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# The Asymmetric Synthesis of Allylic Alcohols Using a Recoverable Chiral Sulphoxide.

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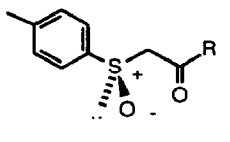
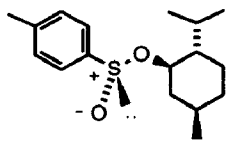
**Abstract:** The enantiomerically pure cyclic sulphinamide $S_{(S)}R$-(+)-**3** reacts with the sodium enolates of ketones to give the corresponding homochiral sulphoxides. Reduction of the carbonyl group in these products using DIBAL-H or DIBAL-H/$ZnBr_2$ gives complementary products of high diastereoisomeric excess. This methodology has been applied to the synthesis of an allylic alcohols in high enantiomeric excess.

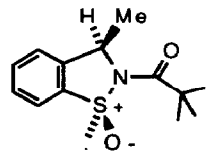
Chiral sulphoxides are known to provide excellent control of the stereoselective reduction of a β–keto group.[1] The reduction substrates **1** are generally prepared by the reaction of methyl magnesium bromide with the chiral menthyl sulphinate (1R,2S,5R)-(-)-menthyl-(S)-p-tolylsulphinate **2**[2] followed by acylation of the resulting methyl sulphoxide.[1] A more convenient approach to compounds such as **1** would be by direct reaction of (S)-**2** with the enolate of a methyl ketone, however the use of sodium and lithium enolates has been shown to cause epimerisation[3] of **2** whilst the use of a magnesium enolate requires forcing reaction conditions.[4] We have recently reported the synthesis and applications to asymmetric synthesis of cyclic sulphinamide $S_{(S)}R$-(+)-**3**, a compound which provides a convenient source of chiral sulphoxide.[5] Sulphinamide $S_{(S)}R$-(+)-**3** possesses a number of practical advantages over (S)-**2**, the most significant of which is that it may be recycled after use.[5] In this paper we describe the application of $S_{(S)}R$-(+)-**3** to the synthesis of β–keto sulphoxides and subsequently enantiomerically pure alcohols *via* diastereoselective reduction of the carbonyl group.




**1**



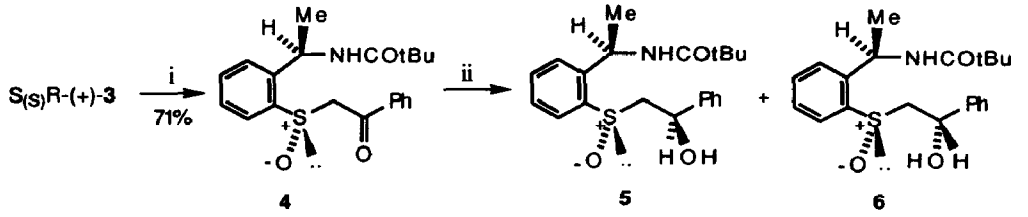

**S-2**




$S_{(S)}R$-(+)-**3**

Treatment of $S_{(S)}R$-(+)-**3** at -78°C with the sodium enolate of acetophenone resulted in formation of sulphoxide **4** as a single diastereoisomer in 71% yield. On the basis of our previous studies on $S_{(S)}R$-(+)-**3** the streochemistry of **4** was assigned as the product of inversion of configuration at sulphur during ring opening (Scheme 1).[5c,6,7] The reduction of **4** with a series of reducing agents was studied (Scheme 1,

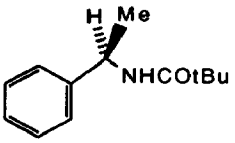
Table). As expected[1] the use of DIBAL-H and DIBAL-H/$ZnBr_2$ gave complementary major diastereoisomers of β-hydroxy sulphoxides in high diastereoselectivity (**5** and **6** respectively). The product stereochemistry was assigned on the basis of the reported reduction selectivities for these reducing agents.[1] The use of DIBAL-H alone also gives a small quantity (ca. 5%) of the corresponding β-hydroxy sulphide resulting from sulphoxide reduction. Two equivalents of reducing agent are needed in these reactions however the pivaloylamide side chain does not appear to otherwise influence the reaction (Scheme 1).




**Scheme 1** Reagents i) PhCOMe, $NaN(TMS)_2$, toluene, -78°C. ii) See Table.

**Table**: Diastereoselective reductions of β-keto sulphoxide **4**

| Reducing agent | Yield | **5 : 6** |
|---|---|---|
| DIBAL-H | 73% | 94 : 6 |
| $NBu_4BH_4$ | quant. | 62 : 38 |
| $NaBH_4$ | quant. | 60 :40 |
| $NaBH_4/CeCl_3$ | quant. | 57 : 43 |
| $NaB(OAc)_3H$ | quant. | 40 : 60 |
| $LiAlH_4$ | 87% | 25 : 75 |
| DIBAL-H/$ZnBr_2$ | 80% | <2 : >98 |

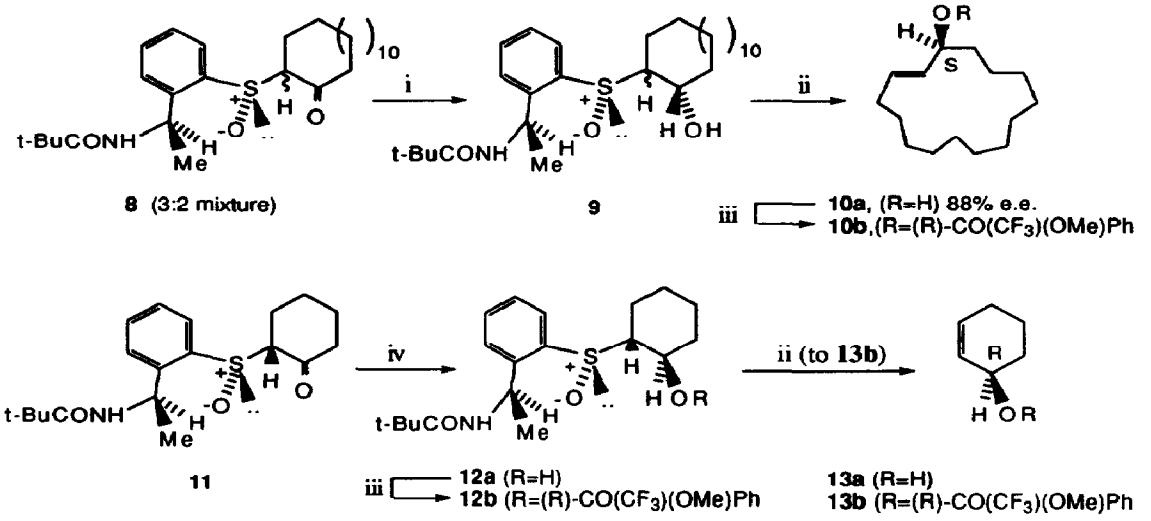



**7**

Attempted reductive cleavage of recrystallised **6** using Raney nickel[1j,k] or nickel boride[8] gave a mixture of amide **7**, racemic 2-phenethylalcohol and ethylbenzene. Raney nickel has been reported to be capable of oxidising benzylic alcohols in a disproportionation reaction.[9] Subsequent reduction of this ketone would would account for the epimerisation of the cleaved alcohol. In view of this disappointing result, we sought an alternative approach which would permit the formation of non-racemic products without compromising the potential recyclability of $S_{(S)}R$-(+)-**3**. We have found that adducts of $S_{(S)}R$-(+)-**3** with ketones undergo a very facile sulphenic acid elimination reaction to give enones.[10] Furthermore several reports have concluded that the reduction of β-keto sulphoxides bearing α-substituents is controlled essentially completely by the configuration of the sulphoxide group.[1c,g,h] Reaction of the sodium enolate of cyclopentadecanone with $S_{(S)}R$-(+)-**3** gave the sulphoxide **8** as a 3:2 mixture of diastereoisomers in 82% yield. Reduction with DIBAL-H/$ZnBr_2$ followed by heating the crude reduction mixture **9** at 60°C in toluene for 5 hours gave the allylic alcohol **10a** in 82% overall yield along with a number of sulphenic acid derived side-products (Scheme 2). The enantiomeric excess of **10a** was shown to be 88% in favour of the S- enantiomer based on the assigned reduction selectivity and by integration of the methoxy signals from the Mosher ester derivatives **10b**[11] by comparison with a sample from racemic modification (270 MHz $^1$H-

NMR). Allylic alcohol **10a** has been employed as a key intermediate in a recent synthesis of enantiomerically pure muscone.[12] The use of DIBAL-H alone for the reduction of **8** followed by the same sequence resulted in the formation of **10a** of only 12% enantiomeric excess in favour of the R- enantiomer. This sequence confirms that with the use of DIBAL-H/$ZnBr_2$ the sulphoxide chirality overrides any control by the configuration at the α-centre, although this is not the case with DIBAL-H alone.

Reaction of $S_{(S)}R$-(+)-**3** with the sodium enolate of cyclohexanone resulted in the formation of a 6:1 mixture of adducts in 78% yield in which the isomer **11** was shown to be the major product by an X-ray crystal structure analysis.[6] Reduction of **11** with DIBAL-H gave a single diastereoisomer of alcohol **12a** in low yield (31%) although 65% unreacted **11** was recovered. Thermally-promoted sulphenic acid elimination was attempted on **12a**, but very little alcohol **13a** was formed (<5%). In the belief that this lack of reactivity was due to stabilisation by an intramolecular hydrogen bond this alcohol was first converted to its Mosher acid derivative **12b** in quantitative yield. Sulphenic acid elimination then proceeded smoothly to furnish the protected alcohol **13b** in quantitative yield, as a single diastereoisomer (Scheme 2). The same sequence of reactions from **11** to **13b** using DIBAL-H/$ZnBr_2$ gave a product in 54% overall yield which was a 1:1 mixture of diastereoisomers. This result is in contrast to the expected result based on the observations on the reduction of the larger ring compound **8** and shows that the factors controlling the relative contributions to the stereochemical control from the sulphoxide and the configuration at the α-centre are complex.




**Scheme 2** Reagents: i) DIBAL-H/$ZnBr_2$, THF, -78°C. ii) Toluene, 60°C, 5 hr. iii) (R)-$HO_2CC(OMe)(CF_3)Ph$, DCC, DMAP. iv) DIBAL-H, THF, -78°C.

In conclusion we have demonstrated that the cyclic sulphinamide $S_{(S)}R$-(+)-**3** may be used as an auxiliary for the enantioselective conversion of methyl ketones into homochiral methyl alcohols. Since we have shown that $S_{(S)}R$-(+)-**3** may be recycled from the sulphenic acid elimination side-products,[5d] it is effectively recoverable in this application.

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