The scope and limitation of the [1,4]-SPh shift in the synthesis of allylic alcohols †

Varinder K. Aggarwal,[a,b] Jason Eames,*[a,c] Maria A. de las Heras,[a] Sara McIntyre[a] and Stuart Warren*[a]

[a] *University Chemical Laboratory, Lensfield Road, Cambridge, UK CB2 1EW*
[b] *School of Chemistry, University of Bristol, Bristol, UK BS8 1TS*
[c] *Department of Chemistry, Queen Mary, University of London, Mile End Road, London, UK E1 4NS*

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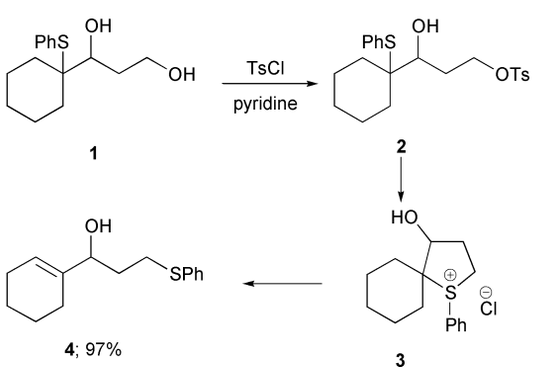
Treatment of a series of 4-phenylsulfanyl-1,3-diols with toluene-*p*-sulfonyl chloride in pyridine gives stereospecifically substituted allylic alcohols in near quantitative yield *via* a [1,4]-SPh shift. We comment on the structural variation at both the migration origin and terminus on the outcome of the title reaction and define its limits.

[1,4]-SR Participation by a sulfur atom *via* a five-membered sulfonium ion intermediate is a well documented effect.[1] The majority of attention has been concerned with the rate of acceleration of simple substitution reactions.[2] Very little is known[3] about the acceptable substitution pattern for such reactions or the product diversity and distribution. It is even rarer that such reactions have been used in synthesis.[4]

We have previously shown that the treatment of the 4-PhS-1,3-diol **1** with toluene-*p*-sulfonyl chloride (TsCl) in pyridine gave instead of the expected tosylate **2**, the allylic alcohol **4** in 97% yield, presumably *via* the sulfonium ion **3** and a [1,4]-SPh shift (Scheme 1).[5] We now report on the rearrangement of



Scheme 1

related 4-PhS-1,3-diols with TsCl in pyridine[6] with structural variation at both the migration origin and terminus and the synthesis of allylic alcohols. We comment on stereochemical effects, structural variation and the Thorpe–Ingold effect[7] on the efficiency and outcome of the reaction. We also disclose methods that allow the isolation of primary tosylate analogues.

The four possible products from this spirocyclic sulfonium salt **3** are the allylic alcohol **4** (by elimination *exo* to the sulfonium ring with [1,4]-SPh shift),[8] the ketone **5** (by *endo* elimination with [1,4]-SPh shift), the rearranged chloride **6** (substitution at the migratory origin with [1,4]-SPh shift), and the unrearranged chloride **7** (substitution at what would be the migratory terminus, but with no SPh migration) (Scheme 2).

The required 4-phenylsulfanyl-1,3-diols **12**, *anti*- and *syn*-**15**, **18**, **21**, **23**, **25**, **27**, **30**, *anti*- and *syn*-**32**, *anti*-**34** and *anti*,*anti*-**38,** *syn* and *anti*-**47**, **60**, **61** and *syn*-**62** for this study were all prepared using known stereoselective aldol methodology with α-PhS substituted aldehydes and most have been reported previously.[9]

We first established, by the rearrangement of the alcohol **12**, that a secondary hydroxy group is unnecessary. This alcohol **12** was synthesised using a two step procedure: refluxing the stabilised Wittig reagent **9**[10] with the aldehyde **8** gave exclusively the (*E*)-enoate **10** in excellent yield (Scheme 3). Non-regioselective reduction with $LiBH_4$ gave the required alcohol **12** in 24% and the allylic alcohol **11** in 74% yield. Treatment of **12** with TsCl in pyridine gave the cyclohexene **14** in 93% yield, by simple *exo*-elimination *via* the sulfonium ion intermediate **13** (Scheme 3).

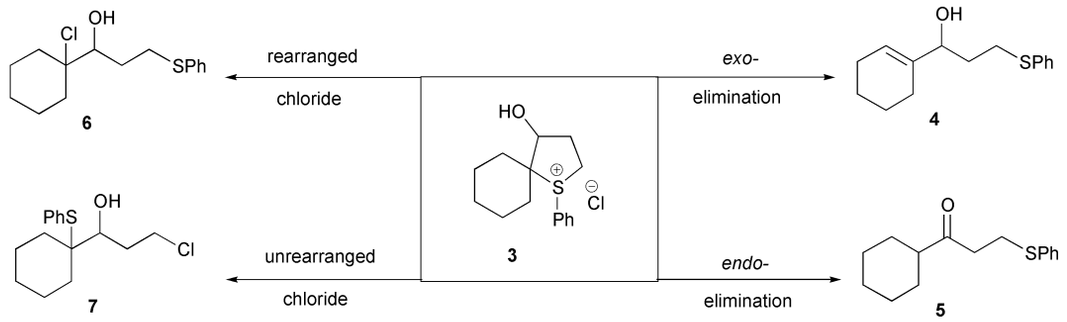
The rearrangement of more substituted cases, like *anti*- and *syn*-1,3 diols **15** occurred as efficiently as the unsubstituted case **12** giving the *anti*- and *syn*-allylic alcohols **17** in excellent yield. The [1,4]-SPh participation occurs independent of the developing stereochemistry within the sulfonium salt: *anti*-diol **15** gives the *anti*-allylic alcohol **17** stereospecifically *via* the sulfonium salt *syn*-**16**, while the *syn*-diol **15** gives the *syn*-allylic alcohol **17** *via* the sulfonium salt *anti*-**16** (Scheme 4).

The effect of ring strain in such sulfonium intermediates as **3** was found to be more dependent on the size of the adjacent spirocarbocyclic ring than on the substitution pattern of the sulfonium ion: the five-membered ring compounds *anti*- and *syn*-**18**, **21** and **23** rearranged in the same way as the six-membered ring compounds to give the allylic alcohols *anti*- and *syn*-**20**, **22** and **24**. The reaction occurs irrespective of whether there is a similar OH group **21**, *gem*-dimethyl groups **23**, or two substituents (OH and Me) on adjacent carbon atoms arranged *anti*- or *syn*- around the sulfonium salt **19** (Scheme 5). A larger medium ring behaves in the same way; treatment of the cyclodecane **25** gave the (*E*)-allylic alcohol **26** in good yield. The (*E*)-stereochemistry was inferred from previous studies on the toluene-*p*-sulfonic acid catalysed [1,2]-SPh rearrangement of similar medium ring carbocycles.[11]

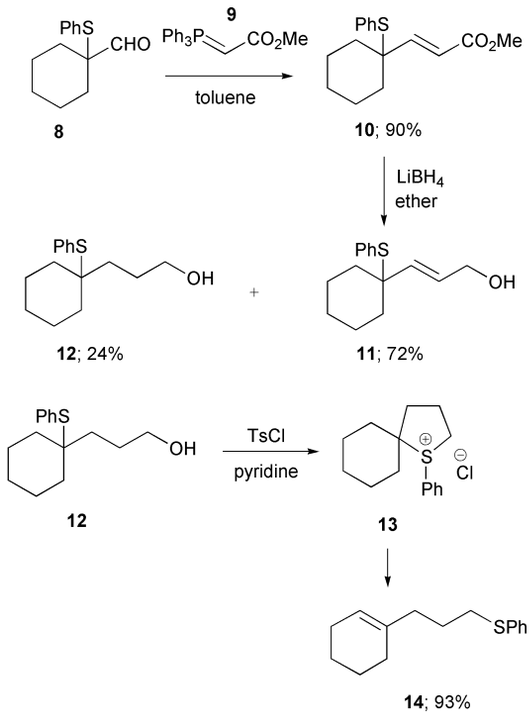
This *exo*-elimination pathway was disfavoured with a cyclobutane since formation of a cyclobutene is indeed disfavoured

† The Experimental section for this paper is available as supplementary data. For direct electronic access see http://www.rsc.org/suppdata/p1/b0/b005349j/

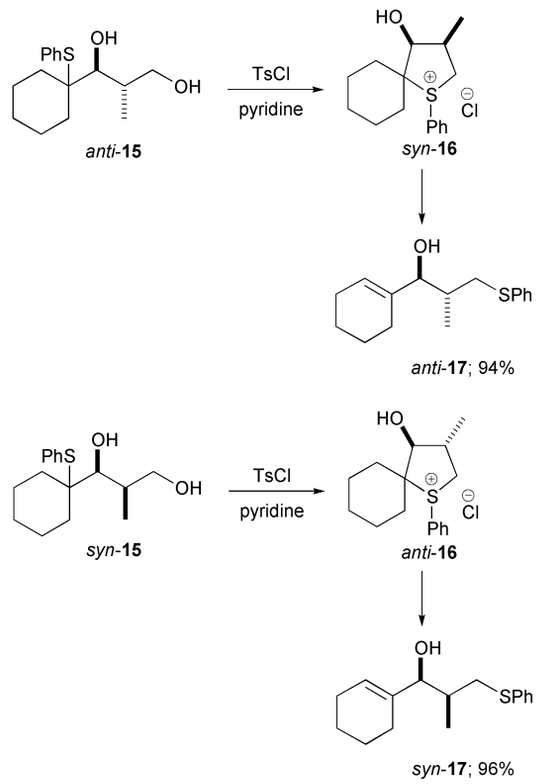
 DOI: 10.1039/b005349j



Scheme 2 Four possible products from the rearrangement of the diol **1** *via* the sulfonium ion **3**.

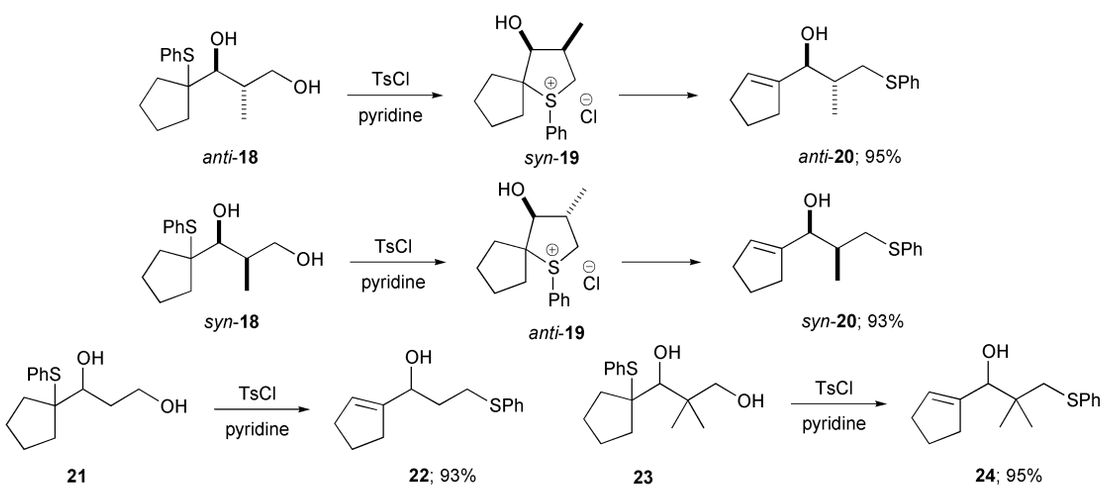


Scheme 3



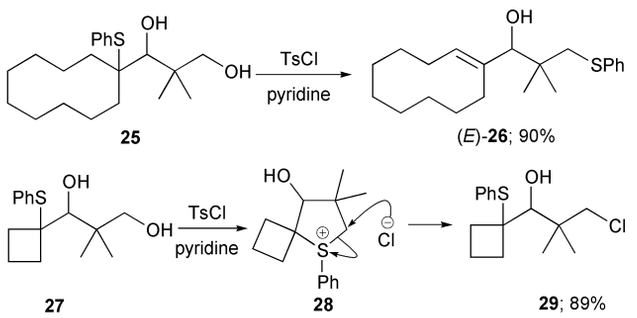
Scheme 4

by ring strain. Reaction of diol **27** under our usual conditions gave the unrearranged chloride **29** in 89% yield with no SPh migration. We believe that formation of the strained sulfonium salt **28** indeed does occur as [1,4]-SPh participation is very efficient, essentially as efficient as [1,2]-SPh migration which can occur even *via* a highly strained episulfonium ion.[1] The chloride **29** must result from a substitution reaction of **28** *via* a tight S_N2 transition state with



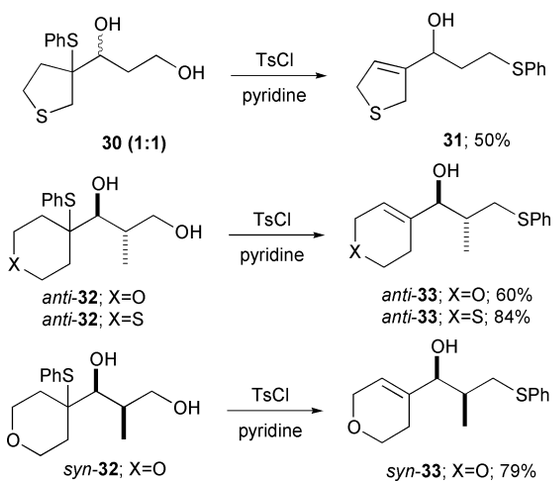
Scheme 5

attack occurring at the less hindered primary carbon of the sulfonium intermediate (Scheme 6). Eliel has observed similar behavour.[12]



Scheme 6

The incorporation of a heteroatom substituent in the ring (X = O or S) did not interfere with the reaction pathway. The five and six-membered ring diols **30**, *syn*- and *anti*-**32** (X = O)[13] and *anti*-**32** (X = S) gave only the expected allylic alcohols **31**, *syn*- and *anti*-**33** (X = O) and *anti*-**33** (X = S) although in reduced chemical yield. It appears that competitive 1,5- and 1,6-participation by the heteroatom X does not occur as it is less efficient than the observed [1,4]-SPh participation (Scheme 7).



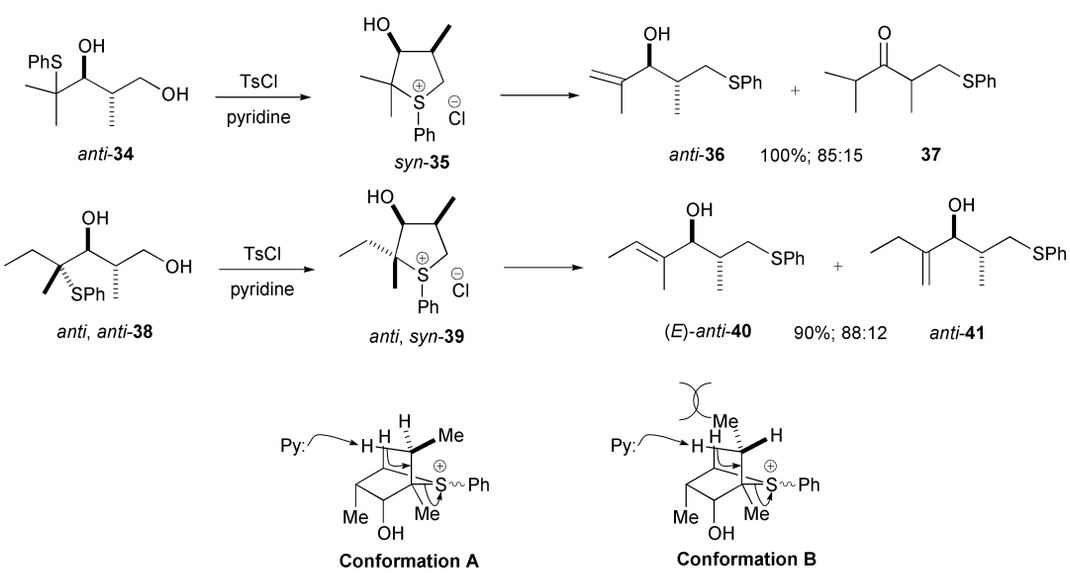
Scheme 7

It appears that the *exo*-elimination pathway was favoured over all other pathways (Scheme 2) due to the near-perfect alignment of the antiperiplanar β-hydrogen required for the *exo*-E2 elimination process in these spirocyclic sulfonium intermediates. The four-membered carbocycle **27** was the exception because the *exo*-elimination pathway was disfavoured due to ring strain. For a more realistic comparison between these *exo*- and *endo*-elimination pathways, we rearranged acyclic 4-PhS-1,3-diols such as *anti*-**34** and *anti*,*anti*-**38**. Treatment of the acyclic diol **34** with TsCl in pyridine gave for the first time two products: the allylic alcohol **36** (major) and ketone **37** (minor) in a 85 : 15 ratio. The ketone **37** was presumably formed *via* an enol, a tetra-substituted alkene, by *endo*-elimination of the sulfonium salt *syn*-**35**. Nevertheless the allylic alcohol *anti*-**36** was the major product.

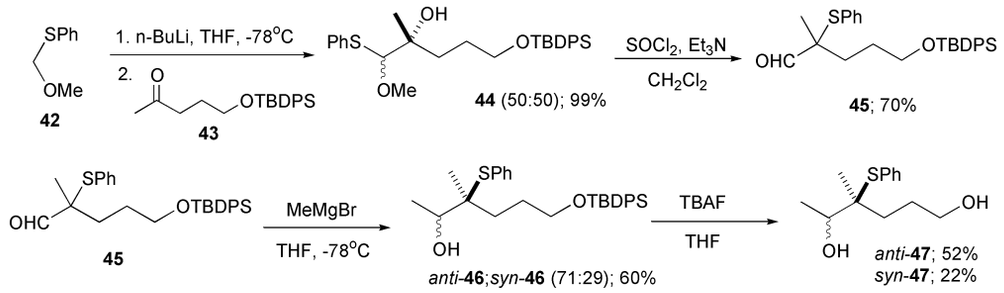
The stereoselectivity in double bond formation in such elimination processes was revealed by rearrangement of the diol *anti*, *anti*-**38** under our usual conditions. It gave the (*E*)-allylic alcohol *anti*-**40** as the major product [(*E*-) : (Z-) 88 : 12—determined by a 500 MHz NOESY spectrum], the most thermodynamically stable of the three (*E*-**40**, *Z*-**40** and the *exo*-methylene compound **41**) possible *exo*-elimination products. This elimination pathway presumably occurs *via* the transition state conformation **A** rather than conformation **B** due to unfavourable 1,3-diaxial interactions (Scheme 8). The alternative *endo*-elimination in **39** to give the ketone is not observed presumably because *exo*-elimination to give (*E*)-**40** is preferred.

The synthesis of ketones by elimination during [1,4]-PhS migration can be achieved if the non-participating secondary alcohol grouping is *exo*- to the sulfonium ring rather than *endo*- as in the previous cases. The diols *syn*- and *anti*-**47** were synthesised by diastereoselective addition of MeMgBr to the α-PhS substituted aldehyde **45**[14] (under Felkin control: *anti* : *syn* = 71 : 29) followed by TBAF deprotection (Scheme 9). The aldehyde **45** was easily synthesised from the protected ketone **43** using the de Groot and Jansen rearrangement.[9,15] Treatment of *syn*- and *anti*-diols **47** separately with TsCl in pyridine gave the same ketone **50** in 96% and 95% respectively, presumably *via exo*-elimination of the sulfonium ions *syn*- and *anti*-**48** and subsequent formation of an enol **49** (Scheme 10).

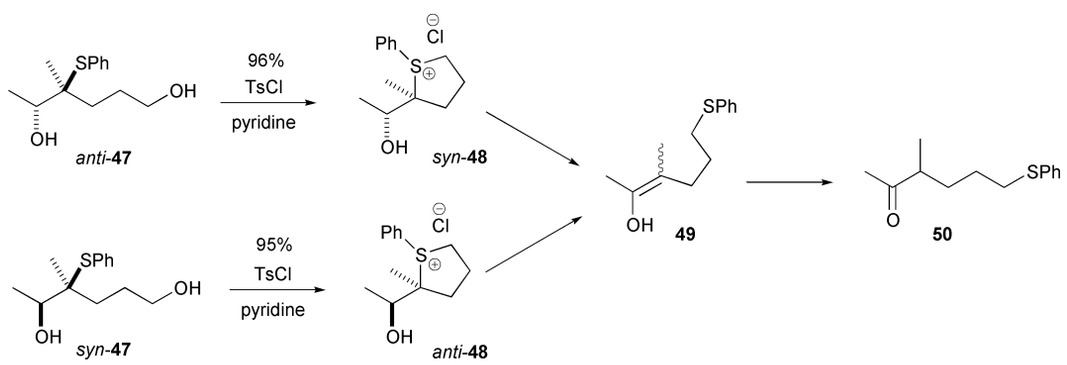
The normal *exo*-elimination pathway is disfavoured if the migration origin is secondary rather than tertiary. The 1,3-diols **60**–**62** were synthesised[9b] using our previously reported aldol and reduction procedure as shown in Scheme 11. Addition of the enolates **54**, (*E*)-**55**[16] and **56** to the 2-PhS-aldehyde **53** gave yields of aldols **57**–**59** which depended on the degree of



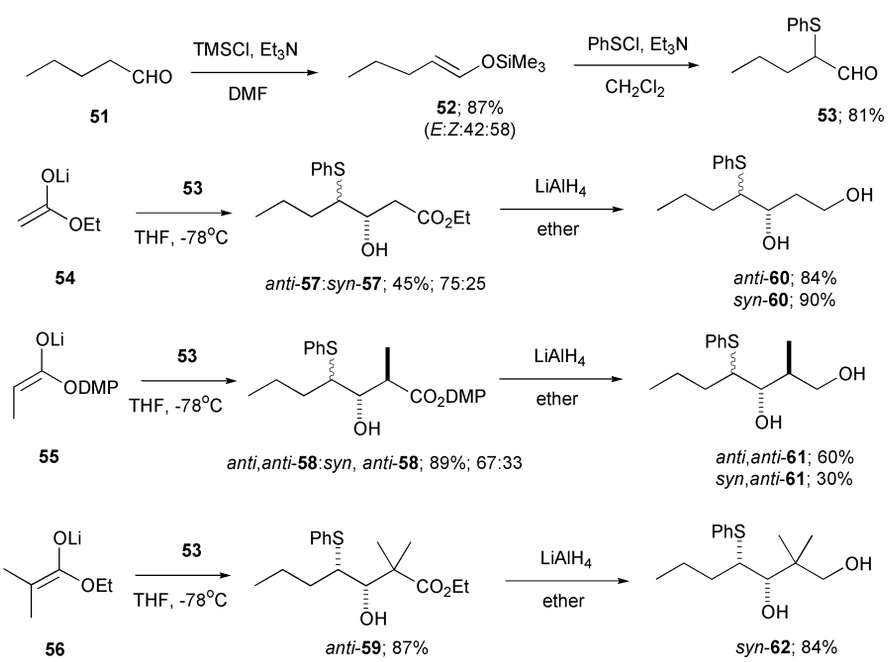
Scheme 8



Scheme 9



Scheme 10



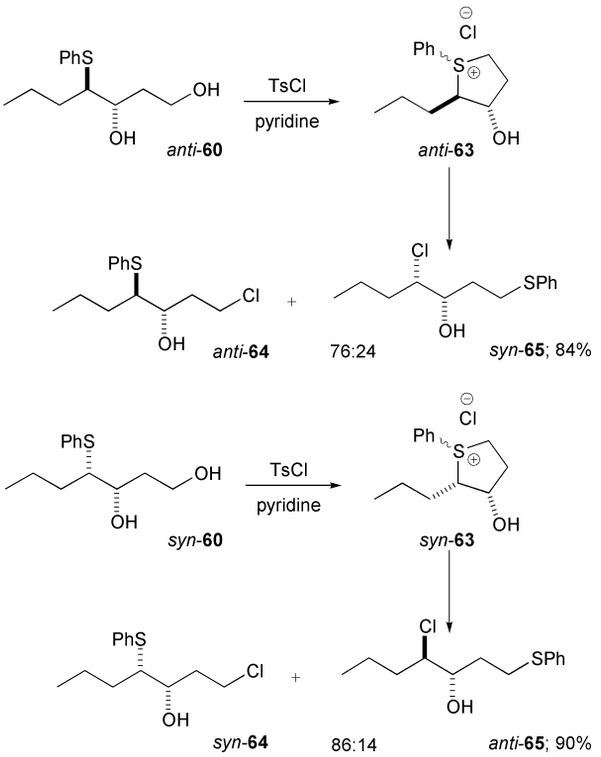
Scheme 11

Table 1 Stereoselectivity in the aldol reactions

Aldol	2,3-*anti*:*syn*	3,4-*anti*:*syn* (Felkin)	Yield (%)
60	—	75:25	45
61	>98:2	67:33	89
62	—	>98:2	87

competitive enolisation of the aldehyde **53** under the reaction conditions. The C(3,4)-Felkin–Anh[17] selectivity was much better (Table 1) for the more sterically demanding[9b] enolate **56**, than for the unsubstituted **54** or mono-substituted (*E*)-**55**, whereas the C(2,3)-selectivity in the aldol **58** was controlled by the enolate geometry.[16] Reduction ($LiAlH_4$) gave the corresponding diols *anti*- and *syn*-**60**, *anti*,*anti*- and *anti*,*syn*-**61** and *syn*-**62** in excellent yield.

Treatment of the *anti*- and *syn*-diols **60** with TsCl in pyridine gave an inseparable regioisomeric mixture of the unrearranged chlorides **64** (major) and rearranged chlorides **65** (minor) in excellent yield: no allylic alcohols were observed (Scheme 12). Presumably these reactions occur *via* a tight S_N2 displacement at the primary carbon of the sulfonium intermediate **63** giving the unrearranged chloride **64** with no SPh migration as the major product. The minor component must come from an S_N2 displacement at the secondary centre in the sulfonium salt to give the rearranged chloride **65** *via* a [1,4]-SPh migration. The displacement is stereospecific because each stereoisomer of **60** gives a single diastereoisomer of the minor rearranged product **65** and we assume the reaction occurs cleanly with inversion.[18]



Scheme 12

These cases are different from previous ones because cleavage of the much weaker C–S in the tertiary carbon in the sulfonium ions like **16** and *syn*-**35** derived from **15** and *anti*-**34** is evidently preferred rather than direct substitution. In comparison the rearrangement of the remaining diols *anti*,*anti*-**61** and *syn*-**62**, gave a reversal of selectivity giving the rearranged chlorides *syn*, *anti*-**68** and *anti*-**72** as the major product (Scheme 13). Presumably, substitution of sulfonium intermediate (*e.g.* **69a**) at the primary carbon is now disfavoured due to the adjacent methyl group. It appears that direct substitution *via* a loose S_N2 reaction at the more substituted secondary centre is evidently preferred. Indeed the substitution at the secondary centre is stereospecific, as we obtain two different stereoisomers in both

Table 2 Allylic alcohols from the rearrangement of 4-phenylsulfanyl-1,3-diols with TsCl in pyridine

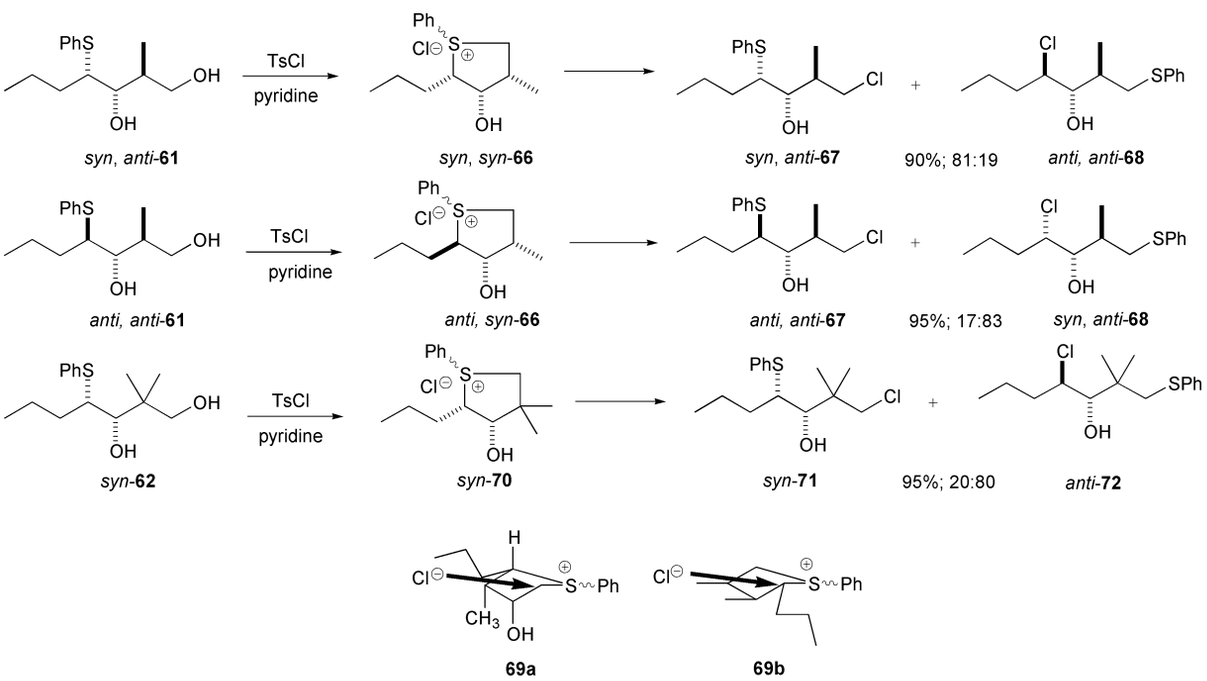
Diol	Allylic alcohol	Yield (%)
anti-**15**	*anti*-**17**	94
syn-**15**	*syn*-**17**	96
anti-**18**	*anti*-**20**	95
syn-**18**	*syn*-**20**	93
21	**22**	93
23	**24**	95
25	(*E*)-**26**	90
30 (1 : 1)	**31**	50
anti-**32**; X = O	*anti*-**33**; X = O	60
anti-**32**; X = S	*anti*-**33**; X = S	84
syn-**32**; X = O	*syn*-**33**; X = O	79
anti-**34**	*anti*-**36**	85
anti,*anti*-**38**	(*E*)-*anti*-**40** : *anti*-**41**	90

reactions of diol **61**. The regioselective substitution of these types of sulfonium intermediates is clearly sensitive to the C3 substituent and the stereochemistry in the sulfonium salts **69a** + **b**.

Attempts to isolate the original tosylate **73** under non-basic conditions proved unsuccessful. Addition of n-BuLi (1 eq.) to a solution of diol *anti*-**15** in THF at −78 °C and reaction with TsCl gave only the allylic alcohol **17** in near quantitative yield (Scheme 14). Isolation of the analogous tosylate was achieved by inhibiting sulfur participation by steric and electronic factors. Reaction of the sulfone *anti*-**74** with TsCl in pyridine gave the primary tosylate *anti*-**75** in 95% yield. Participation by a sulfone is known to be much slower than the more nucleophilic sulfide by at least four orders of magnitude.[19] Reaction of the *anti*-diol **76** containing two secondary alcohols, with TsCl in pyridine gave a 96% yield of a mixture of secondary tosylates **77** and **78** in a ratio 88 : 12. No participation of SPh occurred with these more hindered secondary tosylates.

In conclusion we have shown that the substituted 4-phenylsulfanyl-1,3-diols fall into the following three categories.

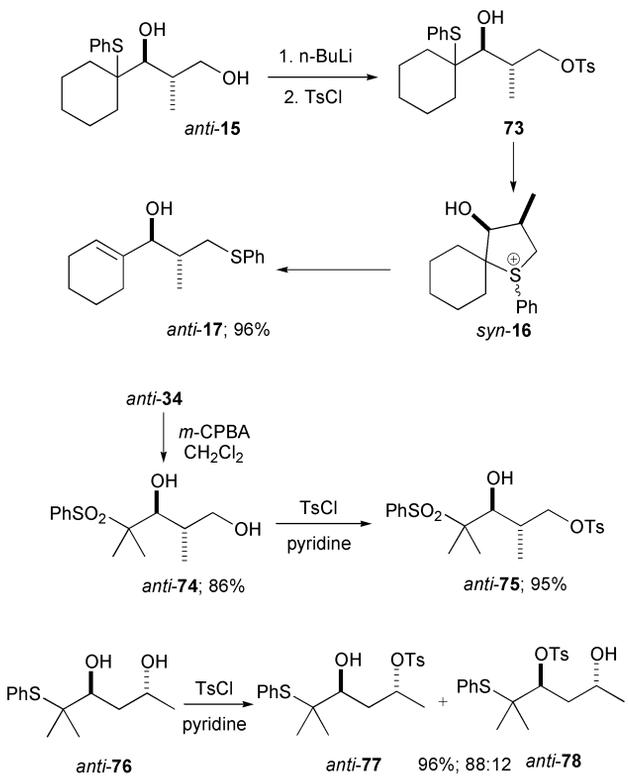
1. Those with a tertiary origin and primary terminus (*e.g.* *anti*-**15**)—all these rearrange to give allylic alcohols in excellent yield (Table 2), except when *exo*-elimination is inhibited, as with cyclobutane **27**.



Scheme 13

Table 3 Alkyl chlorides from the rearrangement of 4-phenylsulfanyl-1,3-diols with TsCl in pyridine

Diol	Unrearranged chloride	Yield (%)	Rearranged chloride	Ratio
27	**29**	89	—	—
anti-**60**	*anti*-**64**	84	*syn*-**65**	76:24
syn-**60**	*syn*-**64**	90	*anti*-**65**	86:14
syn,*anti*-**61**	*syn*,*anti*-**67**	90	*anti*,*anti*-**68**	81:19
anti,*anti*-**61**	*anti*,*anti*-**67**	95	*syn*,*anti*-**68**	17:83
syn-**62**	*syn*-**71**	95	*anti*-**72**	20:80



Scheme 14

2. Those with a tertiary migratory origin and secondary terminus—no rearrangement is observed, instead a regioselective mixture of secondary tosylates was isolated (*e.g. anti*-**76**).

3. Those with a secondary migratory origin and primary terminus—all these rearrange to give a regioisomeric mixture of rearranged and unrearranged chlorides, by substitution on the intermediate sulfonium salt in excellent yield (Table 3).

Experimental

The Experimental section for this paper is available as supplementary data. For direct electronic access see http://www.rsc.org/suppdata/p1/b0/b005349j

Acknowledgements

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References

1 E. L. Eliel, W. H. Pearson, L. M. Jewell and A. G. Abatjoglou, *Tetrahedron Lett.*, 1980, **21**, 331.
2 J. Eames, N. Kuhnert, F. H. Sansbury and S. Warren, *Synlett*, 1999, 1211.
3 M.-J. Villa and S. Warren, *J. Chem. Soc.*, *Perkin Trans. 1*, 1994, 2954.
4 J. Eames, N. Kuhnert and S. Warren, *Synlett*, 1999, 1215.
5 (*a*) L. Djakovitch, J. Eames, R. V. H. Jones, S. McIntyre and S. Warren, *Tetrahedron Lett.*, 1995, **36**, 1723; (*b*) L. Djakovitch, J. Eames, D. J. Fox, F. H. Sansbury and S. Warren, *J. Chem. Soc.*, *Perkin Trans. 1*, 1999, 2771.
6 Preliminary communication: J. Eames, M. A. de las Heras, R. V. H. Jones and S. Warren, *Tetrahedron Lett.*, 1996, **37**, 1117.
7 (*a*) A. J. Kirby, *Adv. Phys. Org. Chem.*, 1981, **17**, 183; (*b*) L. Mandolini, *Adv. Phys. Org. Chem.*, 1986, **22**, 1.
8 What is *exo*- to the sulfonium ring in the spirocyclic intermediate **13** is *endo*- to the cyclohexyl ring and *vice versa.*
9 (*a*) V. K. Aggarwal, I. Coldham, S. McIntyre and S. Warren, *J. Chem. Soc.*, *Perkin Trans. 1*, 1991, 451; (*b*) V. K. Aggarwal, J. Eames, M.-J. Villa, S. McIntyre, F. H. Sansbury and S. Warren, *J. Chem. Soc.*, *Perkin Trans. 1*, 2000, 533.
10 M. S. Wadia, R. S. Mali, S. G. Tilve and V. J. Yadav, *Synthesis*, 1987, 401.
11 M. Hannaby, P. Judson and S. Warren, *J. Chem. Soc.*, *Perkin Trans. 1*, 1992, 2609.
12 E. L. Eliel, R. O. Hutchins, R. Mebane and R. L. Willer, *J. Org. Chem.*, 1976, **41**, 1052.
13 J. Eames, D. J. Fox, M. A. de la Heras and S. Warren, *J. Chem. Soc.*, *Perkin Trans. 1*, 2000, 1903.
14 S. McIntyre, F. H. Sansbury and S. Warren, *Tetrahedron Lett.*, 1991, **32**, 5409.
15 (*a*) A. de Groot and B. J. M. Jansen, *Tetrahedron Lett.*, 1981, **22**, 887; A. de Groot and B. J. M. Jansen, *Synthesis*, 1985, 434; (*b*) J. Otera, *Synthesis*, 1988, 95.
16 C. H. Heathcock, M. C. Pirrung and J. E. Sohn, *J. Org. Chem.*, 1979, **44**, 4294.
17 (*a*) M. Chérest, H. Felkin and N. Prudent, *Tetrahedron Lett.*, 1968, 2199; (*b*) N. T. Anh and O. Eisenstein, *Nouv. J. Chim.*, 1977, **1**, 77.
18 This was calculated by integration of the CH_2Cl signal of the unrearranged chloride and the CH_2SPh signal in the rearranged chloride within the proton NMR spectrum.
19 P. Brownbridge, P. K. G. Hodgson, R. Shepherd and S. Warren, *J. Chem. Soc.*, *Perkin Trans. 1*, 1976, 2024.