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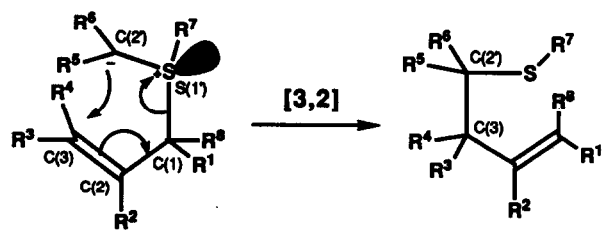
Stereospecificity and Stereoselectivity in the [3,2] Sigmatropic Rearrangement of Open Chain Sulphonium Ylides

Richard C. Hartley and Stuart Warren*
University Chemical Laboratories, Lensfield Road, Cambridge, CB2 1EW.

Ian C. Richards
Schering Agrochemicals Ltd, Chesterford Park Research Station, Saffron Walden, Essex, CB10 1XL.

Abstract The [3,2] sigmatropic rearrangement of sulphonium ylides derived from allyl sulphides with 1,2-related chiral centres was carried out with excellent stereochemical control. 1,4-Related chiral centres across an *E* double bond are set up stereospecifically by this reaction and good 4,5 diastereoselectivity is observed.

The [3,2] sigmatropic sulphonium ylide rearrangement has potential both as a means of transferring chirality within a molecule and of generating stereochemistry.[1] The allyl sulphonium ylide **1** has two chiral centres, at C(1) and S(1'), and a particular double bond geometry. Rearrangement to the homoallylic sulphide **2** destroys both chiral centres but generates two new ones at C(3) and C(2'). The new double bond geometry is generally *E* and complete chiral transfer from C(1) to C(3) has been observed.[2,3,4] While this chiral transfer is believed to be stereospecific in the sense that C(2') of the ylide migrates suprafacially across the allylic system from C(1) to C(3), no demonstration of this in an open chain compound has been reported. Good C(2')/C(3) diastereoselectivities are observed when two of the atoms in the 5-membered ring transition state are linked by a ring.[3,5,6] However, in the absence of such a constraint to rotation C(2')/C(3) diastereoselectivities have been poor (with a single exception[4]).[7,8]



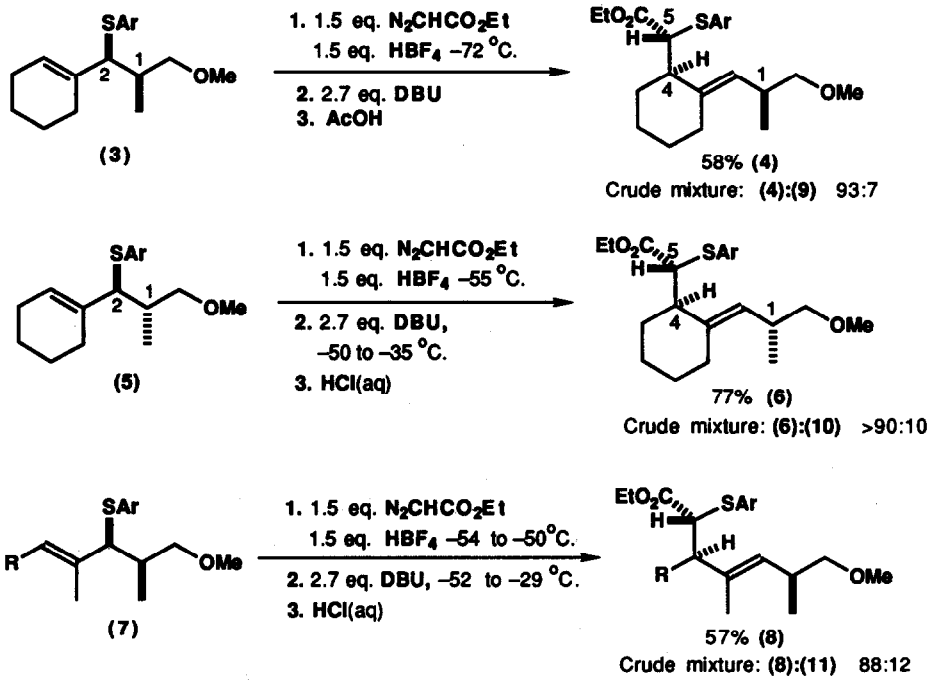
(1) (2)

Scheme 1: Stereochemistry of [3,2] Sigmatropic Rearrangements

We have used stereoselective aldol reactions, PhS migration, and the [3,2] sulphoxide rearrangement to prepare diols with 1,4 related chiral centres across an *E* double bond[9] and now report the extension of these methods to the creation of new carbon-carbon bonds using the [3,2] sigmatropic rearrangement of sulphonium ylides derived from related allyl sulphides (scheme 2). Rearrangement was most efficient when ylides were generated under modified Kurth[5] conditions from 4-methoxyphenylsulphides. The sulphonium salts were prepared at low temperature by five successive and alternate additions of 0.3 equivalents of ethyl diazoacetate and

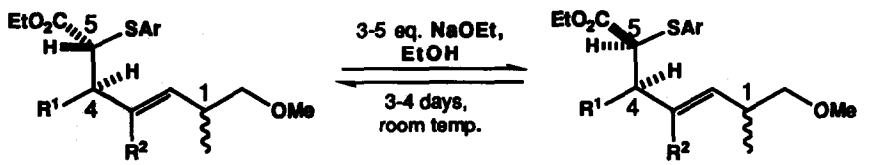
0.3 equivalents of HBF_4. Treatment with DBU gave the ylide, and the reaction was left for 10-20 minutes to allow the [3,2] sigmatropic rearrangement to take place. Addition of acetic acid then quenched the reaction.

The crude products were essentially the pure sulphides **4**, **6**, and **8**, the only impurites being the C-5 epimers **9**, **10**, and **11** in the ratios shown in scheme 2. Control over the relative stereochemistry at C-1 and C-4 was complete (*scheme* 2): the *syn* allyl sulphide **3** gave the 1,4 *syn* homoallylic sulphide **4** while the *anti* allyl sulphide **5** gave the 1,4 *anti* homoallylic sulphide **6**. In neither case was any trace of an *E* homoallylic sulphide with the opposite 1,4 stereochemistry or any *Z* homoallylic sulphide detected. This is the first proof that C(1) to C(3) (*scheme* 1) chiral transfer is stereospecific in the suprafacial sense. The cyclohexenyl ring cannot play a major role in controlling the suprafacial rearrangement as the open chain *syn* allyl sulphide **7** also gave sulphides **8** and **11** with complete control over the relative 1,4 stereochemistry.



Scheme 2: R = $(CH_2)_2Ph$; Ar = 4-methoxyphenylthio

We also found a remarkable degree of control over the relative stereochemistry of the newly created chiral centre at C-5. The ^1H NMR of the crude mixtures showed >90:10 diastereoselectivity in favour of the 4,5 *anti* compounds **4** and **6**. The six-membered ring of the sulphonium ylides derived from allyl sulphides **3** and **5** should not introduce an additional constraint to rotation about the bonds of the 5-membered ring transition state since C(2) and C(3) are already linked by a double bond and the transition state is believed to be early.[10] This was confirmed by the almost equally good diastereoselectivity observed in the formation of the homoallylic sulphide **8**. Equilibration experiments (*scheme* 3) show that there is little difference in the thermodynamic stability of the 4,5-*syn* and 4,5-*anti* isomers and therefore that the preference for the 4,5 *anti* stereochemistry must be kinetic.

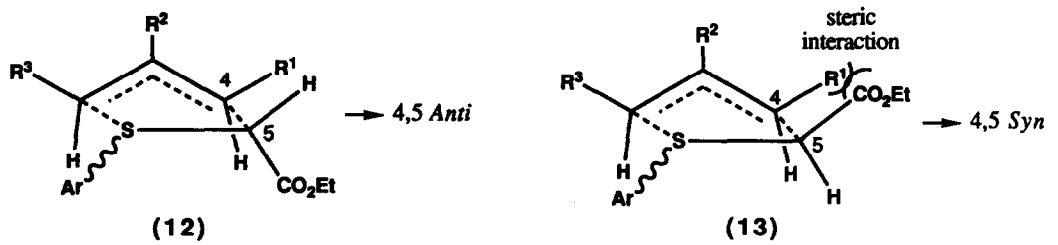


(4) 1,4 *syn*, $R^1,R^2 = (CH_2)_4$, R^3 = 4-methoxyphenyl (9)
(6) 1,4 *anti*, $R^1,R^2 = (CH_2)_4$, R^3 = 4-methoxyphenyl (10)
(8) 1,4 *syn*, $R^1 = Ph(CH_2)_2$, R^2 = Me, R^3 = 4-methoxyphenyl (11)

	Compound				Equilibration ratio
1,4 Stereochemistry	4,5 *Anti*	4,5 *Syn*	R^1	R^2	4,5 *Anti* : *Syn*
Syn	4	9	$-(CH_2)_4-$		36:64
Anti	6	10	$-(CH_2)_4-$		34:66
Syn	8	11	$Ph(CH_2)_2$	Me	52:48

Scheme 3: Equilibration of Products by Enolisation

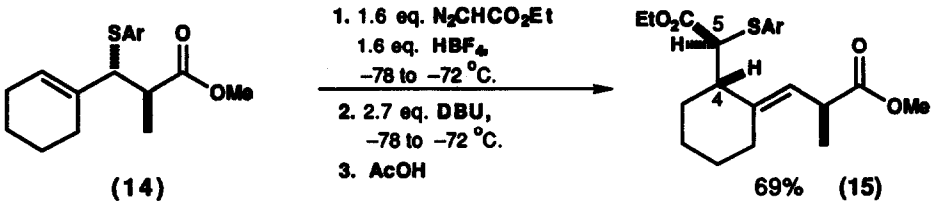
The 4,5 *anti* selectivity can be explained using the folded envelope transition state proposed by Wu and Houk (*scheme 4*).[10] Of the two possible envelope transition states **12** and **13**, the eclipsed substituent (R^1 and CO_2Et) orientation across the developing C(4)-C(5) bond disfavours **13**. Therefore we believe that the reaction proceeds *via* transition state **12** giving the observed 4,5 *anti* stereochemistry. Further support for the nature of the transition state comes from the results of Weinreb,[4] who found that a sulphonium ylide with the *Z* double bond geometry gave the opposite (*syn*) 4,5 stereochemistry. The kinetic selectivity was aided by the low reaction temperature.



Scheme 4: Suggested Transition States for the [3,2] Sigmatropic Rearrangement of Sulphonium Ylides

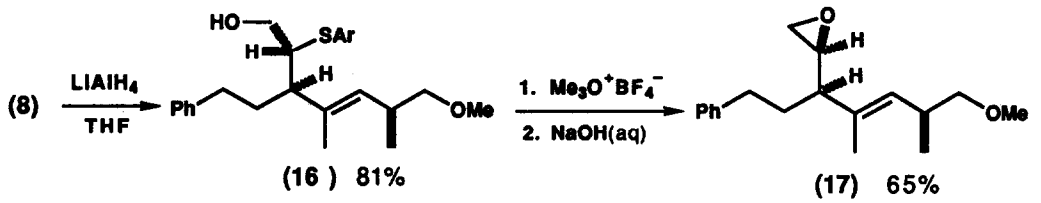
Phenylthio compounds give similar results to 4-methoxyphenylthio compounds. The allyl sulphide **14**, also formed by aldol reaction and rearrangement,[9] was converted to homoallylic sulphide **15** in good yield and with 4,5 diastereoselectivity equal to that of **5** above (*scheme* 4). Thus, the reaction conditions do not affect ester groups or stereochemical integrity at epimerisable centres and elimination of a sulphonium salt β to a carbonyl group is not a problem at the low temperature used.

All the major products of the [3,2] sigmatropic rearrangements were isolated in >89% purity and have satisfactory ^1H NMR, ^{13}C NMR, MS and IR. Stereochemical assignments of starting materials was by NMR correlation to known compounds[9,11] and of products was by COSY and NOE.



Scheme 5: [3,2] Sigmatropic Rearrangement on an Ester

The products of the rearrangement may be further elaborated to give potentially useful synthetic building blocks, for example the homoallylic sulphide **8** was converted stereospecifically (with inversion) to the epoxide **17** by reduction to the β-hydroxysulphide **16**, followed by methylation on sulphur and elimination of thioanisole (*scheme* 6).[12] Products such as **17** have an *E* double bond flanked by three chiral centres and have different functional groups at each end ready for incorporation into larger structures.



Scheme 6: Synthesis of Epoxides by Removal of Sulphur from [3,2] Rearrangement Products

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