The Strain Limit in Intramolecular Nucleophilic Substitution

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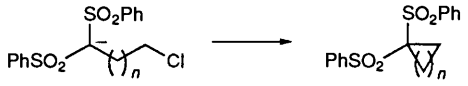
Kinetics and products of reactions of sulfonyl-stabilised carbanions bearing ω-leaving groups have been examined. The intention was to explore the upper limit of strain that can be tolerated for intramolecular nucleophilic substitution in these systems and the effect on enthalpy of activation for carbocycle formation.

In protic solvents, the upper limit of excess enthalpy differential (EED) between starting compound and product is *ca.* 160 kJ mol^{-1}. Above this limit, competing reactions, usually unactivated 1,2-elimination, supervene. As found in earlier work with less strained substrates, cyclisation to give three-membered rings is much faster than for four-membered rings.

In aprotic solvents in which substrates can be completely deprotonated, cyclisation to give very strained products can readily be achieved.

Formation of small rings by intramolecular nucleophilic substitution is a familiar process which has been subjected to much recent investigation.[1] Quantitative data show that for carbon[2] and sulfur[3] nucleophiles, relative rates of formation for the ring sizes are 3 ≫ 4 ≪ 5 > 6, although differing orders of reactivity are observed for oxygen and nitrogen nucleophiles.[4] For carbocycles, strain energies range from 0 in cyclohexane, to 115 kJ mol^{-1} for cyclopropane, yet this differential is clearly not manifest as a large factor in determining the relative rates of cyclisation of 1,1-bis(phenylsulfonyl) stabilised carbanions **1**.



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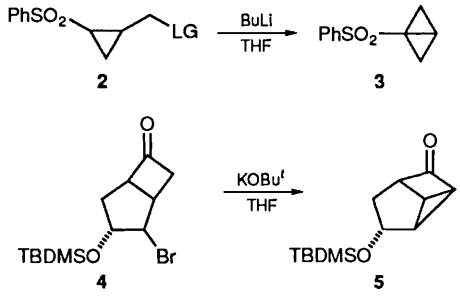
In this system, the range of activation enthalpies[2] spans 23 kJ mol^{-1} and shows little correlation with product strain energies; cyclopropane formation in such cases was demonstrated actually to have a *lower* $\Delta H^{\ddagger}$ than formation of the less strained cyclobutane. Transition structure calculations[5] for cyclisation and the experimental data[6] both suggest a high degree of ring formation in the transition structure for three-, as compared with four-membered and larger rings.

Whilst quantification of cyclisation processes that afford products more strained than cyclopropanes has not, to our knowledge, been previously addressed, there are several examples of carbanion-mediated cyclisations affording highly strained cyclic products. An intriguing example is that of bicyclobutane formation.[7] Factors relating to cyclisation of mesylate **2** (LG = OMes) were recently addressed from these laboratories[8] and competition between the formation of the highly strained 1,2- and 1,3-elimination products was observed. Highly strained products may readily be obtained *via* carbanion-mediated cyclisations (Scheme 1). Gaoni[7] showed that phenylsulfonyl-activated 1,3-elimination led to bicyclobutane **3** and the tricyclic ketone **5** may be formed *via* carbonyl-activated elimination from bromide **4**[9] (Scheme 1). Such observations raise the question of the general feasibility of cyclisations which involve an excess enthalpy differential (EED) greater than 115 kJ mol^{-1} (the value for formation of a cyclopropane from an acyclic starting material) between starting material and product.† We now report on this question using phenylsulfonyl stabilised carbanions potentially able to afford bicyclic or spiro compounds with high strain energies.[10]



Scheme 1

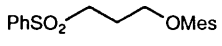
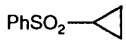
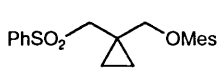
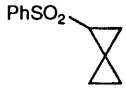
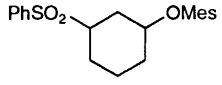
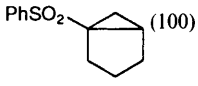
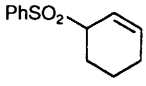
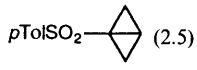
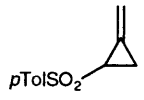
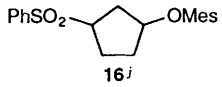
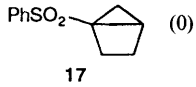
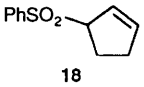
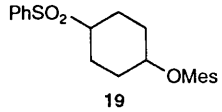
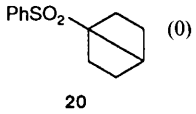
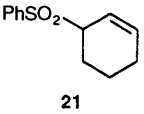
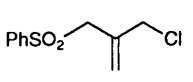
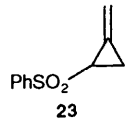
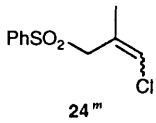
Results and Discussion

Substrates and Products.—Quantitative work was carried out on sulfone mesylates (Table 1). Synthesis of substrates not previously reported was accomplished by the routes in Scheme 2. Cyclopentane **16** and cyclohexane **10** were derived from the enones *via* conjugate addition of thiophenol and *in situ* borohydride reduction, followed by oxidation and mesylation. Cyclopropane **8** was derived from bis-ester **25** *via* the chloride and sulfide. Compounds **13**[11] and **22**[12] were prepared by literature routes. For the substrates in Table 1, carbanions were generated with potassium *tert*-butoxide in *tert*-butyl alcohol. All reactions except that of mesylate **13** and chloride **22** afforded either cyclisation or 1,2-elimination products quantitatively as determined by HPLC. Ring-closure reactions were second order, but kinetics were studied under pseudo-first-order conditions. Kinetic runs were followed by HPLC for both loss of starting material and appearance of product.

Mechanism.—Hydrogen–deuterium exchange experiments support pre-equilibrium formation of α-phenylsulfonyl-stabilised carbanions prior to 1,3-elimination. 'Half reaction' of **6** in Bu^tOK–Bu^tOD allowed recovery of **6** fully deuteriated α- to the phenylsulfonyl group and in the mesyloxy group. In the product **7**, C-1 deuteriation only was observed. The absence of deuterium incorporation at C-2 excludes a carbene-insertion mechanism for the cyclisation (Scheme 3).

† We define the excess enthalpy differential as the excess enthalpy difference between product and starting material, *i.e.*, for conversion of **2** into **3** the difference between bicyclobutane **3** (296 kJ mol^{-1}) and cyclopropane **2** (115 kJ mol^{-1}). In calculations of the excess enthalpy differential the assumption is made that excess enthalpies are independent of ring substitution.

Table 1 Cyclisation *versus* elimination for reactions of sulfones with potassium *tert*-butoxide in *tert*-butyl alcohol

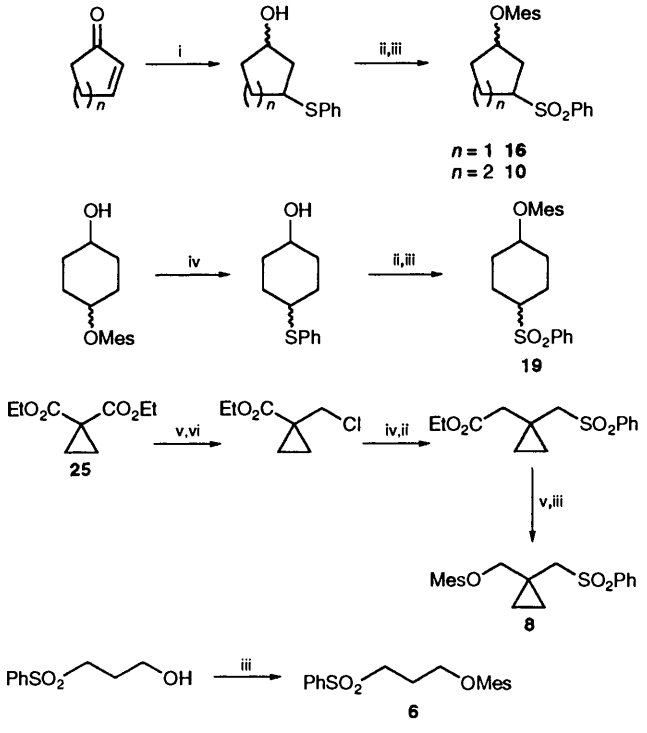
Substrate	Product[a] (%)		Rate constant, k^b				
	Cyclisation	Elimination	Cyclisation[c]	Elimination	$\Delta H^{\ddagger d}$	$\Delta S^{\ddagger e}$	EED[d]
 **6**	 (100) **7**		97	—	65	−46	115
 **8**	 (100) **9**		2.4	—	92	+13	158
 **10**[f]	 (100) **11**	 (0) **12**	0.87	—	97	+21	138
 **13**	 (2.5) **14**[g]	 (96) **15**	0.003[h,i]	0.08[h]	—	—	163
 **16**[j]	 (0) **17**	 (100) **18**	—	6.4[k]	—	—	210
 **19**	 (0) **20**	 (100) **21**	—	0.15[l]	—	—	210
 **22**	(0)  **23**	 (74) **24**[m]	—	—	—	—	171

[a] HPLC yield (unless stated otherwise). For isolated yields see Table 3. [b] 1 $^{-3}$ dm^3 mol^{-1} s^{-1} for reactions in Bu^{t}OK–Bu^{t}OH. [c] Extrapolated to 25 °C. [d] kJ mol^{-1} (for cyclisation) (see ref. 21). [e] J K^{-1} mol^{-1} (for cyclisation). [f] Identical results were obtained for a 9:1 mixture of *cis–trans* **10** as with pure *cis*. [g] Yield determined on the Bu^{t}OH adduct **28** (see the text). [h] At 27.9 °C. [i] Value for 2.5% of the reaction flux. [j] Identical results were obtained from a 3:1 mixture of isomers as from pure *cis* compound. [k] At 28.5 °C. [l] At 26.6 °C. [m] **24** is the product of isomerisation. The isolated yield is recorded.

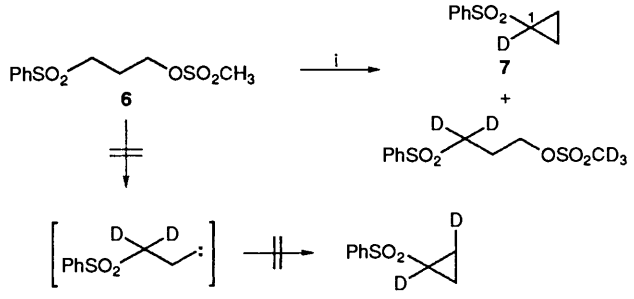
Substrates **10**, **16** and **19** can similarly be recovered fully deuteriated α- to the phenylsulfonyl group, showing α-hydrogen–deuterium exchange to be a far more rapid process than elimination. With reference to the pre-equilibria, the thermodynamic acidities of the systems are similar enough for comparisons despite the range of structural differences. For **6** we assume pK_a^{DMSO} *ca.* 31 as for ethyl phenyl sulfone[13] and no appreciable influence from the β-cyclopropyl group of substrate **8** is expected.[14] Comparisons of **13** with cyclopropyl phenyl sulfone (pK_a^{DMSO} 31.8[15]) and of **10**, **16** and **19** with phenyl 2-propyl sulfone (pK_a^{DMSO} 32[15]) are appropriate.

Pure *cis*-isomers of the cyclopentane **16** and cyclohexane **10** were isolated and used to establish that the rate of epimerisation to a thermodynamic mixture of epimers is much faster than elimination. Under the conditions used equilibration is complete within *ca.* 20 s for **16** and 90 s for **10** with the epimer ratios maintained to at least 90% of reaction.

Activation Parameters and Kinetic Data for Cyclisation and Elimination.—The results of Table 1 show that for comparison of cyclisation of **8** to **9** with the 'unstrained' comparator, cyclisation of **6** to **7**, there is 40-fold inhibition of formation of the more strained product by intramolecular nucleophilic substitution. This retardation is attributable to an increase in $\Delta H^{\ddagger}$ *versus* the 'unstrained' analogue and is manifest despite a change to a positive activation entropy. Cyclopropane **8** may also be considered in relation to *gem*-dialkyl substituted systems; it has been reported that for 1,3-cyclisations using ethoxide in ethanol as base, tosylate **26** equivalent to the 'unstrained' **6** cyclises 12 times more slowly than its *gem*-dimethyl substituted analogue **27** (Table 2).[16] This is a rather modest manifestation of the Thorpe–Ingold effect.[17] Activation parameters for tosylate **26** and mesylate **6** are similar ($\Delta H^{\ddagger}$ 69 *vs.* 65 kJ mol^{-1} and $\Delta S^{\ddagger}$ −38 *vs.* −46 J K^{-1} mol^{-1}) despite the structural and solvent differences. For conversion of **8** into **9**, $\Delta H^{\ddagger}$ falls midway between that for the 'normal' and *gem*-dimethyl substituted substrates, while $\Delta S^{\ddagger}$ is clearly less responsive at + 13 J K^{-1} mol^{-1}. The cyclopropyl group does not appear to act in a Thorpe–Ingold manner. We suggest that the origin of these effects may lie in the widening of the C1,2,3



Scheme 2 Preparation of phenylsulphonyl mesylates. *Reagents:* i, PhSH–Et_3N (5%)–$CHCl_3$, r.t., then $NaBH_4$–EtOH; ii, $(NH_4)_6Mo_2O_7$ (*ca.* 5%)–H_2O_2–MeOH; iii, CH_3SO_2Cl–Et_3N–CH_2Cl_2; iv, PhSNa–EtOH; v, BH_3Me_2S–THF, 66 °C; vi, SO_2Cl_2–CH_2Cl_2.



Scheme 3 *Reagents:* i, 0.5 mol KOBu^t per mole of **6** in Bu^{t}OD

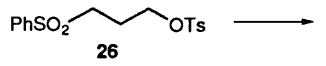
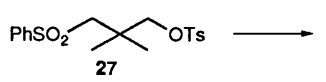
bond angle for **8** compared with **6** (110° to 118° *) while there is *diminution* of this angle on *gem*-dialkyl substitution (110° to 106°*) with a consequent effect on C1, C3 proximity.

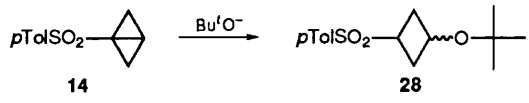
Conversion of **10** into **11** involves an EED comparable to that of **8** into **9** and the activation parameters are similar. The skeletal rigidity of **10** is presumably responsible for the more positive entropy of activation. That this is still smaller than that observed for *gem*-dialkyl substitution points to an entropic origin for the Thorpe–Ingold effect in three-membered-ring cyclisation.

At an EED limit for cyclisation of 163 kJ mol^{-1}, found for the conversion of **13** into **14**, cyclisation, followed by observation of the adduct **28**,[8] is a minor proportion of the reaction flux. Most of the product is methylenecyclopropane **15** derived from unactivated 1,2-elimination. Further increases in the EED for cyclisation, such as those that would be required for conversion of **16** into **17**, **19** into **20**, or **22** into **23** prevent the formation of cyclised products under protic base–solvent conditions. The rate constants for the observed eliminations are of the same

* Bond angle changes estimated from those for analogous systems (see ref. 18)

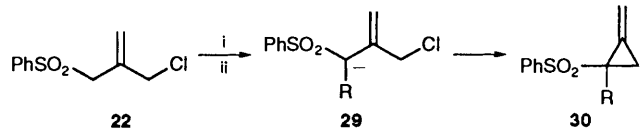
Table 2 The Thorpe-Ingold Effect in cyclisation of sulphonetosylates.[16]

Cyclisation	$\Delta H^{\ddagger}$ kJ mol^{-1}	$\Delta S^{\ddagger}$ J K^{-1} mol^{-1}
 **26**	69	−38
 **27**	115	+134



order of magnitude as for the 'strained' cyclisations. They appear to represent a balance between carbanion-mediated 1,3-eliminations for substrates with an EED (for cyclisation) of 160 kJ mol^{-1} or less and concerted 1,2-elimination for the others. This balance is held by the strain differential. It is noteworthy that cyclopentane **16** undergoes 1,2-elimination a modest seven times *faster* than cyclohexane **10** undergoes 1,3-elimination. It may be that 1,2-elimination is favoured in **16** because of antiperiplanar disposition of β-H and mesylate leaving group. Chloride **22** is incapable of 1,2-elimination and in Bu^{t}OK–Bu^{t}OH is observed to give the isomerised chloride **24**, as a mixture of *E* and *Z* isomers, along with intractable tars. We shall report on the behaviour of **22** and **24** with bases in hydroxylic solvents in a separate publication.

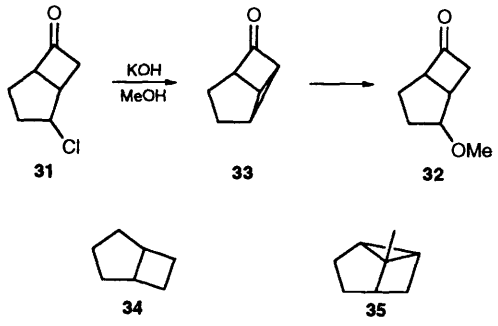
It must be stressed that an EED of 160 kJ mol^{-1} is not an intrinsic barrier to cyclisation. Appropriate base–solvent combinations allow conversions such as **2** into **3** (55–60%[7]) using butyllithium in THF and, in this work, we have found that similar conditions afford bicycle **14** from **13** and **17** from **16** (data in Table 3). A recent report also indicates that methylenecyclopropanes may be formed similarly from analogues of **22** providing that the α-position is mono-alkylated as in conversion of **22** into **30** *via* **29** (Scheme 4).[19]



Scheme 4 *Reagents:* i, 2BuLi–DMPU, −90 °C; ii, RHal (R = alkyl/benzyl) −30 °C ⟶ r.t.

Substrate **19** has not been induced to give the bicyclic product **20**. Using butyllithium in THF it is recovered on quenching; concerted 1,2-elimination is presumably suppressed under conditions of essentially complete conversion into the α-sulfonyl carbanion and it is tempting to suggest that a poorly favoured 1,4-elimination is also extremely slow or not feasible in a system of this type. In relation to this point it should be borne in mind that the C1–C4 through-space distance in the *chair*-form of this rather rigid system is *ca.* 3.7 Å compared with 2.5 Å for a C1–C3 distance. Presumably, reaction would only proceed through a more 'product like' boat form of cyclohexane with a C1–C4 distance of *ca.* 2.8 Å.

Literature examples (Scheme 1)[7,9,20] support our tentative limit for strain differential in cyclisations in hydroxylic solvents. For the conversion of **31** into **32** the EED for formation of the intermediate **33**[20] can be estimated to be 136 kJ mol^{-1}, from the strain energies of the skeletons **34**[21] and **35**,[22] and reaction occurs readily with methanolic potassium hydroxide.



In conclusion, our systems indicate that highly strained cyclopropanes may be formed by carbanion-mediated 1,3-eliminations in hydroxylic solvents provided that an apparent strain-energy differential of *ca.* 160 kJ mol^{-1} is not exceeded. For higher EED values, or larger ring sizes, competing reactions, notably unactivated 1,2-eliminations where these can occur, take precedence.

Experimental

General Directions.—Petrol refers to light petroleum b.p. 40–60 °C. Melting points are uncorrected. ^1H (250 and 400 MHz) and ^{13}C (62.9 MHz) NMR spectra were recorded in $CDCl_3$. For diastereoisomer mixtures, the major ^{13}C chemical shift is italicised. Extractions were with dichloromethane and extracts were dried over Na_2SO_4. Column chromatography refers to flash column chromatography performed on silica gel 60, 230–400 mesh (Merck). 3-(Phenylsulfonyl)propan-1-ol,[23] 1,1-bis(ethoxycarbonyl)cyclopropane **25**,[24] 2-(chloromethyl)-3-(phenylsulfonyl)-propene **22**,[25] 4-tosyloxycyclohexanol[26] and **13**[7] were prepared according to literature routes. Analytical data for substrates and products are in Table 3. *tert*-Butyl alcohol was dried over calcium hydride and distilled before use. Methanesulfonyl chloride was distilled under reduced pressure prior to use.

Kinetics.—Reactions were performed in dry *tert*-butyl alcohol under pseudo-first-order conditions with 1.0 mol dm^{-3} solutions of potassium *tert*-butoxide at known temperatures within the range 17.8–48.4 °C. Reactions were followed by removal of aliquot portions which were quenched (dilute aqueous hydrochloric acid) and submitted to reversed-phase HPLC, on a 5μ Spherisorb ODS (25 cm × 4.6 mm) column; UV detector at 254 nm; in acetonitrile–water, 40:60 v/v for **6** to **7**, **10** to **11** and **16** to **18** and 50:50 v/v for **13** to **14** and **15**, and **19** to **21**. Conversion of **8** into **9** necessitated normal-phase HPLC eluting with hexane–ethyl acetate, 65:35 v/v on 5μ Spherisorb silica (25 cm × 4.6 mm). Each quenched aliquot was extracted into 0.5 cm^3 of dichloromethane (HPLC grade) and injected directly onto the column.

The Reference System.—*1-Mesyloxy-3-phenylsulfonylpropane*, **6**. To a stirred solution of 3-(phenylsulphonyl)propan-1-ol (6.78 g, 33.86 mmol) in dry dichloromethane (55 cm^3) in a flame-dried flask under argon at *ca.* −15 °C were added, sequentially, dry triethylamine (15 cm^3, 10.89 g, 107.6 mmol) and mesyl chloride (3 cm^3, 4.44 g, 38.76 mmol). Stirring was continued for 10 h before careful dropwise addition of water. The organic layer was separated, washed with brine, dried (Na_2SO_4) and concentrated to an off-white semi-solid. Recrystallisation (petrol–ethyl acetate) yielded **6** (6.03 g, 64%), m.p. 48.5–50 °C, R_f 0.42 (petrol–ethyl acetate 1:1); ν_{max}/cm^{-1} 1300 and 1150; δ_H(250 MHz) 7.95–7.80 (2 H, m), 7.74–7.55 (3 H, m), 4.35 (2 H, t, *J* 6 Hz), 3.24 (2 H, t, *J* 8 Hz), 3.02 (3 H, s) and 2.29–2.17 (2 H, m); δ_C(62.9 MHz) 138.60, 133.79, 129.265, 127.72, 67.25, 52.01, 37.10 and 22.72; *m/z* (CI) 296 ($M + NH_4^+$, 20%), 183 ($M^+ - OSO_2CH_3$, 92), 137 ($M^+ - PhSO_2$, 94), 94 (75) and 77 (100).

Formation of Phenylsulfonylcyclopropane **7**.—To a stirred solution of **6** (0.458 g, 1.65 mmol) in dry THF (35 cm^3) under argon was added potassium *tert*-butoxide (3.1 cm^3 of a 1.9 mol dm^{-3} solution in THF, 3.1 mmol). TLC analysis indicated complete loss of starting material after 15 min. Saturated aqueous ammonium chloride (20 cm^3) was added and the whole was subjected to a normal dichloromethane work-up incorporating a brine wash, filtration through a silica pad, drying (Na_2SO_4) and concentration *in vacuo* to give an oil which slowly crystallised on standing. Recrystallisation (ethanol) gave **7** (0.26 g, 87%), m.p. 33–35 °C (lit.,[29] m.p. 35–36 °C), ν_{max}/cm^{-1} 1315 and 1150.

1-Mesyloxymethyl-1-phenylsulfonylmethylcyclopropane, **8**.—*Ethyl 1-(chloromethyl)cyclopropane-1-carboxylate*. To a stirred solution of ethyl 1-(hydroxymethyl)cyclopropane-1-carboxylate (13.2 g, 91 mmol) [prepared from bis(ethyloxycarbonyl)-cyclopropane **25** *via* reduction[31]] under argon, in chloroform (125 cm^3) at 0 °C was added freshly distilled thionyl chloride (12.8 g, 108 mmol). The temperature was allowed to slowly rise to room temperature, stirring was continued for 20 h and then the whole was quenched with saturated aqueous sodium hydrogen carbonate solution. Dichloromethane work-up, incorporating a brine wash followed by concentration and column chromatography yielded pure *chloride* (11.9 g, 80%) as a colourless oil; ν_{max}/cm^{-1} 2680 and 1725 (Found: C, 51.9; H, 7.0. $C_7H_{11}ClO_2$ requires C, 51.7; 6.8%).

Ethyl 1-phenylsulfonylmethylcyclopropane-1-carboxylate. Sodium (0.32 g, 13.33 mmol) was dissolved in ethanol (25 cm^3), followed by thiophenol (1.25 g, 1.17 mol, 11.35 mmol). After 15 min a solution of the chloride (1.68 g, 10.33 mmol) in ethanol (5 cm^3) was added and the whole was stirred at 25 °C for 16 h. The mixture was acidified with dilute hydrochloric acid. Dichloromethane work-up incorporating a brine wash, drying (Na_2SO_4), concentration under reduced pressure and column chromatography (petrol–ethyl acetate 17:3) produced pure *sulfide* (1.96 g, 81%) ν_{max}/cm^{-1} 1720 (Found: C, 65.9; H, 6.7. $C_{13}H_{16}O_2S$ requires C, 66.1; H, 6.8%).

To a stirred solution of the sulfide (1.96 g, 8.36 mmol) in methanol (35 cm^3) was added ammonium molybdate (0.31 g, 0.25 mmol) and hydrogen peroxide (2 cm^3 of a 29% w/v aqueous solution). Stirring was continued for 16 h. Work-up incorporating a brine wash, drying (Na_2SO_4) and concentration under reduced pressure gave a residue which, on recrystallisation (petrol–ethyl acetate), gave the *sulfone* (1.95 g, 88%), m.p. 55–57 °C; ν_{max}/cm^{-1} 1715, 1310 and 1145; δ_H 7.9–7.7 and 7.65–7.45 (2 × m, 5 H), 3.8 (2 H, q), 3.5 (2 H, s) and 1.4–1.0 (7 H, m) (Found: C, 58.4; H, 6.3. $C_{13}H_{16}O_4S$ requires C, 58.2; H, 6.0%).

1-Mesyloxymethyl-1-phenylsulfonylmethylcyclopropane, **8**. To a refluxing solution of the sulfone (1.95 g, 7.3 mmol) in dry THF (25 cm^3) under argon was added dropwise borane–dimethyl sulfide complex in dry THF (1.5 cm^3 of a 10.0 mol dm^{-3} solution, 15.0 mmol). The mixture was heated under reflux for 5 h. After cooling, water was carefully added dropwise, and the whole was then subjected to dichloromethane work-up incorporating a brine wash, followed by drying (Na_2SO_4) and concentration under reduced pressure. Column chromatography (petrol–ethyl acetate 17:3→7:3) yielded the *alcohol* (0.96 g, 68%) m.p. 65–67.5 °C; ν_{max}/cm^{-1} 3510, 1305 and 1150; *m/z* 227 (M + H, 9%) and 67 (100). (Found: C, 58.5; H, 6.3; S, 14.3. $C_{11}H_{14}O_3S$ requires C, 58.4; H, 6.25; S, 14.2%).

To a stirred solution of alcohol (960 mg, 4.94 mmol) in dry dichloromethane (25 cm^3) under argon at −15 °C was added, sequentially, dry triethylamine (1.45 g, 2 cm^3, 14.35 mmol) then

Table 3 Substrates and products

		Found (%)				Required (%)						Found (%)				Required (%)		
Substrate	M.p./°C	C	H	S	Formula	C	H	S	Product[a]	M.p./°C	Yield	C	H	S	Formula	C	H	S
6	48.5–5.50[b]	43.4	5.0	22.8	$C_{10}H_{14}O_5S_2$	43.2	5.1	23.0	**7**	33–35[c,d]	87							
8	90–91.5[b]	47.2	5.4		$C_{12}H_{16}O_5S_2$	47.4	5.3		**9**	54–55[b]	91	63.1	5.8	15.4	$C_{11}H_{12}O_2S$	63.4	5.8	15.4
10	Oil	47.3	5.4	20.9	$C_{12}H_{16}O_5S_2$	47.4	5.3	21.1	**11**	45–46.5[c]	91	64.5	6.2	14.4	$C_{12}H_{14}O_2S$	64.8	6.35	14.2
13	63–64[g]	47.1	5.5		$C_{12}H_{16}O_5S_2$	47.4	5.3		**15**	51–53[h]	96							
									28[i]	Oil	2.5	63.9	7.9		$C_{15}H_{22}O_3S$	63.8	7.85	
									14[e]	90–92[j]	79							
16	124–126[b,f]	48.9	5.6	20.2	$C_{13}H_{18}O_5S_2$	49.0	5.7	20.1	**18**	Oil	93	63.4	5.8		$C_{11}H_{12}O_2S$	63.4	5.8	
									17[e]	Oil	87	63.0	5.9		$C_{11}H_{12}O_2S$	63.4	5.8	
19	147–149.5[b]	49.1	5.6	20.0	$C_{13}H_{18}O_5S_2$	49.0	5.7	20.1	**21**	Oil	79	64.6	6.2	14.3	$C_{12}H_{14}O_2S$	64.8	6.35	14.4
22	55–56[k]	52.2	4.9	14.0	$C_{10}H_{11}ClO_5S_2$	52.1	4.8	13.9	**24**	110–112.5[c,l]	26[m]	52.1	4.6	18.8 15.4[n]	$C_{10}H_{11}ClO_2S$	52.1	4.8	13.9 15.4[n]

[a] Isolated yields from reactions with potassium *tert*-butoxide in *tert*-butyl alcohol unless otherwise stated. [b] From petrol–ethyl acetate. [c] From ethanol. [d] Lit. m.p. 35–36 °C (see ref. 27). [e] From reaction with buyllithium in THF. [f] As a 9:1 mixture of diastereoisomers. [g] From diisopropyl ether–hexane. [h] Lit. m.p. 47.5–48.5 °C (see ref. 28). [i] As a 2:1 mixture of *cis* and *trans* isomers. [j] From hexane. Lit. m.p. 91–92 (see ref. 29). [k] Lit. m.p. 54–55 °C (see ref. 30). [l] Single isomer recrystallised. For the mixture of isomers (2:1) we get m.p. 93–95 °C. Lit. m.p. for an unspecified mixture of isomers 85–87 °C (see ref. 30). [m] Isolated yield for single isomer. 74% recovery for isomer mixture. [n] Analysis for chlorine.

mesyl chloride (0.57 g, 0.38 ml, 4.98 mmol). Stirring was continued for 8 h before dilution with dichloromethane and filtration. The filtrate was carefully treated with water, the organic layer was separated, dried (Na_2SO_4) and concentrated to a viscous oil that solidified upon standing. Recrystallisation (petrol–ethyl acetate) yielded the title compound **8** (1.15 g, 77%), m.p. 90–91.5 °C; δ_H(250 MHz) 7.95–7.83 (2 H, m) and 7.74–7.55 (3 H, m), 4.39 (2 H, s), 3.20 (2 H, s), 0.79–0.71 and 0.69–0.60 (4 H, 2 × m); δ_C 139.84, 133.88, 129.33 and 127.89, 74.80, 59.42, 37.27, 15.58 and 11.16; *m/z* (CI) 304 (M^+, 22%), 209 (M^+ − OMes, 36), 163 (M^+ − $PhSO_2$, 47), 77 (23) and 67 (100).

Formation of the spiropentane **9**.—To a solution of **8** (129.9 mg, 0.43 mmol) in dry THF (5 cm^3) at room temperature under argon was added a solution of potassium *tert*-butoxide (0.45 cm^3 of a 1.0 mol dm^{-3} solution in THF, 0.45 mmol). Stirring was continued for 16 h before the addition of saturated aqueous ammonium chloride solution (10 cm^3). Dichloromethane work-up incorporating a brine wash followed by drying (Na_2SO_4) and concentration yielded an oil which solidified on refrigeration to give phenylsulfonylspiropentane **9** (81 mg, 91%), m.p. 54–55 °C from petrol-ethyl acetate; δ_H(250 MHz) 7.92–7.86 (2 H, m) and 7.68–7.51 (3 H, m), 2.82 (1 H, dd, *J* 7 and 5 Hz), 1.78 (1 H, t, *J* 5 Hz), 1.48 (1 H, dd, *J* 7 and 5 Hz), 1.29–1.12 (2 H, m) and 0.94–0.83 (2 H, m); δ_C 141.25, 133.15, 129.11, 127.29, 38.85, 15.22, 12.68, 5.48 and 4.83; *m/z* (CI) 209 (M + H^+, 17%), 77 (48%) and 67 (M^+ − SO_2Ph, 100).

1-*Mesyloxy*-3-*phenylsulfonylcyclopentanol* **16** *and Reactions with Base*.—3-*Phenylthiocyclopentanol*. To a stirred solution of cyclopent-2-enone (9.85 g, 10.05 cm^3, 120 mmol) in dry chloroform (200 cm^3) at room temperature under argon were added triethylamine (0.73 g, 1 cm^3, 7.17 mmol) and thiophenol (13.41 g, 12.5 cm^3, 122 mmol). The mixture was stirred for 18 h when TLC indicated complete loss of starting material. Sodium borohydride (2.01 g, 53.13 mmol) in ethanol (100 cm^3) was then added. The mixture was stirred for 10 min, quenched with saturated aqueous ammonium chloride and extracted with dichloromethane. Concentration, *in vacuo*, of the organic extract yielded a residue which, on column chromatography (petrol–ethyl acetate 1:1→1:2), yielded 3-phenylthiocyclopentanol as an oil (9.17 g, 39%); R_f, 0.12 (petrol–ethyl acetate 1:1); ν_{max}/cm^{-1} 3325; δ_H(250 MHz) 7.42–7.11 (5 H, m), 4.51–4.41 (0.2 H, m), 4.39–4.28 (0.8 H, m), 3.90–3.76 (0.2 H, m), 3.68–3.56 (0.8 H, m), 2.42–2.25 (1 H, m) and 2.20–1.51 (6 H, m);* δ_C 136.27, *130.25*/130.00, 128.66, *126.16*/125.94, *72.94*/72.59, *44.03*/43.65, 42.96/*42.52*, *34.73*/34.29 and 31.27; *m/z* (EI) 194 (M^+, 27%) and 110 (100) (Found: C, 67.9; H, 7.1; S, 16.3. $C_{11}H_{14}OS$ requires: C, 68.0; H, 7.3; S, 16.5%).

3-*Phenylsulfonylcyclopentanol*. To a stirred solution of 3-phenylthiocyclopentanol (7.96 g, 40.97 mmol) in methanol (100 cm^3), at −10 °C, were added ammonium molybdate (0.5 g, 0.41 mmol) in water (8 cm^3), and aqueous hydrogen peroxide solution (15 cm^3 of a 27.5% w/v solution, 127 mmol). The mixture was stirred (16 h) and quenched with aqueous (10%) sodium metabisulphite solution. Extraction and column chromatography (petrol–ethyl acetate 2:1→1:2) yielded the *sulfone* as an oil (8.22 g, 88%); ν_{max}/cm^{-1} 3425, 1295 and 1145; δ_H(250 MHz) 7.93–7.52 (5 H, m), 4.52–4.43 [m, 0.2 H, C(1′)H], 4.37–4.26 [0.8 H, m, C(1)H], 3.87–3.72 [0.2 H, m, C(3′)H], 3.69–3.54 [0.8 H, m, C(3)H], 2.65 (1 H, br s), 2.40–1.65 (6 H, m);* δ_C 138.03, *133.61*/133.39, *129.14*/129.05, 128.26, 128.09, 72.50/*72.22*, *62.75*/62.37, 36.24/*35.82*, *34.97*/34.28 and *24.37*/24.15; *m/z* (CI) 244 (M + NH_4^+, 100%), 227 (M + H^+, 98), 209 (M^+ − H_2O, 18) (Found: C, 58.3; H, 6.2; S, 13.9. $C_{11}H_{14}O_3S$ requires: C, 58.4; H, 6.2; S, 14.2%).

1-*Mesyloxy*-3-*phenylsulfonylcyclopentane* **16**. To a stirred solution of the sulfone alcohol (6.98 g, 30.85 mmol) in dry dichloromethane (50 cm^3) in a flame-dried flask under argon, were added successively at 0 °C dry triethylamine (3.63 g, 5 cm^3, 35.87 mmol) and methanesulfonyl chloride (4.44 g, 3 cm^3, 38.76 mmol). After 3 h, TLC analysis indicated complete loss of starting material and the reaction was quenched by dropwise addition of water. Extraction, concentration *in vacuo* and chromatographic purification (petrol–ethyl acetate 4:6) gave **16** as an oil, R_f 0.57/0.59 (petrol–ethyl acetate 4:6) (7.32 g, 78%); ν_{max}/cm^{-1} 1300 and 1145; δ_H(250 MHz) 7.94–7.88 (2 H) and 7.73–7.55 (3 H, m), 5.30–5.23 (0.25 H, m), 5.17–5.08 (0.75 H, m), 3.84–3.68 (0.25 H, m), 3.62–3.46 (0.75 H, m), 3.03 (2.25 H, s), 2.99 (0.75 H, s), 2.49–1.88 (6 H, m);† δ_C 138.26, 133.77, 129.33/*129.28*, *128.44*/128.26, 82.98/*80.19*, 61.89, *38.58*/38.34, 34.77/*33.50*, *32.72*/32.67 and *24.92*/24.22; *m/z* (CI) 322 (M + NH_4^+, 100%).

Reactions of 1-*Mesyloxy*-3-*phenylsulfonylcyclopentane* **16** *with Base*.—(*a*) *With potassium* tert-*butoxide in* tert-*butyl alcohol*. To a stirred solution of **16** (0.54 g, 1.77 mmol) in *tert*-butyl alcohol (25 cm^3) and THF (3 cm^3) at 20 °C was added potassium *tert*-butoxide (2.3 cm^3 of a 1.0 mol dm^{-3} solution in THF). The mixture was stirred under argon and when TLC analysis indicated formation of a single new product, the reaction was quenched with saturated aqueous ammonium chloride, extracted and concentrated *in vacuo*. ^1H NMR analysis of the crude products showed 1,2-elimination to form 2-phenylsulfonylcyclopentene **18** (0.345 g, 93%); R_f 0.82 (petrol–EtOAc, 4:6) ν_{max} 1300, 1145 cm^{-1}; δ_H(250 MHz) 7.92–7.86 (2 H, m) and 7.69–7.50 (3 H, m), 6.15–6.08 (1 H, m), 5.70–5.64 (1 H, m), 4.33–4.24 (1 H, m) and 2.55–2.08 (4 H, m); δ_C 140.06, 138.00, 133.46, 128.89, 128.77, 123.56, 72.19, 31.71 and 24.28; *m/z* (EI) 208 (M^+, 3%), 143 and 67 ($C_5H_7^{+\bullet}$, 100).

(*b*) *With Butyllithium in THF*. To a stirred solution of **16** (0.50 g, 1.64 mmol) in dry THF, in a flame dried flask under argon at −10 °C was added butyllithium (1.5 cm^3 of a 1.34 mol dm^{-3} solution in hexanes, 2.01 mmol). After 5 min the mixture was quenched with saturated aqueous ammonium chloride. Extraction and examination of the crude product showed quantitative formation of 1-phenylsulfonylbicyclo[2.1.0]pentane **17**. Chromatography (petrol–ethyl acetate 4:6) yielded **17** as an oil (0.30 g, 87%), R_f 0.76 (petrol–ethyl acetate 4:6); ν_{max}/cm^{-1} 1300 and 1150; δ_H(250 MHz) 7.90–7.83 (2 H, m), 7.68–7.51 (3 H, m), 2.68–2.61 (1 H, m), 2.53 (1 H, tdd, *J* 11, 4 and 2 Hz), 2.28–2.13 (1 H, m), 1.82 (1 H, m), 1.69–1.59 (1 H, m), 1.40 (1 H, m) and 1.25 (1 H, dd, *J* 4.75 and 2.5 Hz); δ_C 139.695, 133.05, 129.02, 127.45, 40.09, 25.16, 22.14, 21.79 and 20.00; *m/z* (EI) 208 (M + NH_4^+, 100%).

1-*Mesyloxy*-3-*phenylsulfonylcyclohexane* **10**.—Using procedures similar to those above for **16**, starting from cyclohex-2-enone (53 mmol) was obtained 3-*phenylsulfonylcyclohexanol* as a viscous oil (10.84 g, 86% from cyclohexenone), R_f, 0.15 (petrol–ethyl acetate 9:11); ν_{max}/cm^{-1} 3400, 1300 and 1140; δ_H(250 MHz) 7.91–7.80 (2 H, m) and 7.73–7.48 (3 H, m), 3.66–3.49 (0.85 H, m), 3.49–3.33 (0.15 H, m), 3.02–2.88 (1 H, m), 2.37–2.22 (1 H, m), 2.19–1.55 (4 H, m) and 1.50–1.08 (4 H, m); δ_C 136.81, *133.60*/133.44, *128.99*/128.92, *128.81*/128.71, *68.98*/64.78, *61.76*/58.29, *34.15*/31.57, *34.08*/31.22, *24.95*/22.45 and *22.46*/18.51; *m/z* (CI) 258 (M + NH_4^+, 22%) and 241 (M + H^+, 100%) (Found: C, 59.5; H, 6.6. $C_{12}H_{16}O_3S$ requires: C, 60.0; H, 6.7%).

1-*Mesyloxy*-3-*phenylsulfonylcyclohexane* **10**. To a stirred solution of 3-(phenylsulfonyl)cyclohexanol (10.04 g, 41.78 mmol) in dry dichloromethane (65 cm^3) in a flame dried flask at −15 °C under argon was added dry triethylamine (4.65 g,

* Diastereiosomer ratio *ca.* 80:20 determined at C(1)H and C(3)H.
† Diastereoisomer ratio *ca.* 75:25 determined at C(1)H and C(3)H.

6.4 cm^3, 45.92 mmol), followed by methanesulfonyl chloride (5.18 g, 3.5 cm^3, 45.22 mmol). Stirring was continued for 4 h and the reaction was quenched by the slow addition of water and extracted to give a semi-solid. Column chromatography (petrol–ethyl acetate 1:1) afforded **10** (8.53 g, 64%) as an oil, which crystallised on standing, m.p. 124–126 °C (ethanol); ν_{max}/cm^{-1} 1340 and 1140; δ_H(400 MHz) 7.90–7.82 (2 H, m), 7.72–7.66 (1 H, m) and 7.64–7.55 (2 H, m), 5.15–5.10 [0.15 H, m, C(1)H minor isomer], 4.57 [0.85 H, tt, *J* 12 and 4 Hz, C(1)H major isomer], 3.10–2.95 [4 H, m including 3.02 (s, SO_2CH_3 major isomer) and 2.99(s)] 2.80–2.46 (0.85 H, m), 2.44–2.37 (0.15 H, m), 2.21–2.14 (1 H, m), 2.11–1.94 (2 H, m), 1.86–1.74 (1 H, m) and 1.60–1.22 (3 H, m);* δ_C 136.645, *133.96*/133.85, 129.23, *128.92*/128.83, *78.38*/76.86, *61.21*/58.02, *38.81*/38.56, *31.89*/30.15, *31.68*/29.89, 24.35/*24.16* and *22.23*/18.70; *m/z* (CI) 336 (M + NH_4^+, 100%), 240 (80), 223 (40) and 81 (61).

Bicyclo[3.1.0]*hexane* **11**.—To a stirred solution of **10** (0.595 g, 1.87 mmol) in dry THF (20 cm^3) at room temperature was added potassium *tert*-butoxide (2 cm^3 of a 1.0 mol dm^{-3} solution in THF, 2.0 mmol). TLC analysis after 2 h showed complete conversion. The mixture was quenched with saturated aqueous ammonium chloride and extraction and concentration under reduced pressure gave an oil, short column filtration of which gave **11** (0.41 g, 90%), m.p. 45–46.5 °C, R_f 0.66 (petrol–ethyl acetate 9:11); ν_{max}/cm^{-1} 1300 and 1130; δ_H(250 MHz) 7.90–7.80 (2 H, m) and 7.65–7.45 (3 H, m), 2.32–2.21 (1 H, m), 2.18–2.07 (1 H, m), 1.87–1.66 (4 H, m), 1.61 (1 H, ddd, *J* 9, 6 and 2 Hz), 1.33–1.18 (1 H, m) and 0.96 (1 H, t, *J* 6 Hz); δ_C 139.76, 132.99, 128.91, 127.93, 48.28, 27.34, 26.55, 26.39, 21.38 and 13.21; *m/z* (EI) 222 (M^+, 13%).

Reactions of **13** *with Base*.—(*a*) Treatment of **13** (1.5 g, 49 mmol) with potassium *tert*-butoxide (0.1 mol dm^{-3} in *tert*-butyl alcohol, 10 equiv) at 20 °C for 6 h gave, after dichloromethane work-up and column chromatography, **15** (0.98 g, 96%), m.p. 51.5 °C.

(*b*) Treatment of **13** (0.5 g, 16.4 mmol) in THF (20 cm^3) at 0 °C with butyllithium (2 cm^3, of a 1.0 mol dm^{-3} solution in hexanes) for 5 min followed by quenching with saturated aqueous ammonium chloride solution, dichloromethane extraction and chromatography gave **14** (0.27 g, 79%), m.p. 90–92 °C.

Treatment of **14** (0.11 g, 0.52 mmol) in dry THF with potassium *tert*-butoxide (10 equiv.) under reflux for 3 h afforded **28** as a mixture of *cis* and *trans* isomers in a ratio of 2:1; δ_H *cis* **28** 7.8 and 7.2 (4 H, d and d), 3.9 (1 H, m), 3.2 (1 H, m), 2.7–2.3 (7 H, m) and 1.1 (9 H, s); δ_H *trans*-**28** 7.8 and 7.2 (4 H, d and d), 4.4 (1 H, m), 3.2 (1 H, m), 2.7–2.3 (7 H, m) and 1.1 (9 H, s). Column chromatography afforded *cis* **28**, m.p. 52–53 °C (pentane); *m/z* (EI) 283 (M + H^+, 100%).

trans-1-*Mesyloxy*-4-*phenylsulfonylcyclohexane* **19**.—cis- *and* trans-4-*phenylthiocyclohexanol*. Thiophenol (12.88 g, 12 cm^3, 116.9 mmol) was added to a stirred solution of sodium ethoxide in ethanol, prepared by dissolving sodium (2.7 g, 117 mmol) in ethanol (150 cm^3) in a flame-dried flask under argon. Stirring was continued for 15 min. before the addition of *cis*- and *trans*-4-mesyloxycyclohexan-1-ol[26] (31.4 g, 116 mmol). Stirring was continued for 16 h. Acidification of the reaction mixture with dilute hydrochloric acid, followed by extraction, drying (Na_2SO_4) and concentration under reduced pressure produced crude sulfide contaminated by starting material. Column chromatography afforded sulfide (2.67 g, 11%, 36% based on recovered monomesylate) as an oil, ν_{max}/cm^{-1} 3500 (Found: C, 69.4; H, 7.7. $C_{12}H_{16}OS$ requires C, 69.2; H, 7.7%), followed by starting material (22.04 g, 70%).

trans-4-*Phenylsulfonylcyclohexanol*. To a stirred solution of 4-phenylthiocyclohexanol (2.05 g, 0.84 mmol) in methanol (45 cm^3) was added ammonium molybdate (0.25 g, 0.21 mmol) in water (5 cm^3), followed by aqueous hydrogen peroxide (7 cm^3 of a 29% w/v solution, 59.7 mmol) at 0 °C. After 16 h, the reaction was quenched with aqueous sodium metabisulfite. Extraction and column chromatography afforded successively: starting material (0.30 g, 13%) as a single diastereoisomer (^1H NMR) followed by trans-4-*phenylsulfonylcyclohexanol* (1.3 g, 54%, 62% based on recovered starting material) as an oil, R_f 0.22 (petrol–ethyl acetate 9:11); ν_{max}/cm^{-1} 3400, 1290 and 1140 cm^{-1}; *m/z* (EI) 241 (M^+ + H, 18%) and 223 (M^+ + H − H_2O, 22) (Found: C, 60.2; H, 6.9. $C_{12}H_{16}O_3S$ requires C, 60.0; H, 6.7%).

1-*Mesyloxy*-4-*phenylsulfonylcyclohexane* **19**. To a stirred solution of the preceding sulfone (0.85 g, 3.54 mmol) in dry dichloromethane (25 cm^3) at −10 °C in a flame-dried flask under argon was added dry triethylamine (1.45 g, 2 cm^3, 14.35 mmol) and methanesulfonyl chloride (0.74 g, 0.5 cm^3, 6.46 mmol). After stirring for 6 h, the reaction was quenched with water. Extraction and concentration under reduced pressure yielded crude product recrystallisation of which (petrol–ethyl acetate) gave the trans-*mesylate* **19** (0.58 g, 52%), m.p. 147–149.5 °C, R_f 0.23 (petrol–ethyl acetate 9:11); ν_{max}/cm^{-1} 1320, 1300, 1150 and 1130; δ_H(250 MHz) 7.92–7.81 (2 H, m) and 7.75–7.50 (3 H, m), 4.98 (1 H, appears as broad quintet) 3.02 (3 H, s), 3.00–2.88 (1 H, m), 2.30–2.18 (2 H, m), 2.02–1.81 (4 H, m) and 1.64–1.49 (2 H, m); δ_C 137.13, 133.77, 129.16, 128.93, 79.485, 61.76, 38.72, 29.78 and 19.70; *m/z* (CI) 336 (M + NH_4^+, 35%), 223 (12), 143 (35) and 81 (100).

Reactions of **19** *with Base*.—(*a*) Reaction of **19** with potassium *tert*-butoxide as before afforded 4-phenylsulfonylcyclohexene, **21** (0.31 g, 79%), as an oil, R_f 0.69 (petrol–ethyl acetate 1:1); ν_{max}/cm^{-1} 1300 and 1145 cm^{-1}; $\delta_H(CDCl_3)$ 7.95–7.80 (2 H, m) and 7.75–7.47 (3 H, m), 5.73–5.68 (2 H, m), 3.24–3.11 (1 H, m), 2.33–2.04 (5 H, m) and 1.74–1.57 (1 H, m); *m/z* (CI) 240 (M + NH_4^+, 100%), 223 (M + H^+, 14), 143 (13), 125 (17) and 81 (38).

(*b*) Reaction of **19** with butyllithium in THF as before gave quantitative recovery of starting material.

Reactions of 2-*Chloromethyl*-3-*phenylsulfonylprop*-1-*ene*, **22**, *with* tert-*butoxide*.—To a stirred solution of **22** (0.71 g, 3.09 mmol) in *tert*-butyl alcohol (50 cm^3) was added potassium *tert*-butoxide (3.3 cm^3, 3.3 mmol). The mixture was stirred at 20 °C for 4 h before addition of saturated aqueous ammonium chloride. Extraction and concentration yielded a residue (0.51 g, 74%) recrystallisation (petrol–ethyl acetate) of which afforded **24a**, m.p. 110–112.5 °C (0.18 g, 26%); ν_{max}/cm^{-1} 1300 and 1150; δ_H 7.95–7.82 (2 H, m), 7.71–7.50 (3 H, m), 5.80–5.79 (1 H, m), 3.79–3.77 (2 H, m) and 1.92–1.90 (3 H, m) (NOE experiments failed to assign the stereochemistry); δ_C 138.24, 133.90, 129.16, 128.36, 127.21, 122.05, 63.28 and 17.22; *m/z* (CI) 248/250 (M + NH_4^+, 100%).

In the ^1H NMR spectrum of crude **24**, additional signals are seen at δ_H 5.97, 4.02 and at 1.95 for the minor isomer **24b**.

* Diastereoisomer ratio determined from C(1)H and OSO_2CH_3 resonances 85:15. Major diastereoisomer determined as *cis*.

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