Additions of benzylsulfonium ylides to aldehydes and ketones: are they under kinetic or thermodynamic control?

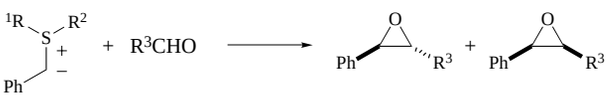
Varinder K. Aggarwal,* Simone Calamai and J. Gair Ford

Department of Chemistry, University of Sheffield, Sheffield S3 7HF, UK

The reaction of benzylsulfonium ylides with aromatic aldehydes gives predominantly *trans* epoxides whilst aliphatic aldehydes give mixtures of *cis* and *trans* epoxides. In order to probe the origin of the diastereoselectivity, single diastereoisomers of betaine intermediates were prepared by independent methods and subjected to ring closure and cross-over experiments. It was found that *anti* betaines derived from aliphatic and aromatic aldehydes gave exclusively *trans* epoxides. *syn* Betaines derived from aromatic aldehydes also gave exclusively *trans* epoxides whilst *syn* betaines derived from aliphatic aldehydes gave mixtures of *cis* and *trans* epoxides. From ring closure experiments in the presence of a more reactive aldehyde (cross-over experiments) it was found that *anti* betaines derived from aliphatic and aromatic aldehydes gave epoxides without incorporation of the more reactive aldehyde. In contrast, *syn* betaines derived from aromatic aldehydes gave exclusively epoxides derived from the more reactive aldehyde whilst *syn* betaines derived from aliphatic aldehydes gave mixtures of epoxides. These experiments indicated that the high *trans* selectivity observed in epoxidation with aromatic aldehydes is a result of irreversible formation of the *anti* betaine and reversible formation of the *syn* betaine. With aliphatic aldehydes the lower selectivity results from only partial reversibility in formation of the *syn* betaine.

Introduction

The reactions of benzylsulfonium ylides with aldehydes has recently received considerable attention since attachment of chiral groups to sulfur can lead to high enantioselectivity in the epoxidation process[1–14] (Scheme 1). However, in addition to the



Scheme 1

issue of enantioselectivity, there is also an issue of diastereoselectivity associated with this method of epoxidation. In this context we and others have found[1–14] that reactions of benzyl sulfur ylides with aromatic aldehydes give largely *trans* epoxides, whilst aliphatic aldehydes give mixtures of *cis* and *trans* epoxides (Table 1, Fig. 1).

In order to understand the origin of the substrate-dependent diastereoselectivity details of the mechanism of the benzyl sulfur ylide reaction are required and, in particular, whether the reaction is under kinetic or thermodynamic control. This issue is not only important for a fundamental understanding of the reaction, but also has major implications in the design of chiral sulfides for asymmetric epoxidation. If the reactions are under kinetic control, then non-bonded interactions in the transition state for the formation of the betaine will determine the stereochemical outcome of the reaction. In contrast, if the reactions are under thermodynamic control, the equilibrium ratio of betaine diastereoisomers and their respective rates of ring closure will influence the ratio of epoxides obtained.

Unfortunately, there are conflicting reports in the literature on whether reactions of benzylsulfonium ylides with aromatic aldehydes are under kinetic or thermodynamic control. For example, Johnson suggested that the high *trans* selectivity in the reaction between diphenylsulfonium benzylide with aromatic aldehydes was a result of rapid but reversible betaine formation followed by slow rate of ring closure. The *syn* betaine **13** ring closes at a much slower rate than the *anti* diastereoisomer **11** leading to high *trans* selectivity in the product epoxide (Scheme 2). The reaction was therefore assumed to be under thermodynamic control.[15] However, recent studies employing chiral benzylsulfonium ylides have focused on non-bonded interactions in the transition states for betaine formation to account for the enantioselectivity of the process. This assumes that

Table 1 Diastereoselectivity in reactions of sulfur ylides with aldehydes

Entry	Ylide	Solvent	Aldehyde	*trans*:*cis*	Proposed mechanism	References
1	**1**	DCM	PhCHO	71:29	Kinetic	Durst[9]
2	**2**	DCM	PhCHO	83:17	Kinetic	Durst[9]
3	**3**	MeCN	PhCHO	>98:2	*a*	Furukawa[14]
4	**4**	MeCN	PhCHO	>98:2	Kinetic	Dai[13]
5	**5**	DCM	PhCHO	>98:2	*a*	Solladié-Cavallo[11]
6	**6**	DCM	PhCHO	>98:2	Kinetic	Aggarwal[6]
7	**7**	THF	PhCHO	>98:2	Thermodynamic	Johnson[15]
8	**8**	DCM	PhCHO	88:12	*a*	Aggarwal[7]
9	**9**	DCM	PhCHO	98:2	*a*	Aggarwal[7]
10	**8**	DCM	*p*-$NO_2C_6H_4CHO$	>98:2	*a*	Aggarwal[7]
11	**8**	DCM	*p*-ClC_6H_4CHO	84:16	*a*	Aggarwal[7]
12	**8**	DCM	C_4H_9CHO	60:40	*a*	Aggarwal[7]
13	**8**	DCM	$C_6H_{11}CHO$[b]	79:21	*a*	Aggarwal[7]
14	**10**	DCM	Bu^tCHO	>98:2	*a*	Ford[26]

[a] Mechanism not indicated. [b] Cyclohexanecarbaldehyde.

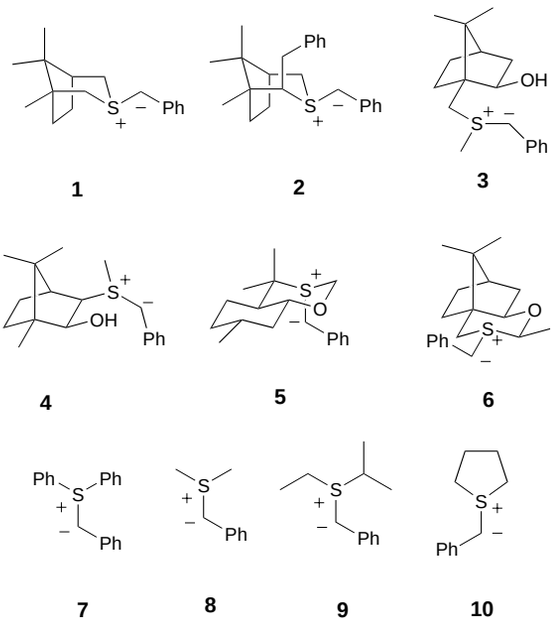
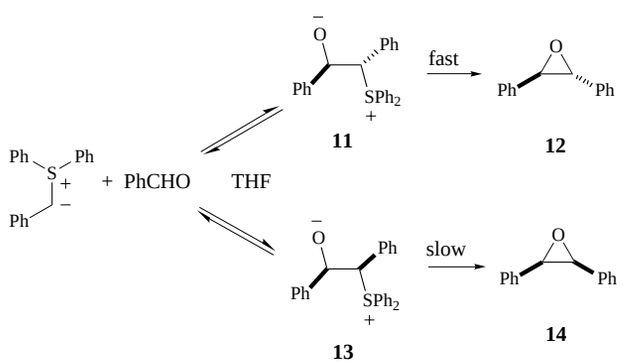


Fig. 1



Scheme 2

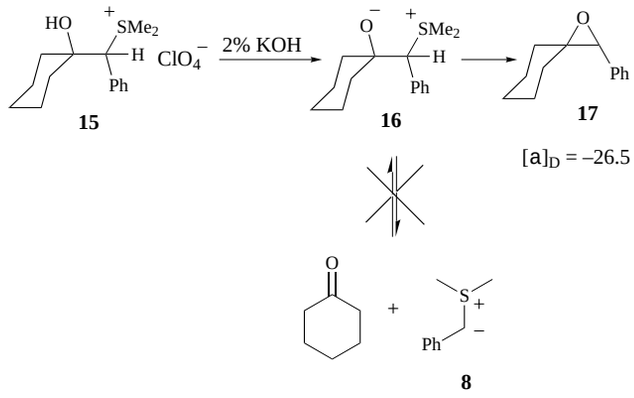
reactions are under kinetic control! In none of the cases has any evidence been presented to support the assumptions made.

Reactions of benzylsulfonium ylides with other carbonyl compounds have also been investigated. For example, Hatch studied the reaction of dimethyl(benzyl)sulfonium ylide with formaldehyde and concluded that betaine formation was slow and irreversible.[16] However, the lack of distinction between the use of paraformaldehyde and formaldehyde in competition and cross-over experiments invalidates the conclusions reached (it was assumed that formaldehyde was in rapid equilibrium with paraformaldehyde but cross-over experiments clearly indicated this was not the case). Durst has studied the reaction of dimethyl(benzyl)sulfonium ylide with cyclohexanone by independent generation of the betaine.[17] The sulfonium salt **15** was prepared in enantiomerically pure form and upon treatment with base gave the corresponding epoxide which rotated plane polarised light (Scheme 3). This indicated that betaine formation was irreversible. However, it did not indicate if the reaction was completely irreversible or only partially so.[18]

Clearly, there was confusion in the literature about whether benzylsulfonium ylides reacted reversibly with aldehydes and this issue therefore had to be addressed. In this paper, we describe our investigations into whether reactions of benzylsulfonium ylides with aromatic/aliphatic aldehydes and ketones are under kinetic or thermodynamic control.

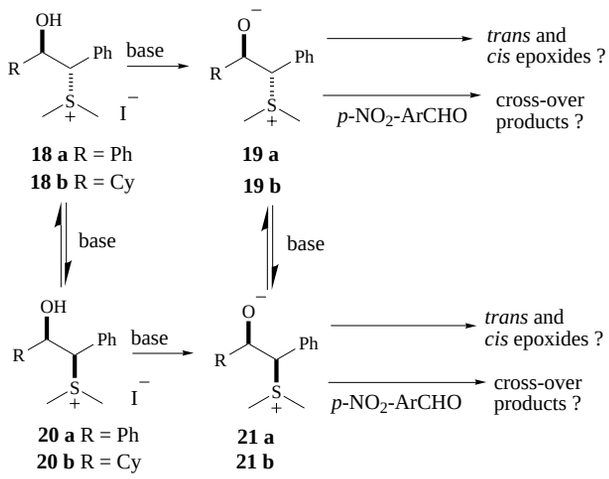
Method

To determine whether sulfur ylide additions to aldehydes and ketones are under kinetic or thermodynamic control, we needed to generate independently the corresponding diastereomerically



Scheme 3

pure intermediate betaines (Scheme 4). Determination of the *cis*:*trans* selectivity in the product epoxides would indicate whether betaine formation was reversible. However, as the sulfonium salt or betaine can undergo base-catalysed epimerisation (Scheme 4), proof of whether betaine formation was



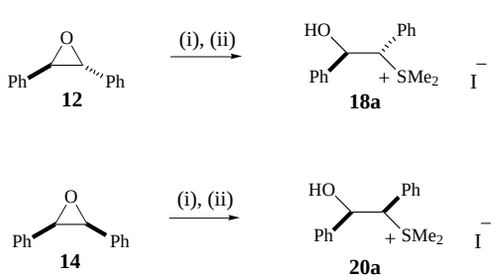
Scheme 4

reversible also needed to be obtained by carrying out the experiment in the presence of a more reactive aldehyde and determining whether cross-over products were formed.

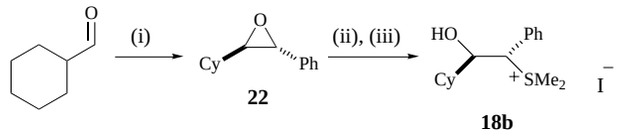
We therefore required the sulfonium salts **15** (for the cross-over study only) and **18a**,**b**, **20a**,**b**. Salts **18a** and **20a** would test reactions of benzylsulfonium ylides with a representative aromatic aldehyde, salts **18b** and **20b** aliphatic aldehydes, and salt **15** ketones. Effects of solvent polarity on reversibility were also examined by carrying out reactions in a strongly polar solvent (dimethyl sulfoxide; DMSO) and in a relatively non-polar solvent (dichloromethane; DCM).

Synthesis of sulfonium salts

Salts **18a** and **20a** were prepared by ring opening *trans*- and *cis*-stilbene oxides with sodium thiomethoxide (IUPAC name: sodium methanethiolate), followed by alkylation with methyl iodide (Scheme 5).



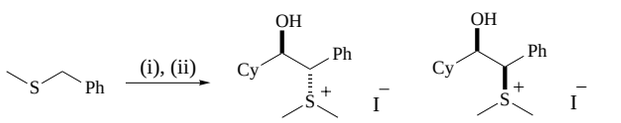
Scheme 5 *Reagents*: (i) NaSMe, EtOH; (ii) MeI



Scheme 6 *Reagents*: (i) $PhCHN_2$, Ph_3As, $Cu(acac)_2$, DCM; (ii) NaSMe, EtOH; (iii) MeI

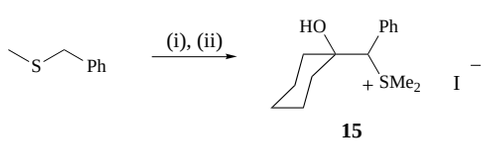
Salt **18b** was obtained in a similar manner (Scheme 6). The required *trans* epoxide **22** was obtained by reaction of cyclohexanecarbaldehyde with triphenylarsonium benzylide using a modification of our catalytic cycle for sulfur ylide epoxidation.[2–4,19] Non-stabilised arsonium ylides react with aldehydes and give epoxides with very high *trans* selectivity.[20]

We were unable to prepare the salt **20b** in diastereoisomerically pure form and so used a mixture of diastereoisomers in the subsequent study. Since we would test both salt **18b** and a mixture of salts **18b** and **20b**, it is possible to calculate the results one would have obtained from a diastereoisomerically pure sample of **20b**. The mixture was prepared according to Scheme 7.



Scheme 7 *Reagents*: (i) TMEDA, BuLi, CyCHO, THF; (ii) MeI

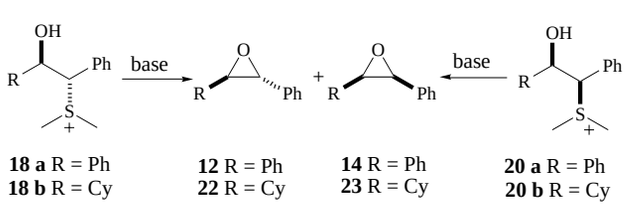
A similar strategy was employed to prepare the salt **15** (Scheme 8).



Scheme 8 *Reagents*: (i) TMEDA, BuLi, cyclohexanone, THF; (ii) MeI

Results

We first tested the diastereoselectivity in ring closure of the sulfonium salts **18a**,**b** and **20a**,**b** in both DCM and DMSO (Scheme 9, Table 2). Solid sodium hydroxide was used in these



Scheme 9

and all subsequent experiments and when reactions were conducted in DCM, a few drops of water were added to aid dissolution of the base.

The results showed that in DMSO, the *trans* epoxide was exclusively obtained from both sulfonium salts, irrespective of which diastereoisomer of the sulfonium salt was used (entries 2, 4, 6, 10). In DCM, mixtures of *cis* and *trans* epoxides were obtained from the *syn* sulfonium salts (entries 3, 9) but only *trans* epoxides were obtained from the *anti* sulfonium salts (entries 1, 5). These results could be accounted for by either base-catalysed equilibration of the betaine diastereoisomers or

Table 2 Ring closure of sulfonium salts in DCM and DMSO

Entry	Salt	Solvent	Product ratio
1	**18a**	DCM	>95:5 (**12**:**14**)
2	**18a**	DMSO	>95:5 (**12**:**14**)
3	**20a**	DCM	42:58 (**12**:**14**)
4	**20a**	DMSO	>95:5 (**12**:**14**)
5	**18b**	DCM	>95:5 (**22**:**23**)
6	**18b**	DMSO	>95:5 (**22**:**23**)
7	**18b** + **20b** (1:1)	DCM	55:45 (**22**:**23**)
8	**18b** + **20b** (1:1)	DMSO	>95:5 (**22**:**23**)
9	**20b**	DCM	15:85 (**22**:**23**)[a]
10	**20b**	DMSO	>95:5 (**22**:**23**)[a]

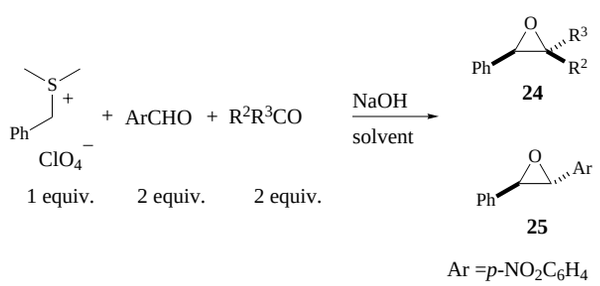
[a] Ratios calculated from entries 5–8.

Table 3 Competition reactions of dimethylsulfonium benzylide with *p*-nitrobenzaldehyde and the test aldehyde/ketone

Entry	Aldehyde or ketone	Solvent	**24**:**25**
1	Benzaldehyde	DCM	<5:95
2	Benzaldehyde	DMSO	<5:95
3	Cyclohexanecarbaldehyde	DCM	<5:95
4	Cyclohexanecarbaldehyde	DMSO	<5:95
5	Cyclohexanone	DCM	<5:95
6	Cyclohexanone	DMSO	<5:95

reversion of the betaine back to the ylide and aldehyde or a combination of both. Evidently equilibration or reversion occurs to a greater extent in DMSO compared to DCM. In order to distinguish between base-catalysed equilibration and reversion we needed to carry out cross-over experiments.

Our proposed cross-over experiments involved the generation of the betaine in the presence of a more reactive trapping agent, *e.g. p*-nitrobenzaldehyde: if betaine formation was reversible then the ylide would react with the trapping agent. Before conducting the cross-over experiments we needed to conduct control experiments to determine if *p*-nitrobenzaldehyde was indeed more reactive than benzaldehyde, cyclohexanecarbaldehyde and cyclohexanone towards benzyl(dimethyl)sulfonium ylide. Competition experiments were therefore carried out between *p*-nitrobenzaldehyde and the corresponding carbonyl compound under investigation in both DCM and DMSO (Scheme 10).



Scheme 10

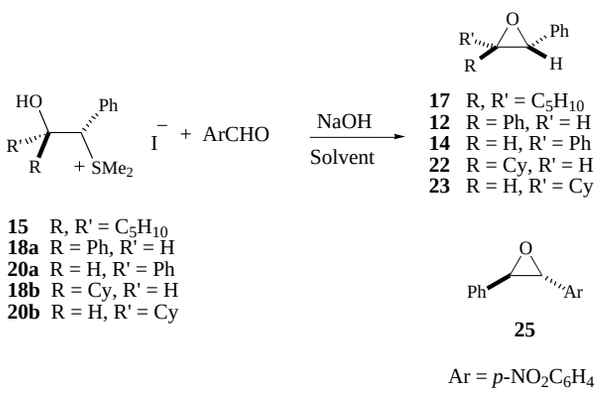
The results clearly showed that in all cases and in either solvent, *p*-nitrobenzaldehyde was the more reactive carbonyl component and was therefore a suitable aldehyde for use in cross-over experiments. Thus, the sulfonium salts **15** and **18a**,**b**, **20a**,**b** were treated with base in the presence of *p*-nitrobenzaldehyde (3 equiv.) in both DCM and DMSO (Scheme 11, Table 4).

The *anti* sulfonium salts **18a**,**b** gave the corresponding *trans* epoxides only, without cross-over products, in either DCM or DMSO (entries 1, 2, 5 and 6) indicating that no reversion of the *anti* betaines **19a**,**b** occurred. The *syn* sulfonium salts **20a**,**b** gave a mixture of the corresponding *cis* epoxides together with cross-over products in DCM (entries 3, 9). The absence of the

Table 4 Cross-over reactions of sulfonium salts in the presence of *p*-nitrobenzaldehyde in DCM and DMSO

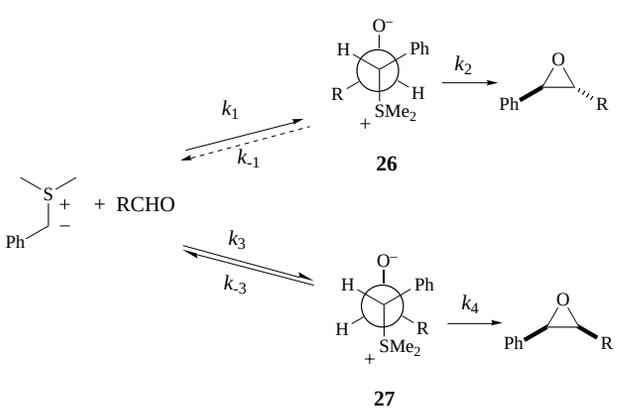
Entry	Salt	Solvent	Product ratios [a]
1	**18a**	DCM	100:0:0 (**12**:**14**:**25**)
2	**18a**	DMSO	100:0:0 (**12**:**14**:**25**)
3	**20a**	DCM	0:22:78 (**12**:**14**:**25**)
4	**20a**	DMSO	0:0:100 (**12**:**14**:**25**
5	**18b**	DCM	100:0:0 (**22**:**23**:**25**)
6	**18b**	DMSO	100:0:0 (**22**:**23**:**25**)
7	**18b** + **20b** (1:1)	DCM	50:40:10 (**22**:**23**:**25**)
8	**18b** + **20b** (1:1)	DMSO	52:0:48 (**22**:**23**:**25**)
9	**20b**	DCM	0:80:20 (**22**:**23**:**25**) [b]
10	**20b**	DMSO	4:0:96 (**22**:**23**:**25**) [b]
11	**15**	DCM	100:0 (**17**:**25**)
12	**15**	DMSO	30:70 (**17**:**25**)

[a] Product ratios are given to ±5% accuracy. [b] Ratios calculated from entries 5–8.



Scheme 11

corresponding *trans* epoxides (coupled with the absence of *cis* epoxides from **18a**,**b**) proves that base-catalysed equilibration of either the sulfonium salts or the betaines does not occur. There was a greater amount of cross-over products in the case of the aromatic containing sulfonium salt **20a** compared to **20b** (compare entries 3, 9). In DMSO, the *syn* sulfonium salts **20a**,**b** only gave cross-over products (entries 4, 10). The small amount of *trans* epoxide **22** obtained from the salt **20b** is zero within experimental error.[21] No cross-over occurred with salt **15** in DCM but substantial amounts of cross-over product **25** was obtained in DMSO (enries 11 and 12).



Scheme 12

From these results it is clear that formation of *anti* betaine **26** (R = Ph/Cy) is irreversible in polar and non-polar solvents and leads directly to the *anti* epoxide ($k_2 > k_{-1}$). The formation of the *trans* epoxide is therefore kinetically controlled. However, the outcome of reactions involving *syn* betaine **27** are more finely balanced. If R = Ph, there is greater potential for reversion to ylide and aldehyde ($k_{-3} > k_4$) compared to R = Cy. The developing conjugation of the π-orbital with the aromatic ring may be increasing the rate of k_{-3}. Reversion of **27** to the ylide and aldehyde will allow formation of betaine **26** and so will result in production of more *trans* epoxide. Reactions with ketones, like those with aliphatic aldehydes, were largely under kinetic control. Again, the lack of stabilisation of the developing π-orbital may reduce the rate of reversion relative to the rate of ring closure of the betaine. Solvent also plays a significant role as non-polar solvents will tend to increase both k_2 and k_4 relative to k_{-1} and k_{-3}. Indeed, in DCM much less reversibility was observed compared to DMSO. The size of the groups attached to sulfur will also influence the amount of the *cis* isomer formed. Considering the betaine **27**, large groups will disfavour the conformation required for elimination and thereby reduce k_4. Large groups attached to sulfur will also enhance k_{-3} and so give a greater preponderance of the *trans* product.

All of our results and the results reported to date can now be understood (Table 1). Reaction of benzylsulfonium ylides with aromatic aldehydes furnish largely *trans* epoxides. The high *trans* selectivity is due to reversible formation of the *syn* betaine **27** and irreversible formation of the *anti* betaine **26** (Table 1, entries 1–11). Higher *trans* selectivity is observed from sulfur ylides bearing larger groups attached to sulfur due to the slower rate of ring closure and greater rate of reversion of the *syn* betaine **27** (Table 1, entries 1, 2 and 7–9). As the *anti* betaine **26** is formed irreversibly the kinetic model for betaine formation is valid and so non-bonded interactions in the transition state are most important.

The formation of mixtures of *cis* and *trans* epoxides from aliphatic aldehydes is a result of irreversible formation of the *anti* betaine and only partially reversible formation of the *syn* betaine (Table 1, entries 12–14). The higher *trans* selectivity observed for pivalaldehyde compared to cyclohexanecarbaldehyde compared to valeraldehyde (Table 1, entries 12–14) is due to greater reversibility of the *syn* betaine. As noted above, larger groups attached to sulfur enhance the rate of reversion. In the same way, larger groups attached to the aldehyde also enhance the rate of reversion. Again because betaine formation is not rapidly reversible, the kinetic model is valid. The same applies to aliphatic ketones.

Conclusion

The addition of benzylsulfonium ylide to an aldehyde/ketone is a remarkably finely balanced reaction. Epoxide formation is essentially under kinetic control. The *trans* epoxide is derived directly from irreversible formation of the *anti* betaine or indirectly from reversible formation of the *syn* betaine (in polar or non-polar solvents). The *cis* epoxide is derived from partial reversible formation of the *syn* betaine. The higher *trans* selectivity observed in reactions involving aromatic aldehydes compared to aliphatic aldehydes is due to greater reversibility in the formation of the *syn* betaine. The degree of reversibility is highly solvent dependent and increases in more polar solvents. As the *trans* epoxide is formed from irreversible formation of the *anti* betaine non-bonded interactions in the transition state for betaine formation are important. This study reinforces the mechanisms put forward to date to account for the enantioselectivities observed and should help in the design of alternative chiral sulfides for asymmetric epoxidation.

Experimental

^{1}H and ^{13}C NMR spectra were recorded using a Bruker ACF-250 spectrophotometer supported by an Aspect 2000 data system. Mass spectra were obtained using a Kratos MS instrument operating in EI, CI mode and on a Kratos MS 80 in +ve FAB mode. Mps were determined using a Kofler hot-stage micro

melting point apparatus and stand uncorrected. Elemental microanalyses were carried out using a Perkin-Elmer 2400 Elemental Analyser CHN, involving classical wet analysis for anions (S, I). Solvents and reagents were dried and purified prior to use according to standard procedures. Thin layer chromatography (TLC) was used routinely to monitor the progress of reactions and purity of compounds. TLC was performed on Merck DC-alufolien Kieselgel 60 F254 sheets containing fluorescent indicator. TLC plates were visualised when possible by wavelength of 356 nm UV light and by treatment with either a solution of phosphomolybdic acid (5 g in 100 ml 95% absolute alcohol) or 0.5% (w/v) aqueous potassium permanganate, followed by warming of the TLC plate using a paint stripper. Chromatographic purification of compounds was achieved by medium-pressure chromatography using Kieselgel 60 F254, 40-63 micron silica gel. Ether refers to diethyl ether.

Preparation of *anti* -1,2-diphenyl-2-hydroxyethyl(dimethyl)-sulfonium iodide 18a from *trans*-stilbene oxide

To a solution of *trans*-stilbene oxide **12** (1.0 g, 5.1 mmol) in absolute ethanol (5 ml) was added sodium thiomethoxide (0.7 g, 10.0 mmol). The resulting solution was heated under reflux for 1 h, stirred overnight at room temperature and then diluted with water (5–10 ml). The ethanol was removed *in vacuo* from the mixture which was then extracted with ethyl acetate (5 × 4 ml). The combined extracts were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the desired *anti*-hydroxy sulfide as an off-white solid (0.9 g, 3.7 mmol, 72%), mp 74.5–75.5 °C (lit.,[22] 74–75 °C). The hydroxy sulfide (0.9 g, 3.7 mmol) was stirred in methyl iodide (5.5 ml, 88 mmol) for 2 h after which the excess of methyl iodide was removed *in vacuo* and the resulting solid was washed with ether to give the desired sulfonium salt **18a** (0.84 g, 2.2 mmol, 59%) as an off-white solid, mp 154–156 °C (decomp.); ν_{max}/cm^{-1} (KBr disc) 3166 (OH), 2986, 2904 and 2800; δ_H[250 MHz; $(CD_3)_2SO$] 2.58 (3 H, s, SCH_3), 3.08 (3 H, s, SCH_3), 5.14 (1 H, d, *J* 4.0, OH), 5.52 [1 H, m, PhC*H*(R)OH], 6.74 [1 H, d, *J* 4.0, PhC*H*(R)SR] and 7.11–7.38 (10 H, m, Ph); δ_C[63 MHz; $(CD_3)_2SO$] 23.71 (CH_3), 24.25 (CH_3), 65.37 (CH), 70.33 (CH), 126.49 (CH), 127.99 (CH), 128.35 (CH), 129.17 (CH), 129.68 (C), 130.11 (CH), 131.06 (CH) and 140.45 (C); *m*/*z* (FAB) 259 ($M^+ - I$, 100%) and 197 ($M^+ - Me_2SI$, 36).

Preparation of *syn*-1,2-diphenyl-2-hydroxyethyl(dimethyl)-sulfonium iodide 20a from *cis*-stilbene oxide

To a solution of *cis*-stilbene oxide **14** (0.7 g, 3.8 mmol) in absolute ethanol (3 ml) was added sodium thiomethoxide (0.5 g, 7.1 mmol). The resulting solution was heated under reflux for 1 h after which the ethanol was removed *in vacuo* and the residue diluted with water and ether. After separation, the aqueous layer was extracted with further volumes of ether before the combined organic extracts were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the desired hydroxy sulfide as an orange oil (0.9 g, 3.7 mmol, 97%). The hydroxy sulfide (0.6 g, 2.4 mmol) was stirred in methyl iodide (4 ml, 60 mmol) for 2 h after which the excess of methyl iodide was removed *in vacuo* and the resulting solid was washed with ether to give the desired sulfonium salt **20a** (0.75 g, 1.9 mmol, 81%) as an off-white solid, mp 124–125 °C (decomp.) (Found: C, 49.65; H, 4.98; I, 32.79; S, 8.45. $C_{16}H_{19}IOS$ requires C, 49.88; H, 4.71; I, 32.94; S, 8.32%); ν_{max}/cm^{-1} (KBr disc) 3299 (OH), 3037, 2982 and 2903; δ_H[250 MHz; $(CD_3)_2SO$] 2.87 (3 H, s, SCH_3), 3.34 (3 H, s, SCH_3), 5.23 (1 H, d, *J* 10.0, OH), 5.47 [1 H, dd, *J* 10.0, 4.0, PhC*H*(R)OH], 6.90 [1 H, d, *J* 4.0, PhC*H*(R)SR], 7.14–7.32 (5 H, m, Ph) and 7.36–7.52 (5 H, m, Ph); δ_C[63 MHz; $(CD_3)_2SO$], 22.53 (CH_3), 26.79 (CH_3), 66.53 (CH), 73.42 (CH), 127.51 (CH), 128.73 (CH), 129.62 (CH), 129.84 (C), 130.49 (CH), 130.81 (CH) and 141.33 (C); *m*/*z* (FAB) 259 ($M^+ - I$, 100%) and 197 ($M - Me_2SI$, 26).

Preparation of *trans*-2-phenyl-3-cyclohexyloxirane 22

A solution of phenyldiazomethane (1.5 mmol) in dichloromethane (1 ml) was added over 6 h, *via* a syringe pump, to a stirred solution of cyclohexanecarbaldehyde (0.12 ml, 1 mmol), triphenylarsine (306 mg, 1 mmol) and copper acetonylacetate (13 mg, 0.05 mmol) in dichloromethane (1 ml). After being left overnight the mixture was evaporated *in vacuo* and the residue purified by chromatography, eluting with 50% dichloromethane in light petroleum (bp 45–60 °C) to give the *trans*-epoxide[7] **22** as a yellow oil (63 mg, 0.31 mmol, 31%); δ_H(250 MHz; $CDCl_3$) 0.76–2.09 (11 H, m, Cy), 2.76 (1 H, dd, *J* 6.8, 2.1, CyC*H*OR), 3.68 (1 H, d, *J* 2.1 PhC*H*OR) and 7.20 (5 H, m, Ph).

Preparation of *anti*-2-cyclohexyl-1-phenyl-2-hydroxyethyl-(dimethyl)sulfonium iodide 18b

To a solution of *trans*-2-phenyl-3-cyclohexyloxirane **22** (108 mg, 0.54 mmol) in absolue ethanol (1 ml) was added sodium thiomethoxide (76 mg, 1.08 mmol). The resulting solution was heated under reflux for 1 h, stirred overnight at room temperature and then diluted with water (5 ml). The ethanol was removed *in vacuo* from the mixture after which the residue was extracted with ethyl acetate (5 × 4 ml). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the desired hydroxy sulfide as an off-white solid (134.8 mg, 0.54 mmol, 100%). Treatment of this solid with methyl iodide (0.4 ml, 6.4 mmol) gave, after removal of the excess of methyl iodide *in vacuo* and trituration with diethyl ether, the desired sulfonium salt **18b** as a white solid (190.1 mg, 0.49 mmol, 90%), mp 144–146 °C (decomp.); ν_{max}/cm^{-1} (KBr disc) 3272 (OH), 2988, 2927 and 2851; δ_H[250 MHz; $(CD_3)_2SO$] 0.71–1.18 (6 H, m, Cy), 1.40–1.72 (4 H, m, Cy), 1.85–2.00 (1 H, m, Cy), 2.95 (3 H, s, SCH_3), 3.34 (3 H, s, SCH_3), 3.84 [1 H, m, PhC*H*(R)OH], 5.00 (1 H, d, *J* 3.0, OH), 6.22 [1 H, d, *J* 6.0, PhC*H*(R)SR], 7.45–7.55 (3 H, m, Ph) and 7.55–7.65 (2 H, m, Ph); δ_C[63 MHz; $(CD_3)_2SO$] 23.32 (CH_3), 23.84 (CH_3), 25.48 (CH_2), 26.16 (CH_2), 28.23 (CH_2), 29.39 (CH_2), 41.12 (CH), 64.15 (CH), 72.70 (CH), 129.59 (CH), 130.28 (C), 130.40 (CH) and 131.18 (CH); *m*/*z* FAB (265) ($M^+ - I$, 100%) and 203 ($M - Me_2SI$, 99).

Preparation of *anti*- and *syn*-2-cyclohexyl-1-phenyl-2-hydroxyethylsulfonium iodide 18b + 20b

To a solution of benzyl methyl sulfide (2.7 ml, 20 mmol) in dry tetrahydrofuran (13 ml) was added tetramethylenediamine (3 ml, 20 mmol) followed by BuLi (1.6 M solution in hexanes; 15 ml) at 0 °C under an atmosphere of nitrogen. After 30 min, the mixture was cooled to −78 °C and a solution of cyclohexanecarbaldehyde (2.43 ml, 20 mmol) in dry tetrahydrofuran (3 ml) was added to it. The solution was allowed to warm to room temperature overnight after which it was quenched with dilute hydrochoric acid (2 M; 40 ml). The aqueous layer was separated and extracted with ethyl acetate (3 × 25 ml) and the combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure. The crude product was purified by chromatography, eluting with 10% ether in light petroleum (bp 60–80 °C) to give the desired hydroxy sulfides as an inseparable mixture of diastereoisomers (4.06 g, 16.2 mmol, 81%). Treatment of this solid with methyl iodide (18 ml, 290 mmol) gave, after removal of the excess of methyl iodide *in vacuo* and trituration with diethyl ether, the desired sulfonium salts **18b**, **20b** as a white solid (3.0 g, 7.7 mmol, 66%), mp 108–110 °C (decomp.); ν_{max}/cm^{-1} (KBr disc) 3300 (OH), 2987, 2928 and 2552; δ_H[250 MHz; $(CD_3)_2SO$] 0.71–1.33 (12 H, m, Cy), 1.39–1.72 (8 H, m, Cy), 1.85–1.98 (2 H, m, Cy), 2.41^{syn} (3 H, s, SCH_3), 2.74^{syn} (3 H, s, SCH_3), 2.98^{anti} (3 H, s, SCH_3), 3.34^{anti} (3 H, s, SCH_3), 3.84^{anti} [1 H, m, PhC*H*(R)OH], 4.17^{syn} [1 H, dd, *J* 10, 6, PhC*H*(R)OH], 5.04^{anti} (1 H, d, *J* 3.0, OH), 5.09^{syn} (1 H, d, *J* 10.0, OH), 6.19 [2 H, m, PhC*H*(R)SR] and 7.43–7.65 (10 H, m, Ph); δ_C[63 MHz; $(CD_3)_2SO$] 21.86^{syn} (CH_3), 23.32^{anti} (CH_3), 23.84^{anti} (CH_3), 24.96^{syn} (CH_2), 25.48^{anti} (CH_2), 25.91^{syn} (CH_2),

26.16^{anti} (CH_2), 26.22^{syn} (CH_2), 26.27^{syn} (CH_2), 26.33^{syn} (CH_3), 28.22^{anti} (CH_2), 29.39^{anti} (CH_2), 29.94^{syn} (CH_2), 41.13^{anti} (CH), 64.13^{anti} (CH), 72.68^{anti} (CH), 74.05^{syn} (CH), 129.60^{anti} (CH), 129.98^{syn} (CH), 130.29^{anti} (C), 130.40^{anti} (CH), 130.46^{syn} (CH), 130.65^{syn} (CH), 130.69^{syn} (C), 131.18^{anti} (CH); *m*/*z* (FAB) 265 ($M^+ - I$, 100%) and 203 ($M - Me_2SI$, 98).

Preparation of 1-[methylsulfanyl(phenyl)methyl]cyclohexanol from cyclohexanone

To a solution of benzyl methyl sulfide (0.5 ml, 3.7 mmol) in dry tetrahydrofuran (3 ml) was added tetramethylenediamine (0.56 ml, 3.7 mmol) followed by BuLi (1.6 M solution in hexanes; 2.7 ml) at 0 °C under an atmosphere of nitrogen. After 30 min, the solution was cooled to −78 °C and cyclohexanone (0.383 ml, 3.7 mmol) was added to it. After being allowed to warm to room temperature overnight, the reaction mixture was quenched with dilute hydrochloric acid (2 M; 5 ml) and the aqueous layer was separated and extracted with ethyl acetate (3 × 10 ml). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude product. This was purified by chromatography, eluting with 5% ethyl acetate in light petroleum (bp 45–60 °C) to give the desired hydroxy sulfide as an oil (531.4 mg, 2.2 mmol, 61%) (Found: C, 71.20; H, 8.58; S, 13.68. $C_{14}H_{20}OS$ requires C, 71.14; H, 8.53; S, 13.56%); ν_{max}/cm^{-1} (thin film) 3474 (OH), 2931, 2857 and 1450; δ_H(250 MHz; $CDCl_3$) 1.27–1.83 (10 H, m, Cy), 1.88 (3 H, s, SCH_3), 3.72 [1 H, s, $MeSCHR_2$], 7.20–7.43 (5 H, m, Ph); δ_C(63 MHz; $CDCl_3$) 15.55 (CH_3), 21.74 (CH_2), 21.93 (CH_2), 25.56 (CH_2), 34.80 (CH_2), 36.09 (CH_2), 65.31 (CH), 73.51 (C), 127.27 (CH), 128.02 (CH), 129.80 (CH) and 139.07 (C); *m*/*z* (EI) 236 (M^+, 3%), 138 (100) and 91 (50).

Preparation of [1-hydroxycyclohexyl(phenyl)methyl]dimethylsulfonium iodide 15

Methyl iodide (1.5 ml) was added to 1-[methylsulfanyl(phenyl)methyl]cyclohexanol (531 mg, 2.2 mmol) and the mixture stirred for 2 h. The precipitate was then filtered off and washed with diethyl ether (3 × 5 ml) to leave the desired sulfonium salt **15** as a white solid (500 mg, 1.32 mmol, 59%), mp 158–160 °C (decomp.) (Found: C, 47.6; H, 6.2; S, 33.4; I, 8.7. $C_{15}H_{23}IOS$ requires C, 47.6; H, 6.1; S, 33.4; I, 8.5%); ν_{max}/cm^{-1} (KBr disc) 3333 (OH), 2986, 2940, 2925 and 2864; δ_H[250 MHz; $(CD_3)_2SO$] 1.13–1.97 (10 H, m, Cy), 2.72 (3 H, br s, SCH_3), 3.36 (3 H, br s, SCH_3), 4.95 (1 H, br s, ROH), 5.82 (1 H, br s, Me_2SCHR_2) and 7.30–8.00 (5 H, m, Ph); δ_C[63 MHz; $(CD_3)_2SO$] 21.64 (CH_2, Cy), 21.84 (CH_2, Cy), 24.39 (CH_3, SCH_3CH_3), 25.22 (CH_2, Cy), 25.57 (CH_3, SCH_3CH_3), 36.09 (CH_2, Cy), 37.53 (CH_2, Cy), 68.07 [CH, $PhCH(SMe_2)$], 74.16 (C, R_2COH), 128.70 (C, Ph), 129.29 (CH, Ph) and 130.37 (CH, Ph); *m*/*z* (EI) 236 ($M^+ - MeI$, 6%), 189 ($M^+ - Me_2SI$, 10) and 138 (100).

General procedure for the preparation of epoxides from sulfonium salts in dichloromethane

To a solution of the desired sulfonium salt (0.25 mmol) in dichloromethane (5 ml) was added aqueous sodium hydroxide (50% solution, 0.5 ml) and the resulting mixture was stirred overnight. It was then washed with water (3 × 5 ml), dried ($MgSO_4$), filtered and evaporated. The crude reaction mixture was analysed by NMR spectrometry to determine the ratios of epoxides produced.[23]

General procedure for the preparation of epoxides from sulfonium salts in dimethyl sulfoxide

To a solution of the desired sulfonium salt (0.13 mmol) in dimethyl sulfoxide (3 ml) was added sodium hydroxide (7.7 mg, 10.19 mmol). The mixture was stirred overnight, and then quenched with saturated aqueous ammonium chloride (added until the solution became pale yellow). After dilution with water, the solution was extracted with dichloromethane. The organic extract was washed with water, dried (Na_2SO_4) and evaporated *in vacuo*. The crude reaction mixture was analysed by NMR spectrometry to determine the ratios of epoxides produced.[23]

Reaction of dimethylsulfonium benzylide with aldehydes or ketones in the presence of *p*-nitrobenzaldehyde in dichloromethane

To a stirred solution of the aldehyde or ketone (1.75 mmol), *p*-nitrobenzaldehyde (264 mg, 1.75 mmol) and benzyldimethylsulfonium perchlorate[24] (252 mg, 0.87 mmol) in dichloromethane (13 ml) was added sodium hydroxide (41.8 mg, 1.05 mmol) and a few drops of water. The mixture was stirred overnight, after which it was diluted with water and the organic layer separated. This was evaporated *in vacuo*. NMR analysis of the crude reaction mixture showed the presence of *trans*-2-(*p*-nitrophenyl)-3-phenyloxirane[7,16] **25** but no other epoxide products; δ_H(250 MHz, $CDCl_3$) 3.85 (1 H, d, *J* 1.9, CH) and 3.98 (1 H, d, *J* 1.9, CH).[7,25]

Reaction of dimethylsulfonium benzylide with aldehydes or ketones in the presence of *p*-nitrobenzaldehyde in dimethyl sulfoxide

To a stirred solution of the aldehyde or ketone (0.4 mmol), *p*-nitrobenzaldehyde (60.4 mg, 0.40 mmol) and benzyldimethylsulfonium perchlorate[24] (50 mg, 0.20 mmol) in dimethyl sulfoxide (3 ml) was added sodium hydroxide (10.3 mg, 0.26 mmol). The mixture was stirred overnight, and then quenched with saturated aqueous ammonium chloride (added until the solution became pale yellow). After dilution with water, the solution was extracted with dichloromethane. The organic extract was washed with water, dried (Na_2SO_4) and evaporated *in vacuo*. NMR analysis of the crude reaction mixture showed the presence of *trans*-2-(*p*-nitrophenyl)-3-phenyloxirane[7,25] **25** but no other epoxide products; δ_H(250 MHz; $CDCl_3$) 3.85 (1 H, d, *J* 1.9, CH) and 3.98 (1 H, d, *J* 1.9, CH).[7,25]

General procedure for cross-over reactions in dichloromethane

To a solution of the desired sulfonium salt or salts (0.51 mmol) and *p*-nitrobenzaldehyde (231 mg, 1.53 mmol) in dichloromethane (15 ml) was added aqueous sodium hydroxide (50% solution; 0.8 ml) and the mixture was stirred overnight. After dilution with dichloromethane, the reaction mixture was washed with water and saturated aqueous ammonium chloride, dried ($MgSO_4$), filtered and evaporated to give the crude reaction mixture which was analysed by NMR spectrometry to determine the ratios of epoxides produced.[23]

General procedure for cross-over reactions in dimethyl sulfoxide

To a solution of the desired sulfonium salt or salts (0.13 mmol) and *p*-nitrobenzaldehyde (59 mg, 0.39 mmol) in dimethyl sulfoxide (3 ml) was added sodium hydroxide (7.7 mg, 0.19 mmol). The mixture was stirred overnight, and then quenched with saturated aqueous ammonium chloride (added until the solution became pale yellow). It was then diluted with water and extracted with dichloromethane. The organic extract was washed with water, dried (Na_2SO_4) and evaporated *in vacuo* to give a crude reaction mixture. This was analysed by NMR spectrometry to determine the ratios of epoxides produced.[23]

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