A Simple C_2 Symmetrical Sulfide for a One-Pot Asymmetric Conversion of Aldehydes into Oxiranes

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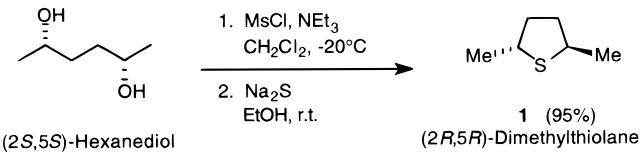
Epoxides are versatile intermediates used to a very large extent in short or multistep syntheses. One of the most important reactions[1,2] is their opening with amines, providing 1,2-amino alcohols of major biological interest, such as adrenergic β-blockers[3,4] or inhibitors of ergosterol synthesis.[5,6] Access to enantiopure oxiranes by Sharpless and Jacobsen type oxidations of alkenes has been the focus of several studies.[7−9] Alternative starting substrates are carbonyl compounds using the reaction of sulfur ylides developed in the 1960s. Initial attempts[10] to achieve an asymmetric epoxidation were disappointing until the advances[11−18] of the 1990s. A pioneering work by Furukawa showed the feasibility of an approach based on chiral sulfides.[19] It was rapidly followed[20,21] by breakthroughs of Durst who reported the first ee's reaching 90%, with a chiral sulfide,[20] obtained in six steps from camphoric acid. Recently the groups of Solladié-Cavallo,[12−14] Aggarwal,[15−17] and Dai[18] have reported major advances in terms of chemical efficiency and ee's, based on chiral sulfonium ylides derived from pulegone or camphor with various reaction conditions. We report[22] a simple chiral auxiliary, which can be prepared in two steps and has C_2 symmetry and low molecular weight (only 6 carbons) tending toward the principle of atom economy.[23] It can be used in a simple one-pot procedure, and it leads to epoxides in high yields and diastereoisomeric and enantiomeric excesses (de and ee).

Scheme 1



The principle of C_2 symmetry[24] has been applied to chiral sulfides by Durst and co-workers with three thiolanes,[21] prepared in five steps with unspecified yields. The reaction of the corresponding sulfur ylides with benzaldehyde as a typical example led to stilbene oxide with yields ranging from 27 to 53% (calculated from the sulfonium salt) and enantiomeric excesses from 15 to 64%. We decided to investigate the use of the very simple enantiopure trans 2,5-dimethylthiolane **1**. It is only mentioned[25,26] in a meeting report in which it was indicated briefly that it did not lead to any asymmetric induction. We have prepared[26] thiolane **1** easily in only two steps from commercially available (2*S*,5*S*)-hexanediol. This diol[27−29] can also be obtained by the enzymatic reduction of the cheap 2,5-hexanedione with baker's yeast.[27] Activation of hydroxyl groups into mesylates[30] and subsequent cyclization with sodium sulfide, by two nucleophilic substitutions with inversion, furnished the C_2 symmetrical sulfide **1** in 95% yield.

The asymmetric benzylidene transfer on aldehydes was investigated. We intended to use a simple epoxidation procedure[18,19] involving a mineral base and mixing all reagents together in one pot at room temperature (Scheme 2). The reaction of benzaldehyde (1 equiv) with benzyl bromide (2 equiv) and thiolane **1** (1 equiv) was carried out with potassium or sodium hydroxide (2 equiv) in various solvents. Experiments in nonpolar or moderately polar solvents, under heterogeneous (toluene/aqueous NaOH, CH_2Cl_2/aqueous NaOH) or homogeneous (THF/aqueous NaOH) conditions, furnished poor yields or

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(1) Gorzynski Smith, J. *Synthesis* **1984**, 629−653.
(2) Rao, A. S.; Paknikar, S. K.; Kirtane, J. G. *Tetrahedron* **1983**, *39*, 2323−2367.
(3) Main, B. G. *Comprehensive Medicinal Chemistry*; Hansch, C., Sammes, P. G., Taylor, J. B., Emmett, J. C., Eds.; Pergamon: Oxford, 1990; Vol. 3, pp 187−228.
(4) Ganellin, C. R.; Roberts, S. M. *Medicinal Chemistry: The Role of Organic Chemistry in Drug Research*; Academic Press: London, 1993.
(5) Schwin, F. J. *Pestic. Sci.* **1983**, *15*, 40−47.
(6) Siegel, M. R. *Plant Disease* **1981**, *65*, 986−989.
(7) Aubé, J. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Schreiber, S. L., Eds.; Pergamon Press: Oxford, 1991; Vol. 1, pp 819−842.
(8) Besse, P.; Veschambre, H. *Tetrahedron* **1994**, *50*, 8885−8927.
(9) Katsuki, T.; Martin, V. S. *Org. React.* **1996**, *48*, 1−299.
(10) Trost, B. M.; Hammen, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 962−964.
(11) Li, A.-H.; Dai, L.-X.; Aggarwal, V. K. *Chem. Rev.* **1997**, *97*, 2341−2372. Aggarwal, V. K. *Synlett* **1998**, 329−336.
(12) Solladié-Cavallo, A.; Adib, A. *Tetrahedron* **1992**, *48*, 2453−2464.
(13) Solladié-Cavallo, A.; Diep-Vohuule, A. *J. Org. Chem.* **1995**, *60*, 3494−3498.
(14) Solladié-Cavallo, A.; Diep-Vohuule, A. *Tetrahedron: Asymmetry* **1996**, *7*, 1783−1788.
(15) Aggarwal, V. K.; Kalomiri, M.; Thomas, A. P. *Tetrahedron: Asymmetry* **1994**, *5*, 723−730.
(16) Aggarwal, V. K.; Thompson, A.; Jones, R. V. H.; Standen, M. C. H. *Tetrahedron: Asymmetry* **1995**, *6*, 2557−2564.
(17) Aggarwal, V. K.; Ford, J. G.; Thompson, A.; Jones, R. V. H.; Standen, M. C. H. *J. Am. Chem. Soc.* **1996**, *118*, 7004−7005.
(18) Li, A.-H.; Dai, L.-X.; Hou, X.-L.; Huang, Y.-Z.; Li, F.-W. *J. Org. Chem.* **1996**, *61*, 489−493.
(19) Furukawa, N.; Sugihara, Y.; Fujihara, H. *J. Org. Chem.* **1989**, *54*, 4222−4224.
(20) Breau, L.; Durst, T. *Tetrahedron: Asymmetry* **1991**, *2*, 367−370.
(21) Breau, L.; Ogilvie, W. W.; Durst, T. *Tetrahedron Lett.* **1990**, *31*, 35−38.
(22) Communicated at the 4th ANORCQ meeting, Southampton (U.K.), April 17, 1997.
(23) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259−281.
(24) Whitesell, J. K. *Chem. Rev.* **1989**, *89*, 1581−1590.
(25) Durst, T. *Phosphorus Sulfur Silicon Relat. Elem.* **1993**, *74*, 215−232.
(26) After this note was submitted for publication, a preparation of thiolane **1** was reported according to the same method as the one used here. Otten, S.; Fröhlich, R.; Haufe, G. *Tetrahedron: Asymmetry* **1998**, *9*, 189−191.
(27) Lieser, J. K. *Synth. Commun.* **1983**, *13*, 765−767.
(28) Burk, M. J.; Feaster, J. E.; Harlow, R. L. *Tetrahedron: Asymmetry* **1991**, *2*, 569−592.
(29) Ikeda, H.; Sato, E.; Sugai, T.; Ohta, H. *Tetrahedron* **1996**, *52*, 8113−8122.
(30) Short, R. P.; Kennedy, R. M.; Masamune, S. *J. Org. Chem.* **1989**, *54*, 1755−1756.

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Scheme 2

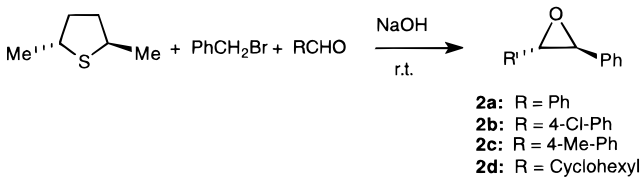
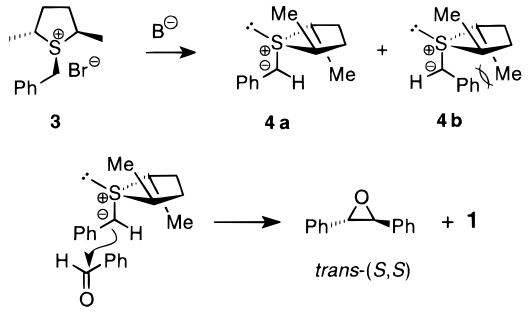


Table 1. Asymmetric Synthesis of Stilbene Oxide 2a in Various Solvents with KOH

entry	solvent	time (days)	yield (%)[a]	de (trans) (%)[b]	ee (*S*,*S*)[c] (%)[d]
1	9:1 CH_3CN:H_2O	1	92	88	84
2	9:1 *t*-BuOH:H_2O	2	92	86	88
3	9:1 *i*-PrOH:H_2O	8	59	86	90
4	9:1 EtOH:H_2O	3	15	84	94
5	H_2O	4	90	74	86

[a] Yield after purification on a silica gel column. [b] Diastereoisomeric excess determined on ^{1}H NMR measurements from the crude product. [c] The major enantiomer (*S*,*S*) is eluted first by chiral HPLC.[17] [d] Enantiomeric excess determined by chiral HPLC using a Chiralsep Chirose-Bond or OD column.

Scheme 3. Asymmetric Induction Model



selectivities. In more polar solvents (DMF, DMSO, MeCN, alcohols) with powdered KOH, we observed various predominant side reactions (Cannizzaro reaction, benzyl bromide solvolysis, Williamson alkylation, solvent reactivity). These could be largely avoided by the addition of 10% of water in the case of MeCN[31] and *t*-BuOH; under these conditions, stilbene oxide was obtained in excellent yields, in 1 or 2 days at ambient temperature (Table 1, entries 1−2). Very remarkable is our observation that this reaction could even be carried out in water (Table 1, entry 5). In all cases, the trans isomer of stilbene oxide **2a** was formed preferentially and the major enantiomer was identified[17] by chiral HPLC as the *trans*-(2*S*,3*S*)-diphenyloxirane. The best enantiomeric excesses (from 84 to 94%) were achieved with MeCN:H_2O, alcohol:H_2O, and H_2O (Table 1).

The high asymmetric induction can be rationalized as shown in Scheme 3. The C_2 symmetry of **1** dictates the formation of the single sulfonium salt **3** by reaction with benzyl bromide. Deprotonation affords the ylide **4** with a planar carbon and a tetrahedral sulfur, the sulfur doublet lying in the plane of the ylide carbon substituents to avoid repulsive interaction with the carbanion doublet.[25,32−34] Out of two possible conformations (**4a** and **4b**), the former is favored as the phenyl group is away from the thiolane ring. Attack of the si face of the ylide **4a** would be preferred; the re face is indeed hindered by the methyl group cis to the benzylidene group. A classical 109° approach of the aldehyde, leading to the trans epoxide, avoids the gauche interaction between the ylide and aldehyde phenyl groups. This model results in the formation of the trans (*S*,*S*) enantiomer, as observed experimentally. It contrasts with the models proposed by Solladié-Cavallo[13] and Dai[18] with the attack of the aldehyde carbonyl being respectively either orthogonal or opposite to ours to provide a coordination with an oxygen atom absent in our inductor.

The excellent data obtained in a mixture of *tert*-butyl alcohol and water (9:1) for the synthesis of stilbene oxide from benzaldehyde (Table 1, entry 2), in terms of yield (92%) and de and ee values (86 and 88%), led us to prefer this solvent for further investigations. The nature of the base (KOH or NaOH) was shown to have no influence on the yield and the stereocontrol. The epoxidation of various aromatic aldehydes and an aliphatic one was then achieved in 9:1 *t*-BuOH:H_2O with NaOH, in 2 days and in yields of about 90% (Table 2, Scheme 2). Trans oxiranes **2** were formed with 85% de for aromatic aldehydes (entries 1−3), and the reduced diastereoselectivity observed for an aliphatic aldehyde (entry 4) was not unexpected according to recent studies.[35] Enantioselectivities from 86 to 94% were observed for the trans isomers. Starting from cyclohexanecarboxaldehyde, we were able to analyze the cis oxirane and measured a 82% ee (entry 4).

An attractive feature of this ylide chemistry is that the initial sulfide is recovered after epoxidation and usable in a catalytic amount.[17−19] The feasibility of a catalytic process was here demonstrated by the use of 0.1 equiv of thiolane **1** for the epoxidation of benzaldehyde (1 equiv) with benzyl bromide (2 equiv) in 9:1 *t*-BuOH:H_2O with NaOH. The reaction was slow as expected (1 month to complete the reaction), but an excellent yield of **2a** (94%) was obtained, and de and ee values were maintained (85 and 90%). Thus the thiolane **1** is robust under the basic conditions which we have used.

In conclusion, we have introduced a very simple sulfide for the asymmetric ylide mediated epoxidation of carbonyl compounds. Thiolane **1** is prepared in a straightforward manner (two steps) and in excellent yield. Attractive conditions have been found for a one-pot procedure, potentially feasible for scaling up. They do not require a strong base, anhydrous solvent, inert atmosphere, preformation of the sulfonium salt,[13,20] or harsh electrophiles (phenyldiazomethane[17] or triflates[13]). Our chiral auxiliary, by its simplicity, efficiency, and robustness, is thus attractive. In the category of one-pot procedures using simple reagents,[18,19] our procedure is excellent: for stilbene oxide the yield is 92% and the ee 88% with a sulfide prepared in two steps and 95% yield. The opposite enantiomer of **1** appears accessible from the known (2*R*,5*R*)-hexanediol.[28,36,37] Extension of this reac-

(31) The reaction reported by Dai and Huang[18] with a camphor-derived sulfide in acetonitrile (from the bottle) could not be reproduced unless we added a few percent of water.

(32) Wolfe, S. *Organic Sulfur Chemistry. Theoretical and Experimental Advances*; Bernardi, F., Csizmadia, I. G., Mangini, A., Eds.; Elsevier: Amsterdam, 1985; pp 133−190.

(33) Fava, A. *Organic Sulfur Chemistry. Theoretical and Experimental Advances*; Bernardi, F., Csizmadia, I. G., Mangini, A., Eds.; Elsevier: Amsterdam, 1985; pp 299−354.

(34) Aggarwal, V. K.; Schade, S.; Taylor, B. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2811−2813.

(35) Aggarwal, V. K.; Calamai, S.; Gair Ford, J. *J. Chem. Soc., Perkin Trans. 1* **1997**, 593−599.

(36) Kim, M.-J.; Lee, I. S.; Jeong, N.; Choi, Y. K. *J. Org. Chem.* **1993**, *58*, 6483−6485.

(37) Nagai, H.; Morimoto, T.; Achiwa, K. *Synlett* **1994**, 289−290.

Table 2. Asymmetric Synthesis of 1,2-Dialkyloxiranes 2 in 9:1 *t*-BuOH:H_2O with NaOH

entry	aldehyde	time (days)	oxirane	yield (%)[a]	de (trans) (%)[b]	ee (trans) (%)[d]	ee (cis) (%)[d]
1	benzaldehyde	2	**2a**	92	86	88 (*S*,*S*)[c]	meso
2	4-chlorobenzaldehyde	2	**2b**	89	84	86 (*S*,*S*)[c]	*e*
3	4-tolualdehyde	2	**2c**	88	84	88 (*S*,*S*)[c]	*e*
4	cyclohexanecarboxaldehyde	2	**2d**	87	30	94	82

[a] Yield after purification on a silica gel column. [b] Diastereoisomeric excess determined on ^{1}H NMR measurements from the crude product. [c] The major enantiomer (*S*,*S*) is eluted first by chiral HPLC.[17] [d] Enantiomeric excess determined by chiral HPLC using a Chiralsep Chirose-Bond or OD column. [e] The enantiomers could not be separated by chiral HPLC.

tion to a variety of substrates for alkylidenation, cyclopropanation, and aziridination will be reported in due course.

Experimental Section

Preparative flash liquid chromatography was performed with Merck 60 silica gel (63−200 μm) in the eluting solvents indicated below. ^{1}H NMR (250 MHz) spectra were recorded on a Bruker AC 250 spectrometer. Data appear in the following order: chemical shift in ppm, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant in hertz, number of protons, assignment. ^{13}C NMR spectra were determined at 62.9 MHz with the same spectrometer, operating with broad band ^{1}H decoupling. The solvent used is $CDCl_3$, and TMS is the internal standard. (2*S*,5*S*)-Hexane-2,5-diol is commercially available (Aldrich) and was also prepared[27] by baker's yeast reduction of 2,5-hexanedione.

(2*R*,5*R*)-2,5-Dimethylthiolane (1). According to ref 30 a solution of (2*S*,5*S*)-hexane-2,5-diol (3.5 g, 29.6 mmol), and triethylamine (10 mL, 72 mmol) in dichloromethane (60 mL) was cooled at −18 °C. Methanesulfonyl chloride (5 mL, 65 mmol) was added dropwise while the temperature was maintained between −20 and −15 °C. After addition the mixture was allowed to warm to 0 °C. A 1 N HCl solution (10 mL) was added. The extraction was carried out with dichloromethane (2 × 30 mL). The organic layer was separated, washed with a saturated $NaHCO_3$ aqueous solution (30 mL), and dried over $MgSO_4$. After filtration and evaporation of the solvent, a colorless oil of (1*S*,4*S*)-4-methanesulfonyloxy-1-methylpentyl methanesulfonate was obtained (8.2 g, quantitative yield). ^{1}H NMR δ: 1.44 (d, J = 6.3 Hz, 6H), 1.75−1.84 (m, 4H), 3.02 (s, 6H), 4.84−4.90 (m, 2H). ^{13}C NMR δ: 21.3, 32.1, 38.8, 78.9.

Sodium sulfide ($Na_2S\cdot 9H_2O$, 14.4 g, 60 mmol) was added to a solution of the preceding dimesylate (8.2 g, 29.6 mmol) in ethanol (75 mL). The mixture was stirred at ambient temperature for 15 days. A milky suspension of sodium methanesulfonate was formed. It was poured into water (50 mL) and extracted with pentane (4 × 25 mL). The combined organic phase was washed with brine (2 × 50 mL) and dried over $MgSO_4$. After filtration, pentane was evaporated with the evaporator water bath being kept at 0 °C to avoid any loss of the volatile thiolane **1**. A pale yellow liquid (3.28 g, 95%) was obtained with an unpleasant odor (storing in the cold in a carefully closed vial and manipulation under hood avoided any discomfort). It appeared unnecessary to further purify (2*R*,5*R*)-2,5-dimethylthiolane **1**. Bp_{12} = 37 °C. $[\alpha]^{25}_D$ = +119° (c = 4,0; pentane). ^{1}H NMR δ: 1.30 (d, J = 6.5 Hz, 6H), 1.49−1.57 (m, 2H), 2.13−2.24 (m, 2H), 3.52−3.65 (m, 2H). ^{13}C NMR δ: 22.8, 39.6, 44.5. HRMS: calcd for $C_6H_{12}S$ 116.06597, found 116.0659.

(2*S*,3*S*)-Diphenyloxirane 2a. To a solution of (2*R*,5*R*)-dimethylthiolane **1** (24 mg, 0.2 mmol) in a 9:1 mixture of *tert*-butyl alcohol and water (0.8 mL) were added benzyl bromide (48 μL, 0.4 mmol), benzaldehyde (20 μL, 0.2 mmol), and powdered NaOH (16 mg, 0.4 mmol). The reaction mixture was stirred for 2 days at room temperature. Water was added. The aqueous phase was extracted with dichloromethane; the combined organic layers were dried over $MgSO_4$ and then concentrated to dryness. NMR analysis[38] of the crude product revealed a 93:7 trans:cis ratio. The crude product was submitted to column chromatography (silica gel, 70:30 petroleum ether/dichloromethane) to afford 36 mg of 2,3-diphenyloxirane **2a** (92%). HPLC analysis[17] (OD column, 99:1 *n*-hexane/2-propanol) showed that the product was a 94:6 ratio of (*S*,*S*):(*R*,*R*) enantiomers [retention times: 5.1 min for the meso oxirane, 6.5 for the (*S*,*S*) enantiomer, and 10.0 for the (*R*,*R*) one].

Oxiranes 2b−d. They are known compounds whose structures (trans and cis) were assigned by comparison with the literature spectroscopic data.[38]

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Supporting Information Available: Chromatographic analysis of the enantiomers of epoxides **2a**−**d** (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(38) Aggarwal, V. K.; Abdel-Rahman, H.; Fan, L.; Jones, R. V. H.; Standen, M. C. H. *Chem. Eur. J.* **1996**, *2*, 1024−1030.