Additions of stabilised and semi-stabilised sulfur ylides to tosyl protected imines: are they under kinetic or thermodynamic control?

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Varinder K. Aggarwal,*[a] Jonathan P. H. Charmant,[a] Cinzia Ciampi,[b] Jonathan M. Hornby,[b] Christopher J. O'Brien,[b] George Hynd[a] and Richard Parsons[b]

[a] *School of Chemistry, Cantocks Close, Bristol University, Bristol, UK BS8 1TS*
[b] *Department of Chemistry, University of Sheffield, Sheffield, UK S3 7HF*

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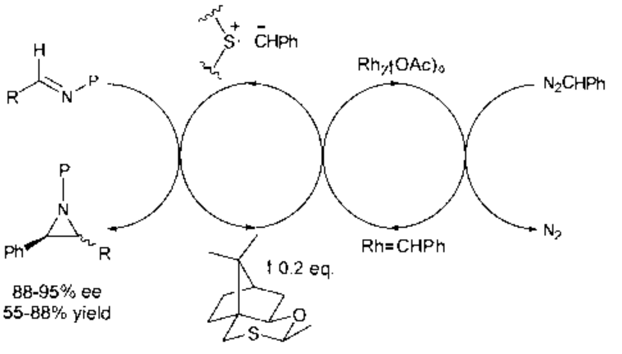
Sulfur ylides react with imines, *via* betaines, to give aziridines. We sought to determine whether betaine formation was reversible in reactions of benzyl-, amide- and ester-stabilised ylides by carrying out cross-over experiments. Thus, the intermediate betaines were generated independently from the corresponding sulfonium salt in the presence of a more reactive imine (*p*-nitrobenzaldimine). It was found that no incorporation of the more reactive imine was observed in reactions with the benzyl-stabilised ylide, whilst >80% incorporation of the *p*-nitrobenzaldimine was observed from the ester- and amide-stabilised ylides. These results indicate that benzyl-stabilised ylides react irreversibly with imines but ester- and amide-stabilised react reversibly. Thus, the stereocontrolling step of the process is dependent on the type of ylide employed and the results are used to account for the different diastereoselectivities observed with the different ylides.

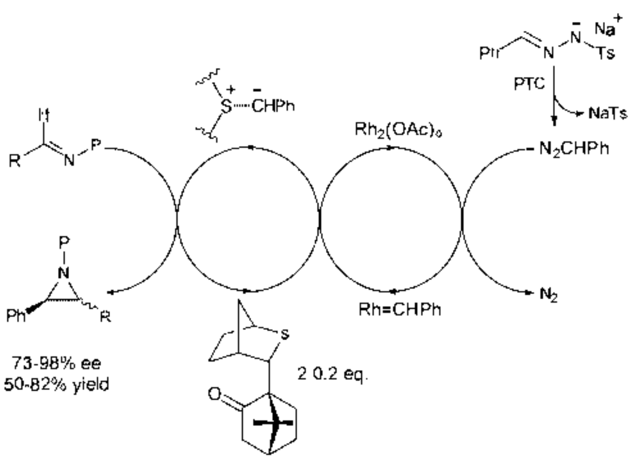
Introduction

The reaction of sulfur ylides with imines to furnish aziridines provides a complementary process to alkene aziridination.[1] We have shown that this process can be rendered both catalytic and asymmetric through a metal-mediated reaction of a chiral sulfide with a diazo compound (Scheme 1).[2] We have also shown that the diazo compounds can be generated *in situ*,[3] thus leading to a practical catalytic asymmetric process for converting imines into aziridines (Scheme 2). Although high enantioselectivity has been achieved in this[3] and the related epoxidation process,[4,5] the diastereoselectivity observed in imine aziridination is much poorer. Furthermore, the use of more stabilised ylides (generated again from the corresponding diazo compounds) led to even lower diastereoselectivity and eventually to a reversal in favour of the *cis* isomer with ester-stabilised ylides. Representative data from our lab and others[6] are provided in Table 1 and Scheme 3.



Scheme 1 Catalytic asymmetric aziridination of imines.

The variation in diastereoselectivity with different sulfur ylides was intriguing and these results raised several questions. Why was the diastereoselectivity much poorer in reactions of benzyl-stabilised ylides with imines compared to the same reactions with aldehydes (Scheme 4)? Why did ester-stabilised ylides lead to predominantly *cis* aziridines whereas less stabilised ylides gave either no selectivity or predominantly *trans* substituted aziridines? In this paper we address these questions and provide an understanding of the relevant factors governing the origin of the diastereocontrol in reactions of sulfonium ylides with imines.



Scheme 2 Catalytic asymmetric aziridination of imines with *in situ* generation of diazo compounds.

Reactions of sulfur ylides with aldehydes are believed to occur *via* intermediate betaines, which subsequently ring close to give epoxides. Indeed, we[7] and others[8,9] have shown that the intermediate betaines can be accessed by deprotonation of β-hydroxy sulfonium salts and this also leads to epoxides. In addition, the mechanism has been further substantiated through recent molecular modelling calculations, from which it was found that end-on approach of sulfur ylides to aldehydes was the favoured mode of addition and betaines were identified as intermediates along the reaction pathway.[10]

In analysing the origin of diastereocontrol in epoxidation reactions,[7] we prepared the *syn* and *anti* β-hydroxy sulfonium salts (**3a** and **3b**, Scheme 5) of benzyl-stabilised ylides and generated the corresponding ylides by treatment with base. This was carried out in the presence of a more reactive aldehyde

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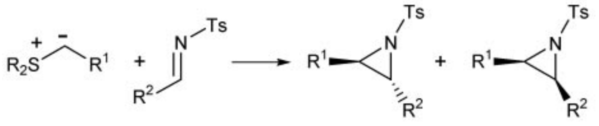
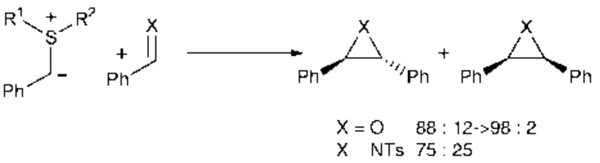
Table 1 Reaction of *N*-tosylbenzaldimine with a variety of sulfonium ylides

Entry	R^1	R^2	Ratio (*trans* : *cis*)[b]	Yield (%)
1[a]	Ph	p-MeOC$_6$H$_4$	3 : 1	96
2[a]	Ph	Ph	3 : 1	82
3[a]	Ph	p-NO$_2$C$_6$H$_4$	3 : 1	43
4[c]	CONEt$_2$	Ph	2 : 1	84
5[d]	CONEt$_2$	Ph	1 : 3	88
6[e]	CO$_2$Et	p-MeOC$_6$H$_4$	2 : 3	62
7[e]	CO$_2$Et	Ph	1 : 3	83
8[e]	CO$_2$Et	p-ClC$_6$H$_4$	1 : 5	41
9[e]	CO$_2$Et	p-NO$_2$C$_6$H$_4$	1 : 12	54
10[e]	CO$_2$Et	C$_6$H$_{11}$	1 : 11	76

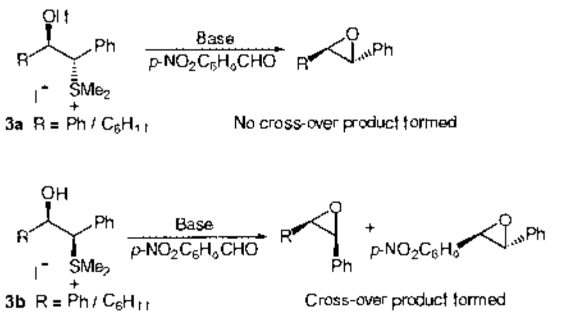
[a] All reactions were performed with 1 mol% $Rh_2(OAc)_4$, 1 equiv. of dimethyl sulfide, 1.5 equiv. phenyldiazomethane in CH_2Cl_2 at RT. [b] Diastereomeric ratios were determined by ^{1}H NMR of the crude reaction mixture. [c] Performed in THF at 60 °C with 1.5 equiv. of *N*,*N*-diethyl diazoacetamide, 1 equiv. of tetrahydrothiophene and 1 mol% $Rh_2(OAc)_4$. [d] Treatment of sulfonium salt with base in the presence of imine (ref. 6). [e] All reactions were performed with 1 mol% $Rh_2(OAc)_4$, 1 equiv. of tetrahydrothiophene, 1.5 equiv. of ethyl diazoacetate in THF at 60 °C.



Scheme 3



Scheme 4 Comparison of diastereoselectivity in reactions of sulfur ylides with aldehydes and imines.



Scheme 5 Cross-over reactions with epoxides.

(cross-over experiment) to determine whether betaine formation was reversible. As no incorporation of the more reactive aldehydes was observed starting from the *anti* β-hydroxy sulfonium salt, we concluded that formation of the *anti* betaine was irreversible. In contrast, partial incorporation of the more reactive aldehyde was observed when we started from the *syn* β-hydroxy sulfonium salt indicating that *syn* betaine formation was partially reversible. The degree of reversibility was dependent on the R group: aromatic groups (leading back to aromatic aldehydes) showed a greater tendency to reversibility than aliphatic groups. The same types of cross-over experiment have also been conducted to analyse whether betaine/oxaphosphetane formation in the Wittig reaction is reversible.[11] We therefore decided to employ the same methods to determine whether ylide additions to imines leading to intermediate betaines were reversible, as this could influence the diastereoselectivity of the product.

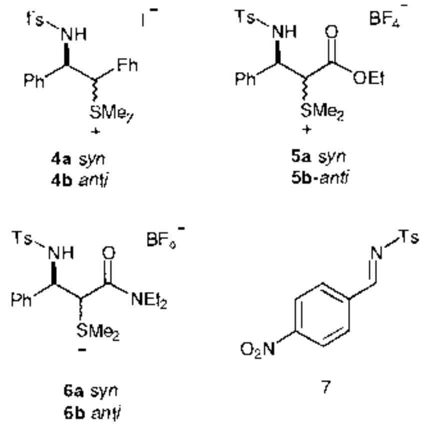


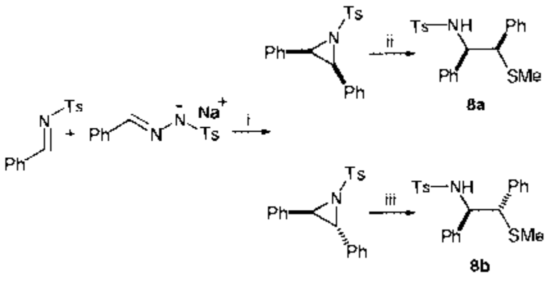
Fig. 1 Targeted sulfonium salts for mechanistic studies.

In addition to answering the questions raised above, the question of whether betaine formation is reversible has important consequences in terms of enantiocontrol. If betaine formation is irreversible, non-bonded interactions in the transition state leading to its formation will be responsible for the stereocontrol (diastereo- and enantio-control). However, if betaine formation is reversible, it will be non-bonded interactions in the transition state of the ring-closing step that will control the relative and absolute stereochemistry of the aziridine product.

As we have employed benzyl-, amide- and ester-stabilised ylides in aziridination processes, we decided to test whether the reaction of each of these ylides with *N*-tosyl imines leading to intermediate betaines was reversible and so we required the corresponding diastereomerically pure sulfonium salts **4a**, **4b**, **5a**, **5b**, **6a** and **6b** (Fig. 1).

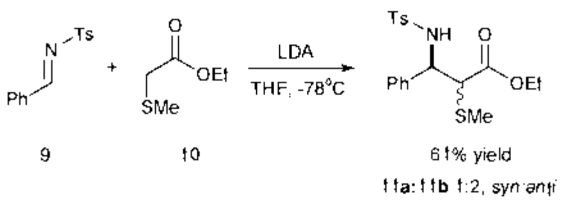
Synthesis of sulfides and sulfonium salts

The *syn* and *anti* sulfonium salts **4a** and **4b** were prepared as shown in Scheme 6. Reaction of the *N*–Ts imine derived from benzaldehyde with the benzaldehyde tosylhydrazone salt in the presence of tetrahydrothiophene and $Rh_2(OAc)_4$ gave a 3 : 1 separable mixture of aziridines in good yield. Although these *cis* and *trans* aziridines could be made stereospecifically from reaction of the *cis* and *trans* stilbenes with PhINTs,[12] we found the above method to be more convenient. Ring opening of the aziridines was effected with NaSMe and interestingly was found to be substantially faster and more efficient for the *trans* isomer compared to the *cis* isomer. We believe that this is due to the greater relief of ring strain inherent in the *trans* isomer (*vide infra*). Alkylation of the sulfide **8b** was carried out with MeI and the salt **4b** was partially characterised although we found it more convenient to prepare the salts and use them directly in subsequent studies.



Scheme 6 *Reagents and conditions*: i, $Rh_2(OAc)_4$ (1 mol%), $BnEt_3N^+Cl^-$ (10 mol%), 1,4-dioxane, tetrahydrothiophene (20 mol%), 40 °C, 84% (3 : 1, *trans* : *cis*); ii, NaSMe, EtOH, reflux 6 h, 56%; iii, NaSMe, EtOH, reflux 1 h, 97%.

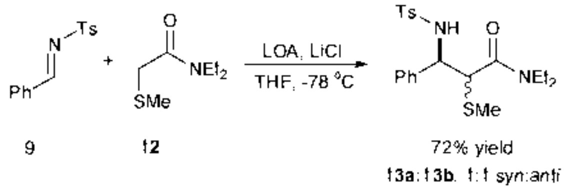
The *syn* and *anti* sulfides **11a** and **11b** were prepared directly by an aldol reaction and furnished a separable 2 : 1 mixture of isomers (Scheme 7). The relative stereochemistry of the *syn* **11a**



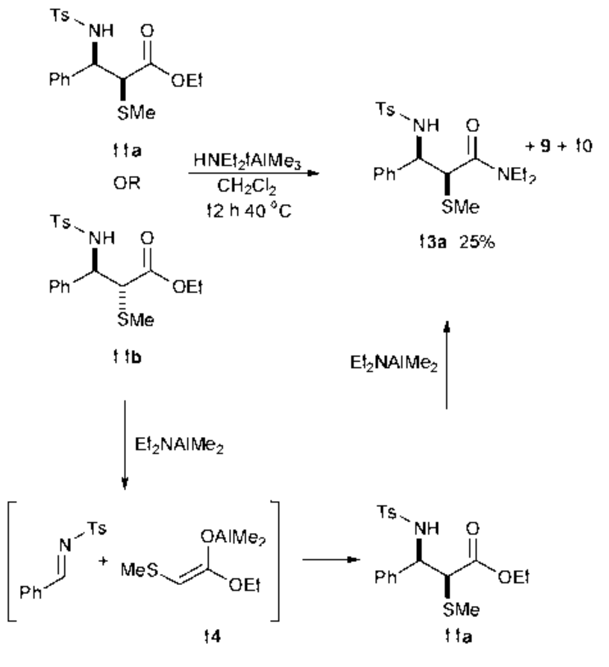
Scheme 7 Formation of the ester aldol adduct.

and *anti* **11b** isomers was determined by X-ray crystallography (Fig. 2). Alkylation of sulfides **11a** and **11b** with Meerwein's reagent gave the sulfonium salts **5a** and **5b**. As these salts were hygroscopic, they were not isolated but generated immediately before use in the cross-over experiments.

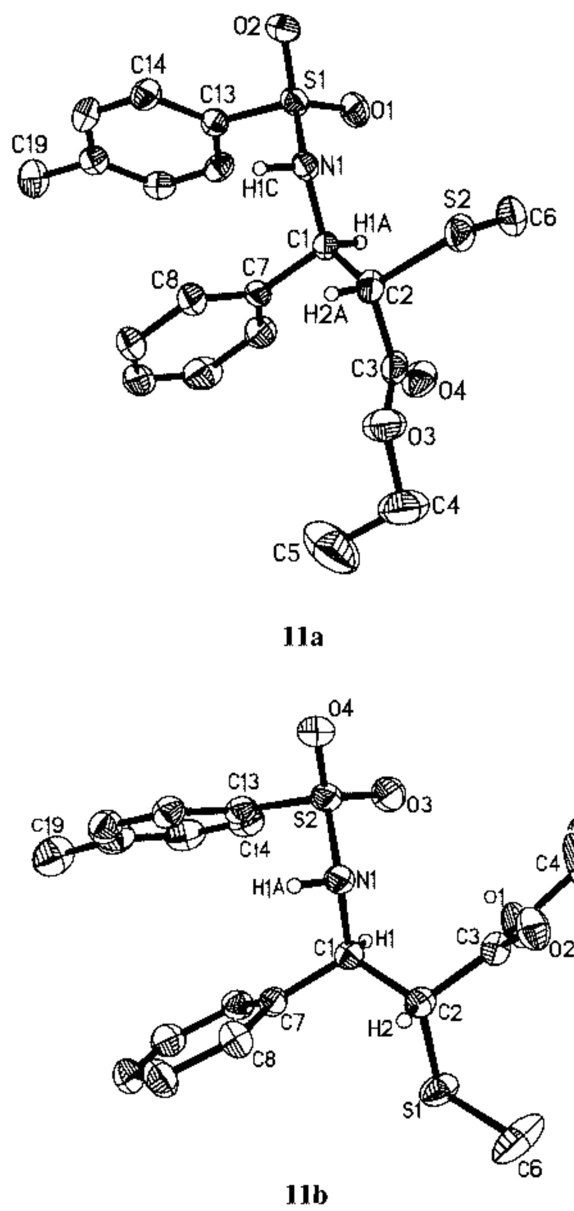
The same strategy was applied to the synthesis of *syn* and *anti* sulfides **13a** and **13b** using an aldol reaction with amide **12**[13] (Scheme 8). In the aldol process involving the amide we found that LiCl was essential to obtain reasonable yields of the aldol adducts.[14] However, in this case we were unable to separate the *syn* and *anti* isomers. We therefore attempted to directly convert the *syn* and *anti* ester aldols adducts **11a** and **11b** into the corresponding amide aldols **13a** and **13b** using $HNEt_2$–Me_3Al (Scheme 9).[15] However both the *syn* and *anti* ester aldols **11a** and **11b** gave the same *syn* amide aldol **13a** in moderate yield; none of the *anti* amide aldol was obtained. As the reaction mixture also contained ester **10** and imine **9** but none of the amide **12**, it is reasonable to conclude that the two ester aldols **11a** and **11b** equilibrate *via* the aluminium enolate **14** to give the *syn* aldol **11a** (Scheme 9). Attempts to generate the aluminium enolate **14** directly from **10** using various aluminium-based reagents to prove this mechanism were unsuccessful. This aldol is subsequently converted into the *syn* amide **13a** using Et_2NAlMe_2. This procedure thereby provides ready access to the *syn* amide **13a** but the pure *anti* isomer **13b** remained elusive. Nevertheless from cross-over reactions involving pure *syn* **13a** and a 1 : 1 mixture of *syn* and *anti* isomers, it would be possible to calculate the results of the pure *anti* isomer.



Scheme 8 Formation of the amide aldol adduct.



Scheme 9 Reaction of esters **11a** and **11b** with Me_3Al–$HNEt_2$.



11a

11b

Fig. 2 Solid state molecular structures of **11a** and **11b** showing one of the four crystallographically independent molecules in each unit cell. Ellipsoids are drawn at the 50% probability level.

Results of cross-over experiments

Treatment of *syn* and *anti* sulfonium salts **4a** and **4b** (formed from **8a** and **8b** by methylation with MeI) resulted in stereospecific ring closure to give exclusively *cis* and *trans* aziridines, respectively (Scheme 10). The fact that no scrambling of stereochemistry was observed indicated that no base-catalysed epimerisation occurred and that the intermediate betaines did not revert back to the corresponding ylide and imine. This was confirmed by carrying out the same reaction in the presence of *p*-$NO_2C_6H_4CH{=}NTs$, but as expected, no incorporation of the more reactive imine was observed. This indicated that reaction of benzyl-stabilised ylides with $PhCH{=}NTs$ leading to the *syn* and *anti* betaine intermediates was irreversible (Scheme 11). The diastereoselectivity of the reaction is therefore set up in the betaine forming step. The preferred formation of the *trans* aziridine can be readily accounted for by analysing the relevant

Table 2 Cross-over experiments with ester aldol adducts

Entry	Solvent	Aldol adduct	**14** (%)[b]	**15** (%)[b]	Ratio[c] (**14** : **15**)	**16** (%)[b]	**17** (%)[b]	Ratio[c] (**16** : **17**)
1	Dioxane	**11a**	4.0	2.0	2 : 1	29.0	5.4	5 : 1
2	Dioxane	**11b**	4.0	1.8	2 : 1	25.0	5.7	5 : 1
3	THF	**11a**	2.5	1.3	2 : 1	27.1	4.5	5 : 1
4	THF	**11b**	5.2	2.4	2 : 1	28.0	3.2	5 : 1
5	CH_3CN	**11a**	10.8	4.7	2 : 1	20.0	—	—
6	CH_3CN	**11b**	4.7	2.1	2 : 1	17.0	—	—
7	CH_2Cl_2	**11a**	4.0	2	2 : 1	24.5	4.5	5 : 1
8	CH_2Cl_2	**11b**	2.8	1.5	2 : 1	28.9	3.2	5 : 1

[a] All sulfonium salts were formed in CH_2Cl_2 at RT using 1 equiv. of Me_3OBF_4. The CH_2Cl_2 was then removed under high vacuum and the solvent of choice added, followed by 1 equiv. of imine and KO^{t}Bu. [b] Yields were determined using 1,3-benzodioxole as a ^{1}H NMR internal standard. [c] Diastereomeric ratios were determined by ^{1}H NMR.

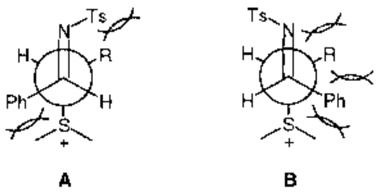
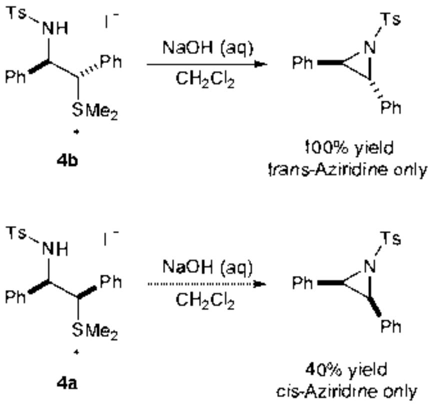
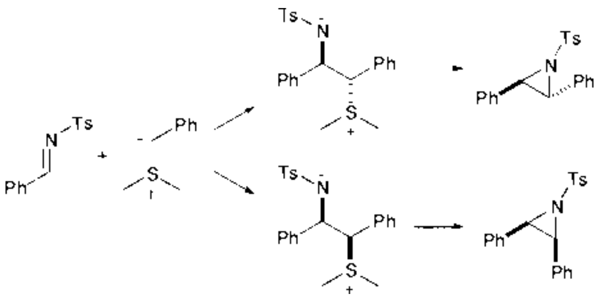


Fig. 3 End-on addition of sulfur ylide to imine.



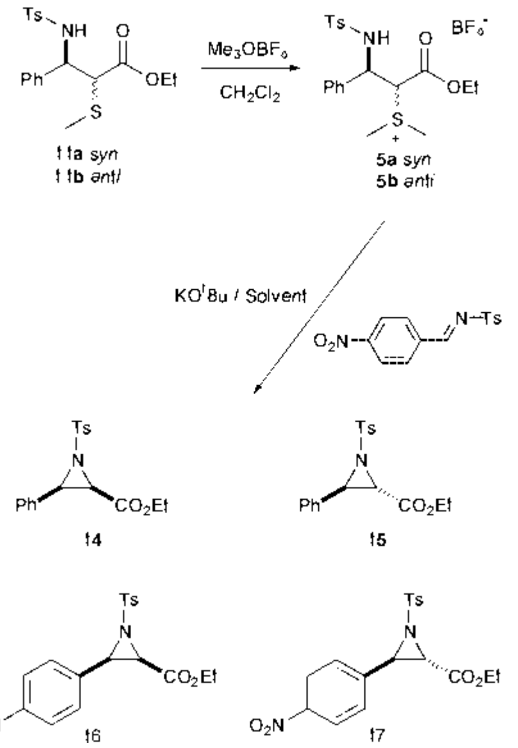
Scheme 10 Ring closure experiments with semi-stabilised sulfur ylide precursors.



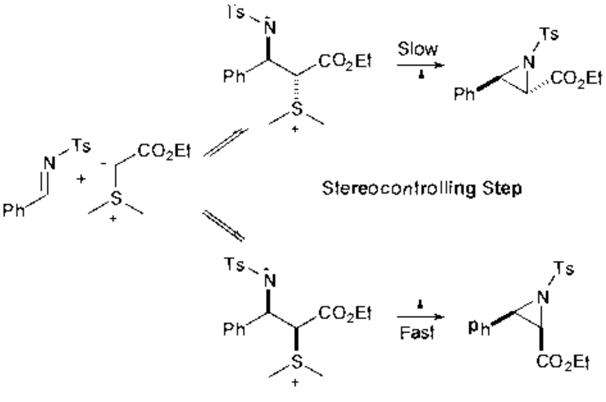
Scheme 11 Mechanism for benzyl-stabilised sulfur ylide aziridination.

transition states (Fig. 3). Assuming an end-on approach of the sulfur ylide to the imine, this will give rise to the two transition states **A** and **B**, which lead to the *trans* and *cis* aziridines, respectively. Clearly transition state **A** is less sterically encumbered than transition state **B**, which accounts for the preferred formation of the *trans* aziridine.

As *syn* and *anti* sulfonium salts **4a**/**4b** and **5a**/**5b** (ester and amide) could more readily equilibrate through base-catalysed epimerisation, we decided to carry out the cross-over experiments on these pairs of substrates rather than to determine whether ring closure was stereospecific. The cross-over experiments were conducted in several different solvents (Scheme 12, Table 2 and Scheme 14, Table 3) to determine whether solvent polarity affected the outcome of the overall process. In the event, treatment of the sulfide **11a** with Meerwein's reagent followed by base in the presence of p-$NO_2C_6H_4CH{=}NTs$ led to a 5 : 1 mixture of *cis* : *trans* aziridines derived from the *p*-nitrobenzaldimine **16** and **17** with only a small amount of aziridines **14** and **15** derived from direct ring closure. As both *syn* and *anti* sulfonium salts **5a** and **5b** (derived from **11a** and **11b**, respectively) essentially gave the same results, this implied that rapid base-catalysed epimerisation of the two diastereoisomers **5a** and **5b** occurred. The cross-over experiments were



Scheme 12 Cross-over experiments with ester-stabilised sulfur ylide precursors.

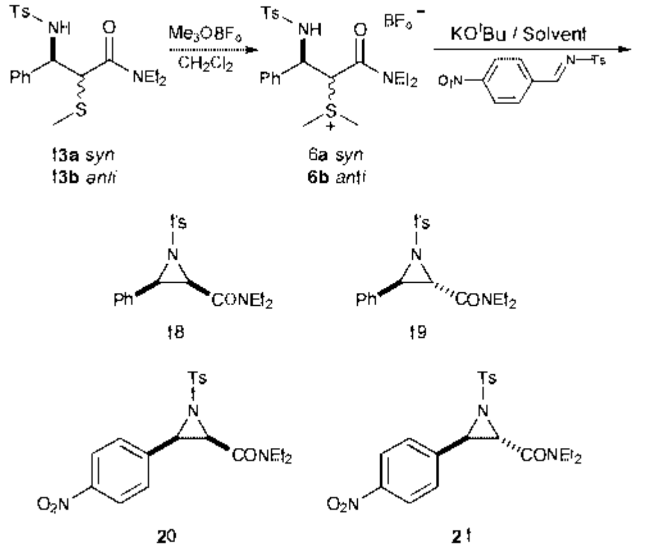


Scheme 13 Mechanism for ester-stabilised sulfur ylide aziridination.

Table 3 Cross-over experiments with amide aldol adducts

Entry	Solvent	Aldol adduct	**18** (%)[b]	**19** (%)[b]	Ratio[c] (**18** : **19**)	**20** (%)[b]	**21** (%)[b]	Ratio[c] (**20** : **21**)
1	Dioxane	**13a**	Trace	1.3	—	16.6	8.3	2 : 1
2	Dioxane	**13a** : **13b** (1 : 1)	3.4	3.8	1 : 1	35.6	22.7	1.6 : 1
3	THF	**13a**	3.1	4.5	1 : 1.5	13.4	7.8	1.7 : 1
4	THF	**13a** : **13b** (1 : 1)	2.8	4.1	1 : 1.5	28.9	17.4	1.7 : 1
5	CH_3CN	**13a**	2.2	7.0	1 : 3	17.8	20.6	1 : 1
6	CH_3CN	**13a** : **13b** (1 : 1)	7.2	10.9	1 : 1.5	30.4	35.3	1 : 1
7	CH_2Cl_2	**13a**	6.8	20.3	1 : 3	16.0	18.2	1 : 1
8	CH_2Cl_2	**13a** : **13b** (1 : 1)	8.6	18.3	1 : 2	23.7	25.4	1 : 1

[a] All sulfonium salts were formed in CH_2Cl_2 at rt using 1 equiv. of Me_3OBF_4. The CH_2Cl_2 was then removed under high vacuum and the solvent of choice added, followed by 1 equiv. of imine and KO^tBu. [b] Yields were determined using 1,3-benzodioxole as a ^1H NMR internal standard. [c] Diastereomeric ratios were determined by ^1H NMR.



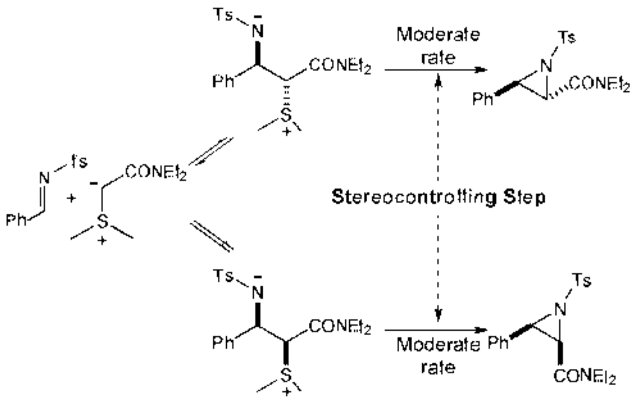
Scheme 14 Cross-over experiments with amide-stabilised sulfur ylide precursors.

carried out in a range of solvents but the outcome of the process was similar in each case (Scheme 12, Table 2). Thus in all the solvents, following betaine formation, reversion to the imine and ylide was faster than direct ring closure and the ylide was subsequently trapped by the more reactive *p*-nitrobenzaldimine.[16] Reversion of the betaine to give the imine and ylide is favoured in this case because the ylide is stabilised by the ester group. Indeed this ylide can, unlike the benzyl- or amide-stabilised ylide, be isolated and stored.[17] There is considerable evidence for the high thermodynamic stability and low reactivity of the ester-stabilised ylide: Ratts[17] found that this ylide does not react with simple aldehydes, only 1,2-dicarbonyl compounds, and indeed Dai was unable to couple the same ylide with *N*-tosyl imines.[6]

As betaine formation is reversible, it is the step involving ring closure of the betaine which controls the stereochemistry of the product aziridine (Scheme 13). The *cis* diastereoselectivity observed indicates that ring closure of the *syn* betaine is *more rapid* than the ring closure of the *anti* betaine. The relative rates of ring closure are determined by non-bonded interactions in the transition state. In related epoxidation, the *trans* isomer is favoured as the product-like transition state for ring closure of the *anti* betaine is less hindered than the transition state leading to the *cis* isomer. As the same factors will also be relevant to ring closure of the *syn* and *anti* betaines, **5a** and **5b**, the preferred formation of the *cis* aziridine implies that this isomer suffers fewer steric interactions than the *trans* isomer.

Indeed, it has been shown experimentally that *cis* aziridines are thermodynamically more stable then the corresponding *trans* isomers: palladium-catalysed isomerisation of unsaturated aziridines[18] and base-catalysed isomerisation of aziridinyl ketones[19] give *cis* aziridines predominantly. The thermodynamic preference for the *cis* aziridine can be understood in terms of steric hindrance. The largest group on the three membered ring is the Ts group and this will prefer to be *anti* to the other substituents to minimise 1,2-steric interactions. Thus, the remaining two groups are *cis* to each other. We can now understand why the *trans* aziridine reacted more rapidly with NaSMe (Scheme 6) than the *cis* isomer: opening of the *trans* aziridine resulted in greater relief of ring strain than opening of the corresponding *cis* isomer.

The amide sulfonium salts behaved in a similar way to the ester derivatives (Scheme 14, Table 3). As with the esters, both the *syn* and the 1 : 1 *syn* : *anti* mixture of amide sulfonium salts **6a** and **6b** gave similar results indicating that rapid base-catalysed epimerisation occurred. As with the ester-stabilised ylides, the major aziridine product incorporated the *p*-nitro benzaldimine indicating that the betaine fragmented to the ylide and imine more rapidly than it underwent direct ring closure. Thus, as with ester-stabilised ylides, ring closure of the betaine rather than betaine formation is again the step which controls the stereochemistry of aziridinations with amide-stabilised ylides (Scheme 15).



Scheme 15 Mechanism for amide-stabilised sulfur ylide aziridination.

The lower diastereoselectivity observed with the amide-stabilised ylides compared to reactions of ester-stabilised ylides is probably due to competing steric interactions. As in the case of ester-stabilised ylides, the two substituents on the aziridine will prefer to occupy a position *anti* to the bulky tosyl group. However, in this case the bulky amide group will prefer to occupy a position *anti* to the other two substituents. These two competing steric interactions lead to low diastereocontrol.

Conclusions

The addition of benzyl-stabilised sulfur ylides to imines is an irreversible process and therefore the selectivity is determined by the relative rates of formation of the *anti* and *syn* betaines.

This is in contrast to the epoxidation process where formation of the *syn*-betaine is partially reversible.[7] Amide- and ester-stabilised ylides react reversibly with imines to give the intermediate betaines which subsequently ring close to give the aziridines. In these cases ring closure of the betaine is therefore the stereocontrolling step.

The change in stereocontrolling step according to the type of ylide employed has an important consequence in the design of chiral sulfonium ylides for asymmetric aziridination. For semi-stabilised (benzyl) ylides, interactions in the transition state leading to betaine formation control the stereochemistry of the aziridine whilst for stabilised (ester/amide) ylides it is interactions in the transition state for ring closure of the betaine that will influence the stereochemistry. It is therefore likely that different sulfides will be required to achieve high stereocontrol for the different classes of ylides.

Experimental

General

Infrared spectra were recorded on a Perkin-Elmer Spectrum One FT-IR spectrometer and only selected absorbancies (ν_{max}) are reported. Mass spectra (*m*/*z*) were recorded on a Micromass Analytical Autospec spectrometer. Microanalyses were performed using a Carlo Erba EA1108. Melting points were determined on a Kofler hot stage. Nuclear magnetic resonance (NMR) were recorded at the field strength shown and on a JEOL Delta GX270, GX400 eclipse400 or Alpha500 instrument. Chemical shifts (δ_H and δ_C) are quoted in parts per million (ppm), referenced to TMS or the appropriate solvent peak. TLC was performed on aluminium backed silica plates (60 F_{254}) which were developed using standard visualising agents. Flash chromatography was performed on silica gel (Merck Kieselgel 60 F_{254} 230–400 mesh). All commercially available reagents and solvents were purified and dried according to standard procedures and all experiments were carried out under an inert nitrogen atmosphere. Literature procedures were used to prepare the following compounds: *N*-benzylidenetoluene-*p*-sulfonamide,[2b] *trans*-*N*-(*p*-tolylsulfonyl)-2,3-diphenylaziridine,[3] *cis*-*N*-(*p*-tolylsulfonyl)-2,3-diphenylaziridine,[3] *N*,*N*-diethyl-2-methylsulfanylacetamide,[13] and trimethyloxonium tetrafluoroborate.[20]

***anti*-[1,2-Diphenyl-2-(toluene-4-sulfonamido)ethyl]dimethylsulfonium iodide 4b**

anti-*N*-(1,2-Diphenyl-l-methylthioethyl)toluenesulfonamide (100 mg, 0.25 mmol) was dissolved in methyl iodide (1 cm^3) and the mixture stirred at rt for 80 h. Excess methyl iodide was removed *in vacuo* and the residue solid was triturated with diethyl ether (5 × 15 cm^3) to afford sulfonium salt **4b** as an off-white solid (85 mg, 63%), δ_H(250 MHz; d^6DMSO) 2.25 (3H, s, ArC*H*$_3$), 2.75 [6H, s, $S(CH_3)_2$], 5.16 (1H, d, *J* 8.0 Hz, CH), 5.32 (1H, m, CH), 7.47–6.97 (14H, m, Ar), 8.73 (1H, d, *J* 10 Hz, NH).

***trans*-*N*-(*p*-Tolylsulfonyl)-2,3-diphenylaziridine (Scheme 10)**

To a stirred suspension of **4b** (60 mg, 0.11 mmol) in dichloromethane (2 cm^3) was added 50% aqueous NaOH (0.5 cm^3). The mixture was stirred at rt before being diluted with dichloromethane (3 cm^3) and partitioned with water (5 cm^3). The organic fraction was dried over $MgSO_4$ and the solvent evaporated *in vacuo* to give the title compound as a white solid (40 mg, 100%). Data (^{1}H NMR and ^{13}C NMR) were identical to those reported.[21,22]

***cis*-*N*-(*p*-Tolylsulfonyl)-2,3-diphenylaziridine (Scheme 10)**

syn-*N*-(l,2-Diphenyl-l-methylthioethyl)toluenesulfonamide (79 mg, 0.2 mmol) was dissolved in methyl iodide (1 cm^3) and stirred at rt for 60 h. The excess methyl iodide was removed *in vacuo* and the solid residue triturated with diethyl ether (10 cm^3). The resultant solid **4a** was dissolved in dichloromethane (3 cm^3) and 50% aqueous NaOH (0.5 cm^3) and the solution stirred at rt for 20 h before being diluted with dichloromethane (7 cm^3). After being washed with water (5 cm^3), the organic fraction was dried over $MgSO_4$ and evaporated *in vacuo* to give the title compound as a white solid (28 mg, 40%). Data (^{1}H NMR and ^{13}C NMR) were identical to those reported.[19,20]

***anti*-[1-Ethoxycarbonyl-2-phenyl-2-(toluene-4-sulfonamido)-ethyl]dimethylsulfonium tetrafluoroborate 5b**

Ethyl *anti*-3-(4-methylphenylsulfonylamino)-2-(methylthio)-3-phenylpropanoate (0.12 g, 0.305 mmol) and trimethyloxonium tetrafluoroborate (0.045 g, 0.305 mmol) were stirred overnight in dichloromethane (4 cm^3) at rt. The resultant solution was frozen in liquid nitrogen and the solvent removed under high vacuum, to yield a very air-sensitive pale brown solid (0.15 g, assuming 100% yield), which was not isolated (pure *anti* by crude ^{1}H NMR); δ_H(250 MHz; DMSO) 0.87 (3H, t, *J* 7.0 Hz, OCH$_2$C*H*$_3$), 2.25 (3H, s, ArC*H*$_3$), 3.08 (3H, s, SC*H*$_3$), 3.11 (3H, s, SC*H*$_3$), 4.00 (2H, q, *J* 7.0 Hz, OC*H*$_2$CH$_3$), 4.72 (1H, m, NC*H*), 5.01 [1H, m, C*H*S(CH$_3$)$_2$], 7.05–7.17 (7H, m, Ar), 7.39–7.47 (2H, m, Ar), 9.08 (1H, d, *J* 3.0 Hz, N*H*); δ_F(235.5 MHz; DMSO) −148 [BF_4^- $^+S(CH_3)_2$].

***syn*-*N*-(1,2-Diphenyl-1-methylthioethyl)toluenesulfonamide 8a**

NaSMe (60 mg, 0.86 mmol) was added to a stirred suspension of *cis*-*N*-(*p*-tolylsulfonyl)-2,3-diphenylaziridine (150 mg, 0.43 mmol) in ethanol (5 cm^3). The mixture was heated at reflux for 6 h before being allowed to cool to rt. The mixture was then diluted with water (5 cm^3) and extracted with ethyl acetate (4 × 10 cm^3). The combined organic fractions were dried over $MgSO_4$ and evaporated *in vacuo* to furnish a yellow oil, which solidified on standing. The residue was purified by column chromatography eluting with 85 : 15, petroleum ether–EtOAc to give the required sulfide **8a** (96 mg, 56%) as an off-white solid mp 133.0–134.5 °C (petroleum ether–EtOAc); ν_{max}(Attenuated total reflection, ATR)/cm^{-1} 3268, 3062, 3029, 2917, and 2891; δ_H(400 MHz; CDCl$_3$) 1.82 (3H, s, SCH$_3$), 2.32 (3H, s, ArC*H*$_3$), 3.94 (1H, d, *J* 8.4 Hz, SC*H*Ph), 4.60 (1H, dd, *J* 5.1 and 8.4 Hz, NC*H*Ph), 5.62 (1H, d, *J* 5.1 Hz, N*H*), 7.15–6.85 (12H, m, Ar), 7.46 (2H, d, *J* 9 Hz, Ar); δ_C(100 MHz; CDCl$_3$) 14.5, 21.5, 58.1, 61.5, 126.9, 127.3, 127.4, 127.6, 127.7, 128.3, 128.5, 128.9, 136.8, 137.2, 137.4, 142.7; *m*/*z* (EI) 349 ($M^+ - SCH_3$, 54%), 260 (100), 194 (33), 155 (61) (Found: $M^+ - SCH_3$, 350.1216. $C_{21}H_{20}NO_2S$ requires M^+, 350.1215).

***anti*-*N*-(1,2-Diphenyl-1-methylthioethyl)toluene-4-sulfonamide 8b**

NaSMe (32 mg, 0.45 mmol) was added to a stirred suspension of *trans*-*N*-(*p*-tolylsulfonyl)-2,3-diphenylaziridine (80 mg, 0.23 mmol) in EtOH (3 cm^3). The mixture was heated to reflux for 45 min before being allowed to cool to rt. The resultant suspension was diluted with water (5 cm^3) and the EtOH was removed *in vacuo*. The remaining solution was extracted with ethyl acetate (5 × 5 cm^3) and the combined organic extracts dried over $MgSO_4$. The solvent was removed *in vacuo* to furnish the title compound **8b** (90 mg, 97%) as an off-white solid, R_f 0.33 (80 : 20 petroleum ether–ethyl acetate); mp 139–141 °C; ν_{max}(ATR)/cm^{-1} 3268, 3062, 3029, 2917, and 2891; δ_H(400 MHz; CDCl$_3$) 1.69 (3H, s, SCH$_3$), 2.30 (3H, s, ArC*H*$_3$), 3.92 (1H, d, *J* 7.0 Hz, SC*H*Ph), 4.55 (1H, t, *J* 7.0 Hz, NC*H*Ph), 5.34 (1H, d, *J* 7.0 Hz, N*H*), 6.86 (2H, m, Ar), 6.96–7.20 (10H, m, Ar), 7.36 (2H, d, *J* 8 Hz, Ar); δ_C(100 MHz; CDCl$_3$) 15.2, 21.5, 58.6, 61.9, 127.2, 127.8, 127.9, 128.0, 128.6, 128.8, 129.3, 137.0, 137.4, 137.5, 142.9; *m*/*z* (EI) 349 ($M^+ - SCH_3$, 54%), 260 (100), 194 (12), 155 (63) (Found: $M^+ - SCH_3$, 350.1207. $C_{21}H_{20}NO_2S$ requires M^+, 350.1215).

2-Methylsulfanyl-3-phenyl-3-(toluene-4-sulfonamido)propionic acid ethyl ester *syn*-11a and *anti*-11b

To diisopropylamine (0.98 cm^3, 6.97 mmol) in THF (10 cm^3) was added *n*-butyllithium (5.02 cm^3, 1.3 M, 6.53 mmol) and the resultant mixture was stirred for 1 h. After this time the reaction mixture was cooled to −78 °C. Ethyl (methylthio)acetate (0.41 cm^3, 3.1 mmol) dissolved in THF (10 cm^3) was added dropwise to the cooled solution over a period of 30 min, and stirred for 1 h. Finally *N*-benzylidenetoluene-*p*-sulfonamide (0.96 g, 3.7 mmol) dissolved in THF (6 cm^3) was added dropwise to the solution at −78 °C and stirred for 40 min. 2 M ethanolic HCl (10 cm^3) was added with rapid stirring, diethyl ether (30 cm^3) was then added and the mixture stirred for 10 min. The vessel and its contents were allowed to warm to rt. The organic phase was washed with water (40 cm^3), saturated aqueous $NaHCO_3$ (2 × 10 cm^3) and brine (20 cm^3). The organic phase was then dried with $MgSO_4$ and the solvent removed *in vacuo* to yield a yellow solid (2 : 1 *anti* : *syn*, ratio by crude ^1H NMR). The solid was purified by flash chromatography (85 : 15, petroleum ether–EtOAc), giving two separate colourless solid diastereoisomers: *anti*: [0.58 g, 40%, R_f 0.43 (80 : 20, petroleum ether–EtOAc)] as a white solid: mp 127–128 °C (from petroleum ether–EtOAc) (Found: C, 58.22; H, 5.76; N, 3.56. $C_{19}H_{23}NO_4S_2$ requires C, 57.99; H, 5.89; N, 3.56%); ν_{max}(ATR)/cm^{-1} 3257, 2925, 1728, 1330 and 1154; δ_H(400 MHz; $CDCl_3$) 0.99 (3H, t, *J* 7.0 Hz, OCH_2CH_3), 2.02 (3H, s, SCH_3), 2.36 (3H, s, $ArCH_3$), 3.39 (1H, d, *J* 10.2 Hz, $CHSCH_3$), 3.93 (2H, q, *J* 7.0 Hz, OCH_2CH_3), 4.54 (1H, dd, *J* 10.2 and 3.3 Hz, NC*H*), 5.70 (1H, d, *J* 3.3 Hz, N*H*), 7.05–7.13 (7H, m, Ar), 7.42–7.51 (2H, m, Ar); δ_C(100 MHz; $CDCl_3$) 12.1, 13.8, 21.5, 52.5, 55.8, 61.4, 127.3, 128.1, 128.2, 128.3, 128.4, 129.3, 137.1, 137.2, 143.2, 168.7; *m*/*z* (EI) 393 (M^+, 100%); *syn*: [0.30 g, 21%, R_f 0.40 (80 : 20, petroleum ether–EtOAc)]; as a white solid: mp 134–136 °C (from petroleum ether–EtOAc) (Found C, 58.14; H, 5.96; N, 3.61. $C_{19}H_{23}NO_4S_2$ requires C, 57.99; H, 5.89; N, 3.56%); ν_{max}(ATR)/cm^{-1} 3257, 3190, 1712, 1333 and 1156; δ_H(400 MHz; $CDCl_3$) 1.11 (3H, t, *J* 7.0 Hz, OCH_2CH_3), 2.09 (3H, s, SCH_3), 2.33 (3H, s, $ArCH_3$), 3.47 (1H, d, *J* 6.0 Hz, $CHSCH_3$), 4.01–4.15 (2H, m, OCH_2CH_3), 4.84 (1H, dd, *J* 6.0 and 9.0 Hz, NC*H*), 6.09 (1H, d, *J* 9.0 Hz, N*H*), 7.06–7.17 (7H, m, Ar), 7.52–7.56 (2H, m, Ar); δ_C(100 MHz $CDCl_3$) 14.2, 15.6, 21.4, 53.9, 59.0, 61.6, 126.7, 127.2, 127.9, 128.5, 129.2, 137.8, 138.0, 139.9, 143.0, 170.8; *m*/*z* (EI) 393 (M^+, 100%).

Crystal structure of 11a †

Crystal data for $C_{19}H_{23}NO_4S_2$; *M* = 393.50; crystal dimensions 0.30 × 0.20 × 0.20 mm^3. Monoclinic, *a* = 22.104(3), *b* = 18.785(3), *c* = 20.095(3) Å, *U* = 7979.2(19) $Å^3$, *Z* = 16, D_c = 1.310 Mg m^{-3}, space group *P*2(1)/*c*, Mo-Kα radiation (λ = 0.71073 Å), μ(Mo-Kα) = 0.290 mm^{-1}, *F*(000) = 3328.

Crystal structure of 11b †

Crystal data for $C_{19}H_{23}NO_4S_2$; *M* = 393.50; crystal dimensions 0.75 × 0.50 × 0.50 mm^3. Monoclinic, *a* = 10.3330(14), *b* = 28.469(3), *c* = 26.751(4) Å, *U* = 7857.9(18) $Å^3$, *Z* = 16, D_c = 1.330 Mg m^{-3}, space group *P*2(1)/*c*, Mo-Kα radiation (λ = 0.71073 Å), μ(Mo-Kα) = 0.295 mm^{-1}, *F*(000) = 3328.

N,*N*-Diethyl-2-methylsulfanyl-3-phenyl-3-(toluene-4-sulfonamido)propionamide *syn*-13a *anti*-13b

To a mixture of LiCl (0.8 g, 18.6 mmol) and diisopropylamine (0.98 cm^3, 6.97 mmol) in THF (10 cm^3) under nitrogen was added *n*-butyllithium (5.02 cm^3, 1.3 M, 6.53 mmol) and the resultant mixture was stirred for 1 h. After this time the reaction mixture was cooled to −78 °C. *N*,*N*-Diethyl-2-methylsulfanylacetamide (0.5 g, 3.1 mmol) dissolved in THF (10 cm^3) was added dropwise to the cooled solution over a period of 30 min and the mixture was stirred for 1 h. Finally *N*-benzylidenetoluene-*p*-sulfonamide (0.96 g, 3.7 mmol) dissolved in THF (6 cm^3) was added dropwise to the solution (at −78 °C) and stirring was continued for 40 min. 2 M ethanolic HCl (10 cm^3) was added with rapid stirring, ether (30 cm^3) was then added and the mixture stirred for 10 min. The vessel and its contents were then allowed to warm to rt. The organic phase was washed with water (40 cm^3), saturated aqueous $NaHCO_3$ (2 × 10 cm^3) and brine (20 cm^3) until neutral. The organic phase was then dried with $MgSO_4$ and the solvent removed *in vacuo* to yield a yellow solid (1 : 1 *anti* : *syn* ratio by crude ^1H NMR). The solid was purified by flash chromatography (R_f 0.41, 60 : 40, petroleum ether–EtOAc), and by recrystallisation, yielding a white solid containing both diastereoisomers, which could not be separated (0.93 g, 72%), as a white powder; mp 149–150 °C (from petroleum ether–EtOAc of 1 : 1 *syn* : *anti*); ν_{max}(ATR)/cm^{-1} 3355, 3261, 2981, 1616, and 1614; δ_H(400 MHz; $CDCl_3$) 0.62^{syn} (3H, t, *J* 7.0 Hz, NCH_2CH_3), 0.72^{anti} (6H, m, 2 × NCH_2CH_3), 0.89^{syn} (3H, t, *J* 7.0 Hz, NCH_2CH_3), 1.77^{anti} (3H, s, SCH_3), 2.07^{syn} (3H, s, SCH_3), 2.27^{anti} (1H, s, $ArCH_3$), 2.33^{syn} (1H, s, $ArCH_3$), 2.80–3.20$^{anti\&syn}$ [8H, m, 2 × $N(CH_2CH_3)_2$], 3.37^{anti} (1H, d, *J* 10.2 Hz, CH_3SCH), 3.56^{syn} (1H, d, *J* 4.0 Hz, CH_3SCH), 4.52^{anti} (1H, dd, *J* 10.2 and 2.2 Hz, NHC*H*), 4.74^{syn} (1H, dd, *J* 8.0 and 4.0 Hz, NHC*H*), 5.78^{anti} (1H, d, *J* 2.2 Hz, N*H*), 7.03–7.77 (18H, m, Ar); δ_C(100 MHz; $CDCl_3$) 10.5, 12.8, 14.1, 14.3, 14.7, 21.4, 21.5, 41.0, 41.1, 42.2, 42.5, 47.8, 48.5, 55.6, 60.2, 126.8, 127.1, 127.5, 127.5, 127.6, 127.8, 128.0, 128.3, 128.4, 129.0, 129.4, 136.5, 138.3, 138.5, 139.2, 142.5, 143.3, 166.2, 168.8; *m*/*z* (EI) 421 (M^+, 10%), 373 (24), 300 (55), 161 (100) (Found: M^+, 420.1528. $C_{21}H_{28}N_2O_3S_2$ requires M^+, 420.1541).

syn-*N*,*N*-Diethyl-2-methylsulfanyl-3-phenyl-3-(toluene-4-sulfonamido)propionamide 13a

A 1.0 M solution of trimethylaluminium in hexane (1.0 cm^3, 1.0 mmol) was slowly added at rt to a solution of diethylamine (103 μl, 1.0 mmol) in 2.5 cm^3 of dry dichloromethane. The mixture was stirred at rt for 15 min and **11a** or **11b** was added in one portion (393 mg, 1.0 mmol). The mixture was warmed to 40 °C until TLC indicated that the reaction had gone to completion. The reaction mixture was diluted with dichloromethane (15 cm^3) and quenched with dilute HCl (1 M), separated and the organic layer dried ($MgSO_4$). The solvent was removed *in vacuo* to afford the crude amide as a pale yellow solid. The solid was purified by flash chromatography (60 : 40, petroleum ether–EtOAc), and by recrystallisation (hexane–EtOAc), to yield the product (106 mg, 25%) as a white solid: mp 161.0–163.5 °C (from petroleum ether–EtOAc); ν_{max}(ATR)/cm^{-1} 3355, 3259, 2980, 1613, 1324, and 1301; δ_H(400 MHz; $CDCl_3$) 0.62 (3H, t, *J* 7.0 Hz, NCH_2CH_3), 0.89 (3H, t, *J* 7.0 Hz, NCH_2CH_3), 2.07 (3H, s, SCH_3), 2.33 (3H, s, $ArCH_3$), 2.80 [1H, dq, *J* 14.0 and 7.0 Hz, $N(CHHCH_3)_2$], 3.05 [1H, dq, *J* 14.0 and 7.0 Hz, $N(CHHCH_3)_2$], 3.22 [2H, q, *J* 7.0 Hz, $N(CH_2CH_3)_2$], 3.56 (1H, d, *J* 4.0 Hz, $CHSCH_3$), 4.74 (1H, dd, *J* 7.3 and 4.0 Hz, NC*H*), (N*H* not visible), 7.06–7.17 (7H, m, Ar), 7.52–7.56 (2H, m, Ar); δ_C(100 MHz; $CDCl_3$) 12.8, 14.1, 14.7, 21.5, 41.0, 42.5, 48.5, 60.2, 126.5, 126.8, 127.1, 127.6, 128.3, 129.0, 129.8, 138.5, 139.2, 142.4, 143.3, 168.8; *m*/*z* (EI) 421 (M^+, 12%), 373 (27), 300 (54), 161 (100) (Found: M^+, 420.1548. $C_{21}H_{28}N_2O_3S_2$ requires M^+, 420.1541).

General method for crossover experiments

The aldol adduct (**11a**/**11b** and **13a**/**13b**) (0.076 mmol) and trimethyloxonium tetrafluoroborate (11.3 mg, 0.076 mmol) were stirred overnight in dichloromethane (1 cm^3) at rt under nitrogen. The resultant solution was frozen in liquid nitrogen and

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† CCDC reference number 169025. See http://www.rsc.org/suppdata/p1/b1/b107275g/ for crystallographic files in .cif format.

the solvent removed under high vacuum, to yield a very hydroscopic pale brown solid (assumed 100% yield). To the sulfonium salt (0.076 mmol) was added dry solvent (1 cm^3) and *N*-(nitrobenzylidene)toluene-*p*-sulfonamide (23 mg, 0.076 mmol) and the mixture was stirred for 5 min. KO^{t}Bu (76 µl, 0.076 mmol, of a 1 M solution in THF) was then added dropwise with rapid stirring. The resultant solution was stirred for 1 h at rt then diluted with dichloromethane (5 cm^3) and the organic layer extracted with water (2 × 5 cm^3). The organic phase was then dried with $MgSO_4$ and the solvent removed *in vacuo* to yield a pale yellow solid. To the solvent-free mixture was added 1,3-benzodioxole (internal standard, 2.6 µl, 0.0226 mmol) and the whole reaction mixture was subjected to NMR analysis to determine yields based on the internal standard.

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