoxides obtained were excellent (entries 1−4), except where a sterically hindered reagent was employed (entry 5). The diastereoselectivities were generally high with only trans epoxides being formed, apart from unhindered tosylhydrazone salts bearing electron-donating substituents (entry 2).

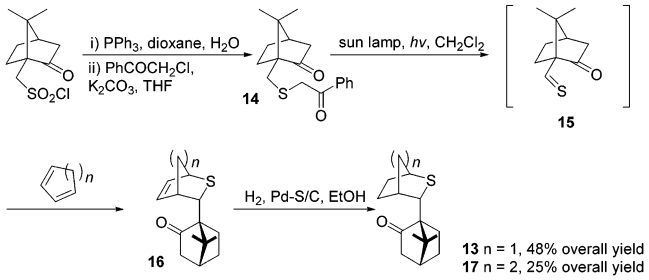
The next group of substrates to be tested was the unsaturated tosyl hydrazone salts. There was some literature precedence for the use of unsaturated sulfonium salts to form α,β-unsaturated epoxides (vide supra),[16] but in some cases, it has been shown that ylide equilibration was followed by [2,3] sigmatropic rearrangement.[30] These substrates were generally more difficult to handle due to their lower stability, but it was possible to carry out deprotonation in situ using Li- or Na-HMDS. In some cases, it was also necessary to replace the tosyl group with the more hindered, and more reactive, triisopropyl benzenesulfonyl group to obtain moderate yields of epoxide. Lower diastereoselectivities and more variable yields were observed with these substrates (Table 2, entries 7−9).[26]

Use of Chiral Sulfides in the in Situ Catalytic Cycle

With this improved methodology in hand, attempts were made to render the process asymmetric by use of a chiral sulfide.[31] Unfortunately, thioacetal **10a**, which had given good levels of enantioselectivity with a range of aldehydes in conjunction with phenyl diazomethane, was unstable under the reaction conditions, and only low yields of epoxide were obtained.

We therefore designed and prepared a range of more stable mono and bicyclic chiral sulfides and, from this extensive study, found that bicyclic sulfide **13**, which could be prepared in four steps and 48% overall yield from camphor sulfonyl chloride (Scheme 7), was highly effective in our epoxidation process.[32]

Scheme 7



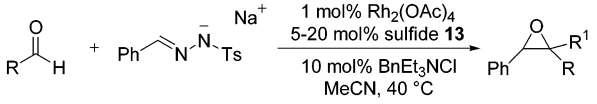
Epoxidation using only 5 mol % of sulfide **13** occurred readily, and high levels of enantioselectivity were observed. Furthermore, the sulfide could be reisolated in good yield after the reaction with no loss of stereochemical purity.

The bicyclic [2.2.2] sulfide **17** was also prepared by the same route and gave similar results in epoxidation. No improvements were observed when sulfide **17** was employed; therefore our studies were continued with sulfide **13** because this sulfide was prepared in higher yield using the inexpensive cyclopentadiene.

We succeeded in scaling up the reaction between benzaldehyde and the benzaldehyde tosyl hydrazone sodium salt to a 50 mmol scale and achieved similar yields and enantioselectivities. On this scale, it was possible to further reduce both the metal catalyst loading (0.5 mol %) and the amount of PTC employed (5 mol %). Due to the potential hazards involved when working with diazo compounds, this large-scale work would not have been contemplated using the process involving the preformed diazo compound, but using the in situ process, the reaction was uneventful.

Chiral sulfide **13** was then employed using the optimized conditions with a range of aromatic, heteroaromatic, and α,β-unsaturated aldehydes, as well as aliphatic substrates (Table 3).[26]

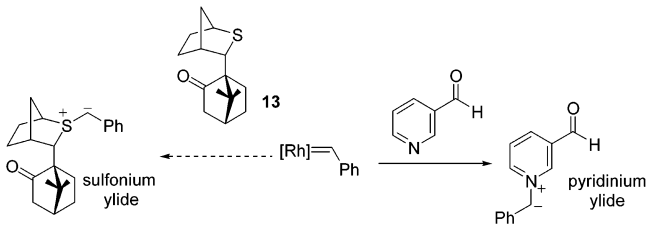
Table 3. In Situ Epoxidation Studies Using Chiral Sulfide with Various Aldehydes



entry	aldehyde	% yield	trans/cis	% ee
1	C_6H_5	82	>98:2	94
2	*p*-$NO_2C_6H_4$	75	>98:2	92
3	*p*-$MeOC_6H_4$	68	>98:2	92
4	furaldehyde	60	>98:2	91
5	valeraldehyde	46	75:25	89
6	(*E*)-cinnamaldehyde	70	>98:2	87

It was found that good yields and high enantio- and diastereoselectivities were observed in most cases (>87% ee), but some curious limitations were uncovered. For example, the hindered mesitaldehyde worked well, but pivaldehyde did not. Phenyl acetaldehyde, which worked well when tetrahydrothiophene was employed, was no longer a good substrate either, perhaps because the more hindered ylide was now less nucleophilic and therefore acted as a base instead. Pyridinecarboxaldehydes, which again worked well when tetrahydrothiophene was employed, were no longer effective with sulfide **13**. In this case, it was thought that competitive formation of a pyridinium ylide occurred (as opposed to formation of the sulfonium ylide) due to the higher nucleophilicity of the lone pair on the nitrogen compared to that of the hindered sulfide (Scheme 8).

Scheme 8

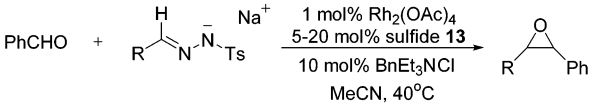


A variety of aromatic tosylhydrazone salts were also successfully employed and again, high yields but more variable levels of enantio- and diastereoselectivity were observed (Table 4).

Electron-rich aromatic tosyl hydrazone salt gave high enantiomeric excess (>93% ee), and high diastereoselectivity was also achieved when they were ortho-substituted. Electron-deficient aromatic tosyl hydrazone salts gave high diastereoselectivity but low enantiomeric excess (61−64% ee). A single ortho-substituent was tolerated but two ortho-substituents resulted in much lower yields. Presumably, this was a result of slow ylide formation due to the reaction of a hindered carbene with a hindered sulfide.

α,β-Unsaturated substrates were less successful in asymmetric epoxidations, often resulting in low product yields with varying degrees of diastereo- and enantioselectivity.

Table 4. In Situ Epoxidation Studies Using Chiral Sulfide with Various Tosylhydrazone Salts



entry	R	% yield	trans/cis	% ee
1	C_6H_4	82	>98:2	94
2	4-$MeOC_6H_4$	95	80:20	93
3	2-$MeOC_6H_4$	70	>98:2	93
4	4-ClC_6H_4	81	>98:2	93
5	4-CNC_6H_4	70	>98:2	64
6	2-furyl	53	90:10	61
7	$C(CH_3)CH_2$	12	>98:2	88

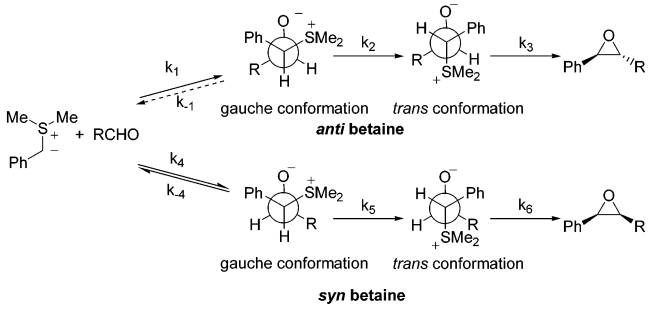
Origins of Diastereoselectivity and Enantioselectivity

Although high levels of diastereo- and enantiocontrol were observed in the reaction of ylides with a variety of substrates, the level of stereocontrol was sometimes lower than expected, and we wanted to understand which features of the sulfide structure, ylide conformation, choice of electrophile, or reaction conditions were responsible for this. It was hoped that with a greater understanding of these factors, we would be able to achieve improved selectivities with our "problem" substrates.[33]

Initially, we looked at the diastereoselectivity of reactions involving semistabilized ylides.[34] Crossover studies were carried out with the syn and anti betaines, which were independently generated by deprotonation of the corresponding hydroxy-sulfonium salt in the presence of a more reactive aldehyde. We observed that while the anti betaine underwent direct formation of stilbene oxide with no incorporation of the more reactive aldehyde, the syn betaine gave almost complete incorporation of the more reactive aldehyde (Scheme 9). Hence, we could conclude that the high trans selectivity observed in most reactions of benzyl-substituted ylides with aromatic aldehydes is a result of the nonreversible formation of the anti betaine and the unproductive, reversible formation of the syn betaine.

These observations were supported by DFT calculations,[35] which showed that in the case of the syn betaine, the barrier to C−C bond rotation (k_5) was higher than the barrier of reversion to starting materials (k_{-4}), whereas for

Scheme 9



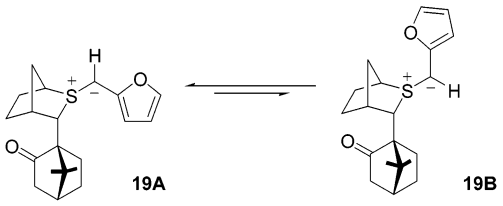
the anti betaine, the barrier to bond rotation (k_2) was lower than the barrier to return to starting materials (k_{-1}).

We concluded that for reactions involving different substrates, the diastereoselectivity can be lowered by four factors that contribute to the reduced reversibility of the syn betaine, which in turns leads to a reduction in trans selectivity: (a) lower stability of the carbonyl group (for example, aliphatic aldehydes give lower diastereoselectivity than aromatic aldehydes); (b) reduced stability of the ylide (for example, the presence of electron-donating groups on the aromatic ring destabilizes the ylide leading to lower diastereoselectivity); (c) reduced steric hindrance of the ylide or aldehyde (for example, the use of acetylenic aldehydes allows rotation about the C−C bond to become more facile and hence the diastereoselectivity is reduced); (d) increased solvation of charges by Li salts or protic solvents leading to a reduction in the barrier to bond rotation and therefore reduced diastereoselectivity.

To control enantioselectivity, it is necessary to (i) form a single diastereomeric sulfonium ylide, (ii) achieve high levels of control in ylide conformation, (iii) achieve high levels of control in face selectivity in the addition of the ylide onto the electrophile, and (iv) ensure that anti betaine formation is nonreversible (Scheme 10).

From data that we had obtained for the corresponding sulfonium salt (vide infra), we were confident that a single diastereomer of the sulfonium ylide was being formed in the alkylation step and that the bulky camphor moiety controlled the facial selectivity of the ylide by effectively blocking one face (as shown in Scheme 10). However, the degree of control in the ylide conformation was a concern. We believe that cases where we observed low enantioselectivity with nonhindered ylide substrates, such as with the 2-furaldehyde tosyl hydrazone salt (61% ee) or one of the α,β-unsaturated tosylhydrazone salts, were due to low control over ylide conformation (Scheme 11). In contrast, in the case of the benzylide substrate, which is a significantly larger group, there is a much greater preference for conformer **18A** where the 1,4-steric interactions are minimized, and thus, the enantioselectivity is much higher (94% ee, Scheme 10).

Scheme 11



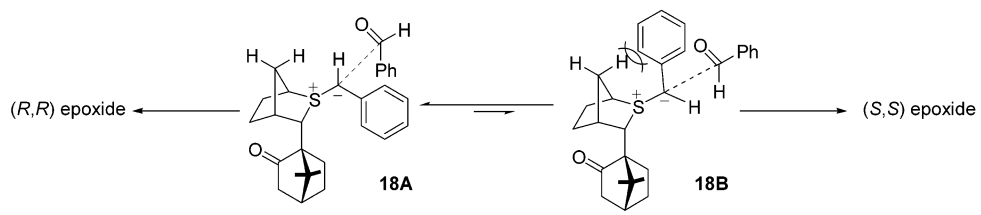
The degree of reversibility of the reaction is also important and is governed by the relative rates of bond rotation from the gauche to the trans betaine conformations versus the rate of reversion to the ylide and aldehyde. It was observed that more stable or hindered ylides gave reduced enantioselectivities, and we believe that this is due to partial reversibility of the betaines. In the former case, this is due to increased rates of reversion (k_{-1}) and in the latter case this is due to an increased barrier to bond rotation (k_2), which converts the gauche into the trans betaine.[35]

It would also seem that temperature is an important factor to take into consideration. While the catalytic sulfur ylide reactions have to be conducted at room temperature or above (usually 40 °C) to allow efficient decomposition of the tosyl hydrazone compound, stoichiometric sulfur ylide reactions can be carried out at lower temperatures. This has been shown to lead to higher levels of both diastereo- and enantioselectivity, although we believe this is not solely due to the effect of temperature on the ratio of conformers. Reactions carried out with ylide **18** at −78 °C gave enantioselectivities higher than expected on the basis of Boltzmann calculations, so clearly, even at low temperature, the other factors (e.g., reduced reversibility) are also important.

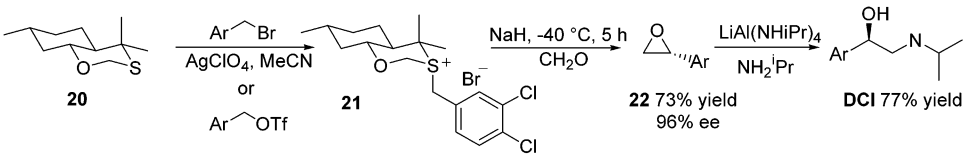
Development of a Stoichiometric Process

Although the metal carbene process has quite broad scope, like most catalytic processes, it also has its limitations (although it is less limited than the alkylation/deprotonation approach discussed above). For example, aldehydes with basic groups (e.g., pyridyl carboxaldehydes) were poor electrophiles, and α,β-unsaturated hydrazones were poor carbene precursors. Unfortunately, these two very useful classes of epoxide are also difficult to prepare by oxidative means, and therefore, a different approach was sought.

Scheme 10



Scheme 12



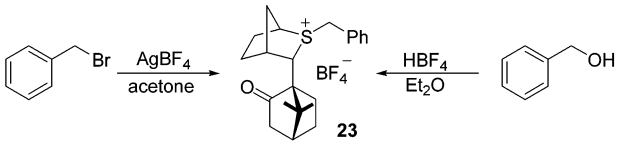
As an alternative, we considered the use of a stoichiometric process, ideally involving efficient recovery of the chiral transfer reagent. Although the use of stoichiometric quantities of sulfide had previously been described, through initial formation of a sulfonium salt, the substrate scope remained rather limited,[17] and the sulfides that had been reported were not readily available in both enantiomeric forms.

One of the best sulfides is Eliel's oxathiane **20**, used and developed by Solladié-Cavallo for ylide epoxidation.[36] This methodology has been extended to the preparation of the β-adrenergic compound (−)-(*R*)-dichloroisoproterenol (DCI), which was derived from the terminal epoxide **22** (Scheme 12). Excellent levels of stereocontrol were observed.[37]

In the initial studies, NaH was used to form the ylide[38] (other bases were tested but this was found to be superior in terms of yield and selectivity); however, it was later found that the use of a phosphazene (EtP_2) base gave increased levels of selectivity because it could be used effectively at low temperatures.[39]

Although excellent selectivities were achieved, a serious limitation is that only a single enantiomer of sulfide **20** is readily available. In contrast, both enantiomers of sulfide **13** are equally accessible, so stoichiometric ylide reactions were explored to plug the gaps in the catalytic process.

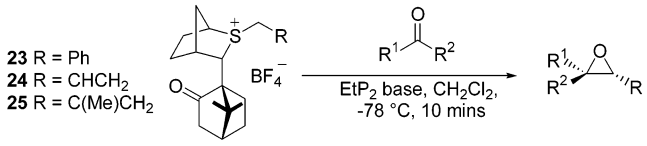
Scheme 13



The desired chiral sulfonium salt **23** was prepared by alkylation with either an alkyl bromide in the presence of $AgBF_4$ or the corresponding alcohol in the presence of HBF_4 (Scheme 13).[40] Subsequently, the sulfonium salt **23** was treated with either KOH at room temperature, the phosphazene base (EtP_2)[39] at −78 °C, or KHMDS at −78 °C to form the ylide. Only substrates that performed poorly in the catalytic cycle (vide supra) were tested, and high yields, high diastereoselectivities, and almost perfect enantioselectivities were usually observed (Table 5). Except when the epoxide was unstable to chromatography, the sulfide could be recovered in high yield. Ketones were also found to be good substrates, and the methodology could even be applied to α,β-unsaturated sulfonium salts.

In each case, the phosphazene base at low temperature gave higher selectivities than the KOH reaction, which had to be carried out at room temperature due to the use of water as a cosolvent. However, the cost of the phosphazene base prohibits large-scale use and so deprotonation with other bases at low temperature was investigated. From a series of bases tested, KHMDS was found to be particularly effective.

Table 5. Scope of Sulfonium Salt Epoxidation



entry	salt	electrophile	% yield	trans/cis	% ee
1	**23**	2-pyridinecarboxaldehyde	88	98:2	99
2	**23**	valeraldehyde	64	92:8	97
3	**23**	methacrolein	55	>99:1	99
4	**24**	benzaldehyde	43	91:9	89
5	**25**	benzaldehyde	26	>99:1	93

Although acrolein was a rather poor substrate, other unsaturated aldehydes performed very well. Furthermore, the chemistry could be extended to α,β-unsaturated sulfonium salts to give epoxides with high levels of selectivity.

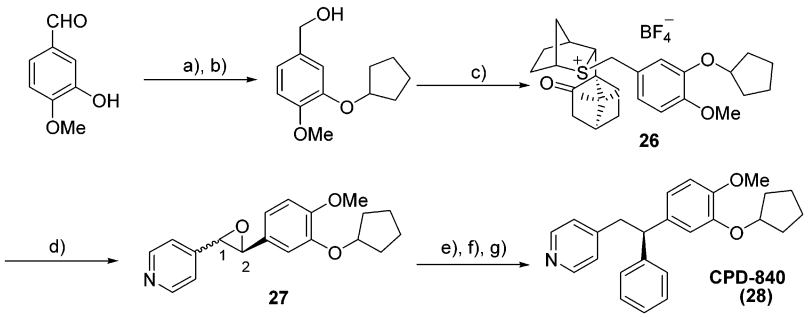
Application of the Methodology in Synthesis

The asymmetric sulfur ylide methodology was applied to the synthesis of the antiinflammatory agent CDP-840. Chiral sulfonium salt **26** was reacted with 4-pyridine carboxaldehyde using the phosphazene (EtP_2) base and the desired epoxide (**27**) was obtained as a 7:3 mixture of diastereoisomers with almost complete control of enantioselectivity (>98% ee for each diastereoisomer, Scheme 14). The sulfide itself was recovered in near quantitative yield. A mixture of cis and trans epoxides was acceptable because they were both obtained with the same high enantioselectivity at C2, and following ring opening and removal of the hydroxyl group, CDP-840 (**28**) was obtained in enantiomerically pure form.[40]

Enantioselective Preparation of Aziridines, Cyclopropanes, Terminal Epoxides and Glycidic Amides.

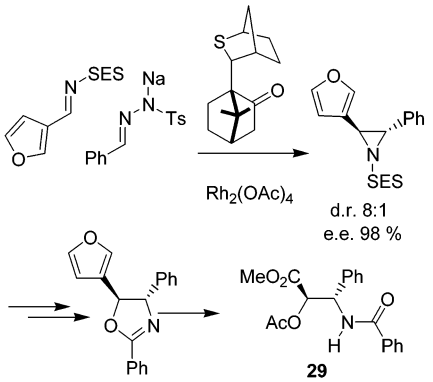
The asymmetric ylide-mediated epoxidation process has also been extended to the preparation of aziridines[41,42] and cyclopropanes[42,43] for a variety of substrates, and high enantio- and diastereoselectivity has been achieved. Furthermore, the aziridination methodology has been applied to the synthesis of the side chain of taxol **29** (Scheme 15),[44] while the cyclopropane methodology has been applied to the preparation of cyclopropylamino acids **30** (Scheme 16).[42]

Scheme 14



Reagents and conditions: a) K_2CO_3, cyclopentyl bromide, DMF, 97%; b) $NaBH_4$, MeOH, 99%; c) **ent-13,** HBF_4, Et_2O, room temperature, 1 h, 99%; d) EtP_2 base, CH_2Cl_2, -78 °C, 15 min, then pyridinecarboxaldehyde, -78 °C, 1 h, 89%, (trans:cis = 7:3), >98% ee; e) PhMgBr, CuI, THF, 85%; f) Et_3N, MsCl, CH_2Cl_2; g) Zn, AcOH, 80% (two steps)

Scheme 15



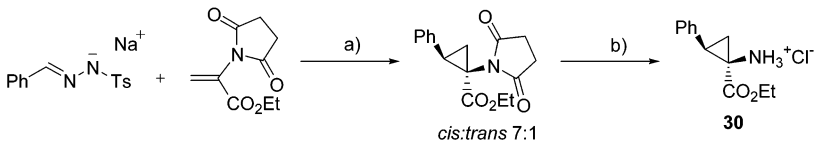
No practical process for preparing terminal epoxides through methylidene transfer has been developed.[45] However, very high enantioselectivity has been achieved in the synthesis of glycidic amides using the chiral amide-stabilized sulfur ylide **31** (Scheme 17). The reaction shows good substrate scope and has been applied in the synthesis of the leukotriene D_4 antagonist SK&F 104353 (**32**), which is active in the treatment of bronchial asthma.[46]

Conclusions

Two catalytic, asymmetric sulfur ylide-mediated epoxidation processes have been developed. The method involving reaction of a chiral sulfide with an alkyl halide and base in the presence of an aldehyde is generally limited to the synthesis of stilbene oxide derivatives. This is because reactive halides are required, and the aldehydes should not undergo significant side reactions (e.g., aldol reactions). Nevertheless, this method has delivered high levels of enantioselectivity for this class of epoxide.

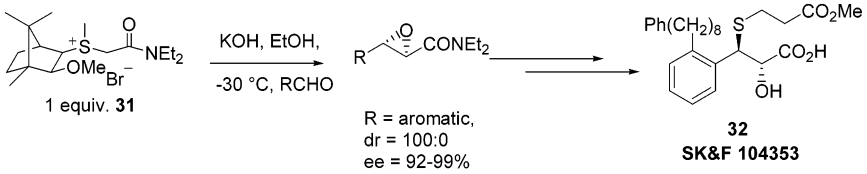
The method involving reaction of a chiral sulfide with a diazo precursor in the presence of a PTC, metal catalyst, and aldehyde shows broader scope. Aromatic, heteroaromatic (but not pyridyl), aliphatic, and unsaturated aldehydes have been employed together with a range of aromatic and heteroaromatic diazo precursors. The broader scope results from the increased electrophilicity of the metal carbene relative to an alkyl halide, the neutral reaction conditions, and the regiospecific formation of the intermediate ylide. Certain aldehydes and diazo precursors gave rather low yields of epoxides, so a stoichiometric process was developed to fill the gaps. In particular, heteroaromatic epoxides bearing basic groups and α,β-unsaturated epoxides, which are difficult classes of epoxides to prepare by oxidative methods, were easily synthesized using the stoichiometric process with high stereocontrol. The combined catalytic and stoichiometric processes allow access to a very broad range of epoxides including glycidic amides and α,β-unsaturated epoxides, aziridines, and cyclopropanes with control of both relative and absolute stereochemistry in many instances. This

Scheme 16



Reagents and conditions: a) Sulfide **17** (20 mol%), $Rh_2(OAc)_4$ (1 mol%), PTC (20 mol%), 1,4-dioxane, 40 °C, 24 h, 55%; b) 6N HCl, reflux, 90%

Scheme 17



broad substrate scope of the process now allows the sulfur ylide disconnection to be applied with confidence in total synthesis.

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