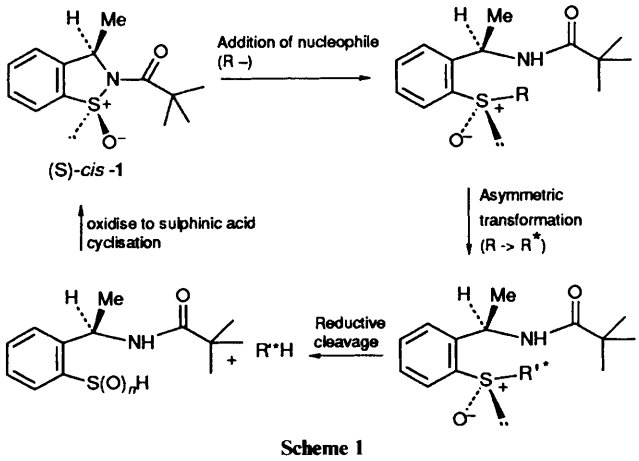
Dependence of Ring Closure Stereoselectivity on the Nature of the Leaving Group: Application to the Synthesis of a New Class of Chiral Sulfoxide for the Control of Asymmetric Aldol Reactions

Martin Wills,*[a] Roger J. Butlin,[b] Ian D. Linney[a] and Richard W. Gibson[a]
[a] *School of Chemistry, University of Bath, Claverton Down, Bath, BA2 7AY, UK*
[b] *ICI Pharmaceuticals, Mereside, Alderley Park, Macclesfield, Cheshire, SK10 4TG, UK*

Enantiomerically pure cyclic sulfinamide ($S_{(S)}R$)-(+)-**1** [(*S*)-*cis*-**1**], which has application to the control of asymmetric aldol reactions *via* a derived sulfoxide, has been prepared in diastereoisomerically pure form from the sulfinic acid (*R*)-(−)-**5** using thionyl chloride–4-dimethylaminopyridine (DMAP); replacement of DMAP with pyridine or triethylamine gave both diastereoisomers of **1** in low diastereoisomeric excess.

As part of a programme directed at the development of improved chiral sulfoxides for the control of asymmetric reactions,[1-4] we envisaged the use of an enantiomerically pure cyclic sulfinamide such as (*S*)-*cis*-**1**[5] as a source of sulfoxide *via* heterocyclic ring opening with a nucleophile. Since this process would be expected to take place with inversion at sulfur[2b] the resultant sulfoxide should be enantiomerically pure and serve as a control element for asymmetric functionalisations of the adjacent groups. The sulfoxide may be subsequently removed by reductive cleavage[6] and, potentially, recycled *via* oxidation[7] and cyclisation to (*S*)-*cis*-**1** (Scheme 1).[5]† This approach, if



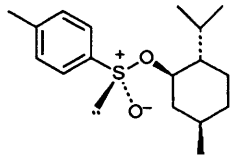
Scheme 1

successful, would represent a significant improvement over similar methodology involving the use of (1*R*,2*S*,5*R*)-(−)-menthyl (*S*)-toluene-*p*-sulfinate **2**,[2-4,9] which, purified *via* a complex series of crystallisation steps, is prone to epimerisation during reactions[10] as well as during storage[11] and is not recyclable after use. The success of this approach depends crucially on the availability of an efficient method for the synthesis of (*S*)-*cis*-**1**[5,11] in enantio- and diastereo-isomerically pure form. The meeting of this objective is described in this paper, as well as the ring opening of (*S*)-*cis*-**1** by nucleophiles and application to asymmetric aldol reactions.

The first step in the preparation of (*S*)-*cis*-**1** was the acylation of readily available (in both enantiomeric forms) inexpensive amine (*R*)-(+)-**3** with pivaloyl chloride and triethylamine to give (*R*)-(+)-**4** which was *ortho*-lithiated using *tert*-butyllithium and treated with sulfur dioxide to yield the sulfinic acid (*R*)-(−)-**5**.[5] The cyclisation of (*R*)-(−)-**5** to ($S_{(S)}R$)-(+)-**1** [(*S*)-*cis*-**1**, structure proven by X-ray crystal structure analysis,[5] no *trans*-isomer detected] using thionyl chloride and sodium hydride has been described,[5] however we sought an experimentally more reproducible alternative method.‡ Towards this end we have found that treatment of a tetrahydrofuran (THF) solution of (*R*)-(+)-**5** with thionyl chloride and a tertiary amine effects its facile conversion into *cis*- and *trans*-**1** in a ratio dependent on the nature of the base (Scheme 2, Table 1).§

Table 1 Synthesis of *cis*- and *trans*-**1**

Amine	Yield of **1** (%)	*cis*-**1**:*trans*-**1**
DMAP	67	100:0
Triethylamine	63	85:15
Pyridine	60	60:40



2

The remarkable range of diastereoselectivities observed in the above reactions is presumably a consequence of the leaving group abilities of the amines used to catalyse the cyclisation.¶ The initial reaction of (*R*)-(−)-**5** with thionyl chloride will give a mixture of epimeric sulfinyl chlorides **I** and **II** which cyclise (following amide deprotonation) at disparate rates ($k_1 \gg k_2$ assuming inversion at sulfur in this process)[2b,5,9] such that (*S*)-*cis*-**1** is formed in excess (Scheme 3). The *cis* product may be favoured in the cyclisation because the methyl, pivaloyl and sulfur oxygen groups can all be oriented pseudo-*trans* in the transition state, thereby minimising unfavourable steric interactions relative to the transition state leading to the *trans*-isomer. Addition of a tertiary amine results in the formation of

† Several reports have appeared on potentially recoverable sulfoxides which have application to asymmetric synthesis, principally *via* a stereocontrolled sulfide oxidation directed by a nearby chiral centre.[8]

‡ Sulfinamides have been prepared by a related oxidative cyclisation.[12]

§ All new compounds gave satisfactory spectroscopic and physical data.

¶ To our knowledge the nature of the base used to promote cyclisations of this type has not previously been examined in detail. A number of reports have appeared on the preparation of diastereoisomeric 1,2,3-oxathiazolidine 2-oxides.[13] In each case the precursor amino alcohol or diol was treated with thionyl chloride and triethylamine, resulting in a stereoselective cyclisation in which the existing chiral centres of the heterocycle controlled the configuration of the new sulfur chiral centre with selectivities of 2:1 to 9:1.

Table 2 Ring opening reactions of (*S*)-*cis*-**1**

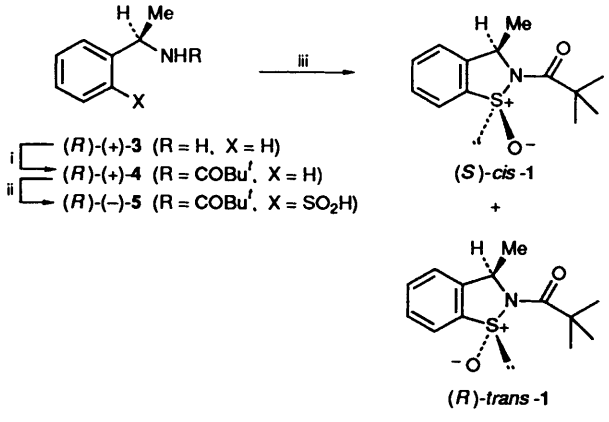
6	RM	Yield (%)
a	MeLi	89
b	BuLi	71
c	$PhCH_2MgBr$	89
d	$Bu^tO_2CCH_2MgBr$	87

a small concentration of highly reactive ammonium sulfinates **II** and **IV** which cyclise at faster rates than **I** and **II** and, therefore dominate the selectivity. Presumably $k_4 = k_3$ for pyridine, $k_4 > k_3$ for triethylamine and $k_4 \gg k_3$ for 4-dimethylaminopyridine (DMAP). The pK_a differences* between pyridine (5.21), triethylamine (11.01) and DMAP (9.65) may explain the low selectivity obtained with pyridine since low pK_a suggests a better leaving group which will be less sensitive to the structure of the cyclisation transition state. Although the reason for the high selectivity of DMAP relative to triethylamine is unclear, the two bases are fundamentally different in structure. The non-reversibility of the cyclisation was demonstrated by addition of an excess of DMAP to a THF solution of a 3:2 mixture of *cis*- and *trans*-**1**, which showed no change to the ratio after being stirred overnight, quenched with saturated aqueous ammonium chloride, and extracted. Treatment of a sample of pure (*S*)-*cis*-**1** in the same way with an excess of triethylamine failed to generate any *trans*-isomer. It should be noted that cyclisation *via* a trigonal bipyramidal species, with pseudorotation processes occurring at sulfur, cannot be ruled out.

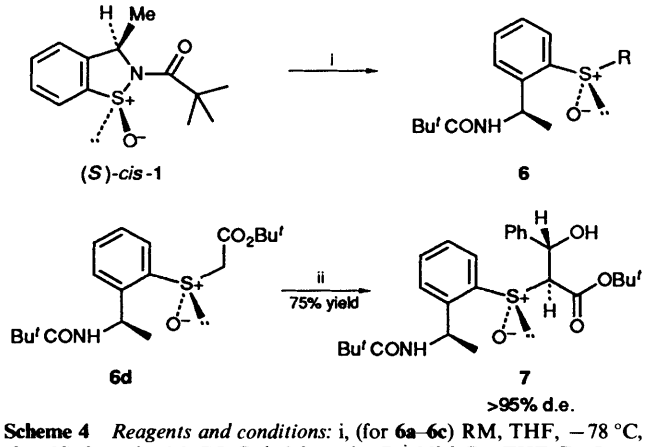
Having developed an efficient synthesis of enantiomerically pure (*S*)-*cis*-**1** we have studied its application to the control of asymmetric reactions. Initial experiments with alkyllithium and Grignard reagents showed that the heterocyclic ring could be clearly opened, with presumed inversion of configuration at sulfur,[2b] to the diastereoisomerically pure products **6a–d** (Scheme 4, Table 2).† The product from the ester anion reaction, **6d**, was a tar which solidified with time and could be recrystallised from dichloromethane–hexane. As a test of the synthetic significance of (*S*)-*cis*-**1**, the aldol reaction of **6d** with benzaldehyde was carried out using *tert*-butylmagnesium bromide as the base.[2b,c] 270 MHz ^1H NMR analysis of the crude reaction mixture, after removal of an excess of benzaldehyde by flash chromatography, showed that one predominant diastereoisomer of product **7** (therefore assumed to be of at least 95% diastereoisomeric excess) had been formed which was isolated in 75% yield, presumably as a single diastereoisomer after recrystallisation from dichloromethane–hexane (Scheme 4). The stereochemistry of **7** has not yet been determined but we predict that it is the diastereoisomer formed *via* the

* D. D. Perrin, *Dissociation Constants of Organic Bases*, Plenum Press, NY, 1965.

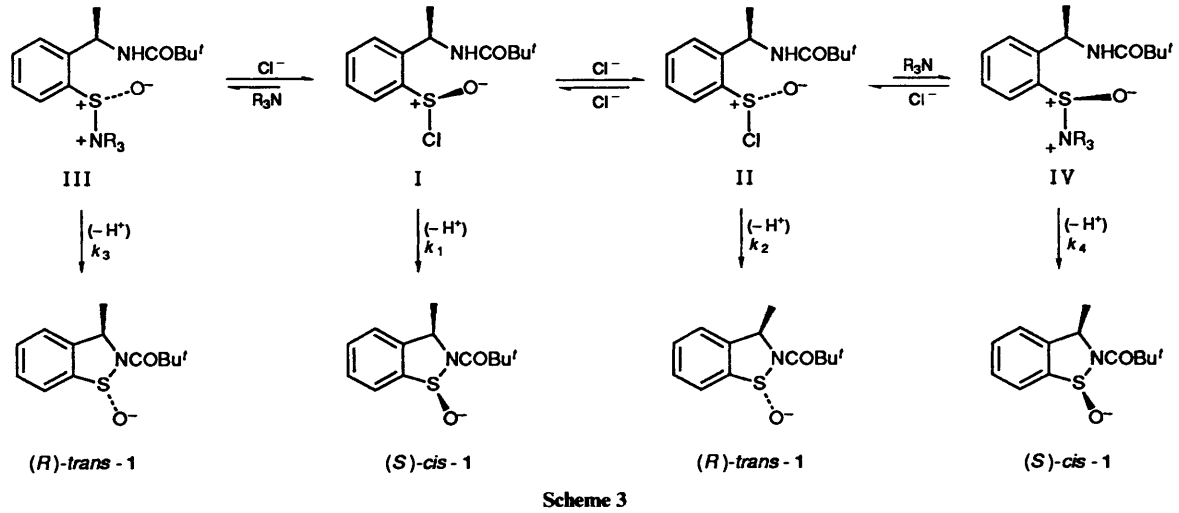
† See footnote § on p. 3383.



Scheme 2 *Reagents and conditions:* i, 1.1 equiv. Et_3N, 1.1 equiv. Bu^tCOCl, CH_2Cl_2, 0 °C, 16 h (94% yield); ii, 2.2 Bu^tLi, Et_2O, −78 °C 1 h, 0 °C 1 h, then SO_2, −78 °C (90% yield); ii, 1.5 equiv. $SOCl_2$, 1 equiv. R_3N, THF, 0 °C 1 h, room temp., 15 h, then 2 equiv. R_3N, 0 °C 2 h (yields in Table 1)



Scheme 4 *Reagents and conditions:* i, (for **6a–6c**) RM, THF, −78 °C, (for **6d**) 2 equiv. $MeCO_2Bu^t$, 3.2 equiv. Pr^i_2NMgBr, THF–Et_2O, −78 °C, 3 h; ii, 5 equiv. Bu^tMgBr, 3.0 equiv. PhCHO, THF, −78 °C, 6 h, then room temp. 6 h



Scheme 3

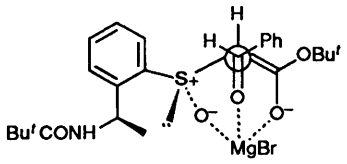
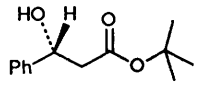


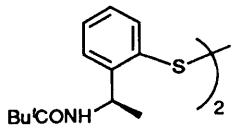
Fig. 1

magnesium chelated transition state in Fig. 1, in accord with that observed with the analogous *p*-tolyl sulfoxides.[2] The absolute configuration at the β-centre in the product was confirmed by treatment of **7** with mercury/aluminium amalgam, which resulted in reductive cleavage of the C(alkyl)–S bond to give enantiomerically enriched (>95% enantiomeric excess)* β-hydroxy ester (*R*)-(+)-**8** (85% yield) and disulfide **9** (80% yield).

In conclusion, we have demonstrated that enantiomerically pure sulfinate (*S*)-*cis*-**1** is available *via* a remarkably stereoselective DMAP-promoted cyclisation of a sulfinic acid precursor. The diastereoselectivity of the cyclisation is



(*R*)-(+)-**8**



9

dependent upon the nature of the tertiary amine used to catalyse the reaction and an explanation for this dependence has been provided. The *tert*-butyl sulfinylacetate **6d** derived from (*S*)-*cis*-**1** undergoes stereoselective aldol reaction with benzaldehyde, therefore efficiently creating a new chiral centre at the β-position.

Experimental

Preparation of (*S*)-(+)-cis-**1**.—Thionyl chloride (2.50 ml, 34.27 mmol) was added dropwise to a stirred and cooled (0 °C) solution of (*R*)-(−)-**5** (5.00 g, 18.59 mmol) and DMAP (2.43 g, 19.92 mmol) in THF (50 ml) under nitrogen. The mixture was stirred at room temperature for 16 h. Further DMAP (5.00 g, 40.98 mmol) was added portionwise and the mixture stirred at room temperature for a further 2 h. After this time it was quenched by the addition of saturated aqueous ammonium chloride (50 ml), the organic phase was separated and the aqueous solution was extracted with ethyl acetate (3 × 50 ml). The combined organic phases were washed with brine (50 ml), dried (sodium sulfate) and the solvent removed to give a yellow oil which solidified with time. ($S_{(S)}R$)-(+)-*cis*-**1** was isolated by flash chromatography [light petroleum (b.p. 60–80 °C)–EtOAc] as a white solid which was recrystallised from dichloromethane–hexane (3.13 g, 67%), m.p. 115–117 °C. Physical and spectral data matched those of authentic material.[5]†

* (*R*)-(+)-**8** above; $[\alpha]_{20}^{D}$ +13° (*c* 0.15, ethanol), reported (*S*)-(−)-**8** $[\alpha]_{20}^{D}$ −16.6 (*c* 0.545, ethanol).[2c] Enantiomeric purity of (*R*)-(+)-**8** was confirmed using the chiral shift reagent tris-[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III) derivative **10** (Aldrich). Addition of *ca.* 0.2 equiv. of **10** to a [$^2H_1$]chloroform solution of racemic **8** (prepared from the reaction between *tert*-butoxycarbonylmethyllithium and benzaldehyde) resulted in splitting of the *tert*-butyl signals due to each enantiomer. The same experiment on a solution of (*R*)-(+)-**8** isolated from the above reaction resulted in formation of only one singlet. Since baseline resolution was possible the enantiomeric excess was assumed to be in excess of 95%.

† See footnote § on p. 3383.

Acknowledgements

We thank the SERC and ICI Pharmaceuticals Ltd for a CASE award (to I. D. L.).

References

1 For a recent review see *The Chemistry of Sulphones and Sulphoxides*, S. Patai, Z. Rappaport and C. J. M. Stirling, Wiley Interscience, 1988, ch. 8 (J. Drabowicz, P. Keilbasinski and M. Mikolajcyk), 12 (S. Oae and Y. Uchida) and 16 (G. Posner).
2 (*a*) G. Solladie in *Asymmetric Synthesis*, ed. J. D. Morrison, Academic Press, 1983, vol. 2, ch. 6; (*b*) G. Solladie, *Synthesis*, 1981, 185; (*c*) G. Solladie and C. Mioskowski, *Tetrahedron*, 1980, **36**, 227; (*d*) E. J. Corey, L. O. Weigel, A. R. Chamberlin, H. Cho and D. Hua, *J. Am. Chem. Soc.*, 1980, **102**, 6615.
3 (*a*) G. Posner in ref. 2*a*, ch. 8; (*b*) G. H. Posner, *Acc. Chem. Res.*, 1987, **20**, 72 and references therein.
4 (*a*) G. Solladie, *Pure Appl. Chem.*, 1988, **60**, 1699; (*b*) H. Kosugi, H. Konta and H. Uda, *J. Chem. Soc., Chem. Commun.*, 1985, 211; (*c*) K. Ogura, M. Ishida and M. Fujita, *Bull. Chem. Soc. Jpn.*, 1989, 3987.
5 W. Oppolzer, M. Wills, C. Starkemann and G. Bernardinelli, *Tetrahedron Lett.*, 1990, **31**, 4117.
6 E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, 1965, **87**, 1345.
7 W. G. Filby, K. Gunther and R. D. Penzham, *J. Org. Chem.*, 1973, **38**, 4070.
8 (*a*) O. DeLucchi, *Tetrahedron Lett.*, 1987, **28**, 107; (*b*) M. R. Binns, R. J. Goodridge, R. K. Haynes and D. D. Ridley, *Tetrahedron Lett.*, 1985, **26**, 6381; (*c*) S. G. Pyne, P. Bloem and R. Griffith, *Tetrahedron*, 1989, **45**, 7013; (*d*) O. DeLucchi, V. Lucchini, C. Marchioro, G. Valle and G. Modena, *J. Org. Chem.*, 1986, **51**, 1457; (*e*) O. DeLucchi and D. Fabri, *Synlett*, 1990, 287; (*f*) S.-H. Hung, D.-S. Lee and T.-K. Yang, *Tetrahedron, Asymmetry*, 1990, **1**, 873.
9 K. K. Andersen, *Tetrahedron Lett.*, 1962, **18**, 93; (*b*) K. K. Andersen, W. Gaffield, N. E. Papanikoloau, J. W. Foley and R. I. Perkins, *J. Am. Chem. Soc.*, 1964, **88**, 5637; (*c*) Method involving epimerisation by HCl in acetone see ref 2(*b*) and G. Solladie, A. Girardin and J. Hutt, *Synthesis*, 1987, 173; (*d*) other routes to chiral sulphoxides; H. B. Kagan and F. Rebiere, *Synlett*, 1990, 643.
10 K. Hirio and N. Matsuyama, *Synthesis*, 1986, 65.
11 H. Phillips, *J. Chem. Soc.*, 1925, **127**, 2552; K. Zeigler and A. Wenz, *Justus Liebigs Ann. Chem.*, 1934, **511**, 109.
12 (*a*) J. T. Doi and W. K. Musker, *Tetrahedron Lett.*, 1985, **50**, 1; (*b*) B. J. Wagner, J. T. Doi and W. K. Musker, *J. Org. Chem.*, 1990, **55**, 4156.
13 (*a*) F. Wudl and T. B. K. Lee, *J. Chem. Soc., Chem. Commun.*, 1972, 61; (*b*) F. Wudl and T. B. K. Lee, *J. Am. Chem. Soc.*, 1973, **95**, 6349, related six membered heterocycles; (*c*) K. Hiroi, S. Sato and R. Kitayama, *Chem. Lett.*, 1980, 1595; (*d*) K. Hiroi, S. Sato and R. Kitayama, *Chem. Pharm. Bull.*, 1983, **31**, 3471, and cyclic sulphites; (*e*) H. B. Kagan and F. Rebiere, *Tetrahedron Lett.*, 1989, **30**, 3659.

Paper 1/04383H
Received 21*st August* 1991
Accepted 25*th September* 1991