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Synthesis and Hydride Reductions of Chiral Cyclic β-Iminosulfoxides

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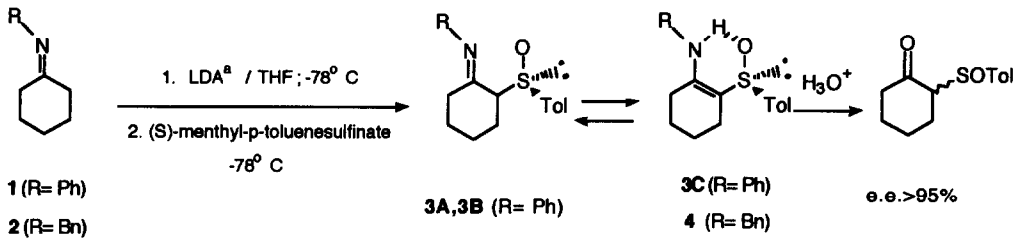
ABSTRACT: The hydride reductions of chiral N-(2-*p*-tolylsulfinyl)cyclohexylidene phenyl amines **3A** and **3B** (epimers at C-2), and of N-1-(2-*p*-tolylsulfinyl)cyclohexenyl benzyl amine, **4**, are highly stereoselective, yielding only the corresponding *cis*-aminosulfoxides.

Chiral 2-aminosulfoxides are useful compounds for asymmetric synthesis[1]. The addition of α-sulfinyl carbanions to imines[1h,2] (d.e. ranged from 14 to 90%), which is the most general method to obtain such compounds, cannot be used to prepare cyclic aminosulfoxides. These products could be available by conjugate addition of amines to chiral vinyl sulfoxides, but the d.e. reported for such reactions on acyclic compounds are not higher than 74%[1e,1g]. Taking into account the good stereochemical results obtained in the hydride reductions of cyclic β-ketosulfoxides,[3,4,5] we envisioned the reduction of their corresponding β-iminosulfoxides (surprisingly not reported so far) as a diastereoselective method to synthesize chiral cyclic 2-aminosulfoxides. In the present paper, the synthesis of the chiral N-phenyl and N-benzyl imines derived from 2-*p*-tolylsulfinylcyclohexanone, as well as the results obtained in their hydride reductions, are reported.

RESULTS AND DISCUSSION

Several methods have been described to synthesize optically active 2-iminosulfoxides. The addition of chiral sulfinyl carbanions to nitriles[1b] did not give access to the desired cyclic substrates. The condensation of chiral 2-ketosulfoxides with amines gave poor yields[6], and the asymmetric oxidation of compounds 2-iminothioether structures proceeded with poor enantiomeric excesses[6]. Once again the method of choice is the Andersen type synthesis[7] already applied to acyclic[8] and endocyclic imines[9].

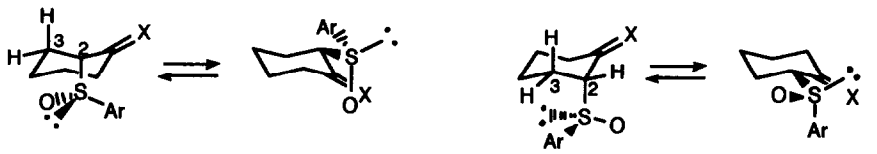
The reaction of the N-cyclohexylidene phenyl amine (**1**) with (*S*)-(-)menthyl-*p*-toluenesulfinate, in the presence of LDA,[10] afforded a 2:1 mixture of N-(2-*p*-tolylsulfinyl)cyclohexylidene phenyl amines, **3A** and **3B**, epimers at C-2, in 70% yield[11] after chromatography (Scheme 1). When the crude material is directly crystallized from a mixture of acetone and methanol, it is possible to isolate the enamine tautomer, N-1-(2-*p*-tolylsulfinyl) cyclohexenyl aniline, **3C**, as a solid, which slowly changed in solution into a 2:1 mixture of imines **3A** and **3B** . This suggests that these imine tautomers are in equilibrium through the enamine form **3C**, which must be the less stable.



[a] For **2** see experimental part.

Scheme 1

When the N-cyclohexylidene benzyl amine (**2**) was treated with LDA and (*S*)-(-)menthyl-*p*-toluenesulfinate, only compound **4**, with enamine structure, was obtained in 65% yield (Scheme 1).As the reaction of carbonyl compounds with menthyl sulfinate in the presence of LDA took place with partial racemization at sulfur,[3,12] it was necessary to check the optical purity of the resulting imino and enamino sulfoxides. The rotatory power of pure compounds **3A-C** could not be measured because of the equilibrium in solution, and the observed value for **4** was very low ($[\alpha]_D$= -5.3, $CHCl_3$, c=1). This prompted us to hydrolyze these substrates to the ketosulfoxides whose rotatory powers and optical purity (>95%e.e.)were known.[4] Compound **3** yielded a 75:25 mixture of ketosulfoxides whose rotatory power ($[\alpha]_D$= +258, $CHCl_3$, c=1) and composition were identical to those obtained by direct sulfinylation of cyclohexanone.[4,5] On the other hand, hydrolysis of **4** afforded a mixture of the same ketosulfoxides, with very low rotatory power ($[\alpha]_D$= +17.9, $CHCl_3$, c=1) indicating that epimerization at sulfur had taken place. In order to avoid this, the sulfinylation of the benzylimine **2**, was carried out using as base magnesium diisopropylamide bromide instead of LDA. The hydrolysis of the enamine **4** so obtained, once more yielded a partially racemized ketosulfoxide mixture ($[\alpha]_D$= +27.5, $CHCl_3$, c=0.8). The slightly higher value of the rotatory power obtained in the later case indicates a lower racemization in the presence of magnesium. Finally, optically pure **4** was synthesized by treating the lithium enolate of cyclohexylidene benzylamine (**2**), generated with LDA, with a high excess of magnesium bromide, before adding the menthyl sulfinate. The ketosulfoxides obtained from hydrolysis of the enamino sulfoxide **4** resulting in these conditions, showed a $[\alpha]_D$= +258 ($CHCl_3$,c=1), identical to that measured for the authentic enantiomerically pure sample.



	Isomer S_2R_S		Isomer R_2R_S	
	X= O	X= NPh	X= O	X= NPh
δ- C(2)	74.0	73.3	72.9	70.5
δ- C(3)	24.2	26.9	27.5	28.1
δ– H(2)	3.37	3.55	3.56	3.60
$J_{2,3}$(Hz)	9.4/5.6	6.7/4.6	6.6/6.6	5.6/5.6

Scheme 2

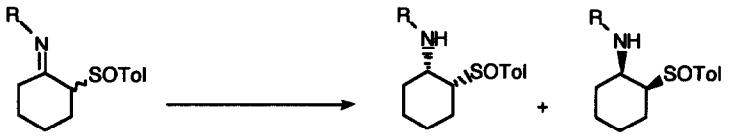
The imine and enamine structures assigned to compounds **3** and **4**, as well as the configurational assignment of **3A** (major) and **3B** (minor), are based in their nmr data. Compounds **3A** and **3B** exhibit signals at 3.55 (dd, J=6.7 and 4.6 Hz) and 3.60 ppm (t, J=5.6 Hz) respectively, which can only be assigned to H-2 of the imine tautomer and indicate that the conformational equilibrium is mainly shifted to the conformer with the sulfinyl group in the axial arrangement (the low values for the coupling constants agree with the equatorial arrangement of H-2). On the other hand, the comparison with the nmr parameters obtained for the 2-phenylsulfinyl cyclohexanone epimers at C-2[3] collected in Scheme 2 suggests the configurations ***S_2R_S*** (lower chemical shift for H-(2) and C-(3), higher for C-(2) and larger participation of the conformer with sulfinyl group in equatorial position) for **3A** and ***R_2R_S*** for **3B**(for a more detailled discussion see reference 3). The configuration of the C=N bond is *E* in both compounds.[13]

Compounds **3C** and **4** are in the enamine tautomeric form (Scheme 1). They do not exhibit any signal in the 3-4 ppm range, and the signal corresponding to the amine proton (desappiers with D_2O), is strongly deshielded (**3C**: δ=8.57 ppm, broad singlet; **4**: δ=5.90 ppm, triplet, J=6.4 Hz), which suggests that it could be involved in hydrogen-bonding with the sulfinyl oxygen. These data indicate that the phenyl substituent on the nitrogen stabilizes the imine tautomers (**3A** and **3B**), whereas the benzyl group favours the enamine form. This different behavior, is in accordance with that observed for several acyclic 2-iminosulfoxides previously studied,[6,8] and can be due to the conjugation of the phenyl ring with the lone electron pair at nitrogen, which is reinforced by the chemical shifts of the aniline ring *ortho*-protons (6.5 and 6.6 ppm).

The results obtained in the reactions of the **3A+3B** mixture[14]and the enamine **4** with different reducing agents are shown in Table 1.

The configurational assignment of the amines **5**, **6**, **7** and **8** was carried out on the basis of their spectroscopic data mainly ^{1}H-NMR (Table 2). The *cis*-stereochemistry for all of them could be deduced from the values of the vicinal coupling constant $J_{1,2}$, and the equatorial arrangement of the *p*-tolylsulfinyl group (and therefore the axial one for the NHR group) from the typical J_{anti} values obtained for $J_{2,3a}$ (12.0-10.2 Hz, see Table 2).

Table 1. *Diastereoisomeric ratios obtained in the reduction of 3 and 4 with different hydrides.*



3(R=Ph) **5**(R=Ph) **6**(R=Ph)
4(R=Bn) **7**(R=Bn) **8**(R=Bn)

Substrates	**Reducing agent**[a]	**5**[b,c]	**6**[b,c]	**Yield(%)**[d]
3A+3B (R=Ph)	DIBAL	0	100	89
	DIBAL/$ZnCl_2$	0	100	87
	$LiAlH_4$	0	100	83
	$Li(s\text{-}Bu)_3BH$	0	100	97
	$LiEt_3BH$	20	80	95
	$NaBH_4$	30	70	99
	$NaBH_4/ZnCl_2$	16	84	98
	B_2H_4	33	67	95
4 (R=Bn)		**7**[b,c]	**8**[b]	**Yield(%)**[d]
	DIBAL	0	100	87
	$LiEt_3BH$	25	75	95
	$NaBH_4$	32	68	96
	B_2H_6	35	65	95

[a] All reactions were carried out in THF at 0°C with excess of hydride (see experimental part).[b]Diastereomer ratios from ^{1}H-NMR of the crude reaction mixture. [c] ee>95%, determined by ^{1}H-NMR with chiral shift reagent Eu(tfc)$_3$. [d] isolated yield after chromatographic purification.

The chemical shifts observed for protons H(1), H(3a) and H(3e) (Table 2), can be justified taking into account the anisotropic effects of the phenyl and sulfinyl groups[3] in the favoured rotamers around the C-S bond for diastereoisomeric sulfoxides which are those depicted in Figure 1.[15] The higher δ-H(1) and lower δ-H(3e) values observed for compounds **5** and **7** with respect to those of their epimers **6** and **8**, are in accordance with the spatial arrangement of the *p*-tolylsulfinyl group in the favored conformations of each sulfoxide represented in Figure 1.

Therefore, we assign the configuration ***S*$_1$*R*$_2$*R*$_S$** to compound **5** and **7** and ***R*$_1$*S*$_2$*R*$_S$** to compounds **6** and **8**. Thus, the well known deshielding effect of the sulfinyl oxygen[3,16] and the shielding effect of the aromatic rings, both on the protons in 1,3-parallel arrangement, satisfactorily explain the observed values for the H-(1), H-(3a) and H-(3e) chemical shifts. Additionally, the smaller δ value observed for C-3 in **6** with respect to **5** is in accordance with the shielding effect of the lone electron pair at sulfur on those carbons in antiperiplanar arrangement[17] (like C-3 in **6A**, see Fig. 1). Although δ of C-3 in compound **7** coud not be determined, the chemical shifts of C-3 and C-5 in compound **8** are very close to those of the sulfoxide **6** (see Table 2) Thus, on this basis, and considering that compound **8** was obtained from **4** as major product in the same

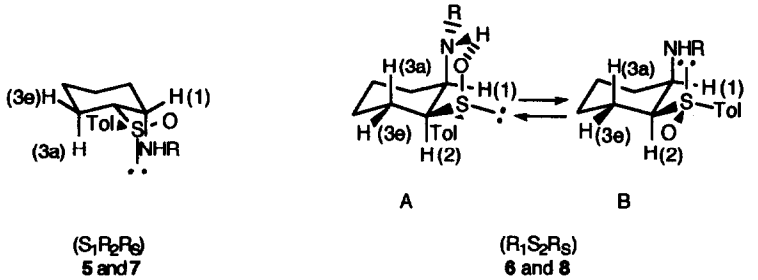
conditions that **6** was obtained from **3** (see Table 1), we can assign the configurations shown in Figure 1 for compounds **5** and **8**.

Table 2. *Significant NMR parameters for the configurational assignment of aminosulfoxides* ***5, 6 ,7 and 8.***

	Comp. **5**	Comp. **6**	Comp. **7**	Comp. **8**
$J_{1,2}$	3.8	4.3	3.5	3.5
$J_{2,3a}$	10.2	11.8	12.0	11.6
$J_{2,3e}$	3.8	4.3	3.5	4.3
δ-H(1)	4.10	3.59	3.44	2.82
δ-H(2)	2.86	2.76	2.58	2.68
δ-H(3a)	1.65	1.93.	1.65	1.86-2.0
δ-H(3e)	1.50	2.20	1.41-1.70	1.86-2.0
δ-C(3)	22.7	20.6	a	20.7
δ-C(5)	20.7	19.6	a	19.3

[a] Data not available

In order to explain the stereochemical course of these reactions, two different facts must be considered: the exclusive formation of the *cis*-aminosulfoxides, whatever the configuration of the starting imine **3** or enamine **4**, and the fact that only one amine (**6**) was obtained starting from the **3A+3B** mixture, with DIBAL, DIBAL/$ZnCl_2$, $LiAlH_4$ and Li(s-Bu)$_3$BH. The complete stereoselectivity observed for all hydrides is surprising considering their different electrophilic (DIBAL) or nucleophilic ($LiAlH_4$, L-Selectride) nature and the steric bulkiness (small: DIBAL, $LiAlH_4$ and bulky: L-Selectride), which contrast with our previous results on 2-*p*-tolylsulfinylcyclohexanones where the stereochemical outcome of the reactions was dramatically changed with either the electronic nature and/or the steric bulkiness of the reducing system[3].



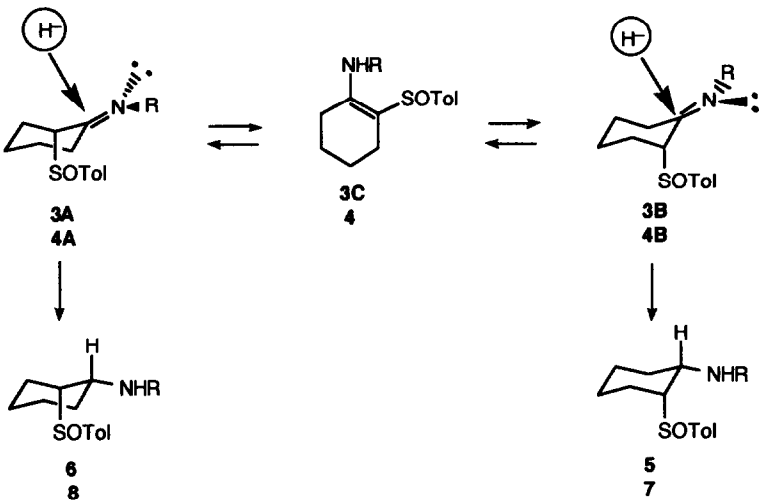
$(S_1R_2R_S)$
5 and **7**

$(R_1S_2R_S)$
6 and **8**

Fig. 1. *Favored rotamers for* **5** and **7**-**($S_1R_2R_S$)** *and* **6** and **8**-**($R_1S_2R_S$)** *sulfoxides.*

The axial hydride approach on the conformation with the sulfinyl group in axial position (Scheme 3), yielding the *cis*-aminosulfoxides, must be favoured for all hydrides in the case of the imines. Since we have demonstrated that these conformers are the major ones for both, **3A** and **3B** (*vide supra*) the results obtained suggest the axial attack as the major pathway for the evolution of the imines **3A** and **3B**. A similar explanation has been proposed in other reduction of

cyclic imines[18]. On the other hand, we must assume that both starting imines must be in fast equilibrium in the reaction medium (probably through the enamine **3C**), the reduction of one of them being much faster than the rate of production of the other, in order to explain the results obtained in the entries 1-4 (Table 1). Taking into account that the absolute configuration of **6** is ***R*1*S*2*R*S**, and that the reaction conditions do not affect the absolute configuration at C-2 and the sulfur atom, we can state that **6** comes from **3A** (***S*2*R*S** configuration), whose reduction must therefore be faster than that of **3B**. This rationale is reinforced by the result of the reduction with $LiEt_3BH$ and B_2H_6 (Table 1), which are the most reactive reagents (shortest reaction times), since in these cases each diastereoisomeric imine gives rise to a different amine in a ratio that closely resembles the proportion of the imines in the mixture used as starting material (**3A** /**3B** :2/1). $NaBH_4$ exhibits the same low selectivity of the more reactive hydrides.



Scheme 3

Despite the influence of $ZnCl_2$ in the ketosulfoxide reduction,[3] its presence does not modify substantially the results obtained in the reduction of imines with DIBAL and $NaBH_4$ (see Table 1), indicating that this Lewis acid does not exert any chelating effect on the β-iminosulfoxides. This has been demonstrated by recording the ^{1}H-NMR spectra of the mixture of imines **3A+3B** and $ZnCl_2$, in which no shifts of the signals corresponding to the imines has been observed.

The results obtained in the reduction of **4** are completely similar to the ones observed for **3**. Therefore we must assume that, in the reaction conditions, only the imine tautomer **4A** and **4B**, in equilibrium with the most stable enamine form **4** (see Scheme 3), is reduced with DIBAL, and both **4A** and **4B** reacted with $LiEt_3BH$, $NaBH_4$ and B_2H_6 (Table 1), giving always the *cis* aminosulfoxides.

Although it is necessary to prepare model substrates to clearly elucidate the mechanism of the reduction we have demonstrated the synthetical usefulness of this reaction which allows the preparation of only one enantiomerically pure aminosulfoxide from a mixture of diastereisomeric

imines. At present, we are working on the application of these reactions to acyclic imines and on the transformation of the sulfinyl function in order to obtain chiral functionalized cyclohexylamines.

EXPERIMENTAL SECTION

Melting points were obtained in open capillary tubes and are uncorrected. Microanalyses were performed by the Instituto de Química Orgánica of the CSIC in Madrid with a Perkin Elmer Model 240 analyzer.Mass spectra were recorded at 70 eV in a Hewlett-Packard 5985 spectrometer. The IR spectra were obtained on a Philips PU 9716. ^{1}H and ^{13}C-NMR spectra were recorded at 200.1 and 50.3 MHz. Diastereomeric ratios were established by integration of well-separated signals of both diastereomers in the mixtures of the aminosulfoxides. Optical purity was determined by ^{1}H-NMR analysis using the chiral shift reagent Eu(tfc)$_3$. The racemic compounds required for this determination were obtained from methyl *p*-toluenesulfinate for **5** and **6** following the same procedure. Thin layer chromatography was performed using precoated sheets of silica gel 60 (230-400 mesh) of Macherey-Nagel. Eluting solvents are indicated in the text. Dry THF was distilled from sodium/benzophenone ketyl. Apparatus for all experiments was dried by flaming in a stream of dry argon and all reactions were carried out under an argon atmosphere and were monitored by TLC. Unless otherwise indicated, routine workup was as follows: The crude mixtures resulting from hydrolysis were extracted with methylene chloride, dried over anhydrous sodium sulfate, and concentrated in vacuo. Diastereomeric ratio and yields of reductions are collected in Table 1.

Preparation of 2-iminosulfoxides. Method I. To a solution of LDA (31.3 mmol) in THF (25 ml) a solution of the corresponding imine (**1** or **2**) (36.7 mmol) in THF (25 ml) at -78°C was slowly added *via* syringe. The mixture was then placed in an ice-bath and stirred for 30 min. After this time, the mixture was recooled to -78°C, and a solution of (*S*)-(-)-menthyl *p*-toluenesulfinate (13.6 mmol) in THF (25 ml) was quickly added *via* syringe. The reaction mixture was stirred for 15-30 min at -78°C and then quenched with NH_4Cl (20 ml). **Method II.** To a solution of LDA (31.3 mmol) in THF (25 ml) was slowly added *via* syringe a solution of the imine **4** (36.7 mmol) in THF (25 ml) at -78°C. The mixture was then placed in an ice-bath and stirred for 30 min. After this time, a solution of $MgBr_2$ (generated from 3 ml of 1,2-dibromoethane and 0.9g of magnesium) in 100 ml of THF, was added through a double tipped needle by means of argon pressure. The mixture was then stirred for 1h. and recooled to -78°C, and a solution of (*S*)-(-)-menthyl *p*-toluenesulfinate (13.6 mmol) in THF (25 ml) was quickly added *via* syringe. The reaction mixture was then treated as in method I.

N-(2-*p*-tolylsulfinylcyclohexylidene) aniline (3A+3B) was prepared from cyclohexylidene aniline (**1**), following methods I and II; purified by flash chromatography on silica gel (acetone/hexane:1/2, and 10% Et_3N), yield 70% of a 2:1 mixture of **3A+3B.** Compound **3A** was isolated pure by crystallization from acetone-hexane; m.p. 110-111 °C: MS, m/z (rel. intensity) 311 (4.4) M^+, 263 (64.8), 172 (100.0), 143 (31.1), 130 (39.4), 91 (19.5), 77 (51.8); ^{1}H-NMR δ 7.63 and 7.33 (AA'BB' system, 4H, Tol), 7.25 (m, 2H, Ph), 7.05 (m, 1H, Ph), 6.49(m, 2H, Ph), 3.55 (dd, 1H, J= 6.7 and 4.6 Hz CHSO), 2.42 (s, 3H, CH_3), 2.51-1.30 (m, 8H, $(-CH_2-)_4$); ^{13}C-NMR 168.7 , 149.2 , 141.5 , 139.7 (139.6), 129.4 , 128.6, 125.2 , 123.4 , 119.0 , 73.3 , 31.0 , 26.9 , 26.5 , 22.7 , 21.1 ; IR (film) 2940, 1700, 1600, 1490, 1090, 815, 755 cm^{-1}. Compound **3B** could not be isolated pure and was characterized as a 2:1 mixture of **3A** and **3B.** ^{1}H-NMR δ 7.6 and 7.3 (AA'BB' system, 4H, Tol), 7.2 (m, 2H, Ph), 7.1-6.9 (m, 1H, Ph), 6.6-6.5 (m, 2H, Ph), 3.60 (dd, 0.3 H, J= 5.6 and 5.6 Hz, CHSO), 3.55 (dd, 0.6 H,J= 6.7 and 4.6 Hz, CHSO), 2.42 (s, 3H, CH_3), 2.5-1.1 (m, 8H, $(-CH_2-)_4$);^{13}C-NMR (values of **3B** in brackets)168.7 (168.9), 149.2 (149.4), 141.5 (141.4), 139.7 (139.6), 129.4 (129.3), 128.6 (128.3), 125.2 (125.4), 123.4 (123.3), 119.0 (119.3), 73.3 (70.5), 31.0 (31.1), 26.9 (28.1), 26.5 (26.5), 22.7 (22.7), 21.1 (21.1). N-1(2-*p*-tolylsulfinyl) cyclohexenyl aniline **3C** was isolated when the crude reaction mixture was crystallized from an

acetone/methanol mixture, m.p. 135-136°C. MS, m/z (rel. intensity) 311(2.7) M^+, 294(3.9), 263(100.0), 220(17.4), 172(75.8), 143(34.4), 130(39.0), 117(18.3), 91 (33.7), 77(74.1). ^{1}H-NMR (C_6D_6) δ 8.57 (*s broad*, 1H, NHPh), 7.65 and 6.88 (AA'BB' system, 8H, Tol), 7.03 (2H), 6.84 (1H) and 6.74 (2H) (multiplets of the phenyl ring), 2.28-2.00(*m*, 4H, protons at C(3) and C(6) in the cyclohexene ring), 1.93 (*s*, 3H, CH_3-C_6H_4) and 1.50-1.00 (m, 4H, protons at C(4) and C(5) in the cyclohexene ring); IR (KBr) 3300, 1620, 1590, 1480, 1295, 1010, 990, 795, 735 and 680 cm^{-1}; Anal.: Calculated from $C_{19}H_{21}NOS$: C, 72.90; H, 6.76; N, 4.47. Found: C, 73.05; H, 6.81; N, 4.78). In solution, this compound generates a mixture of imines **3A+3B**, as can be seen by nmr.

N-1-(2-*p*-tolylsulfinyl)cyclohexenylbenzylamine (4) was prepared from cyclohexylidene benzylamine (**2**) following methods I and II; purified by flash chromatography on silica gel (acetone/hexane:1/2, and 10% Et_3N), yield 65%: $[\alpha]_D$ =-21.0° ($CHCl_3$, c=1) MS, m/z (rel. intensity) 325 (2.7) M^+, 307 (2.2), 277 (50.6), 186 (25.8), 91 (100.0); ^{1}H-NMR δ 7.45 and 7.25 (AA'BB' §§system, 8H, Tol), 7.4-7.1 (*m*, 5H, Ph), 5.91 (t, J=6.4 Hz, 1H, NH), 4.3 (d, J=6.4 Hz, 2H, CH_2-N), 2.39 (s, 3H, CH_3), 2.5-1.2 (m, 8H, (-CH_2-)$_4$); IR (film) 3320, 2940, 1620, 1500, 1035, 820, 740 cm^{-1}.

General Procedures for Hydride Reductions. They have been previously reported[3] for **i-Bu_2AlH** (Method A), **i-Bu_2AlH/$ZnCl_2$** (Method B), **LiAlH$_4$** (Method C), **NaBH$_4$** (Method F) and **NaBH$_4$/$ZnCl_2$** (Method G). For **3** and **4** the hydride was added at -78°C and the resulting mixture strred at 0°C until completion.

Reductions with **Li(s-Bu)$_3$BH** (Method D) and **Li(Et)$_3$BH** (Method E): A solution of 0.22 mmol of a 1M hexane solution of the hydride is added to a mixture of 0.11 mmol of 2-iminosulfoxide in 5 ml of anhydrous THF at -78°C. The resulting solution was stirred at 0°C upon completion (4-8 h) and decomposed as in method C.

Reduction with **B_2H_6** (Method H): A solution of 0.45 mmol of a 1M hexane solution of B_2H_6 in THF was added to a mixture of 0.11 mmol of 2-iminosulfoxide in 5 ml of anhydrous THF at -78°C. The resulting solution was stirred at 0°C and upon completion (2-4 h) and then workup as in method C.

(*S*$_1$*R*$_2$*R*$_S$)-*cis*-N-phenyl-2-*p*-tolylsulfinylcyclohexylamine (5). Reduction of the mixture **3A+3B** with the following procedures E, F, G and H yielded a mixture of diastereomers **5** and **6** (Table 1). Amine **5** was isolated by flash chromatography ($CHCl_3$/acetone: 9/1 as eluent) and subsequently crystallized from hexane:acetone, mp 123-4°C; $[\alpha]_D$= +266° ($CHCl_3$, *c*=1) : MS, m/z (rel. intensity) 315 (2.2) M^++2, 313 (34.4) M^+, 296 (6.1), 174 (100.0), 139 (20.3), 132 (27.4), 106 (55.4), 91 (19.1), 77 (42.3) ; ^{1}H-NMR δ 7.52 and 7.27 (AA'BB' system, 4H, Tol), 7.18 (m, 2H, H-3 and H-3', Ph), 6.72 (m, 3H, H-4, H-2 and H-2', Ph), 4.8 (broad s, 1H, NH), 4.10 (dt, J=5.5 and 2.7 Hz, 1H, CHN), 2.86 (dt, J=10.2 and 3.8 Hz, 1H, CHSO), 2.40 (s, 3H, CH_3), 2.2-1.2 (m, 8H, (-CH_2-)$_4$); ^{13}C-NMR 146.9, 141.8, 139.0, 129.6, 129.0, 125.3, 117.5, 113.9, 66.5 (CHSO), 49.8 (CHN), 28.9 (C-6), 24.3, 22.7, 21.3 (CH_3), 20.7; IR (KBr) 3330, 2920, 1600, 1495, 1250, 1010, 810, 690 cm^{-1}. Anal. Calcd for $C_{19}H_{23}NOS$: C, 72.90; H, 7.41; N, 4.47. Found: C, 72.98; H, 7.44; N, 4.80.

(*R*$_1$*S*$_2$*R*$_S$)-*cis*-N-phenyl-2-*p*-tolylsulfinylcyclohexylamine (6). Reduction of the mixture **3A+3B** with DIBAL (Method A) yielded pure **6** (Table 1) which was crystallized from hexane:acetone, mp 118-9°C; $[\alpha]_D$= -103° ($CHCl_3$, c=1) : MS, m/z (rel. intensity) 315 (2.2) M^++2, 313 (24.0) M^+, 296 (6.5), 174 (100.0), 139 (11.4), 132 (25.3), 106 (53.9), 91 (23.4), 77 (45.1) ; ^{1}H-NMR δ 7.45 and 7.25 (AA'BB'system, 4H, Tol), 7.17 (m, 2H, H-3 and H-3',Ph), 6.73 (m, 1H, H-4), 6.52 (m, 2H, H-2 and H-2', Ph), 4.2 (broad s, 1H, NH), 3.59 (dt, J=6.9 and 3.4 Hz, 1H, CHN), 2.76 (dt, J=11.8 and 4.3 Hz, 1H, CHSO), 2.41 (s, 3H, CH_3), 2.3-1.1 (m, 8H, (-CH_2-)$_4$); ^{13}C-NMR 145.7, 141.2, 138.5, 129.4, 128.9, 124.7, 117.4, 113.4, 67.1 (CHSO), 48.5 (CHN), 28.1, 24.6, 21.1, 20.6,

19.6. IR (KBr) 3330, 2930, 1600, 1520, 1490, 1250, 1080, 1020, 810, 690 cm^{-1}. Anal. Calcd for $C_{19}H_{23}NOS$: C, 72.90; H, 7.41; N, 4.47. Found: C, 72.72; H, 7.44; N, 4.82.

(*S*1 *R*2 *R*S)-*cis*-N-benzyl-2-*p*-tolylsulfinylcyclohexylamine (7). Reduction of **4** following procedures E, F and H yielded a mixture of diastereomers **7** and **8** (Table 1). Amine **7** was isolated pure by flash chromatography (hexane/ethyl acetate : 1/1 as eluent) as an oil. $[\alpha]_D$ =+170.25° ($CHCl_3$, c=0.4) : ^{1}H-NMR δ 7.50 and 7.25 (AA'BB' system, 4H, Tol), 7.40-7.20 (m, 5H Ph), NH), 3.83 and 3.75 (AB system, J=12.9 Hz, 2H, CH_2N), 3.44 (dt, J=6.7 and 3.5 Hz, 1H, CHN), 2.58 (dt, J= 12.0 and 3.5 Hz , 1H, CHSO), 2.35 (s, 3H, CH_3), 1.8-1.1 (m, 8H, $(-CH_2-)_4$);

(*R*1 *S*2 *R*S)-*cis*-N-benzyl-2-*p*-tolylsulfinylcyclohexylamine (8). Reduction of the **4** with DIBAL (Method A) yielded **8** that was purified by flash chromatography (hexane/ethyl acetate :1/2) MS, m/z (rel. intensity) 327 (1.4) M^+, 310 (24.3),188 (11), 139 (11.2), 91 (100), ^{1}H-NMR δ 7.60 and 7.25 (AA'BB' system, 4H, Tol), 7.30 (m, 5H, Ph), 3.8 and 3.47 (AB system, J=13.3 Hz, 2H, CH_2N), 2.82 (dt, J=7.1 and 3.7 Hz, 1H, CHN), 2.68 (dt, J= 11.6 and 4.3 Hz, 1H, CHSO), 2.40 (s, 3H, CH_3), 2.2-1.1 (m, 8H, $(-CH_2-)_4$). IR (film) 3310, 3030, 2930, 2855, 1595, 1495, 1455, 1085, 1035, 1015, 810, 730, 700 cm^{-1}.

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10.- The reaction conditions are very critical. The enolate, which must be used in excess with respect to the sulfinate, has to be prepared by using a slight deficiency of LDA with respect to the starting imine to avoid the formation of the sulfinamide resulting from the direct attack of LDA on the sulfur). The best results were obtained with a 2.3/2.7/1 molar ratio of LDA:imine:menthyl sulfinate.
11.- This yield was obtained after chromatographic purification from the crude (see experimental) with an eluent containing Et_3N to avoid the easy hydrolysis of the imine to the corresponding ketosulfoxide .
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13.- A mixture of the four possible diastereomeric imines (**3A**, **3B** with (E)-configuration and their corresponding Z-isomers) could be isolated in one of the trials. The ^{13}C-nmr spectrum of this mixture showed the signals corresponding to C-2 at 73.1, 70.5, 67.4 and 64.7 ppm, and those of

C-6 at 31.1, 31.0, 37.2 and 38.0 ppm, being the two first in each series much more intense. Taking into account that a-carbons in E-imines have a downfield shift of more than 6 ppm relative to the Z imines (see H.O. Kalinowski, S. Berger and S. Braun in "*Carbon-13 nmr spectroscopy*" John Wiley & Sons Ltd., Chichester, 1988, p.242), we assign the E-stereochemistry to the two major components of the mixture, easily separated by chromatography, which were the only isolated in the other experiments (**3A** and **3B**).

14.- The crystallization of this mixture yielded **3A** diastereomerically pure. Nevertheless, in solution, this compound is immediately equilibrated, which determined that all reduction studies were made on the mixture **3A+3B.**

15.- In other alkyl (or aryl)-amino sulfoxides studied by us (see E. Brunet, M.T. Gallego, J.L. García Ruano and F. Alcudia, *Tetrahedron*, **1986**, *42*, 1423 and E. Brunet, M.C. Carreño, M.T. Gallego, J.L. García Ruano and F. Alcudia, *J. Chem. Soc. Perkin Trans. II*, **1983**, 937) the diastereoisomers exhibiting the same relative configuration at sulfur and C β than that of **5**, showed almost complete conformational shift towards the rotamer with the nitrogen and the lone electron pair at sulfur adopting an 1,3-parallel arrangement (presumably stabilized by n-d donor acceptor interactions) Figure 1. On the contrary, diastereoisomers with the relative configuration of sulfur and C β corresponding to that of **6** display a lower conformational preference.

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