Asymmetric Selection *via* Addition. Part 2.[1] Optically Active Sulphoximides

By **Rita Annunziata** and **Mauro Cinquini**, Centro C.N.R. and Istituto di Chimica Industriale dell'Università, Via C. Golgi 19, 20133 Milano, Italy

The kinetic resolution of the unsaturated sulphoximides (6)—(10) *via* addition of the chiral amines (11)—(13) has been examined. The rate of reaction depends strongly on steric effects, to the point that a different reaction, involving breaking of the S–N bond, may occur.

OPTICALLY active sulphur derivatives are generally prepared from optically active sulphinates *via* the Andersen synthesis.[2] However this elegant method is limited by the availability of the starting sulphinates, and there is accordingly continuing interest in alternative routes to optically active sulphur compounds.[3]

We recently reported [1] that reaction of chiral racemic allenic sulphones with a deficiency of optically active amines results in asymmetric selection *via* addition to the unsaturated sulphur system. A similar approach can be applied, in principle, to any system where a chiral sulphur unit activates an adjacent multiple bond towards nucleophilic addition. We report here results for αβ-unsaturated sulphoxides and *N*-phthalimidosulphoximides.

$R^1SOCH{=}CHR^2$ $\qquad$ $R^1{-}S(=O)(=NPhth){-}CH{=}CHR^2$

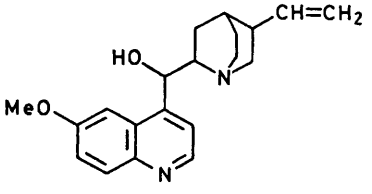
	R^1	R^2	
(1)	*p*-MeC_6H_4	H	(6)
(2)	$PhCH_2$	H	(7)
(3)	α-$C_{10}H_7$	H	(8)
(4a) (*Z*), (4b) (*E*)	*p*-MeC_6H_4	Me	(9a) (*Z*), (9b) (*E*)
(5a) (*Z*), (5b) (*E*)	*p*-MeC_6H_4	Ph	(10a) (*Z*), (10) (*E*)

$PhCHOHCHMeNHMe$ (11) $\qquad$ $PhCH_2CHMeNH_2$ (12)

$PhCHMeNH_2$ (13) $\qquad$ *p*-$MeC_6H_4{-}SO{-}C_{10}H_7$-α (14)

p-$MeC_6H_4{-}S(=O)(=NPhth){-}C_{10}H_7$-α (15)

Phth = phthalimido; α-$C_{10}H_7$ = α-naphthyl



(16)

The racemic sulphoxides (1)—(5) were prepared by standard methods and converted into the corresponding sulphoximides (6)—(10) by the Rees procedure.[4] The optically active *N*-phthalimido-*S*-*p*-tolyl-*S*-vinyl sulphoximide (6) had previously been prepared [5] by reaction of the optically active sulphoxide (1) with *N*-aminophthalimide and lead tetra-acetate, and was chosen as reference compound. The sulphoximide group greatly enhances the electrophilic reactivity of the adjacent double bond, so that addition of amines to (6) proceeds smoothly, even at low temperatures, to afford 1 : 1 adducts. Reaction of (6) with a deficiency of chiral bases resulted in kinetic resolution of the sulphoximide when (−)-(1*R*,2*S*)-ephedrine (11) was used.

Asymmetric selection was shown to be dependent on the reaction temperature, the best result, corresponding to an enantiomeric excess of 46%, being obtained at −30 °C (see Table 1). Surprisingly the racemic sulphoximide (6) was recovered in the case of (−)-(*R*)-amphetamine (12) and (+)-(*R*)-α-phenylethylamine (13).

TABLE 1

Kinetic resolution of sulphoximides *via* addition of chiral amines

Sulphoximide	Amine [a]	Time/day	*T*/°C	Recovered sulphoximide $[\alpha]_D^{25}$	Optical purity (%)
(6)	(−)-(11)	2	25	−11.5° [b]	38
(6)	(−)-(12)	2	25	0	
(6)	(+)-(13)	2	25	0	
(6)	(−)-(11)	2	−30	−13.8° [b]	46
(7)	(−)-(11)	2	−30	+14.7° [c]	45
(8)	(−)-(11)	3	−30	−3.0° [c]	12
(9a)	(−)-(11)	10	25	−6.1° [b]	*d*
(9b)	(−)-(11)	10	25	0	

[a] 0.5 mol. equiv.; the reactions were carried out in chloroform as solvent. [b] In ethanol. [c] In chloroform. [d] Unknown.

Other vinylic sulphoximides, namely (7) and (8), were examined, and in both cases kinetic resolution was achieved with (−)-(11). The optical purity of (6) was estimated on the basis of the highest reported $[\alpha]_D$ value: +30.0° (*c* 1 in $CHCl_3$); [5] enantiomeric excesses of the recovered (7) and (8) were estimated by ^1H n.m.r. spectroscopy with the aid of the chiral shift reagent Eu(tfc)$_3$ [tris(trifluorocamphorato)europium].

The rate of reaction of unsaturated sulphoximides with amines depends strongly on the steric requirements of the unsaturated system, as anticipated from the behaviour of the analogous sulphones, extensively studied by Stirling.[6] Indeed reaction of the propenyl sulphoximides (*Z*)-(9a) and (*E*)-(9b) is much slower than

that of (6)—(8), while the styryl sulphoximides (*Z*)-(10a) and (*E*)-(10b) failed to react with (−)-(11) under conditions comparable to those previously used.

With longer reaction times or at higher temperatures a different reaction occurs, involving breaking of the sulphur–nitrogen bond and formation of the corresponding sulphoxide (see Table 2). The latter reaction is, of course, not limited to unsaturated sulphoximides, and was extended to different compounds such as *S*-naphthyl-*S*-*p*-tolyl sulphoximide (15). Tertiary amines such as triethylamine and (−)-quinine (16) also proved to be effective.

TABLE 2

Kinetic resolution of sulphoximides *via* breaking of the sulphur-nitrogen bond

Sulphoximide [a]	Amine	Mol. equiv. of amine	Time/day	*T*/°C	$[\alpha]_D^{25}$	Sulphoxide: Absolute configuration	Sulphoxide: Optical purity (%)
(10a)	(−)-(11)	0.5	19	25	+14.8°	*S*	2.0
(10b)	(−)-(11)	1.0	0.5	60	+2.0°	*R*	1.2
(10b)	(−)-(16)	1.0	1.5	60	+10.0°	*R*	6.0
(15)	(−)-(11)	0.5	5	60	+11.0°	*R*	2.7
(15)	(−)-(16)	0.5	5	60	+33.0°	*R*	8.0

[a] The reactions were carried out in chloroform as solvent.

When a chiral base is used and the reaction is stopped before completion, it eventually results in asymmetric selection, optically active sulphoxides being recovered (see Table 2), albeit of low optical purity.

While asymmetric synthesis in the addition of amines to optically active αβ-unsaturated sulphoxides has been reported,[7] to the best of our knowledge kinetic resolution of vinylic sulphoxides by chiral amines has not been investigated.

In reactions of the vinyl sulphoxide (1) with a deficiency of (−)-(11) and of (+)-(13), the (*R*)-, $[\alpha]_D^{25}$ +11.3°, and (*S*)-sulphoxides (1), $[\alpha]_D^{25}$ −7.8°, respectively, corresponding to 3 and 2% optical purities, respectively, were recovered. The sulphoxides (4a, b) and (9a, b) failed to react under comparable conditions.

A comparison of the results for sulphoxides and sulphoximides indicates that the stereoelectronic effect of the sulphur unit plays a dominant role in determining the extent of asymmetric selection.

EXPERIMENTAL

General.—Light petroleum had b.p. 40—60 °C. Extractions were performed with chloroform and extracts were dried over Na_2SO_4. ^1H N.m.r. spectra were recorded with Varian A-60 and/or Varian HA 100 instruments; i.r. spectra were recorded on a Perkin-Elmer 377 spectrometer. Optical rotations were measured with a Perkin-Elmer 141 polarimeter. (*R*)-α-Phenylethylamine, $[\alpha]_D^{20}$ +40.1° (neat), (*R*)-amphetamine, $[\alpha]_D^{15}$ −40.2° (*c* 9 in C_6H_6), and (1*R*,2*S*)-ephedrine, $[\alpha]_D^{20}$ −35.0° (*c* 5 in H_2O–HCl), were commercial products. *p*-Tolyl vinyl sulphide,[8] (*Z*)- and (*E*)-propenyl *p*-tolyl sulphide,[9] (*Z*)- and (*E*)-styryl *p*-tolyl sulphide,[10] benzyl vinyl sulphide,[11] and α-naphthyl vinyl sulphide [12] were obtained by literature methods.

Synthesis of αβ-Unsaturated Sulphoxides.—*p*-Tolyl vinyl sulphoxide, b.p. 90 °C at 0.2 mmHg, n_D^{20} 1.578 0 (lit.,[8] b.p. 90 °C at 0.2 mmHg, n_D^{20} 1.578 0), *α-naphthyl vinyl sulphoxide*, m.p. 74—75 °C (Found: C, 71.2; H, 4.9. $C_{12}H_{10}OS$ requires C, 71.25; H, 5.0%), and *benzyl vinyl sulphoxide*. m.p. 34—35 °C (Found: C, 65.1; H, 6.1. $C_9H_{10}OS$ requires C, 65.0; H, 6.1%) were prepared by periodate oxidation [13] of the corresponding sulphides. Oxidation of a mixture of (*E*)- and (*Z*)-propenyl *p*-tolyl sulphides afforded a mixture of (*E*)- and (*Z*)-propenyl *p*-tolyl sulphoxides, which was separated by column chromatography (silica; light petroleum–ether, 7 : 3): (*E*)-propenyl *p*-tolyl sulphoxide had n_D^{25} 1.570 1, and (*Z*)-propenyl *p*-tolyl sulphoxide had n_D^{25} 1.565 0 (lit.,[9] b.p. 106 °C at 0.1 mmHg, n_D^{13} 1.578 4 for the 1 : 1 diastereoisomeric mixture). Oxidation of a mixture of (*E*)- and (*Z*)-styryl *p*-tolyl sulphide afforded a mixture of (*E*)- and (*Z*)-styryl *p*-tolyl sulphoxides, which was separated by column chromatography (silica; light petroleum–ether, 7 : 3); (*Z*)-styryl *p*-tolyl sulphoxide had m.p. 60—61 °C (lit.,[10] m.p. 60 °C); (*E*)-styryl *p*-tolyl sulphoxide had m.p. 34—35 °C (lit.,[10] m.p. 34—35 °C).

Synthesis of αβ-Unsaturated N-Phthalimidosulphoximides (6)—(10).—Compounds (6)—(10) were prepared from the corresponding sulphoxides (1)—(5) by reaction with *N*-aminophthalimide and lead tetra-acetate according to the Rees procedure.[4] *N*-Phthalimido-*S*-*p*-tolyl-*S*-vinylsulphoximide had m.p. 191 °C (lit.,[5] m.p. 191.5 °C), *N-phthalimido*-S-(*Z*)-*propenyl*-S-p-*tolylsulphoximide*, m.p. 174 °C (from ethanol) (Found: C, 63.2; H, 4.8; N, 8.5. $C_{18}H_{16}N_2O_3S$ requires C, 63.5; H, 4.7; N, 8.2%), *N-phthalimido*-S-(*E*)-*propenyl*-S-p-*tolylsulphoximide*, m.p. 140—141 °C (from ethanol) (Found: C, 63.7; H, 4.9; N, 8.0%), *N-phthalimido*-S-(*Z*)-*styryl*-S-p-*tolyl sulphoximide*, m.p. 163 °C (from ethanol) (Found: C, 68.5; H, 4.5; N, 7.0. $C_{23}H_{18}N_2O_3S$ requires, C. 68.6; H, 4.5; N, 7.0%), *N-phthalimido*-S-(*E*)-*styryl*-S-p-*tolyl sulphoximide*, m.p. 175—176 °C (from ethanol) (Found: C, 68.8; H, 4.3; N, 6.9%), *S-benzyl-N-phthalimido*-S-*vinylsulphoximide*, m.p. 136—137 °C (from ethanol) (Found: C, 62.5; H, 4.3; N, 8.6. $C_{17}H_{14}N_2O_3S$ requires C, 62.6; H, 4.3; N, 8.6%), and S-α-*naphthyl*-N-*phthalimido*-S-*vinylsulphoximide*, m.p. 182—183 °C (from ethanol) (Found: C, 66.2; H, 3.8; N, 7.5. $C_{20}H_{14}N_2O_3S$ requires C, 66.3; H, 3.9; N, 7.7%).

Addition of Chiral Amines to the N-Phthalimidosulphoximides (6)—(9).—*General procedure.* (−)-Ephedrine (11) (0.5 mol. equiv.) was added to a stirred solution of the *N*-phthalimido-sulphoximide (1 mol. equiv.) in chloroform (5 ml). The mixture was stirred at −30 or 25 °C for the appropriate time (see Table 1), poured into water, and acidified with dilute hydrochloric acid. The organic layer was separated off, washed with water, dried, and evaporated. The crude mixture was separated by column chromatography (silica; ether); 50% of the starting sulphoximide was recovered in the case of compounds

(6)—(8). Optical rotations and enantiomeric excesses of the sulphoximides are reported in Table 1.

The following products were recovered: S-2-(N-*methyl*-β-*hydroxy*-α-*methylphenethylamino*)*ethyl*-N-*phthalimido*-S-p-*tolylsulphoximide*, m.p. 30—40 °C, $[\alpha]_D^{25}$ −4.4° (*c* 1 in $CHCl_3$) (Found: C, 65.9; H, 6.0; N, 8.5. $C_{27}H_{29}N_3O_4S$ requires C, 66.0; H, 5.95; N, 8.55%); S-*benzyl*-S-2-(N-*methyl*-β-*hydroxy*-α-*methylphenethylamino*)*ethyl*-N-*phthalimidosulphoximide*, m.p. 50—60 °C, $[\alpha]_D^{25}$ −7.0° (*c* 1 in $CHCl_3$) (Found: C, 65.9; H, 6.0; N, 8.5%); S-2-(N-*methyl*-β-*hydroxy*-α-*methylphenethylamino*)*ethyl*-S-*naphthyl*-N-*phthalimidosulphoximide*, m.p. 55—65 °C, $[\alpha]_D^{25}$ +14.0° (*c* 1 in $CHCl_3$) (Found: C, 68.3; H, 5.5; N, 8.0. $C_{30}H_{29}N_3O_4S$ requires C, 68.3; H, 5.5; N, 8.0%). Under these conditions reaction of the sulphoximide (6) with either (+)-α-phenylethylamine (13) or (−)-amphetamine (12) did not result in kinetic resolution. From the reaction of the sulphoximides (9a) and (9b) and (−)-ephedrine (11), 75% of starting material was recovered. It was not possible to obtain the adducts in pure form.

Conversion of the N-*Phthalimidosulphoximides* (10) *and* (15) *into Sulphoxides by Reaction with Amines.—General procedure.* The appropriate chiral amine (0.5 mol. equiv.) was added to a stirred solution of the *N*-phthalimidosulphoximide (1 mol. equiv.) in chloroform or ethanol (5 ml). The mixture was stirred at +25 or +60 °C for the appropriate time (see Table 2), evaporated, and chromatographed (silica; light petroleum–ether, 1 : 1) to afford the sulphoxide together with unchanged sulphoximide.

In the reaction of the sulphoximide (15) with (−)-quinine (16) and (−)-ephedrine (11), respectively, 47 and 15% of the sulphoxide (14) together with 40 and 85%, respectively, of starting sulphoximide were recovered. The sulphoximide (10a) with (−)-ephedrine (11) gave 18% of the sulphoxide (5a) and 67% of a mixture of the sulphoximides (10a) and (10b) in a 9 : 1 ratio. The sulphoximide (10b) with (−)-ephedrine (11) and (−)-quinine (16) gave 40 and 10%, respectively, of the sulphoxide (5b), and 43 and 85%, respectively; of the starting sulphoximide (10b). Optical rotations of the sulphoxides are reported in Table 2, the enantiomeric excesses being calculated on the basis of the highest reported values: $[\alpha]_D^{25}$ +166° (*c* 1 in $CHCl_3$) [14] for (5b); $[\alpha]_D^{25}$ −736° (*c* 1 in $CHCl_3$) [15] for (5a); $[\alpha]_D^{25}$ −414° (*c* 1 in Me_2CO)[2] for (14).

The recovered sulphoximides (10a), (10b), and (15) were optically active. The enantiomeric excess of the sulphoximide could be determined in the case of compound (15) on the basis of the highest reported value, $[\alpha]_D^{25}$ −26.8° (*c* 1 in Me_2CO),[5] and was in close agreement with the optical purity of the sulphoxide. The reaction of the sulphoxide (15) with triethylamine (1 mol. equiv.) in refluxing ethanol for 5 days afforded the *p*-tolyl sulphoxide (14) in quantitative yield.

Addition of the Chiral Amines (11) *and* (13) *to the* αβ-*Unsaturated Sulphoxide* (1).—The chiral amine (0.75 mol. equiv.) and sulphoxide (1 mol. equiv.) were stirred in methanol at 25 °C for 6 days. The mixture was evaporated and chromatographed (silica; ether). In the reaction with the amines (+)-(13) and (−)-(11), 32 and 40% respectively of the starting sulphoxide was recovered, $[\alpha]_D^{25}$ +11.3° (*c* 1 in EtOH) and $[\alpha]_D^{25}$ −7.8° (*c* 1 in EtOH), respectively The enantiomeric excess values, calculated on the basis of the highest reported values, $[\alpha]_D^{25}$ +396° (*c* 1 in EtOH),[7] were 3 and 2% respectively.

[8/1128 *Received*, 19*th June*, 1978]

REFERENCES

[1] Part 1, M. Cinquini, S. Colonna, and F. Cozzi, *J.C.S. Perkin I*, 1978, 247.
[2] K. K. Andersen, W. Gaffield, N. E. Papanikolaou, J. W. Foley, and R. I. Perkins, *J. Amer. Chem. Soc.*, 1964, **86**, 5637; M. Cinquini and F. Cozzi, *J.C.S. Chem. Comm.*, 1977, 502, and references therein.
[3] M. Mikolajczyk and J. Drabowicz, *Phosphorus and Sulfur*, 1976, **1**, 301 and references therein; G. Marchese, F. Naso, and L. Ronzini, *J.C.S. Chem. Comm.*, 1974, 830.
[4] C. W. Rees and M. Yelland, *J.C.S. Perkin I*, 1972, 77.
[5] S. Colonna and C. J. M. Stirling, *J.C.S. Perkin I*, 1974, 2120.
[6] S. T. McDowell and C. J. M. Stirling, *J. Chem. Soc.* (*B*), 1967, 351.
[7] D. J. Abbott, S. Colonna, and C. J. M. Stirling, *J.C.S. Perkin I*, 1976, 492.
[8] W. E. Truce, J. J. Breiter, and J. E. Tracy, *J. Org. Chem.*, 1964, **29**, 3009.
[9] C. J. M. Stirling and D. J. Abbott, *J. Chem. Soc.* (*C*), 1969, 818.
[10] E. P. Koehler and H. Potter, *J. Amer. Chem. Soc.*, 1935, **57**, 1316.
[11] M. Protiva, *Coll. Czech. Chem. Comm.*, 1949, **14**, 354.
[12] M. Reppe and F. Nicolai, Swed. P. 82 699/1934 (*Chem. Abs.*, 1936, **30**, 733).
[13] N. J. Leonard and C. R. Johnson, *J. Amer. Chem. Soc.*, 1962, **84**, 3701.
[14] G. Tsuchihashi, S. Mitamura, S. Inoue, and K. Ogura, *Tetrahedron Letters*, 1973, 323.
[15] M. Mikolajczyk, N. Midura, S. Grzejszczak, A. Zatorski, and A. Chefczynska, *J. Org. Chem.*, 1978, **43**, 473.