

# The complexity of catalysis: origins of enantio- and diastereocontrol in sulfur ylide mediated epoxidation reactions

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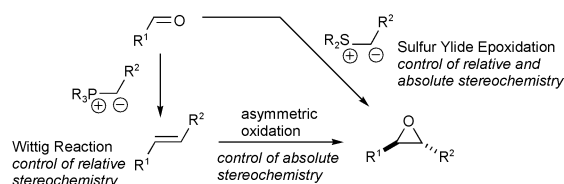
The reaction of chiral sulfur ylides with aldehydes and ketones has emerged as a useful asymmetric process for the synthesis of epoxides. Processes employing either catalytic or stoichiometric amounts of sulfides have been developed. Although a large number of chiral sulfur ylides have been tested in the epoxidation process, only a few have delivered high diastereo- and enantio- selectivity. This review examines the factors that influence stereocontrol (steric hindrance of the sulfide, ylide conformation, ylide face selectivity, reversibility of betaine formation, solvent, and metal salts). This analysis leads to the conclusion that high reversibility in betaine formation leads to high diastereoselectivity but low enantioselectivity, and non-reversible betaine formation leads to low diastereoselectivity and high enantioselectivity (provided that other criteria are met). To achieve both high diastereoselectivity and high enantioselectivity simultaneously, requires non-reversible formation of the *anti*-betaine and reversible formation of the *syn*-betaine. Thus, factors that influence the degree of reversibility in betaine formation are critically important since with subtle changes in reaction conditions (solvent, temperature, metal ions) both high enantio- and diastereoselectivity can often be achieved.

## Introduction

Asymmetric catalysis is one of the most intellectually attractive and practical ways in which to synthesise chiral compounds.<sup>1</sup> Many different methods have been developed to effect useful

synthetic transformations in this way. In most cases, transfer of asymmetry is produced by introducing chirality into the catalyst, usually as a non-symmetric ligand. Obtaining an effective asymmetric transformation is often done largely by trial and error, but increasingly, chemists attempt to use rational design methods to develop possible ligands or auxiliaries. To be able to do this, it is necessary to have a very detailed understanding of the reaction mechanisms underlying the asymmetric transformation. One of our principal research interests lies in the asymmetric synthesis of epoxides using a catalytic variant of the reaction between sulfonium ylides and aldehydes/ketones. The chiral catalyst involved in this asymmetric transformation is a chiral sulfide, and we have synthesised and tested a large number of these during the past few years. Our studies have shown us how intricate the design process is, and have caused us to revisit, both experimentally and computationally, the details of the reaction mechanism and examine how different steps impact upon selectivity and reactivity.

The sulfur ylide mediated process for generating epoxides is complementary to the process involving alkene oxidations where notable successes include the Sharpless epoxidation of allylic alcohols,<sup>2,3</sup> the manganese salen catalysts developed by Jacobsen and coworkers and Katsuki<sup>4,5</sup> and the ketone based catalysts developed by Shi and coworkers.<sup>6–8</sup> If the alkene itself is derived from a carbonyl compound, then two steps are required to make an epoxide (Scheme 1): a Wittig reaction or



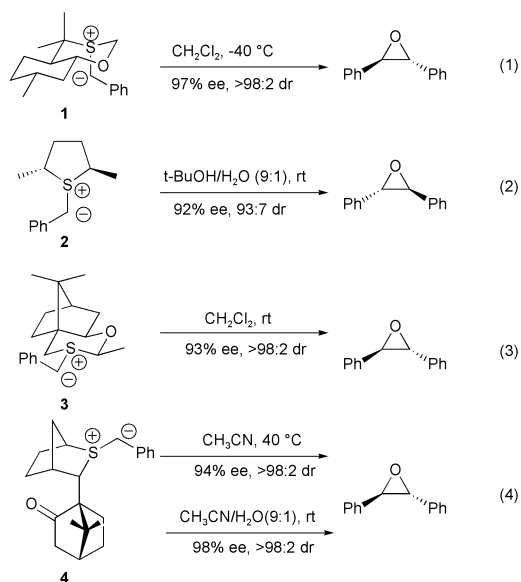
Scheme 1 Routes to epoxides from carbonyl compounds.

related olefination, which controls relative stereochemistry, and an asymmetric oxidation, which controls absolute stereochemistry. It is interesting to note that in this conventional strategy, the first step removes an oxygen atom and the second step adds an oxygen atom. Using a sulfur ylide to generate an epoxide from a carbonyl compound, the oxygen present in the starting carbonyl compound is retained in the product epoxide.<sup>9</sup> However, for this method to be competitive with the conventional protocol the sulfur ylide reaction has to control both relative and absolute stereochemistry. A number of sulfides have been developed which achieved this goal. Eliel's oxathiane was employed by Solladié-Cavallo in stoichiometric sulfur ylide mediated epoxidation and very high levels of enantioselectivity and diastereoselectivity were achieved with a narrow range of substrates (Scheme 2, eqn. 1).<sup>10,11</sup>

Durst<sup>12</sup> and later Metzner<sup>13,14</sup> used  $C_2$  symmetric 2,5-disubstituted tetrahydrothiophenes to effect the asymmetric epoxidation of aldehydes. Metzner applied the Furukawa protocol to render the process catalytic with respect to sulfide (Scheme

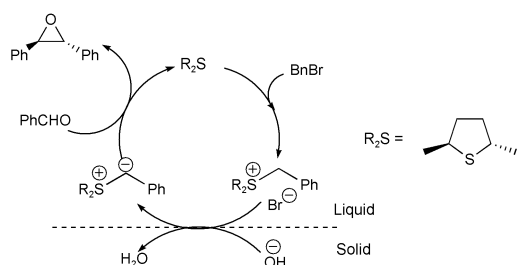
Varinder K. Aggarwal was born in Kalianpur in North India in 1961 and emigrated to the United Kingdom in 1963. He received his B.A. (1983) and Ph.D. (1986) from Cambridge University, the latter under the guidance of Dr Stuart Warren. He was subsequently awarded a Harkness Fellowship to carry out postdoctoral work with Professor Gilbert Stork at Columbia University, NY (1986–1988). He returned to a lectureship at Bath University and in 1991 moved to Sheffield University, where in 1997, he was promoted to Professor of Organic Chemistry. In 2000, he moved to the University of Bristol to take up the Chair of Synthetic Chemistry. He is recipient of the AstraZeneca award, Pfizer Award, GlaxoWellcome award, Novartis lectureship, RSC Hickinbottom Fellowship, Nuffield Fellowship, RSC Corday Morgan Medal and the Liebig's Lectureship.

Jeffery Richardson was born in Truro in the United Kingdom in 1978 and studied chemistry at Sheffield University, performing an undergraduate research project under the supervision of Professor Aggarwal. In 2000, he obtained his MChem degree and was awarded the Haworth medal for chemistry, before beginning his Ph.D. studies with Professor Aggarwal at the University of Bristol.

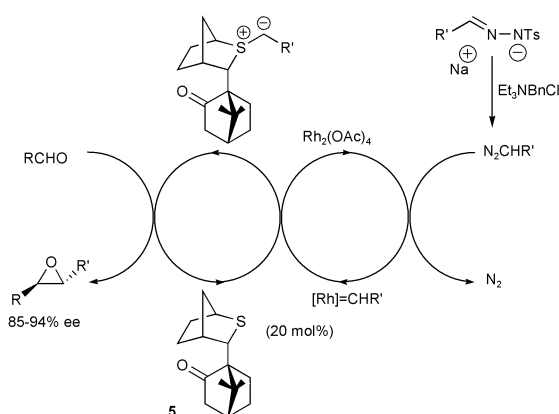


**Scheme 2** Sulfonium ylides used in asymmetric epoxidation reactions.

3).<sup>15</sup> Although Durst only achieved moderate enantiocontrol, considerably higher enantioselectivity was obtained by Metzner (Scheme 2, eqn. 2). Finally, we have described the application of oxathiane derived ylide **3**<sup>16,17</sup> and the ylide **4** based on bridged bicyclic sulfide **5** in catalytic asymmetric epoxidation (Scheme 4).<sup>18,19</sup> Although only a small number of examples were reported with ylides **1–3**, we have explored a very much broader range of substrates with ylide **4**.<sup>20</sup> Indeed, 29 different carbonyl compounds have been employed with ylide **4** and 19 ylides related to **4** have been tested with benzaldehyde.<sup>20</sup>



**Scheme 3** Catalytic asymmetric epoxidation by sulfide alkylation/treatment with base.



**Scheme 4** Catalytic asymmetric epoxidation by carbene transfer from diazocompounds generated *in situ*.

High levels of diastereo- and enantiocontrol were observed in reactions of ylides **1–4** with most substrates, but occasionally the levels of stereocontrol were reduced. So what features of the sulfide, ylide, electrophile, or reaction conditions are responsible for stereocontrol? Why did the C<sub>2</sub> symmetric ylide analogue

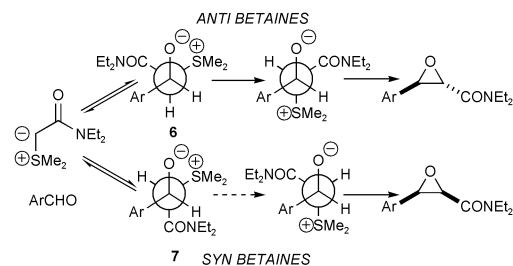
of **2** bearing CH<sub>2</sub>OBn groups in place of methyl groups give 60% ee whilst **2** gave 92% ee – was it due to the change in structure of the sulfide or to the change in reaction conditions? In this short review we attempt to answer these questions and provide a general understanding of the factors that influence stereocontrol in sulfur ylide reactions. In particular, we have come to the conclusion that factors which influence relative stereochemistry have a major impact on control of absolute stereochemistry, the two are inextricably linked.

The discussion is divided into three parts relating to stabilised, semi-stabilised and non-stabilised ylides. As there is almost a continuum of stabilities of different ylides, those close to the borderlines could clearly belong to either camp. We will indicate which classes of ylides belong to which category.

## Stabilised ylides

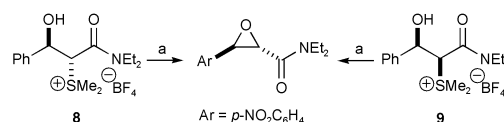
In this category are sulfur ylides bearing an additional anion stabilising group.

Ester stabilised ylides are highly stabilised and do not react with aldehydes; they only react with highly activated 1,2-dicarbonyl compounds.<sup>21,22</sup> Less stable ylides such as those stabilised by an amide group do react with aldehydes and give exclusively *trans*-epoxides for all aromatic and aliphatic aldehydes.<sup>23–25</sup> The mechanism of epoxidation involves three distinct steps: formation of the betaine with charges adjacent to each other, followed by bond rotation to the *trans*-conformation, and finally ring closure (Scheme 5).



**Scheme 5** Origin of high *trans* selectivity for stabilised ylides.

To determine whether betaine formation is reversible, cross-over experiments were conducted (Scheme 6).<sup>26</sup> Treatment of

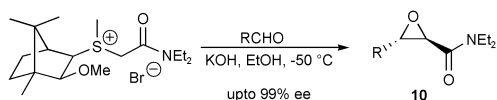


**Scheme 6** Reagents and conditions: a. 3 eq. *p*-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>CHO, 1.5 eq. NaOH, CH<sub>2</sub>Cl<sub>2</sub>, rt.

either the *anti*-(**8**) or *syn*-sulfonium salts (**9**) with base in the presence of the more reactive aldehyde, *p*-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>CHO, furnished only the *trans*-epoxide incorporating the more reactive aldehyde. This indicated that both the *syn*- and *anti*-betaines were formed reversibly. Thus, the high *trans* selectivity observed is a consequence of reversible formation of the intermediate betaines but where only formation of the *anti*-betaine **6** is productive. Based on our studies on the diastereoselectivity of epoxidation reactions using semi-stabilised sulfonium ylides, we believe that C–C bond rotation of the *syn* betaine (**7**) has a much higher activation barrier than bond rotation of the *anti*-betaine (**6**), as two large groups must pass one another as the charges are separated. This results in the barrier for torsional rotation of the *syn*-betaine being larger than the barrier for reversal to starting components. However, for the *anti*-betaine it is possible for the large substituents to pass over a small substituent during bond rotation. Thus, the barrier to torsional rotation for the *anti*-betaine is smaller than for the *syn*-betaine. This results in the C–C bond rotation–ring closure

sequence being faster and thus the *trans*-epoxide predominates.

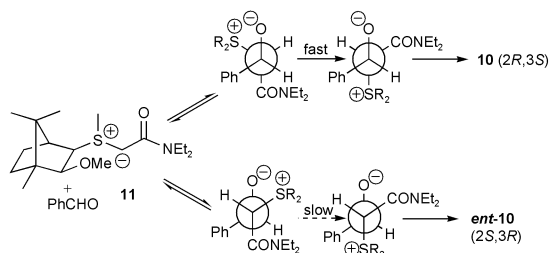
Using chiral sulfonium ylides very high enantioselectivity has been achieved particularly in reactions with aromatic aldehydes (Scheme 7).<sup>27</sup> Although the precise interactions



**Scheme 7** Highly enantioselective synthesis of glycidic amides.

governing enantiocontrol have not yet been established, a general understanding of the mechanism has been advanced.

Using chiral sulfides, two diastereomeric *anti*-betaines can be formed which will lead to the two enantiomeric epoxides (Scheme 8). As the betaines are formed reversibly, the ratio of



**Scheme 8** Possible origin of high enantioselectivity for ylide **11**.

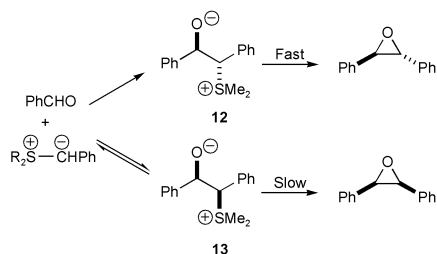
enantiomers obtained will depend on the equilibrium ratio of the betaines and their relative rates of bond rotation (Curtin Hammett). The near perfect levels of asymmetric induction achieved with ylide **11** (up to 99% ee) suggest that there is a significant difference in energy between the diastereomeric betaines and a significant difference in their relative rates of bond rotation. Presumably, to achieve the high levels of enantioselectivity observed, the two differences must be working in concert, favouring the same major enantiomer (Scheme 8).

There are no examples of successful sulfone-, phosphonate- or cyano-stabilised ylides in epoxidation reactions.

### Semi-stabilised ylides

This category comprises of ylides bearing weakly anion-stabilising groups such as substituted benzyl or allyl groups.

Like stabilised ylides, semi-stabilised ylides react with aldehydes *via* betaine intermediates to give epoxides. However, unlike stabilised ylides, the reaction of benzyl-stabilised ylides with aldehydes is remarkably finely balanced. In reactions with benzaldehyde, the *anti*-betaine is formed non-reversibly whilst the *syn*-betaine is formed reversibly (Scheme 9). These

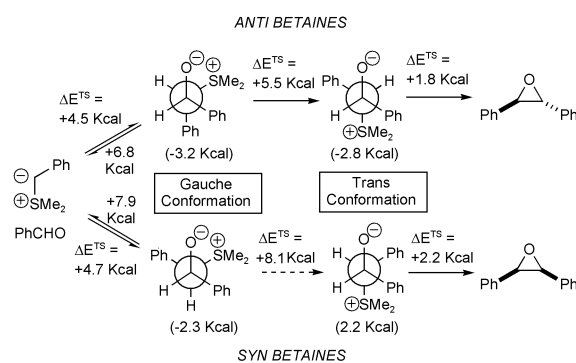


**Scheme 9** Partial reversibility in betaine formation for semi-stabilised ylides.

conclusions were derived from cross-over experiments.<sup>28</sup> When the *anti*-betaine **12** was generated by deprotonation of the corresponding hydroxysulfonium salt in the presence of a more reactive aldehyde, no incorporation of the more reactive aldehyde was observed. In contrast, conducting the same

experiments with the *syn*-betaine **13**, gave essentially complete incorporation of the more reactive aldehyde. Thus, the high *trans* selectivity observed in most reactions of benzyl-stabilised ylides with aromatic aldehydes is a result of productive, non-reversible formation of the *anti*-betaine and unproductive, reversible formation of the *syn*-betaine (Scheme 9).

These experimental observations were underpinned by DFT calculations.<sup>29</sup> Furthermore, the DFT calculations revealed that whilst all the activation barriers to the individual steps were small, the highest activation barriers along the route leading to either the *trans* or *cis* epoxides were C–C bond rotations of the intermediate betaines (Scheme 10). In the case of the *syn*-

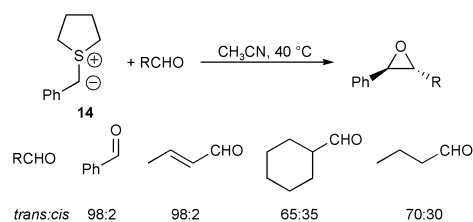


**Scheme 10** Energetic profile (DFT calculations) of ylide reaction with benzaldehyde giving stilbene oxide.

betaine the barrier to bond-rotation was higher than reversal to starting materials whereas for the *anti*-betaine, the barrier to returning to starting materials was higher than bond rotation to the *trans*oid conformation. The calculations thus supported our observations derived from cross-over reactions.

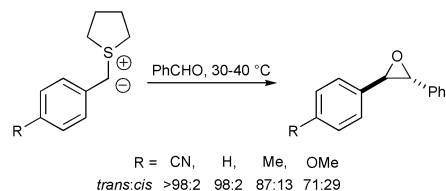
In reactions involving different substrates, the diastereoselectivity can be low if *syn*-betaine formation is non-reversible or only partially reversible. Four factors contribute to reduced reversibility of the betaine back to the original starting materials, which in turn leads to reduced *trans* selectivity:

(i) Lower stability of the carbonyl group, which reduces the tendency for the betaine to revert back to the ylide and carbonyl group. For example, aliphatic aldehydes generally give considerably lower levels of diastereoselection than aromatic and unsaturated aldehydes (Scheme 11).<sup>20</sup>



**Scheme 11** Effect of aldehyde structure on diastereoselectivity.

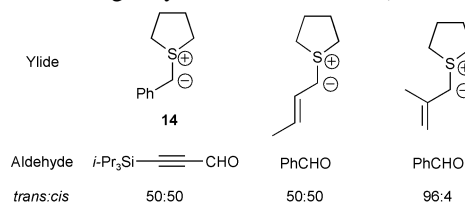
(ii) Reduced stability of the ylide reduces reversibility of betaine formation. Electron-donating groups on the aromatic ring destabilise the ylide and therefore lead to lower diastereoselection (Scheme 12).<sup>20,30</sup>



**Scheme 12** Effect of electronic structure of ylide on diastereoselectivity.

(iii) Reduced steric hindrance of the ylide/aldehyde allows more facile bond rotation from the *gauche* to the *trans*

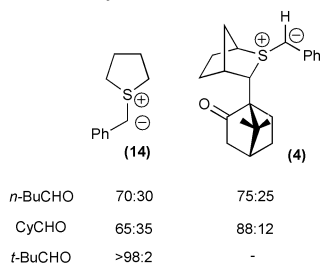
conformation of the betaine and therefore reduces reversibility and thus diastereoselectivity. Low diastereocontrol was observed with acetylenic aldehydes, and  $\alpha,\beta$ -unsaturated sulfonium ylides bearing only an  $\alpha$ -H substituent (Scheme 13).<sup>20,31</sup>



**Scheme 13** Effect of steric hindrance in the ylide/aldehyde component on diastereoselectivity of epoxide formation at 40 °C.

It follows then that more hindered substrates with respect to either the ylide or the electrophile will lead to increased barriers to bond rotation of the initially formed gauche conformers of the betaines and will result in increased reversibility, thus leading to increased *trans* diastereoselectivity.

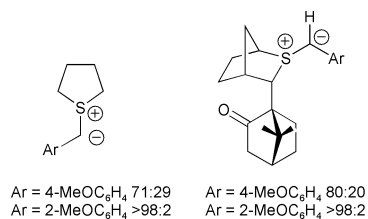
Indeed, the considerably more hindered substrate, pivalaldehyde, gave much higher selectivity than valeraldehyde and cyclohexanecarboxaldehyde (Scheme 14).<sup>20</sup> Furthermore, in-



**Scheme 14** Effect of steric hindrance in aldehyde and sulfonium moieties on diastereoselectivity of epoxidation at 40 °C in  $\text{CH}_3\text{CN}$ .

creased *trans* selectivity was observed with the more hindered sulfonium ylide **4** compared to **14**.<sup>18,20</sup>

Ylides bearing electron-donating groups on the aromatic ring also show increased diastereoselectivity with increasing size of the sulfide moiety (compare Fig. 1 row 1) and a further



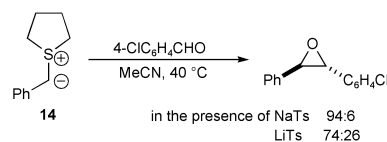
**Fig. 1** Combination of steric and electronic effects in epoxidation of benzaldehyde in  $\text{CH}_3\text{CN}$  at 40 °C.

substantial increase in diastereoselectivity if the electron-donating group is in the *ortho*- position (Fig. 1, columns 1 and 2).<sup>20</sup> This interesting example showed that reversibility due to restricted rotation of the betaine as a result of increased steric hindrance outweighed the expected non-reversibility due to the intermediacy of a less stable ylide *i.e.* that steric effects dominated over electronic effects. In general, the selectivity is governed by both the electronic and steric properties of the ylide and aldehyde.

(iv) Increased solvation of charges of the betaine by Li salts or protic solvents leads to a reduction in the barrier to bond rotation of the intermediate betaine. This results in reduced reversibility and a corresponding decrease in diastereoselectivity (Scheme 15 and Table 1).<sup>20,29</sup>

### Control of enantioselectivity

This has been the most active area of research in the sphere of asymmetric sulfur ylide mediated epoxidations.<sup>32</sup> As stated



**Scheme 15** Effect of metal ions on diastereoselectivity.

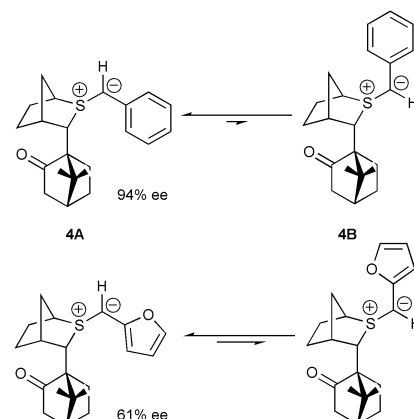
**Table 1** Effect of protic solvents on the diastereoselectivity of stilbene oxide formation<sup>33</sup>

Entry	Conditions	<i>trans</i> : <i>cis</i>
1	$\text{C}_6\text{H}_6$	98 : 2
2	$\text{C}_6\text{H}_6$ + 1 eq. MeOH	96 : 4
3	$\text{C}_6\text{H}_6$ + 2 eq. MeOH	92 : 8
4	$\text{C}_6\text{H}_6$ + 3 eq. MeOH	90 : 10
5	$\text{C}_6\text{H}_6$ + 5 eq. MeOH	86 : 14

above, benzyl sulfonium ylides react with aromatic aldehydes giving *trans*-epoxides with high diastereoselectivity. The reaction occurs *via* the *anti*-betaine which is formed non-reversibly. As such, the transition state leading to the *anti*-betaine is also the enantiodifferentiating step. To achieve high 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 of the ylide and (iv) ensure that *anti*-betaine formation is non-reversible. Indeed, high enantioselectivity has been achieved with a number of chiral sulfides (e.g. **1–4**) that clearly meet criteria (i)–(iii). The fourth criterion is much harder to engineer in the design of chiral sulfides and as such, it is often ignored. However, we believe that this fourth criterion plays a vital role in the stereochemical outcome of a number of asymmetric reactions. This is illustrated with several examples.

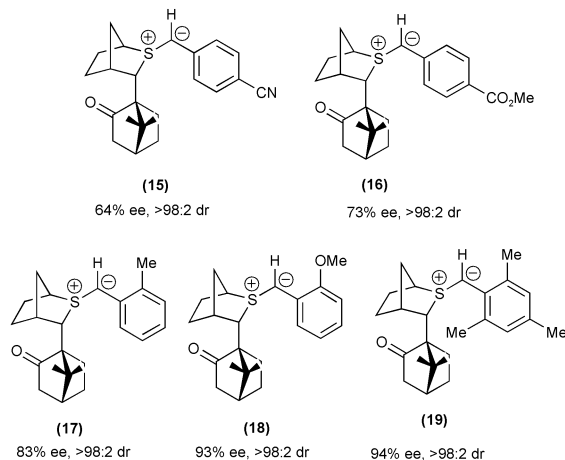
We believe that criteria (i)–(iv) are satisfied with ylides **1–4** and high enantioselectivity results. Indeed, ylide **4** consistently gave high enantioselectivity ( $91 \pm 3\%$  ee) with a broad range of different aldehydes (16 were tested) showing that the nature of the electrophile is less important than the four criteria detailed above.<sup>20</sup> However ylides with different steric or electronic properties give different selectivities.

For example, ylides bearing a smaller group than phenyl (*e.g.* 2-furyl, Scheme 16) gave reduced enantioselectivity as ylide conformation [criterion (ii)] is less well controlled (compare eqn. 1 and 2). More stable (**15** and **16**) or hindered ylides (**17** and



**Scheme 16** Effect of ylide conformation on the enantioselectivity in reactions with benzaldehyde in  $\text{CH}_3\text{CN}$  at 40 °C.

**18**) led to lower enantioselectivity because formation of the *anti*-betaine was reversible–partially reversible [criterion (iv)] (Fig. 2). In these cases, the enantioselectivity is determined by



**Fig. 2** Steric and electronic effects on enantioselectivity in the reaction of chiral sulfonium ylides with benzaldehyde.

the equilibrium ratio of the ylide conformers **4A** and **4B** and the degree of reversibility in the formation of *anti*-betaines **20** and **21** (Scheme 17). If the enantioselectivity was determined solely by the equilibrium ratio of conformers **4A** and **4B** very high enantioselectivity would be expected.<sup>34</sup> The lower enantioselectivity observed indicates that conformer **4B** is expressed to a greater degree than **4A** and we believe that this is due to the lower extent of reversibility in formation of betaine **21** from **4B**. There are two possible reasons why betaine **21** could be formed less reversibly: i) the barriers for torsional rotation in these diastereomers are different, resulting in reversion to starting materials of betaine **20** being more favourable than for **21**. ii) Ylide conformer **4B** is more hindered and therefore higher in energy than **4A**.<sup>35</sup> Reversion of betaine **21** back to ylide conformer **4B** is thus considerably less favourable than reversion of betaine **20** back to **4A**.

Clearly, the issue of steric hindrance on the carbon substituent of the ylide results in a dichotomy, as it is difficult to simultaneously satisfy conditions (ii) and (iv). To obtain high enantioselectivity, a high level of steric hindrance is required to control ylide conformation [criterion (ii)]. However, high steric hindrance of the ylide can result in reversibility even in formation of the *anti*-betaine leading to lower enantioselectivity. Although this might suggest that high enantioselectivity can only be obtained with a small number of substrates where the balance of steric properties for simultaneously satisfying criteria (ii) and (iv) are met, in fact the scope is still quite broad. For example, highly hindered substrates will result in essen-

tially complete control in ylide conformation and so the ratio of betaines **20** : **21** will be very high. The lower enantioselectivity expected for reversible reactions can be offset by a very high ratio of betaine diastereoisomers since the enantioselectivity is determined by the equilibrium ratio and the degree of reversibility in their formation. This is exemplified with the hindered ylide **19**, which gave higher enantioselectivity than the less hindered ylide **17** (Fig. 2).

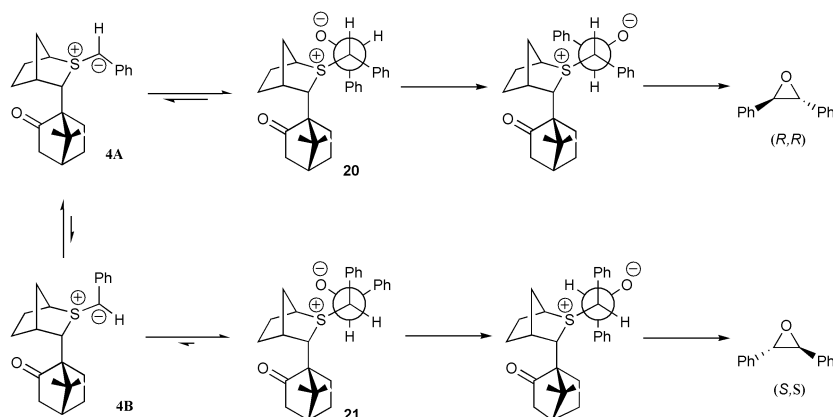
### Effect of temperature

The *catalytic* sulfur ylide reactions have to be conducted at room temperature or above as such temperatures are required for sulfonium salt formation or for decomposition of the tosylhydrazone salt to generate the intermediate diazocompound (Schemes 3 and 4). However, stoichiometric sulfur ylide reactions are not subject to the same constraints and indeed increased diastereoselectivity and enantioselectivity are achieved at lower temperatures. Indeed, the reaction of the stabilised ylide **15** at  $-78$  °C showed very high levels of enantioselectivity (>99% ee).<sup>36</sup> In fact, the enantioselectivity observed is higher than expected based on simple Boltzmann calculations, suggesting that the degree of reversibility is also reduced at low temperature and that criterion (iv) is also subject to temperature control.<sup>37</sup>

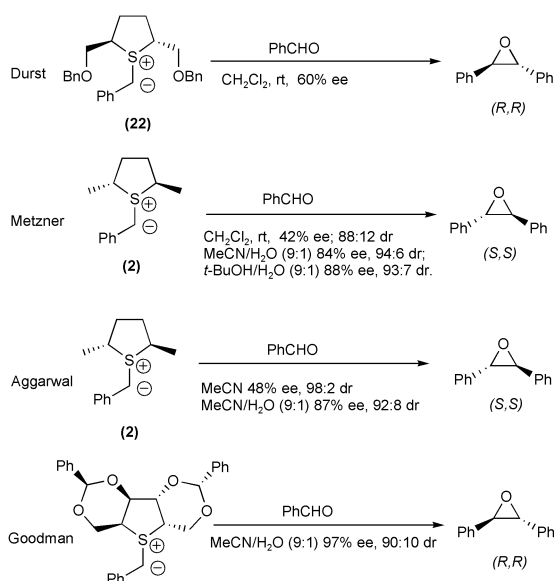
### The importance of criterion (iv): reversible/non-reversible formation of the *anti*-Betaine

Over 10 years ago Durst reported the reaction of  $C_2$  symmetric ylide **22** with PhCHO which gave stilbene oxide with 60% ee (Scheme 18).<sup>12</sup> The reaction was conducted in  $CH_2Cl_2$ . The related  $C_2$  symmetric ylide (**2**) was employed by Metzner but gave lower enantioselectivity (42% ee) in the same solvent.<sup>13</sup> Optimisation of the reaction conditions by Metzner led to high enantioselectivity when the reaction was conducted in MeCN– $H_2O$  or *t*-BuOH– $H_2O$ . Metzner was not able to conduct reactions in pure MeCN due to hydroxide promoted addition of MeCN to PhCHO and Cannizzaro side reactions.

Our method for the generation sulfur ylides allowed us to test this sulfide in anhydrous MeCN and MeCN– $H_2O$  and we also observed a dramatic increase in enantioselectivity in the protic solvent mixture. Although models have been advanced to account for the high enantioselectivity observed,<sup>13</sup> the dramatic effect of protic solvent on enantioselectivity has not been discussed. We believe that the effect can be readily accounted for based on criterion (iv). In aprotic solvent, *anti*-betaine formation is partially reversible and low enantioselectivity but high diastereoselectivity results. However, in protic solvent the increased solvation of the charges of the betaine results in a reduced barrier to bond rotation and therefore reduced reversibility. Under these conditions, *anti*-betaine formation could



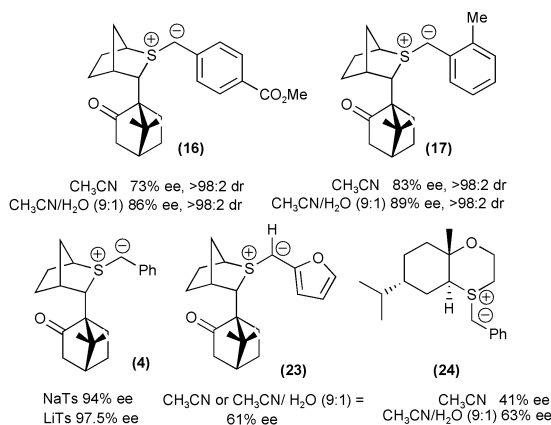
**Scheme 17** Effect of small degree of reversibility in *anti*-betaine formation on enantioselectivity.



**Scheme 18** Effect of protic solvents on stereoselectivity using structurally related sulfur ylides.

become non-reversible and all four criteria are met leading to high enantioselectivity. The reduced reversibility, of course results in reduced diastereoselectivity, which is also observed. Goodman has also reported a highly enantioselective  $C_2$ -symmetric tetrahydrothiophene for asymmetric epoxidation (Scheme 18).<sup>38</sup> The moderate diastereoselectivity observed is indicative of criterion (iv) being satisfied *i.e.* that *anti* betaine formation is non-reversible, again because of the protic solvent employed. The higher enantioselectivity observed compared to Metzner's less hindered sulfide must therefore result from either improved face selectivity (criterion iii) or improved control in ylide conformation (criterion ii).

The use of protic media or lithium cations to reduce reversibility can be used as a test for determining whether the fourth criterion is being satisfied or not. For example, ylides **16**, **17** and **23** all gave lower enantioselectivity than ylide **4** (Fig. 3).



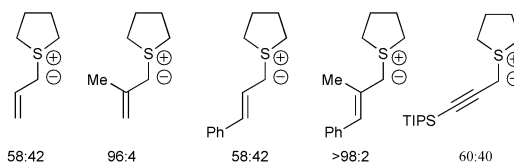
**Fig. 3** Effect of protic solvent and counterions on stereoselectivity of reactions of sulfur ylides with benzaldehyde.

But why? Which of the criteria were not satisfied? The use of protic media revealed the answer. Whilst an increase in enantioselectivity was observed with ylides **16** and **17**, no increase was observed with **23**. This indicates that the reduced enantioselectivity observed with **16** and **17** is due to partial reversibility in betaine formation [criterion (iv)] whereas in the case of ylide **23** the lower enantioselectivity is not due to reversibility. In the case of ylide **23**, as criteria (i) and (iii) are not expected to alter relative to the benzyl ylide **4**, it must be criterion (ii) (ylide conformation) which is not satisfied.

We previously reported the synthesis of a large number of chiral sulfides for which we expected to achieve high enantioselectivity as (in most cases) they were designed to fulfil criteria (i)–(iii).<sup>39</sup> However in most cases only moderate selectivity was observed and at the time we believed that this was due to conformational changes in the ylide (flattening of the ring leading to reduced control in ylide conformation). However, recent calculations did not support this theory and we now believe that the low selectivity was probably due to our inability to control criterion (iv): the degree of reversibility. Sulfide **24** was therefore re-examined and we used our protic media test to determine whether higher enantioselectivity could be achieved in this alternative medium. Indeed, the enantioselectivity increased from 41% ee in MeCN to 63% ee in MeCN–H<sub>2</sub>O.<sup>40</sup>

### Reactions of $\alpha,\beta$ -unsaturated sulfonium ylides

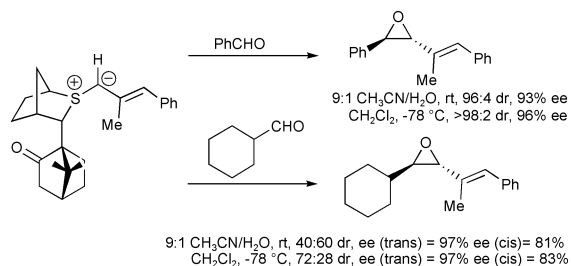
Reactions of  $\alpha$ -unsubstituted allyl and propargyl sulfonium ylides with aromatic aldehydes gave low diastereocontrol.<sup>20,31</sup> Presumably, the low steric hindrance associated with these ylides provides low barriers to C–C bond rotation of the initially formed *gauche* betaine leading to non-reversible betaine formation, and thus low diastereocontrol (Fig. 4). As the steric



**Fig. 4** *Trans* : *cis* diastereoselectivity in reactions of  $\alpha,\beta$ -unsaturated sulfur ylides with benzaldehyde.

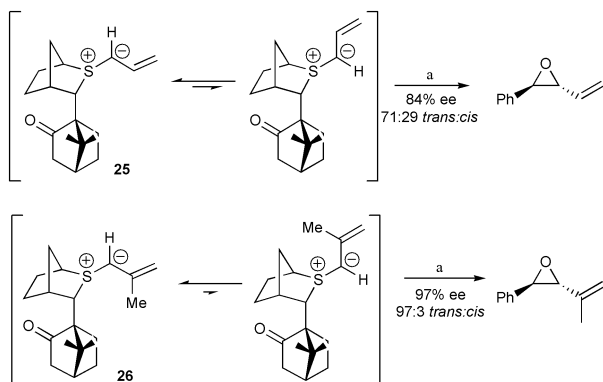
hindrance of the ylide is increased by incorporating an  $\alpha$ -substituent, the diastereocontrol increases markedly. We believe that the same arguments used to account for the high diastereoselectivity observed in the reaction of benzyl sulfonium ylides can also be used in the case of  $\alpha$ -substituted- $\alpha,\beta$ -unsaturated sulfonium ylides. The high diastereocontrol is a result of unproductive, reversible formation of the *syn* betaine and productive, non-reversible formation of the *anti*-betaine. In fact, the  $\alpha$ -substituted allyl sulfonium ylide is sterically similar to the benzyl sulfonium ylide and hence it is not surprising that it gives similar results.

Like benzyl sulfonium ylides, lower diastereoselectivity was observed in the reaction of the  $\alpha$ -substituted allyl sulfonium ylides with aliphatic aldehydes compared to aromatic aldehydes, probably for the same reasons as discussed above in the benzyl case (Scheme 19).<sup>41</sup>



**Scheme 19** Enantioselectivity in epoxidation reactions involving  $\alpha,\beta$ -unsaturated sulfur ylides.

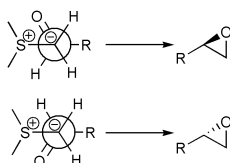
High enantioselectivity was also achieved in the case of the  $\alpha$ -substituted ylide **26** whilst lower enantioselectivity was observed with the  $\alpha$ -unsubstituted ylide **25**. In these cases it is the second criterion, control of ylide conformation, which is achieved with the former ylide **26** (which, again behaves like benzyl) but not with ylide **25** (Scheme 20). Both conformations of the less substituted ylide can be more easily accommodated due to reduced steric hindrance.<sup>41</sup>



**Scheme 20** Effect of ylide conformation on enantioselectivity. Reagents and conditions: a PhCHO, rt,  $\text{CH}_3\text{CN}-\text{H}_2\text{O}$  (9 : 1).

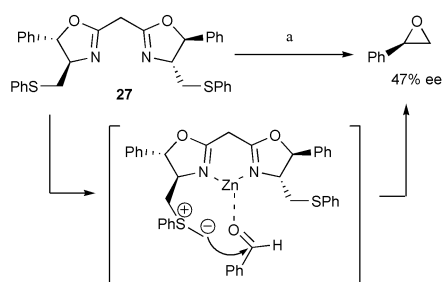
### Reaction of non-stabilised ylides

These ylides bear groups that are not capable of stabilising negative charge (*i.e.* alkyl or H). There has been little work done on the alkyl substituted ylides but some attempts have been made to effect asymmetric methylene transfer. In every case the enantioselectivity is < 5%.<sup>42,43</sup> This is because betaine formation is non-reversible and selectivity arises from control over which face of the aldehyde is attacked. This is rarely achieved in substituted ylides and is clearly not achieved in the unsubstituted ylide (Scheme 21).



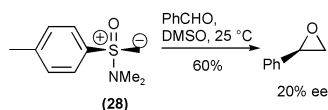
**Scheme 21** Modes of addition for unsubstituted ylides leading to the two enantiomers of terminal epoxides.

The only case where moderate asymmetric induction was achieved *via* sulfonium ylides was using the rather elaborate sulfide **27**. In this case it is believed that the moderate selectivity arose from complexation of the aldehyde with the zinc atom which was followed by a pseudo-intramolecular attack by the intermediate non-stabilised ylide (Scheme 22).<sup>44</sup>



**Scheme 22** Reagents and conditions: a. 1 eq.  $\text{Et}_2\text{Zn}$ , 1 eq.  $\text{CICH}_2\text{I}$ , 0.5 eq. PhCHO,  $\text{CH}_2\text{Cl}_2$ .

Chiral aminosulfonium ylides have been studied by Johnson and co-workers to generate enantiomerically enriched terminal epoxides.<sup>45–47</sup> For example, using aminosulfonium ylide **28** styrene oxide was prepared with 20% ee (Scheme 23).



**Scheme 23** Epoxidation of aldehydes with aminosulfonium ylides.

The formation of the intermediate diastereomeric betaines has been shown to be reversible.<sup>48</sup> This suggests that the low enantioselectivity is a consequence of either a low equilibrium

ratio of the diastereomeric betaines or similar rates of ring closure.

An alternative, albeit related, method for the preparation of terminal epoxides employs chiral sulfimide anions as ylide-like reagents for epoxidation of carbonyl compounds. Terminal epoxides have been obtained with considerably higher enantioselectivities using such species (upto 70% ee).<sup>49,50</sup>

### Conclusion

This review charts the important factors responsible for controlling both relative and absolute stereochemistry in reactions of stabilised and semi-stabilised sulfur ylides with aldehydes. Stabilised ylides give *trans* epoxides exclusively *via* intermediate betaines which are formed reversibly. The high diastereocontrol results from the *anti*-betaine diastereomer undergoing bond rotation and ring closure more rapidly than the *syn* isomer, which reverts to starting materials. Enantioselectivity is governed by Curtin–Hammett principles and is determined by the diastereomeric ratio of the *anti*-betaines and their relative rates of bond rotation. For semi-stabilised ylides, factors controlling enantioselectivity are more complex, but at the same time more easily understood. Four factors are responsible for controlling enantioselectivity: (i) formation of a single diastereomeric sulfonium ylide, (ii) control of ylide conformation, (iii) control of facial selectivity of the ylide and (iv) non-reversible formation of *anti*-betaines. If factor (iv) is not met and *anti*-betaine formation is reversible lower levels of enantioselectivity can result. A further consequence of reversible formation of the *anti*-betaine is that, high diastereoselectivity invariably results. If factor (iv) is satisfied (together with the other three factors) and *anti*-betaine formation is non-reversible it is possible that *syn*-betaine formation is also (partially) non-reversible and so whilst high enantioselectivity may be observed, low diastereoselectivity may result. Thus, factors that control diastereoselectivity also impact on enantioselectivity: the two are intimately linked. Nevertheless, conditions can be found in which the reaction of benzyl sulfonium ylides (and many substituted analogues) or  $\alpha,\beta$ -unsaturated sulfonium ylides with a range of aromatic, heteroaromatic, aliphatic and  $\alpha,\beta$ -unsaturated aldehydes and ketones furnish epoxides with high levels of diastereoselectivity and enantioselectivity.

If low enantioselectivity is observed, the use of protic solvents or lithium cations should increase enantioselectivity as the reaction becomes less reversible. If low diastereoselectivity is observed, the use of aprotic solvent and avoidance of species capable of solvating an alkoxide should increase diastereoselectivity as these conditions increase the barrier to bond rotation, thereby making the reaction more reversible.

In this study, we have shown how many complex and intricate factors combine to produce the final, observed, selectivity of the epoxidation reaction of aldehydes and ketones using chiral sulfonium ylides. This was in contrast to our initial expectations, in which enantioselectivity could be attributed to the single, carbon–carbon bond-forming step. It is easy to suspect that our observations may not be limited to this particular example, and that many other asymmetric catalysis processes may involve an analogous level of kinetic complexity. We therefore believe that the kind of detailed analysis of an asymmetric process reported here could be of great value in many other cases, and that the resulting more rational approach to design could ultimately lead to the generation of greatly simplified, highly efficient and selective catalysts for stereoselective synthesis.

### Future outlook

Although we have successfully developed a catalytic sulfur ylide mediated process for converting carbonyl compounds into

epoxides employing very low sulfide loadings (5–20 mol%), the range of substrates that simultaneously give high yields, high diastereoselectivity and high enantioselectivity is somewhat limited. Sulfide **5** shows the broadest scope to date but limitations in both the electrophile and ylide were encountered.<sup>20</sup> Heteroaromatic aldehydes with basic groups were not compatible with the catalytic cycle in the presence of the hindered sulfide and certain  $\alpha$ -unbranched aliphatic aldehydes gave low diastereoselectivity. Although,  $\alpha,\beta$ -unsaturated tosylhydrazone salts gave moderate-high selectivities, in general low yields in epoxidation were observed. We have therefore begun to examine the stoichiometric sulfur ylide reaction and found that high yield, diastereoselectivity and enantioselectivity are indeed achievable with a much broader range of substrates.<sup>41</sup> One can therefore envisage the sulfur ylide mediated epoxidation process being exploited in two modes: a catalytic one with rather limited scope and a stoichiometric one with very broad scope. Although the sulfide for our studies was highly effective, was prepared in 48% overall yield in four steps from camphorsulfonyl chloride and is readily available in both enantiomeric forms, sulfides that are even more easily accessible are desirable especially for the stoichiometric process. This review highlights the factors responsible for diastereo- and enantio- control and should aid the design of cheaper and more accessible chiral sulfides. Studies in this area are on-going.

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