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Catalytic Activity of Chiral β-Hydroxysulfoxides in the Enantioselective Addition of Diethylzinc to Benzaldehyde.

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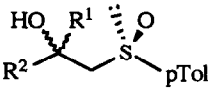
Abstract: The first examples of the use of readily available β-hydroxysulfoxides **1-8** as chiral catalysts in the enantioselective addition of diethylzinc to benzaldehyde are reported. The increase of the steric hindrance around the chirai ligand OH group improves the e.e. of the obtained 1-phenylpropanol, which is higher with tertiary alcohols (25-45%) than with secondary ones (<23%). The addition of $MeAl_3$ also affords better e.e. (55%).

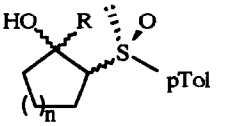
Enantioselective catalytic alkylation of prochiral aldehydes has been widely studied by using a combination of dialkylzinc compounds and optically active ß-aminoalcohols[1], diamines[2] and 1,2-diols[3] as chiral auxiliaries. The observed stereoselectivity in these reactions was justified by assuming the existence of a rigid transition state formed by association of ligands and the organometallic species.[1-4] In order to become efficient catalysts, the presence of the two basic centers in the ligands seems to be essential. β-Hydroxysulfoxides have also two basic oxygens,[5] which suggests that they could act as chiral bidentated ligands. Nevertheless, to the best of our knowledge, optically active β-hydroxysulfoxides have never been used as a chiral source in this kind of reaction.[6] Taking into account that these compounds are readily available in enantiomerically pure form by stereoselective nucleophilic addition to chiral β-ketosulfoxides, we decided to investigate their catalytic activity. This paper reports our results in the use of enantiomerically pure ß-hydroxysulfoxides as chiral ligands in the enantioselective alkylation of benzaldehyde with diethylzinc to obtain optically active 1-phenylpropanol.

Results and discussion.

The structures of the hydroxysulfoxides considered in this study are recorded in scheme 1. As can be seen, we have studied secondary and tertiary alcohols with cyclic and acyclic skeleton. With these structural variations we treated to determine the role that the substitution around the chiral centers of the ligand plays on the enantioselectivity of the process which, according to the published reports, is sometimes contradictory.[7]



compound	R^1	R^2
1a-[2S,(S)R]	^{t}Bu	H
1b-[2R,(S)R]	^{t}Bu	H
2-[2R,(S)R]	^{t}Bu	CH_3
3a-[1S,(S)R]	Ph	H
3b-[1R,(S)R]	Ph	H
4-[2R,(S)R]	Ph	CH_3
5-[5R,(S)R]	$H_3CO_2C(CH_2)_2CH_2$	H

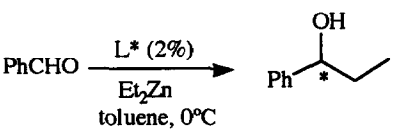


compound	n	R
6a-[1S, 2S, (S)R]	1	H
6b-[1R, 2S, (S)R]	1	H
7a-[1S, 2S, (S)R]	2	H
7b-[1R, 2S, (S)R]	2	H
8-[1R, 2S, (S)R]	2	CH_3

Scheme 1

Secondary alcohols **1**[8,9], **3**[9], **5**[10], **6**[11] and **7**[12] were obtained by reduction of the corresponding chiral β-ketosulfoxides with DIBAL or DIBAL / $ZnCl_2$, whereas the tertiary carbinols **2**, **4** and **8**[13], derive from the stereoselective $AlMe_3$ addition to the adequate precursors in the presence of $ZnCl_2$. The high optical purity (ee>97%) of all the β-hydroxysulfoxides used in this study (**1-8**) was established by nmr, using Eu $(hfc)_3$ as chiral shift reagent.

Reactions of diethylzinc with benzaldehyde were conducted at 0°C in toluene and in the presence of catalytic amounts (2 mol %) of the ß-hydroxysulfoxide (L*) used as chiral auxiliary (Scheme 2).



Scheme 2

Hydroxysulfoxides were easily recovered from the reaction mixtures by flash column chromatography with virtually the same optical purity in every case. Both, the enantiomeric excess of the resulting 1-phenylpropanol and the absolute configuration of the major enantiomer were deduced from the value of the optical rotation of the samples obtained, after purification by flash chromatography. The results are reported in Table I.

A detailed analysis of this table indicates that the enantiomeric excess of the resulting 1-phenylpropanol increases when the hydroxylic center of the chiral ligand became more crowded. Thus, when acyclic secondary carbinols **1**, **3** and **5** were used as catalysts, the best result was obtained with the ligand **1b**–[2R,(S)R] having

the bulky ^{t}butyl substituent on the hydroxylic carbon (Table I, entry 2). Better results were obtained using the sulfinylcyclohexanols **7** (entries 10 and 11) than the corresponding cyclopentanol derivatives **6** (entries 8 and 9).

Table I: Asymmetric Addition of Diethylzinc to Benzaldehyde[a].

entry	ligand	$[\alpha]^{25}$, (c, $CHCl_3$)	ee (conf.)[b]	r[c]
1	**1a**-[2S,(S)R]	+4.2, (2.62)	9 (R)	4.3
2	**1b**-[2R,(S)R]	-10.1, (3.48)	22 (S)	7.6
3	**2**-[2R,(S)R]	-15.8, (2.40)	35 (S)	2.0
4	**3a**-[1S,(S)R]	+8.0, (8.00)	18 (R)	2.1
5	**3b**-[1R,(S)R]	-7.1, (2.12)	16 (S)	1.6
6	**4**-[2R,(S)R]	-11.1, (2.20)	25 (S)	1.2
7	**5**-[5R,(S)R]	-3.1, (4.60)	7 (S)	3.2
8	**6a**-[1S, 2S, (S)R]	-0.7, (6.00)	2 (S)	5.8
9	**6b**-[1R, 2S, (S)R]	-4.8, (2.80)	11 (S)	2.5
10	**7a**-[1S, 2S, (S)R]	-4.5, (1.00)	10 (S)	5.7
11	**7b**-[1R, 2S, (S)R]	-10.6, (4.20)	23 (S)	2.2
12	**8**-[1R, 2S, (S)R]	-20.4, (4.40)	45 (S)	3.5
13[d]	**8**-[1R, 2S, (S)R]	-4.8, (4.40)	11 (S)	3.0
14[e]	**8**-[1R, 2S, (S)R]	-9.2, (5.27)	21 (S)	5.2
15[f]	**Al-8**-[1R, 2S, (S)R]	-24.8, (1.10)	55 (S)	4.2
16[g]	**B-8**-[1R, 2S, (S)R]	-16.1, (3.10)	36 (S)	1.8
17[h]	**Li-8**-[1R, 2S, (S)R]	-15.5, (1.98)	35 (S)	1.3

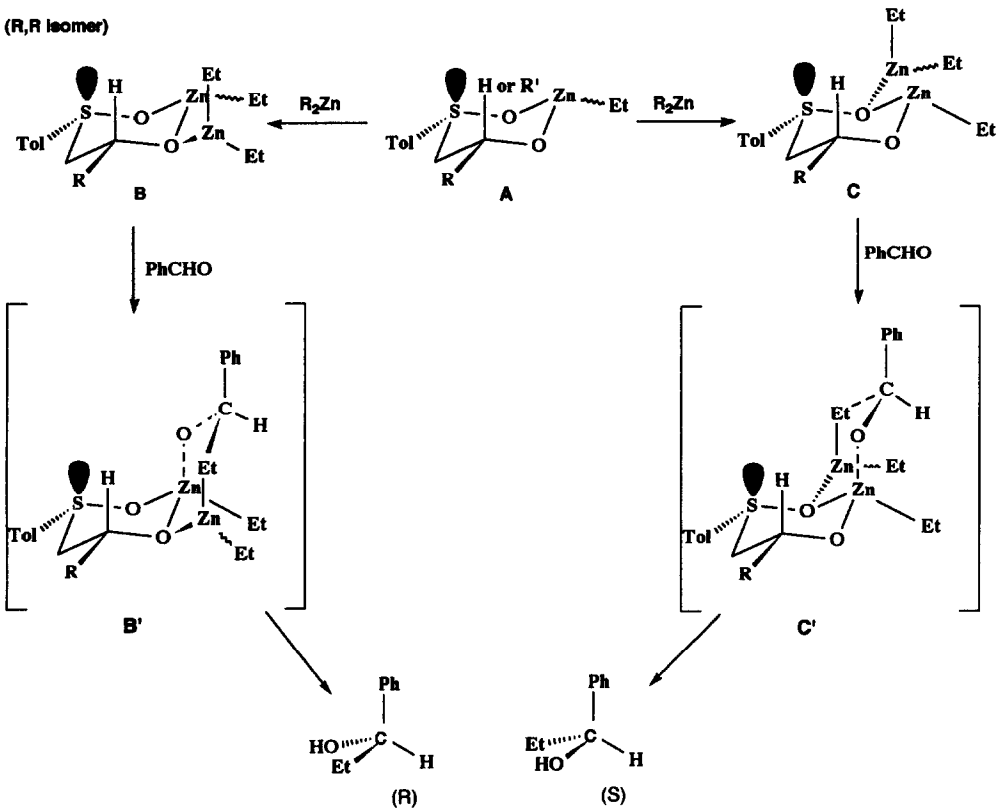
[a] Reaction was carried out in toluene at 0°C using 2 mol % of β-hydroxysulfoxide and a ratio alkylating agent/aldehyde=1.2 .[b]Determined on the basis of the optical rotation of (S)-1-phenylpropanol: $[\alpha]^{25}$ -45.45(c 5.15, $CHCl_3$)[14].[c] Ratio 1-phenylpropanol/ benzyl alcohol (determined by ^{1}H-NMR analysis).[d] Reaction carried out in CH_2Cl_2.[e] Reaction carried out in toluene / hexane.[f] Complex formed by chiral ligand and $AlMe_3$.[g] Complex formed by chiral ligand and $BH_3.SMe_2$.[h] Complex formed by chiral ligand and n-BuLi.

The tertiary carbinols (entries 3, 6 and 12) yielded much better results than the secondary ones, being the hydroxysulfoxide **8** which afforded the highest e.e. (entry 12). The influence of the steric hindrance around the basic centers had been already observed in other enantioselective additions using chiral aminoalcohols.[1]

The configuration of the hydroxylic carbon in the ligand is also important. It seems that the use as catalysts of secondary and tertiary carbinols having the ***R*** configuration at this carbon favours the formation of the (S)-enantiomer. This preference decreases when the catalysts have the ***S*** configuration at the hydroxylic carbon, even the formation of the (R)-enantiomer becomes favoured using acyclic sulfoxides (entries 1 and 4).

All these results can be explained from the model depicted in Scheme 3, which is based on that proposed by Noyori et al.[15] to explain the catalytic effect of ß-aminoalcohols, but assuming that the transfer of the ethyl group takes place throught a chair-like six membered ring (instead of the four membered ring suggested in ref. 15) as transition state, according to the mechanism suggested by Soai et al.[16]

In the case of the acyclic (or cyclic) sulfoxides with ***R*** configuration at the hydroxylic carbon, the initial reaction of diethylzinc with the OH group of the catalysts affords the corresponding zinc monoalkoxides A[17], which must be stabilized by association with the sulfinylic oxygen (its most stable conformation is depicted in Scheme 3).



Scheme 3

The species A contains two basic oxygens, both able to coordinate with a second molecule of the dialkylzinc forming the intermediates B and C. Further association of the aldehyde on the zinc joined to both oxygens (more acidic that the other one) affords respectively (R) and (S) 1-phenylpropanol through the transition states B' and C'. Taking into account that B' must be slightly less stable than C' (the steric interaction $(H/Et)_{1,3\text{-}p}$ present in B' is more destabilizing than the $(:/Et)_{1,3\text{-}p}$ in C' and the $S^{\delta+}/O^{\delta-}$(aldehydic) attraction must be larger in

C' than in B'[18]), the enantiomer (S) will be obtained as the major one. In the case of the tertiary alcohols the relative stabilities of both, the C intermediate and the transition state C', are substantially higher than those of B and B', determining that the proportion of the enantiomer (S) was larger than using secondary alcohols as catalysts.The slight predominance of the (R) enantiomer starting from the epimers with *S* configuration at the hydroxylic carbon must be readily explained by using a similar model to that depicted in Scheme 3.

The situation must be similar for cyclic alcohols, but they are more efficient than the acyclic ones and yield better e.e. (the same has been observed in aminoalcohols[15]), being the stability and the steric constraint of the bicyclic chelated species (that also depends on the size of the cycle) responsible of the observed changes in stereoselectivity.

Analogously to other catalyzed diethylzinc additions, variable amounts of benzyl alcohol resulting from reduction of benzaldehyde were obtained under the usual alkylation conditions. The values for the ratio phenylpropanol/benzylic alcohol (r in Table I) range from 1.1 to 7.6. Unfortunately when the e.e. becomes better the r values are usually worse.

We have evaluated the influence of several factors, such as the concentration of the catalyst, the temperature and the solvent, on the asymmetric induction in the case of the sulfoxide **8**. The increase of concentration of **8** up to 20%, strongly improves the yield in phenylpropanol (conversion of the starting product is 90% and r=21) but the stereoselectivity is not reproducible (e.e. range between 3 and 55%). On the other hand, no reaction was observed when the temperature ranged from -40°C to -20°C. The best stereoselectivity is obtained at 0°C, despite at higher temperatures the r values are better. Similar effects of the temperature and concentration have been observed by using aminoalcohols as catalysts.[15] As far as the solvent is concerned (Table I, entries 13 and 14), the use of CH_2Cl_2 instead of toluene decreases the enantioselectivity.

In many cases, the use of lithium, boron and aluminum complexes of the chiral catalysts have made possible to increase their effectiveness.[1b,4] The influence of different metallic atoms was also studied on compound **8**. The results of benzaldehyde alkylation in the presence of previously generated lithium-, boron-, or aluminum-hydroxysulfoxide complexes are collected in Table I. The reactions were carried out by addition of a mixture of diethylzinc and benzaldehyde to the solution resulting in the treatment of compound **8** with 1.2 eq.of n-BuLi, $BH_3.SMe_2$ or $AlMe_3$ respectively, in toluene at room temperature. The best enantioselectivity was achieved with $AlMe_3$ (Table I, entry 15, 55% ee and r=4.2). This result suggested that the Al atom must be involved in the catalytic process.[19]

In conclusion, we can affirm that enantiopure ß-hydroxysulfoxides are effective chiral catalysts to the asymmetric synthesis of 1-phenylpropanol by reaction of benzaldehyde with Et_2Zn. Despite the structural analogy of these compounds with ß-aminoalcohols (usually used as catalysts in these processes), the e.e. obtained with sulfoxides ranges from low to moderate, contrasting with the results reported[1] with the former. This can be attributed to the double possibility of coordination for the second $ZnEt_2$ molecule, exhibited by the initially formed zinc monoalkoxide A (only one, the oxygen, in the case of the aminoalcohols).

Experimental

Melting points were determined on a Gallenkamp capillary apparatus and are uncorrected. The ^{1}H-NMR (200 MHz) and ^{13}C-NMR (50.3 MHz) were registered on a Bruker WP-200-SY spectrometer. All NMR spectra were obtained using $CDCl_3$ as solvent and TMS as an internal standard. Optical rotations were recorded on a

Perkin-Elmer 241 MC automatic polarimeter in a 1dm tube; concentrations are given in g/100 ml. Infrared spectra were recorded on a Philips PU-9716 spectrophotometer.Toluene was dried over sodium pentoxide and kept over sodium wire. Tetrahydrofuran was distilled from sodium-benzophenone under argon. All reactions reported were carried out under argon atmosphere. Flash chromatography was performed on silica gel Merck (MN-Kieselgel 60, 230-400 mesh).

[2R,(S)R]-2,3,3-trimethyl-1-p-tolylsulfinylbutan-2-ol, (2).

A mixture of [(S)R]-3,3-dimethyl-1-p-tolylsulfinylbutan-2-one[8,9] (214 mg, 0.9 mmol) and anhydrous zinc chloride (180 mg, 1.2 mmol) in dry THF (8 ml) was submitted to sonication for 20 min at room temperature. The resulting solution was added dropwise to a 2M hexane solution of trimethyl aluminum (1.8 ml, 3.6 mmol) in THF and stirred for 15 min at room temperature. The mixture was decomposed by careful addition of methanol (4 ml) at 0°C. The solvents were evaporated at vacuo, and the residue was diluted with a 5% aqueous sulfuric acid solution. The aqueous solution was extracted with methylene chloride and the organic layer was washed with brine. The organic phase was dried over sodium sulfate and evaporated under reduced pressure to yield compound **2** as a 95:5 mixture of [2R,(S)R] and [2S,(S)R] isomers (83% yield) from which diastereomerically pure **2**-[2R,(S)R] was isolated by crystallization from ethyl acetate -hexane as a white solid. mp: 116-117°C ; $[\alpha]^{25}$= +213.6 (c 1.2 $CHCl_3$); ^{1}H NMR, δ: 7.60 and 7.31 (AA'BB' system, 4H), 5.60 (s, br, 1H), 2.87 (AB system, 2H, J=13 Hz), 2.43 (s, 3H), 0.91 (s, 12H) ppm; ^{13}C NMR, δ: 141.7, 140.3, 129.9, 123.7, 76.2, 63.7, 38.2, 24.6, 21.9, 21.2 ppm. I.R.(KBr) (cm^{-1}): 3440, 2980, 1470, 1380, 1020, 820, 740. Found C, 66.40; H, 8.61; S, 12.50. $C_{14}H_{22}O_2S$ requires C, 66.10; H, 8.72; S, 12.60.

[2R,(S)R]-2-phenyl-1-p-tolylsulfinylpropan-2-ol, (4).

This was prepared from [(S)R]-1-phenyl-2-p-tolylsulfinyletan-2-one[9] in a manner analogous to the preceding preparation, affording 4 as a 86:14 mixture of [2R,(S)R] and [2S,(S)R] isomers (78% yield) from which diastereomerically pure 4-[2R,(S)R] was isolated as a colourless oil by cromatographyc pufication (ether/hexane 5/2); $[\alpha]^{25}$= +150 (c 2 $CHCl_3$); ^{1}H NMR, δ: 7.60 and 7.10 (m, 9H), 3.14 (dc, AB system part A, 1H,J_{AB}=13.3 Hz, J_{AMe}=0.6 Hz), 2.96 (AB system part B, 1H, J_{AB}=13.3 Hz), 2.39 (s, 3H), 2.00 (d, 3H, J_{AMe}=0.6 Hz) ppm; ^{13}C NMR, δ: 146.2, 141.5,139.9, 129.8, 128.0, 126.9, 124.4, 123.7, 73.7, 68.6, 28.4, 21.1 ppm. I.R.(KBr) (cm^{-1}): 3580, 3400, 1600, 1500, 1060, 1010, 818. Found C, 69.89; H, 6.74. $C_{16}H_{18}O_2S$ requires C, 70,04; H, 6.61.

General Procedure for the Enantioselective Alkylation of Benzaldehyde using $ZnEt_2$.

A dry 50 ml Schlenk flask containing a small Teflon-coated stirring bar was evacuated and filled with argon. The flask was charged with a solution of chiral β–hydroxysulfoxide (2 mol%, 0.2 mmol) in dry toluene (20 ml), and degassed by freeze-thaw cycles. An hexane solution of diethylzinc (1M,12 ml, 12 mmol) was added at room temperature. After stirring for 30 min, the mixture was cooled to -78°C and benzaldehyde (10 mmol) was added over a period of 5 min and was kept at 0°C for additional 15-20 h. at 0°C. Saturated aqueous ammonium chloride solution was added to quench the reaction mixture. After extraction with ethyl acetate, the combined organic layers were washed with 5% aqueous hydrochloric acid solution and brine. The extracts were

dried over anhydrous sodium sulphate and evaporated under reduced pressure. Purification of the residue by flash columm chromatography (ethyl acetate/hexane 1/4) afforded optically active 1-phenylpropanol.

General Procedure for the Enantioselective Alkylation of Benzaldehyde, using n-BuLi, $BH_3.SMe_3$ or $AlMe_3$ and $ZnEt_2$.

To a toluene solution of the chiral β–hydroxysulfoxide (0.2 mmol) was added dropwise a solution of n-BuLi (0.24 mmol) in hexane, $BH_3.SMe_2$ (0.24 mmol) or Me_3Al in hexane (0.24 mmol), respectively at room temperature. After stirring for 30 min, an hexane solution of diethyl zinc (1M, 12 ml, 12 mmol) was added and the mixture was kept at room temperature for 30 min. Benzaldehyde (1.01 ml, 10 mmol) is then added at -78°C over a period of 5 min and stirring prolonged for additional 15-20h. Quenching, extraction and purification were performed as described above.

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11. Compound **6** had been previously obtained in our laboratory following the procedure described in reference 12.

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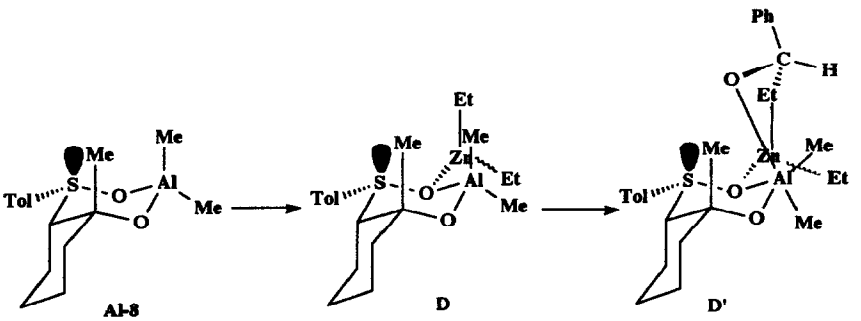
17. Dimeric structures has been demonstrated in the reactions catalyzed by 3-*exo* (dimethylamino)isoborneol (See ref. 15).

18. The association of the Et_2Zn on the sulfinyl oxygen decreases its n-backbonding effect on the sulfur in C', that increases the positive charge at sulfur and consequently make stronger the S/O electrostatic attraction.

19. By reaction with Me_3Al, compound **8** must evolve into the complex **Al-8** depicted in Scheme 4. The ^{1}H-NMR spectrum of the 1:1 mixture of compound **8** and $AlMe_3$ in C_6D_6 showed the disappearance of the signals corresponding to methyl groups and to the hydroxylic proton, whereas a broad six protons singlet at δ=-0.013ppm, and a significant upfield shift (Δδ=0.1ppm) of the signals corresponding to the protons of the p-tolylsulfinyl group can be observed. This complex must be able to catalyze the addition of $ZnEt_2$ to benzaldehyde. The sense of induction in the alkylation reaction could be explained through the intermediate D, where a diethylzinc molecule is activated[15] by coordination with the sulfinyl oxygen (the association on the alkoxide oxygen is less favored by steric grounds, see discussion about Scheme 3). It is able to transfer the ethyl moiety to the benzaldehyde associated to the more Lewis acidic aluminum atom, giving rise to the pentacoordinate aluminum species[20] which mainly evolves through D' into the (S) 1-phenylpropanol.



Scheme 4

It is evident that in this reaction on **Al-8**, the ethyl group must be transferred from the Et_2Zn activated by association on only one oxygen. This is the base to assume that the same can happen from intermediates B and C (Scheme 3) and therefore it is not strictly necessary that the migration of the Et group take place from the the zinc atom supported by the two oxygens (suggested by Noyori in ref. 15).

20. Although organoaluminum complexes prefer tetracoordination (Evans, D.E.; *Science*, **1988**, *240*, 420), pentacoordinated species such as **D'** have also been proposed to explain the stereoselectivity of catalyzed Diels-Alder reactions (Rebière, F., Riant, O, and Kagan. H. B. *Tetrahedron Asymmetry*, **1990**, *1*, 199.) or cyanohydrin formation (García Ruano, J.L., Martín, A.M., Rodriguez, J.H., *J. Org. Chem.* **1992**, *57*, 7235).