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# Stereocontrol in the Nucleophilic Epoxidation of α-(1-Hydroxyalkyl)-α,β-Unsaturated Sulfones

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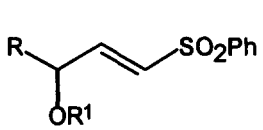
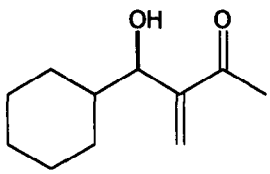
*Key Words:* Michael Addition; Vinylsulfone; Epoxidation; 1,3-Allylic Strain

***Abstract:*** Epoxidation of β-unsubstituted-α-(1-hydroxyalkyl)-α,β-unsaturated sulfones **3** with lithium *t*-butylperoxide proceeds with high diastereoselectivity to give the *syn* epoxy alcohols **6**. Epoxidation of the triisopropylsilyl ethers **5**, however, leads to the *anti* epoxy ethers **9** with moderate to good selectivity. In contrast to this, epoxidation of (*E*)-β-phenyl-α-(1-hydroxyalkyl)-α,β-unsaturated sulfones **4** proceeds with high diastereoselectivity to give the *anti* epoxy alcohols **13** . Epoxidation of the corresponding triisopropylsilyl ethers leads to a reversal in diastereofacial selectivity, giving the *syn* epoxy ethers **14** with moderate selectivity. A rationalisation for these results, based on the principle of 1,3-allylic strain, is proposed.

We have recently described the the results of an investigation into the nucleophilic epoxidation of γ-oxygenated-α,β-unsaturated sulfones **1** using lithium *t*-butylperoxide.[1] In view of recent reports on the epoxidation of α-(1-hydroxyalkyl)-α,β-enones (*e.g.* **2**) using both nucleophilic and metal catalysed epoxidation conditions,[2] we have undertaken a study to determine the diastereofacial selectivity of epoxidation of both β-unsubstituted-α-(1-hydroxyalkyl)-α,β-unsaturated sulfones **3** and (*E*)-β-phenyl-α-(1-hydroxyalkyl)-α,β-unsaturated sulfones **4**. We now report that stereocomplementary results are obtained in all the examples that we have examined provided that a proper choice of protecting group is made.




**1**

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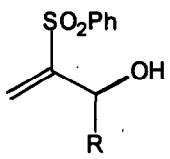


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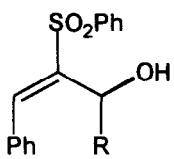
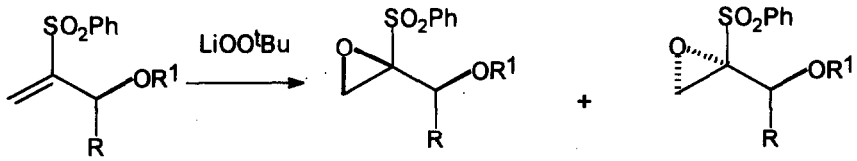



**4**

The required β-unsubstituted-α-(1-hydroxyalkyl)-α,β-unsaturated sulfones **3a-c** were obtained by treatment of phenyl vinylsulfone with the appropriate aldehyde using diazabicylo[2.2.2]octane as catalyst.[3] Protection of the hydroxyl group was effected using triisopropylsilyl trifluoromethanesulfonate/lutidine to give the silyl ethers **5a-c**. Treatment of the free alcohols **3a-c** with lithium *t*-butylperoxide in THF at -20 °C proceeded smoothly to give the corresponding *syn* and *anti* epoxides **6a-c** and **7a-c**. Epoxidation of the silyl ethers **5a-c** was very slow at -20 °C and the reaction was therefore carried out at room temperature to give the *syn* and *anti* epoxides **8a-c** and **9a-c**. The diastereoisomeric ratios were determined by proton nmr of the crude reaction products, and the results are summarised in Table 1.




*syn* *anti*

**3**, $R^1$ = H **6**, $R^1$ = H **7**, $R^1$ = H

**5**, $R^1 = (^iPr)_3Si$ **8**, $R^1 = (^iPr)_3Si$ **9**, $R^1 = (^iPr)_3Si$

Table 1. Epoxidation of Vinyl Sulfones **3** and **5** with Lithium *t*-Butylperoxide

| Vinylsulfone | R | Epoxides | *Syn/Anti* Ratio | Yield, % |
|---|---|---|---|---|
| **3a** | Me | **6a/7a** | 25:1 | 62 |
| **3b** | $^nPr$ | **6b/7b** | 25:1 | 65 |
| **3c** | $^iPr$ | **6c/7c** | 25:1 | 62 |
| **5a** | Me | **8a/9a** | 1:12 | 73 |
| **5b** | $^nPr$ | **8b/9b** | 1:25 | 61 |
| **5c** | $^iPr$ | **8c/9c** | 1:4 | 79 |

The relative stereochemistry of the *syn* epoxide **6c** (Figure 1),[4] and of the *anti* epoxide **9a** (Figure 2)[5] were determined by X-ray crystal structure analysis, and the relative stereochemistry of the major products from epoxidation of vinylsulfones **3a** and **5c** were determined by chemical correlation. The epoxides **7b** and **8b** were shown to possess opposite relative stereochemistry by chemical correlation, and have been assigned the relative configurations shown based on the other examples. Since the bulk of the propyl group is intermediate between a methyl group and an isopropyl group, we feel confident of the stereochemical assignments for these compounds.

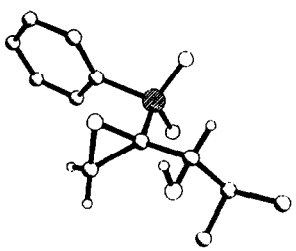


**Figure 1** X-ray Structure of **6c**

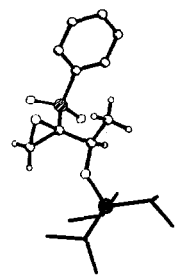
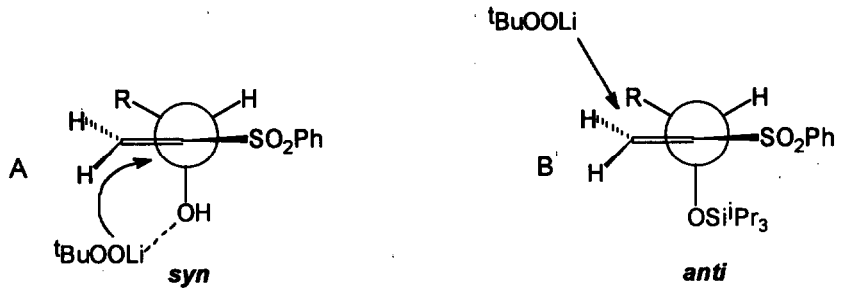


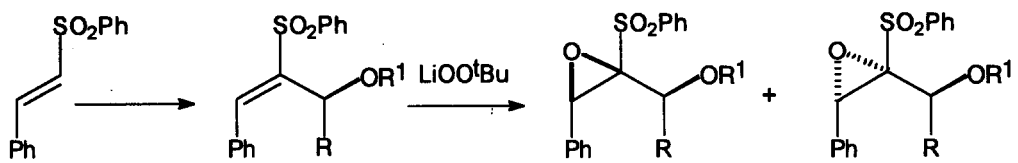
**Figure 2** X-ray Structure of **9a**

The stereochemical outcome of these epoxidation reactions can be rationalised on the basis of a reactive conformation in which the alkyl substituent R occupies the inside position and the carbon-oxygen bond is parallel to the π-bond thus activating the double bond towards nucleophilic attack.[6] This reduces any destablising interaction between the alkyl substituent and the phenylsulfonyl group. In the case of the free alcohols **3a-c**, interaction between the hydroxyl group and lithium *t*-butylperoxide, either by coordination of the lithium atom or by hydrogen bond formation from the alcohol proton to the *t*-butylperoxide anion, allows delivery of reagent from the same face (**A**). In the case of the triisopropylsilyl ethers **5a-c**, a similar

conformation, combined with nucleophilic attack of lithium *t*-butylperoxide from the opposite face (**B**), yields the observed stereoisomer. Support for this hypothesis is provided by the observation that the diastereoselectivity is lowest when the alkyl substituent is largest, when a destabilising interaction might be expected between this substituent and the incoming nucleophile.




Having established the steric course of nucleophilic epoxidation of β-unsubstituted-α-(1-hydroxyalkyl)-α,β-unsaturated sulfones, we then investigated the effect of introducing a substituent at the β-position. The required substrates **4a-c** were prepared by lithiation of phenyl styryl sulfone **10** with MeLi followed by treatment with $MgBr_2.Et_2O$ and then an aldehyde, according to the procedure of Eisch.[7] The alcohols **4a-c** were protected to give the triisopropylsilyl ethers **11a-c**. Treatment of the free alcohols **4a-c** with lithium *t*-butylperoxide in THF at -20 °C proceeded smoothly to give the corresponding *syn* and *anti* epoxides **12a-c** and **13a-c**. Epoxidation of the silyl ethers **11a-c** required the reaction to be conducted at room temperauture and gave the *syn* and *anti* epoxides **14a-c** and **15a-c**. The results are summarised in Table 2.




**10** **4**, $R^1$ = H **12**, $R^1$ = H **13**, $R^1$ = H

**11**, $R^1 = (^iPr)_3Si$ **14**, $R^1 = (^iPr)_3Si$ **15**, $R^1 = (^iPr)_3Si$

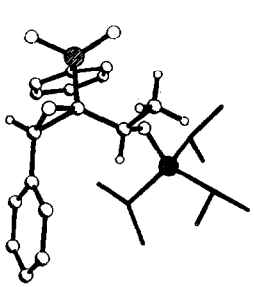
Table 2. Epoxidation of Vinyl Sulfones **4** and **11** with Lithium *t*-Butylperoxide

| Vinylsulfone | R | Epoxides | *Syn/Anti* Ratio | Yield, % |
|---|---|---|---|---|
| **4a** | Me | **12a/13a** | 1:12 | 72 |
| **4b** | $^nPr$ | **12b/13b** | 1:20 | 63 |
| **4c** | $^iPr$ | **12c/13c** | 1:25 | 53 |
| **11a** | Me | **14a/15a** | 5:1 | 90 |
| **11b** | $^nPr$ | **14b/15b** | 4:1 | 91 |
| **11c** | $^iPr$ | **14c/15c** | 4:1 | 80 |

The relative stereochemistry of the *syn* epoxide **14a** was determined by X-ray crystal structure analysis (Figure 3),[7] and the relative stereochemistry of the *anti* epoxide **13a** was established by conversion to the

*anti* epoxide **15a**, of opposite relative configuration to **14a**. Although we have no unambiguous proof of stereochemistry of the other examples, silylation of the mixture of stereoisomers derived from epoxidation of the free alcohol **4b** established that the major isomer from this reaction was of opposite relative configuration to the major isomer derived from direct epoxidation of the silyl ether **11b**. Similarly, the major isomers derived from epoxidation of the free alcohol **4c** and from the silyl ether **11c** were again established to possess opposite relative stereochemistry.

The reversed stereoselectivity observed for epoxidation of compounds **4a-c** and **11a-c** when compared with the β-unsubstituted examples **3a-c** and **5a-c** is easily rationalised by assuming that the presence of the phenyl substituent *syn* to the allylic stereocentre destabilises conformations in which the alkyl group is inside. Thus, 1,3-allylic strain becomes the main influence,[9] and overrides the interaction between the alkyl group and the sulfone. The observed stereochemical outcome can now be rationalised by direction of lithium *t*-butylperoxide by the free hydroxyl group (**C**), or by attack *anti* to the bulky triisopropylsilyloxy group (**D**).



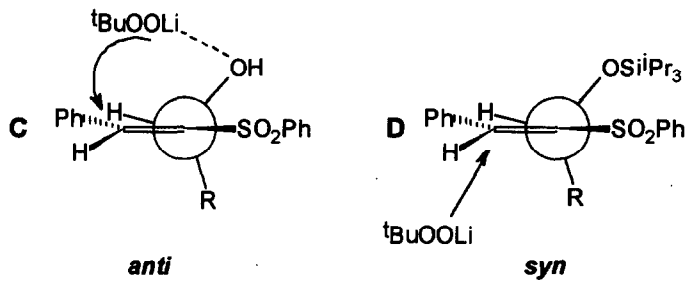



**Figure 3** X-ray Structure of **14a**

**Acknowledgements:** We thank SERC for a postgraduate studentship (SPS) and for a research grant (WC), ICI plc for a grant from their strategic research fund (RFWJ), and Mathias Wenig and Luca Vangelista for experimental contributions.

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4. Compound **6c** forms monoclinic crystals, a = 8.538(6), b = 20.829(14), c = 14.621(8) Å, β = 106.16(6)°, Z = 8, space group $P2_1/n$. The structure was solved from 2312 observed diffractometer reflections ($2\theta < 45°$, MoKα radiation) and refined to R = 0.0560 and $R_w$ = 0.0522.
5. Compound **9a** forms orthorhombic crystals, a = 17.213(8), b = 11.605(6), c = 20.932(8) Å, Z = 8, space group Pbca. The structure was solved from 3021 observed diffractometer reflections ($2\theta < 50°$, MoKα radiation) and refined to R = 0.0351 and $R_w$ = 0.0516.
6. Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199-2204. Chérest, M.; Felkin, H. *Tetrahedron Lett.* **1968**, 2205-2208. Anh, N.T.; Eisenstein, O. *Nouv. J. Chem.* **1977**, *1*, 61-70.
7. Eisch, J.J.; Galle, J.E. *J. Org. Chem.* **1979**, *44*, 3279-3280.
8. Compound **14a** forms triclinic crystals, a = 9.0816(8), b = 9.4779(8), c = 15.6504(18) Å, α = 86.947(9), β = 88.644(9), γ = 73.596(6)°, Z = 2, space group $P\bar{1}$. The structure was solved from 3791 observed diffractometer reflections ($2\theta < 50°$, MoKα radiation) and refined to R = 0.0518 and $R_w$ = 0.0762.
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