Tetrahedron Letters,Vol.31,No.1,pp 35-38,1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

Preparation of Optically Active Stilbene Oxides Via Sulfonium Salts Derived from C_2 Symmetric Thiolanes.[1]

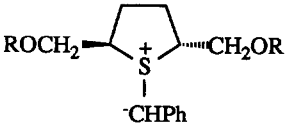
L.Breau[a], W.W. Ogilvie[b] and T. Durst[*]

Ottawa-Carleton Chemistry Institute, Department of Chemistry, University of Ottawa, Ottawa,
Canada K1N 6N5

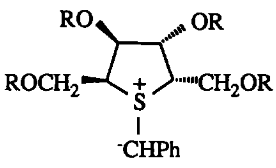
Abstract : Trans-stilbene oxides have been obtained in up to 83% enantiomeric excess via reaction of S-benzyl ylides prepared from optically active trans-2,5-disubstituted thiolanes.

The potential of sulfur ylides for the preparation of optically active epoxides was first recognized and investigated by Trost and Hammen in 1973.[2] Unfortunately their system, reaction of the ylide from optically active adamantylethylmethylsulphonium tetrafluoroborate with benzaldehyde, yielded styrene oxide with essentially no enantiomeric excess.

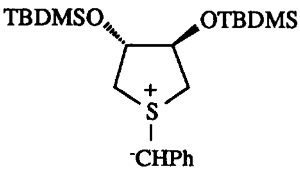
We have been investigating the reaction of the S-benzyl ylides derived from the optically active C_2 symmetric thiolanes (**1**), (**2**) and (**3**) with benzaldehyde, and in the case of (**2**) and (**3**) with substituted benzaldehydes, and find that trans-stilbene oxides are produced in up to 83% enantiomeric excess. Very recently, Furukawa and co-workers[3] have reported the preparation of several stilbene oxides in about 10-45% ee using an optically active sulfonium salt prepared by modification of 10-camphorsulphonic acid. These results represent the first examples of the preparation of optically active epoxides in which both a carbon-carbon and a carbon-oxygen bond rather than only carbon-oxygen bonds are formed in an asymmetric manner.[4]



1



2



3

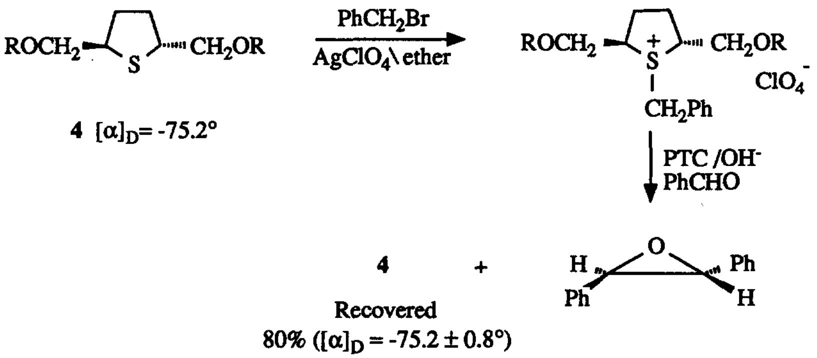
R = $PhCH_2$

---

[a] NSERC Scholarship holder 1986-1989.

[b] NSERC 67 Scholar 1985-1988.

The overall reaction scheme for the preparation of (R,R)-trans-stilbene oxide using the ylide (**1**) is shown below.



The thiolanes required for the preparation of the above ylides were synthesized by standard procedures. The precursor for (**1**), thiolane (**4**), was obtained by resolving thiolane-trans-2,5-dicarboxylic acid with brucine[5] followed by reduction and benzylation[6], that leading to (**2**) by benzylation of the corresponding tetraol[7a,b]. The thiolane leading to (**3**) was prepared by reduction of the isopropylidene tartrate[8a], obtained from *l*-tartaric acid followed by tosylation, deprotection, silylation and cyclization with Na_2S in DMF.[8b]

Sulfonium salt formation was carried out by treatment of the precursor thiolane with $PhCH_2Br$ in ether followed by addition of $AgClO_4$. Purification was accomplished by evaporating the ether, adding CH_2Cl_2 and filtering to remove the insoluble silver salt(s). The filtrate was evaporated and triturated with ether to remove any unreacted thiolane and benzyl bromide. It is important to remove silver salt(s) impurities since their presence results in black reaction mixtures during the ylide reaction and very low recovery of the thiolane auxiliary. The salts thus obtained were characterized by proton and carbon nmr which showed clearly that only one sulfonium salt had formed as expected on the basis of the C_2 symmetry of the thiolanes. The yields ranged from 60 - 75%. These sulfonium salts became brownish on standing at room temperature suggesting limited stability.

We have used NaOH under phase transfer conditions and NaH in DMSO as base in our initial epoxidation studies. The results for the reaction of the reaction of the ylides (**1**), (**2**), and (**3**) with benzaldehyde, and several substituted benzaldehydes in the case of ylides (**2**) and (**3**), are shown in the Table. As can be seen the highest enantiomeric excess was obtained with ylides derived from thiolanes having substituents close to the ylide reaction center, i.e., at C-2 and C-5.

Interestingly and somewhat surprisingly the ylides (**1**) and (**3**) afforded trans-stilbene oxide with the same absolute configuration despite the fact that the substituents at C-3 and C-4 in (**3**) have the opposite sense of chirality compared to C-2 and C-5 in (**1**). The results obtained with the ylide (**2**) derived from 2,3,4,5-tetrasubstituted thiolane suggest that the C-2 and C-5 substituents are dominant in determining the extent of asymmetric induction in the product.

In order to have the potential for synthesis of optically active epoxides the chiral auxiliary thiolane. must be recoverable and recyclable without loss of optical activity. This point was proven in the reaction of the ylide (**1**) and (2) with benzaldehyde. In addition to the 53% yield of (R,R)-trans stilbene oxide (60%ee) the thiolane (4) was recovered in 80% yield with essentially no loss of optical purity.

Table. Preparation of stilbene oxides via optically active sulfur ylides.

Ylide	Aldehyde	Reaction Condition	Epoxide Yield (%)	e.e.[1] (%)
1	PhCHO	A	53	60 (63)[2]
2	PhCHO	A	27	64
2	4-$NO_2C_6H_4CHO$	A	41	83
3	PhCHO	B	30	15
3	4-MeC_6H_4CHO	B	49	11
3	4-ClC_6H_4CHO	B	94	7
3	4-$NO_2C_6H_4CHO$	B	72	13

Method: A) NaOH 50% / cat. $BnEt_3NHCl$ / CH_2Cl_2 - 0°C .
B) $NaCH_2S(O)CH_3$ / THF - 10°C.

1. Based on $[\alpha]_D$ measurements[9].
2. Based on the 95% optical purity of (4).

We feel that it is somewhat premature at this point to try to draw mechanistic conclusion which might be used to explain our results.[10] We are confident that more effective chiral auxiliaries can be designed and synthesized which will allow for the preparation of a variety of optically active epoxides via the sulfur ylide + carbonyl compound route. The preparation of optically active cyclopropanes resulting from the reaction of sulfur ylides with electron deficient alkenes is also being examined.

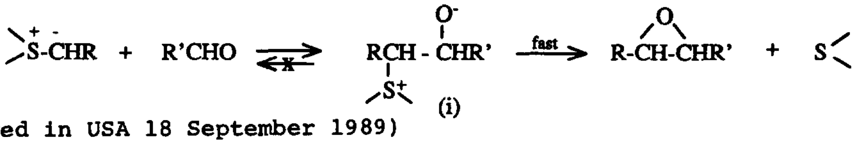
Acknowledgments: Support for this work by NSERC (Canada) is gratefully acknowledged.

References and Footnotes

1. Presented in preliminary form at the 3rd North American Chemical Congress, Toronto, Canada, June 1988, Abstract 125 and at the 72nd Canadian Chemical Conference; Victoria, Canada, June 1989, Abstract 599.

2. B.M. Trost, R. F. Hammen. *J. Am. Chem. Soc.* **1973,** 95, 962.
3. N. Furukawa, Y. Sugihara and H. Fujihara, *J. Org. Chem.*, **1989,** 4222.
4. For a review of the Sharpless asymmetric epoxidation see: (a) B.E. Rossiter in *Asymmetric Synthesis;* Morrison, J.D., Ed.; Academic Press: New Yord, 1985; Vol. 5, Chapter 7, 193; (b)Y. Gao, R.M. Hanson, J.M. Klunder, S.Y. Ko, H.Masamune, and K.B. Sharpless, *J. Am. Chem. Soc.*,**1987,**109,5765.
5. A. Fredga, *J. Prakt. Chem.*, **1938,** 150, 124. Absolute stereochemistry of (-)-thiolane-2,5-dicarboxylic acid was determined to be (2R),(5R) by conparison of its specific rotation with literature : K. Achiwa, Y. Morimoto, Y. Terao, *Chem. Pharm. Bull.*, **1987,** 35 (6), 2266.
6. The thiolane (4) gave the following spectroscopic data: $[\alpha]_D^{23}$ -75.2° (c .625, CH_2Cl_2); IR (neat) 2940,1365, 1120-1070, 740 and 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.86 (m, 2H), 2.08(m, 2H), 3.46(m, 4H), 3.60(m, 2H), 4.51(d, 1H, J=12Hz), 4.58(d, 1H, J=12Hz) and 7.28(m, 10H); EIMS:m/z(%), 328(M^+,1.2), 221(77), 220(77), 131(69), 99(98) and 92(100). Anal. Calc. for $C_{20}H_{24}O_2S$: C, 73.14; H, 7.36; S, 9.76. Found: C, 72.94; H, 7.36; S, 9.89.
7. a) A.V.R. Rao, K.A. Reddy, M.K. Gurjar and A.C. Kunwar; *J. Chem. Soc., Chem. Commun.*, **1988,** 1273. b) The parent thiolane gave the following spectroscopic data: $[\alpha]_D^{23}$ -32.7 (c 1.25, CH_2Cl_2); IR (neat) 3040, 2850, 1365, 1210, 1140-1050, 740 and 705cm^{-1}; ^1H NMR ($CDCl_3$) δ ppm 3.56(dd, 2H, J=8.05 and 5.1Hz), 3.78 (d, 2H, J=8.05Hz), 3.86 (dd, 2H, J= 5.3 and 3.2Hz), 4.08 (d, 2H, J= 2.9Hz), 4.47 (s, 4H), 4.48(s, 4H), 7.23 (m, 20H); CIMS:m/z(%), 433 (M^{+}- OBn, 6.6).
8. a) D. Seebach, H.O. Kalinowski, B.Bastani, G. Grass, H. Daum, H. Dorr, N.P. DuPreez, V. Ehrig, W. Langer, C Nussler, H. Oei and M. Schmidt; *Helv. Chim. Acta,* **1977,** 60, p.301; b) The corresponding thiolane gave the following spectroscopic data: $[\alpha]_D^{23}$ +29.0° (c = 2.98, acetone); I.R. (neat) 1255, 1070 cm^{-1}; ^1H NMR ($CDCl_3$) δ ppm 0.06(s,12H), 0.86(s, 18H), 2.62(dd, 2H, J=10.72 and 2.39Hz), 3.03(dd, 2H, J=10.72 and 3.39Hz) and 4.11(dd, 2H, J=3.39 and 2.39Hz); EIMS:m/z 291(M^+-57, 61%).
9. M. Imuta, H. Ziffer, *J. Org. Chem.*, **1979,** 44, 2505.
10. The following aspects are pertinent to any mechanistic discussion. The structure of stabilized ylides such as $(CH_3)_2S^+$-$C^-(CN)_2$ has been established by X-Ray diffraction [a) A.F.Cook and J.G. Moffatt, *J. Amer. Chem. Soc.*, **1968,** 90, 740; b) A.T. Christensen and W.G. Whitmore, *Acta Cript.*, **1969** 25B, 73.]. The sulfonium sulfur was pyramidal, the carbanion planar, and the $S(CH_3)_2$ angle bisected by the plane made by the $C(CN)_2$ group.

    It is also known that the reaction of a sulfonium ylides such as (1)-(3) with a carbonyl compound to generate a betaine (i) is essentially irreversible [c) C.R. Johnson, C.W. Schroeck, J.R. Shanklin., *J. Am. Chem. Soc.*, **1973,** 95, 7424; d) T.Durst, R.Viau, R.Van Den Elzen, C.H. Nguyen., *J. Chem. Soc., Chem. Commun.*, **1971,** 1334; e) J.M.Townsend, K.B.Sharpless., *Tetrahedron Lett.*, **1972,** 3313.] and thus the final stereochemistry of the epoxide is fixed in this step. However the mode of addition of the ylide to a carbonyl group, whether a 2 + 2 cycloaddition analogous to the phosphorus ylide reaction [f) E.Vedejs and C.F.Marth., *J. Am. Chem. Soc.*, **1989,** 111, 1519.] or a head to tail addition leading directly to the betaine (i) has not been established.



(Received in USA 18 September 1989)