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Asymmetric Methylene Transfer Reactions I : Asymmetric Synthesis of Oxiranes from Carbonyl Compounds by Methylene Transfer Reaction Using Chiral S-Methyl-S-neomenthyl-N-tosyl Sulfoximines +

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Abstract : The use of ylides prepared from (-)-S-methyl-S-neomenthyl-N-tosyl sulfoximine, **10a**, and its epimer at sulfur, **10b**, as methylene transfer reagents for the conversion of prochiral carbonyl compounds to oxiranes has yielded chiral oxiranes with 56-86% enantiomeric excess.

INTRODUCTION

The methodologies currently available for the chemical enantioselective synthesis of oxiranes have mostly centered around the epoxidation of alkenes. Two major routes are : 1. The Sharpless epoxidation[1] applicable to allylic alcohols, and, 2. Epoxidation with catalysts such as metal complexes[2], certain porphyrins[3], etc., mainly studied with phenyl alkenes (styrenes).

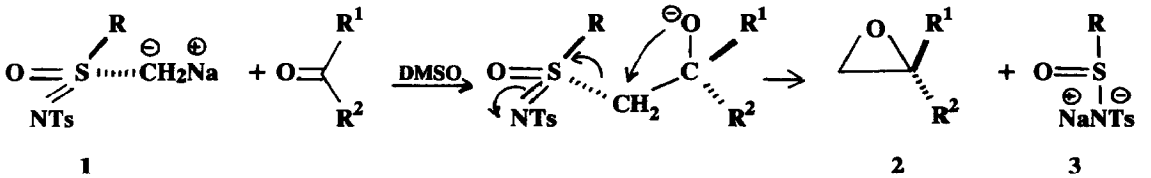
The synthesis of oxiranes by methylene transfer from dimethyl sulfoxonium methylide (Corey's reagent) and related reagents to carbonyl compounds has been known for over 30 years.[4] Various attempts to achieve the enantioselective synthesis of oxiranes by the use of chiral reagents have resulted[5] in chiral products with less than 30% enantiomeric excess (ee). In cases involving the transfer of benzyl groups using sulfur containing chiral auxiliaries, however, syntheses of oxiranes with higher ee (70-100%) have been reported.[6,7]

Sulfoximines[8,9] are another class of methylene transfer reagents used for the synthesis of oxiranes. Attempts at the asymmetric synthesis of oxiranes using sulfoximines having a stereogenic sulfur have not been very successful (ee, < 40%).[10] We felt that sulfoximines with suitable chiral ligands could be exploited for the synthesis of chiral oxiranes. In this and subsequent papers we present the results of our studies on the enantioselective synthesis of oxiranes in fairly good enantiomeric excess using chiral sulfoximines possessing stereogenicity both on a sulfur atom and on carbon atoms of substituent groups.

RESULTS AND DISCUSSIONS

The methylene transfer from a S-methyl sulfoximine to a carbonyl substrate leading to the formation of an oxirane can be represented as in Scheme 1.

+ MRC Communication No. 69

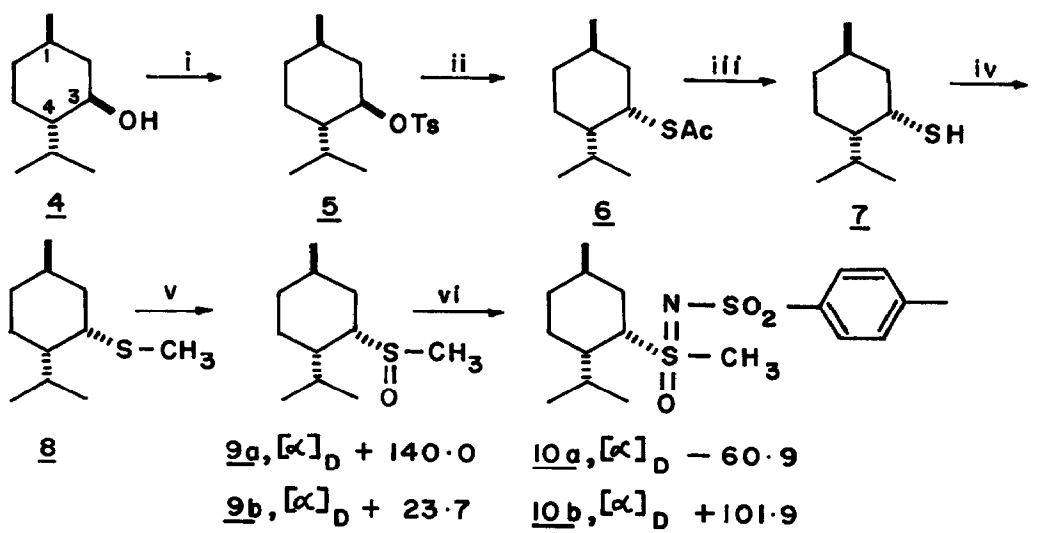


Scheme - 1

The stereochemical outcome will be influenced by the stereochemistry of the transition state which in turn will be dependent on the stereochemistry of the reactant sulfoximine. As earlier work[10] has shown that chirality on sulfur of the sulfoximine does have some effect on the chirality of the product oxirane, we felt that this effect could be enhanced significantly by having suitable chiral ligands on sulfur. Initially we focussed our attention on the use of (-)-menthol, **4**, to provide the menthyl group possessing three stereogenic centres as a ligand on sulfur.

As substrates for this study on asymmetric methylene transfer reactions, we chose phenyl ketones (and benzaldehydes) believing that the resulting chiral oxiranes could be excellent intermediates for preparing a large number of chiral 2-aryl propionic acids (*via* the corresponding aldehydes)[11] which in turn are the most sought-after chirons for the synthesis of a variety of commercially important pesticides such as (S)-fenvalerate, and drugs such as (S)-ibuprofen, (S)-naproxen, etc.

(1R,3R, 4S)-(-)-Menthol, **4**, was converted[12] *via* its tosylate, thioacetate and thiol to (1R,3S,4S)-(+)-S-methyl-S- neomenthyl sulfide, **8**, which on oxidation with hydrogen peroxide gave an epimeric (at sulfur) pair[13] of sulfoxides, **9a** and **9b** (Scheme 2). One of the diastereomers could be isolated from the mixture



Reagents : i. TsCl, Py; 10°C/12 hr; ii. KSAc, DMSO; 45°C/44 hr; iii. LAH, Et_2O; 35°C/6 hr; iv. MeONa/MeOH, MeI; 30°C/10 hr; v. H_2O_2, AcOH; 25°C/50 hrs; vi. p-TsN_3, Cu, MeOH; 65°C/64 hrs.

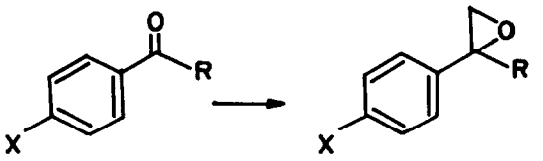
Scheme 2

by crystallisation and purified to 100% enantimoric purity (Chiral GC) by recrystallisation to give **9a**[14], $[\alpha]_D$ + 140.06. By repeated chilling and separation of the solids by filtration, the mother liquor could be enriched to 98% diastereomeric excess of **9b**, $[\alpha]_D$ + 23.75.

The solid sulfoxide, **9a**, on treatment with p-toluene sulfonyl azide gave sulfoximine, **10a**, $[\alpha]_D$ -60.9. The liquid diastereomer **9b** on similar treatment followed by chromatographic purification and crystallisation gave pure sulfoximine, **10b**, $[\alpha]_D$ + 101.9.

The diastereomeric purities of both sulfoximines were above 99% as easily judged from their high-resolution ^{1}H NMR spectra. In **10a**, the -S-C*H*$_3$ protons appear as a sharp singlet at δ 3.45 and *H*C-S-proton appear as a quartet centered at δ 3.78. The corresponding signals in **10b** are seen at δ 3.50 and at δ 3.57.

The methylene transfer reactions were carried out on four selected carbonyl compounds, **11** -**14**.



11 – 14 15 – 18

	X	R
11, 15	H	H
12, 16	Cl	H
13, 17	H	CH_3
14, 18	Cl	i-Pr

Reaction of sulfoximine, **10a**, with sodium hydride in DMSO gave sodium S-neomenthyl-N-tosyl oxosulfonium methylide to which was added the carbonyl compound at ambient temperature (30-32°C). The epoxide formed was isolated and distilled under reduced pressure. The asymmetric induction achieved with sulfoximine **10a** is given in Table 1.

Table 1

No.	Substrate	Product			
		Identity	Yield(%)	$[\alpha]_D^{25}$	ee(%)GC*
1	Benzaldehyde, **11**	(R)-(+)-phenyl oxirane, **15**	42	+28.57 (c,1.85;Bz)	66.2 (a)
2	4-Chloro-benzaldehyde, **12**	(R)-(+)-(4-chloro-phenyl)-oxirane, **16**	55	+12.27 (c,1.3;Bz)	55.8 (a)
3	Acetophenone, **13**	(-)-2-Methyl-2-phenyl oxirane, **17**	65	- 11.30 (c,0.7;Ac)	82.3 (a)
4	1-(4-Chloro-phenyl)-2-methyl propane-1-one, **14**	(-)-2-(4-Chloro-phenyl)2-isopropyl oxirane, **18**	80	- 31.22 (c,3.78; chf)	86.0 (b)

* Cyclodextrin B, capillary column, 25M x 0.25 mm
"a" denotes the enantiomer, a, with lower retention time in excess and
"b" the enantiomer, b, with higher retention time in excess

When sulfoximine **10b** was used, the enantiomeric ratios (a:b, by GC) of the products were found reversed and the oxiranes obtained showed specific rotations nearly equal in magnitude but opposite in sign to those of oxiranes prepared with sulfoximine **10a**.

Conclusion

We have presented a very useful method, with good scope for further improvement, for the synthesis of chiral oxiranes in fairly high enantiomeric excess by the reaction of prochiral carbonyl compounds with chiral sulfoximines. As anticipated at the outset, the chirality of the ligand on sulfur did influence the extent of ee achieved in the methylene transfer reaction. The absolute configuration at sulfur appears to be the guiding factor in deciding the absolute configuration of the oxirane formed.

EXPERIMENTAL

General : All melting points are uncorrected. Optical rotations were measured at 25° C in chloroform (unless otherwise stated) on a JASCO model DIP-370 digital polarimeter. Chiral GC analyses were done on a Cyclodex B capillary column, 30M x 0.25mm (J & W Scientific) using a Hewlett-Packard model 5890 Gas Chromatograph. The various spectra were obtained using the following instruments : **IR** Spectra : Perkin Elmer Model 781; ^{1}H **NMR** spectra : Perkin-Elmer R-32 (90 MHz); High resolution ^{1}H **NMR** spectra and ^{13}C **NMR** spectra:GE NMR QE-300, Brucker AC-200 and Varian XL 300; Mass Spectra : TRIO-1 GC MS and Finnigan Mat-1020; HRMS : VG-ZAB-E.

(+)-S-Methyl-S-neomenthyl sulfide, **8**

This was prepared as per published procedure[12] as depicted in Scheme 2 starting from (1R,3R,4S)-(-)-Menthol, $[\alpha]_D$ - 49.5 (c,2.2; EtOH). The yields and specific rotations of intermediates were as follows :

Name	Structure	Molar yield, %	$[\alpha]_D^{25}$ observed	$[\alpha]_D^{20}$ reported[12]
(-)-Menthyl p-toluenesulfonate	**5**	91.0	- 69.5 (c,3.12)	- 69.5 (c,2.99)
(+)-Neomenthyl thioacetate	**6**	61.0	+75.18 (c,2.60)	+64.0 (c,2.66)
(+)-Neomenthane thiol	**7**	92.0	+54.84 (c,2.27)	+53.9 (c,1.85)
(+)-S-Methyl-S-neomenthyl sulfide	**8**	94.0	+95.79 (c,3.85)	+90.3 (c,3.52)

(+)-S-Methyl-S-neomenthyl Sulfoxides, **9a** *and* **9b**

To a solution of (+)-S-methyl-S-neomenthyl sulfide, **8** (10.13g; 54.5 mmol) in acetic acid (3.2 ml) was added (1 hr) aqueous hydrogen peroxide (30% w/v; 6.2 ml; 54.7 mmol) at 18°C and the mixture stirred at 20-30°C until the oxidation was complete (50 hrs; monitoring by ^{1}H NMR). The product was taken up in chloroform (50 ml), washed with water (50 ml) aqueous potassium carbonate (5%; 2x15 ml) finally with water (20 ml), dried (Na_2SO_4) and freed from solvent. The residue (10.61g), $[\alpha]_D$ + 78.08 (c,1.46) was found to be a mixture of diastereomeric sulfoxides (35:65; chiral GC, cyclodex B column; 150°C). Crystallisation of the product mixture from n-hexane-chloroform (97:3; 20 ml) gave a solid which after recrystallisation to constant m.p. weighed 2.3g, m.p. 125-26°. The mother liquor was freed from the solid diastereomer by repeated chilling and filtration. Distillation at 120°C (bath)/0.5 mm gave a colourless liquid, 5.06 g (diastereomeric ratio, 1:99; chiral GC).

Solid sulfoxide, **9a**. m.p. 125-26°C; $[\alpha]_D$ + 140.06 (c,1.48) (Reported[12] : $[\alpha]_D$ + 136.7; c,1.35); **IR** (nujol) : 1390, 1330, 1320, 1265, 1030, 1020, 1005, 965, 940, 700 cm^{-1}. ^{1}H **NMR** ($CDCl_3$) : 0.7-1.2 (9H, m, -C*H*$_3$), 2.58 (3H, s, -S-C*H*$_3$), 2.81 (1H, t, *H*C-S-).

Liquid sulfoxide, **9b**. $\eta_{D(25^{\circ}C)}$ 1.4950; solid below 15°C; $[\alpha]_D$ + 23.75 (c, 2.1); **IR** (liq. film) : 2960, 2920, 2880, 1480, 1455, 1425, 1385, 1370, 1035, 930, 660 cm^{-1}; ^1H **NMR** ($CDCl_3$) : 0.7-1.2 (9H,m,-C*H*$_3$), 2.60 (3H, s, S-C*H*$_3$), 3.28 (1H, broad s, *H*C-S-).

(-)-S-Methyl-S-neomenthyl-N-tosyl Sulfoximine, **10a**

A mixture of solid sulfoxide, **9a**, (7.07g; 35 mmol), p-toluene sulfonyl azide[15] (13.74g; 70 mmol) precipitated copper powder (1.85 g) and anhydrous methanol (50 ml) was refluxed for 64 hrs (about 80% conversion; ^1H NMR). Methanol was distilled off and the residue was stirred (15 min) with a saturated solution (125 ml) of Na_2EDTA. The reaction mixture was extracted with chloroform (150 ml) organic extract was treated with activated charcoal (2 g), filtered (using hyflo super cel as filter aid) and the filtrate washed with aqueous sodium hydroxide (5%; 2x20ml) and water (3x40ml), dried (Na_2SO_4) and was freed from solvent. The residue (12.1g) on column chromatography over SiO_2 (500 g) and eluting with n-hexane-acetone (80:20) gave pure sulfoximine **10a**, (8.4 g) and unreacted sulfoxide (1.0 g) (yield of sulfoximine, 75.4%, based on consumed sulfoxide). Sulfoximine, **10a**, m.p. 115-16°C, $[\alpha]_D$ - 60.9 (c, 2.54) did not show any change in m.p. or specific rotation even after three recrystallisations (hexane-acetone; hexane-chloroform).

Sulfoximine, **10a**. **IR** (nujol) : 1600, 1278, 1232, 1205, 1150, 1080, 1022, 785, 718 cm^{-1}. **UV** (EtOH), max (ε): 237(3900), 257(680), 263(760), 268(640), and 274(550) nm. ^1H **NMR** ($CDCl_3$) : δ 0.82, 0.89, 1.02 (3H each; d, J = 6.6, 6.3, 6.3 Hz resp.; HC-C*H*$_3$), 2.42 (3H, s, Ar-C*H*$_3$), 3.45 (3H, s, S-C*H*$_3$), 3.78 (1H, q, J = 3.6 Hz, *H*C-S-), 7.27 (2H, d, J = 7.8 Hz, Ar-C*H*), 7.84 (2H, d, J = 8.4 Hz, Ar- C*H*). ^{13}C **NMR** ($CDCl_3$) : δ 21.24, 21.41, 21.98, 22.33, 44.06 (all *C*H$_3$), 23.76, 34.48, 35.76 (all -*C*H$_2$-), 26.50, 28.80, 49.24, 64.32 (all -*C*H-), 126.34, 129.01 (four aromatic -*C*H), 141.12, 142.39 (Ar-*C*-). **EIMS**, m/z (%) : 371(M^+, 2), 234(100), 216(20), 155(94), 138(97), 123(29), 95(72), 91(96), 82(54), 79(32). Anal. calcd for $C_{18}H_{29}NO_3S_2$: C, 58.18; H, 7.87; N, 3.77; Found : C, 58.04, H, 8.21, N, 3.56.

(+)-S-Methyl-S-neomenthyl-N-tosyl Sulfoximine, **10b**

The liquid sulfoxide, **9b**, (9.1g; 45 mmol), p-toluene sulfonyl azide (17.7g; 90 mmol), precipitated copper powder (2.31 g) and methanol (55 ml) were refluxed for 46 hrs (about 90% conversion; ^1H NMR). The reaction product was worked up as in the case of **10a**. The column eluted product (13.5 g; yield, 80.5%) was crystallised to constant m.p. (3 times from n-hexane-acetone) to provide sulfoximine **10b** of 100% optical purity (^1H *NMR* : no detectable signals due to **10a**, m.p. 74-5° C; $[\alpha]_D$ + 101.9,(c, 3.88). **IR** (nujol): 1602, 1330, 1320, 1305, 1205, 1155, 1070, 820, 732, 688, 650 cm^{-1}. **UV** (EtOH) max (ε) : 238(3770), 257(680), 263(750), 268(640), 274(550) nm. ^1H-**NMR** ($CDCl_3$) : 0.76, 0.80, 0.92 (3H, each; d; J = 6.3, 6.4, 6.3, Hz resp.; HC-C*H*$_3$), 2.32 (3H, s, Ar-C*H*$_3$), 3.50 (3H, s, S-C*H*$_3$), 3.57 (1H, q, J = 3.0 Hz), 7.18(2H, d; J = 8.1 Hz, Ar-C*H*), 7.74 (2H; d; J = 8.4 Hz; Ar-C*H*). ^{13}C **NMR** ($CDCl_3$) : 21.20, 21.29, 21.92, 22.09, 44.92 (all *C*H$_3$); 23.55, 34.44, 36.22, (all -*C*H$_2$), 25.62, 28.66, 48.62, 64.17 (all -*C*H-), 125.03, 128.70, (4 aromatic *C*H), 141.00, 141.34, (2 aromatic -*C*-) **EIMS**, m/z (%) : 372 (M^+ + 1, 33), 370(29), 236(54), 235(50), 234(100), 218(25), 217(20), 216(100), 155(19), 152(21), 139(31), 105(15); Exact mass, M^+ + 1 : 372.1644, $C_{18}H_{30}NO_3S_2$ requires, 372.1667.

General Procedure for the preparation of Oxiranes

To a mixture of sodium hydride (0.127 g; 50% dispersion in oil; 2.64 mmol washed with Na-dry n-hexane) and anhydrous DMSO (5 ml) was added a solution of (-)-S-methyl-S-neomenthyl-N-tosyl sulfoximine, **10a**, $[\alpha]_D$ - 60.9 (0.89g, 2.4 mmol) in DMSO (10 ml) and the mixture stirred under N_2 at ambient temp. (30-32°C) for 4 hrs. To the sodium methylide formed was added the carbonyl compound (2 mmol) in DMSO (2 ml) and the reaction mixture was stirred at room temp. The reaction takes about 2-18 hrs to complete (GC:disappearance of carbonyl compound). The reaction mixture was cooled (5°C), diluted with water (25 ml), extracted with n-hexane (5x10 ml), the extract washed with water (2 x 20 ml), dried (Na_2SO_4), freed from solvent and the residue distilled under reduced pressure (2-10 mm; bulb to bulb distillation). The products were identified by spectroscopic methods (IR, ^1H NMR) and enantiomeric excess determined by GC on cyclodex B capillary column.

The yields of the product oxiranes, their specific rotations and ee as determined by GC are given in Table 1.

Oxiranes using (+)-S-Methyl-S-neomenthyl-N-tosyl sulfoximine, **10b.**

The above general procedure was used to prepare oxiranes from carbonyl compounds using sulfoximine **10b**. In all cases the enantiomeric ratios (GC) of the oxiranes were in the reverse order compared to oxiranes prepared with sulfoximine, **10a.**

(S)-(-)-phenyl oxirane (prepared from **11**) : $[\alpha]_D$ - 26.33 (c, 2.16; Benzene); ee, 61.0%.

(-)-2-(4-chloro-phenyl) oxirane (from **12**) : $[\alpha]_D$ - 10.77 (c, 2.37; Benzene); ee, 49.3%.

(+)-2-(4-chloro-phenyl)-2-isopropyl oxirane (from **14**) : $[\alpha]_D$ + 29.04 (c, 4.0); ee, 80.4%

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13. The Absolute configuration at sulfur is not determined. Hence diastereomers are referred to as **9a** and **9b** with specific rotation characterising them. Determination of absolute configuration at sulfur of the sulfoxides **9a** and **9b**, and of the sulfoximines **10a** and **10b** and relating this with the configuration of the oxiranes will form the subject matter of a subsequent paper in this series.
14. The most significant difference in the ^{1}H NMR spectra of these diastereomeric sulfoxides is that the C-3 proton of the crystalline isomer **9a**, appears at δ 2.80 whereas in the liquid isomer, **9b**, it appears at δ 3.28.
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