β-Hydroxy Sulfoximines as Catalysts for the Enantioselective Alkylation of Aldehydes

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Optically active β-hydroxy sulfoximines are catalysts for the enantioselective ethyl transfer from diethylzinc to aldehydes affording secondary alcohols with high enantioselectivity; the structure of a dimeric zinc alkoxide has been determined by X-ray diffraction analysis.

The addition of diorganozinc reagents to aldehydes can be accelerated by a wide range of chiral catalysts affording secondary alcohols with high asymmetric induction.[1] To date the most successful catalysts have been sterically congested β-amino alcohols possessing a bulky substituent at the chiral hydroxy-bearing carbon atom. In general, the highest rate enhancements and enantioselectivities have been observed with amino alcohols that are able to form a five-membered chelate ring. In this communication we report on the use of a novel type of catalyst containing a chiral sulfur atom and the crystallographic characterization of a sulfoximine-containing dimeric zinc alkoxide.

The synthesis and reactivity of sulfoximine derivatives have been extensively studied by Johnson *et al.*[2] and others.[3–5] We have now found that catalytic amounts of β-hydroxy sulfoximines accelerate the ethylation of aldehydes leading to the alkylated products with high enantiocontrol. The catalytically active compounds **1–6** were synthesized by the addition of the appropriate sulfonimidoyl lithium reagent to ketones with subsequent aqueous work-up and purification by column chromatography.[6]

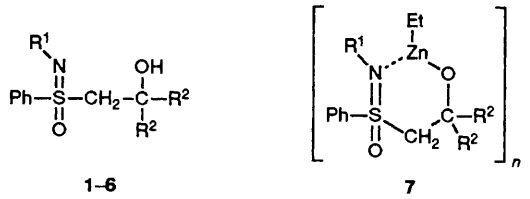
In order to make comparisons with previous results,[7] we chose the catalysed enantioselective ethyl transfer from diethylzinc to benzaldehyde **8a** as the standard model reaction. In the presence of 5–10 mol% of β-hydroxy sulfoximines ethyl transfer occurred even below room temperature, and **9a** was obtained with up to 88% enantiomeric excess (e.e.). In all cases, the (*S*)-enantiomer of **9** was the major product when (*S*)-β-hydroxy sulfoximines were used.

The asymmetric induction was highly dependent on the structure of the catalyst. The best selectivities were achieved with sulfoximines having two alkyl substituents at the hydroxy bearing β-carbon (Table 1). Sulfoximines **1**, **2** and **3**, derived from cyclobutanone, cyclodecanone and acetone, respectively, gave the most selective catalysts. Changes in the size and electronic properties of the imine nitrogen revealed that *N*-methylsulfoximines gave catalysts leading to the highest e.e. values of **9a**.

Substituted aryl aldehydes, such as **8b** and **8c**, were alkylated almost equally well to give the corresponding products with 79 and 75% e.e., respectively. Ethyl transfer to **8d** occurred with lower enantioselectivity (61% e.e.).

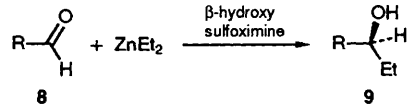
Treatment of a hexane solution of *rac*-**3** with diethylzinc resulted in the formation of a dimeric aggregate of zinc alkoxide **7** (R^1 = R^2 = Me, n = 2). Its structure was determined by single crystal X-ray diffraction (Fig. 1). In this dinuclear zinc complex two heterochiral zinc alkoxides are bridged *via* their zinc and oxygen atoms to form a four-membered Zn_2O_2 heterocycle.

The non-monomeric nature of the species formed in solution was indicatd by the asymmetric amplification in the catalysis with a β-hydroxy sulfoximine of low optical purity.[1,7,8] The use of 10 mol% of **3** of only 23% e.e. resulted in the formation of **9a** with 64% e.e. in 70% yield.†



1–6

7



8 **9**

a; R = Ph
b; R = *p*-ClC_6H_4
c; R = *p*-$MeOC_6H_4$
d; R = CH_2CH_2Ph

Table 1 Enantioselective addition of $ZnEt_2$ to aldehydes catalysed by β-hydroxy sulfoximines

Sulfoximine	Mol%	Aldehyde **8**	R^1	$(R^2)_2$	Yield of **9** (%)[a]	E.e. of **9** (%)[b]
1	10	**a**	Me	$[CH_2]_3$	55	84
2	5	**a**	Me	$[CH_2]_9$	50	88
3	10	**a**	Me	Me_2	73	85
4	10	**a**	Et	Me_2	94	68
5	5[c]	**a**	Tos[d]	Me_2	52	1
6	5	**a**	TBS[d]	Me_2	7	4
3	5	**b**	Me	Me_2	79	79
3	5	**c**	Me	Me_2	48	75
3	5	**d**	Me	Me_2	50	61

[a] Standard reaction conditions: $ZnEt_2$ (2 equiv.), hexane, 0 °C, 2–36 h; low yields due to incomplete conversion of **8** and formation of benzyl alcohol; after column chromatography. [b] Optical purities determined by HPLC using a chiral stationary phase (Chiralcel OD) or ^1H NMR spectroscopy of the corresponding methoxy(trifluoromethyl)phenylacetyl (MTPA) esters. [c] Use of 1.5 equiv. of $ZnEt_2$. [d] TBS = *tert*-butyldimethylsilyl; Tos = tosyl.

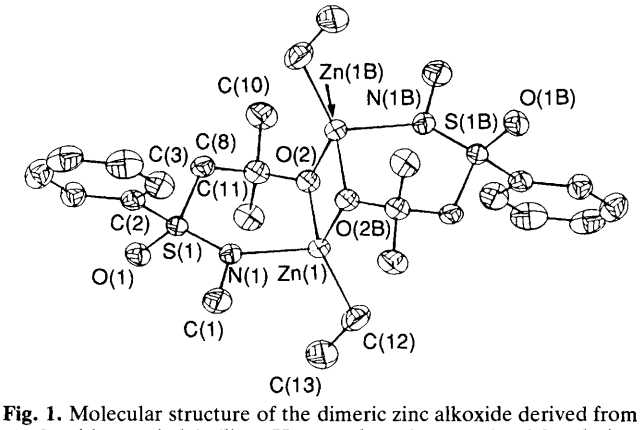


Fig. 1. Molecular structure of the dimeric zinc alkoxide derived from *rac*-**3**, with atomic labelling. H atoms have been omitted for clarity. *Crystal data*: $C_{26}H_{42}N_2O_4S_2Zn_2$, M = 641.512, monoclinic, $P2_1/n$, a = 8.447(7), b = 9.246(2), c = 19.514(9) Å, β = 100.29(6)°, U = 1499.5(16) Å^3, Z = 2, Mo-Kα radiation (λ = 0.71069 Å), θ_{max} = 28°, R = 0.028 (R_w = 0.033) for 3136 unique observed reflections. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors. Issue No. 1.

† The optical purity of the catalysts (≥95% e.e.) is based on the e.e. value obtained by ^1H NMR shift experiments of the synthetic precursor *S*-methyl-*S*-phenylsulfoximine. In the amplification studies, the e.e. of **3** was determined by HLPC using a chiral stationary phase (Chiralcel OD).

Further investigation into the use of optically active sulfoximine–metal complexes in asymmetric catalysis is currently being pursued in our laboratories.[9]

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