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Spectroscopic Studies on the β-Hydroxysulfoximine-Catalyzed Enantioselective Alkylation of Aldehydes ¥

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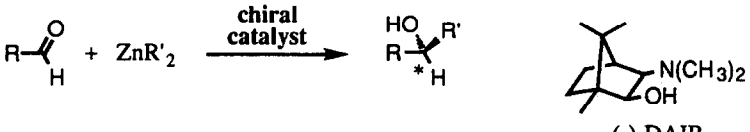
Abstract: The asymmetric β-hydroxysulfoximine-catalyzed alkyl transfer from diethylzinc to benzaldehyde has been studied by NMR spectroscopy.

INTRODUCTION

Asymmetric alkyl transfer from dialkylzinc to aldehydes is efficiently catalyzed by a number of chiral reagents affording optically active addition products with high enantiomeric excess.[2] Rapid progress has followed the initial reports by *Oguni* et al.,[3] and in 1986 a major landmark in this field, the use of the sterically congested β-amino alcohol 3-*exo*-(dimethylamino)isoborneol (DAIB) in this catalytic transformation, was described by *Noyori* and coworkers.[4] Since then, several studies have focused on the development of new catalyst systems with high enantioselectivities and improved practicality. Modified transmetallation



(-)-DAIB

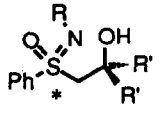
Scheme 1

procedures introduced by *Seebach, Knochel, Oppolzer,* and others,[5] now even allow the preparation of zinc reagents which give a wide range of *functionalized* secondary alcohols with high optical purities by catalyzed asymmetric aldehyde additions.

¥ Dedicated to Professors K. Barry Sharpless and R. Noyori to honor their outstanding contributions to asymmetric catalysis.

The main aim in this research has been the achievement of high enantioselectivities. In a careful mechanistic study, *Noyori* et al. investigated the dimethylzinc addition to benzaldehyde in the presence of catalytic amounts of DAIB, and an explanation of the origin of the enantioselection in this reaction has been given.[2,4] Accordingly, the alkyl transfer proceeds via an assembly in which the chiral zinc alkoxide, derived from DAIB and dialkylzinc controls the overall three-dimensional arrangement and activates reactants. Besides the efficient *multiplication of chirality*, a phenomenon described as *asymmetric amplification*[2a,4b,6] became a matter of major interest. Mutual enantiomer recognition and differential chemical behavior of diastereomeric dinuclear zinc alkoxides have been proposed to be the basis of the strong nonlinear relationship between the optical purities of the chiral auxiliary and the product.

Recently, we have reported that enantioselective alkylation of aldehydes with diethylzinc was achieved by using catalytic amounts of readily available β-hydroxysulfoximines **1**.[7,8] The corresponding secondary alcohols were obtained in good yields with enantioselectivities up to 88% ee. Variation of the optical purity of the β-hydroxysulfoximine revealed an asymmetric amplification in the ethyl transfer to benzaldehyde using a catalyst of low ee. A dinuclear zinc alkoxide was obtained by treatment of racemic β-hydroxysulfoximine **1a** with diethylzinc, and its molecular structure was determined by single-crystal X-ray diffraction (Figure 1).



1: R, R' = Alkyl
1a: R, R' = Methyl

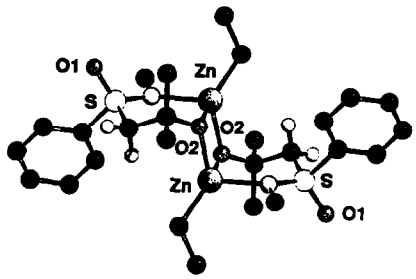


Figure 1

We now report variable-temperature NMR spectroscopic investigations on this catalyst system. We also provide evidence that the *addition product* of diethylzinc to benzaldehyde (an optically active ethylzinc alkoxide) can interact with intermediate complexes effecting the aggregation state of the active zinc catalyst.

RESULTS AND DISCUSSION

For solution studies of zinc alkoxides derived from **1**, the colorless crystals obtained by treatment of a hexane solution of *rac*-**1a** with diethylzinc, followed by recrystallization of the crystalline precipitate from toluene (Figure 1: solid state structure), were dissolved in toluene-d_8 under argon and NMR spectra were first recorded at room temperature in a sealed tube. In Figure 2a the ^{1}H NMR spectrum of this solution is reproduced. It shows that *two* species, in a ratio of about 9:1, were formed. Carrying out the same reaction with enantiopure *(R)*-**1a** and comparing the ^{1}H- and ^{13}C-spectra of the resulting complexes[9] revealed that the signals of the *minor* species were identical to those of the *optically active* zinc alkoxide derived from *(R)*-**1a**

(Figure 2b). This result was confirmed by recording spectra of various mixtures of enantiomerically enriched **1a** and diethylzinc.

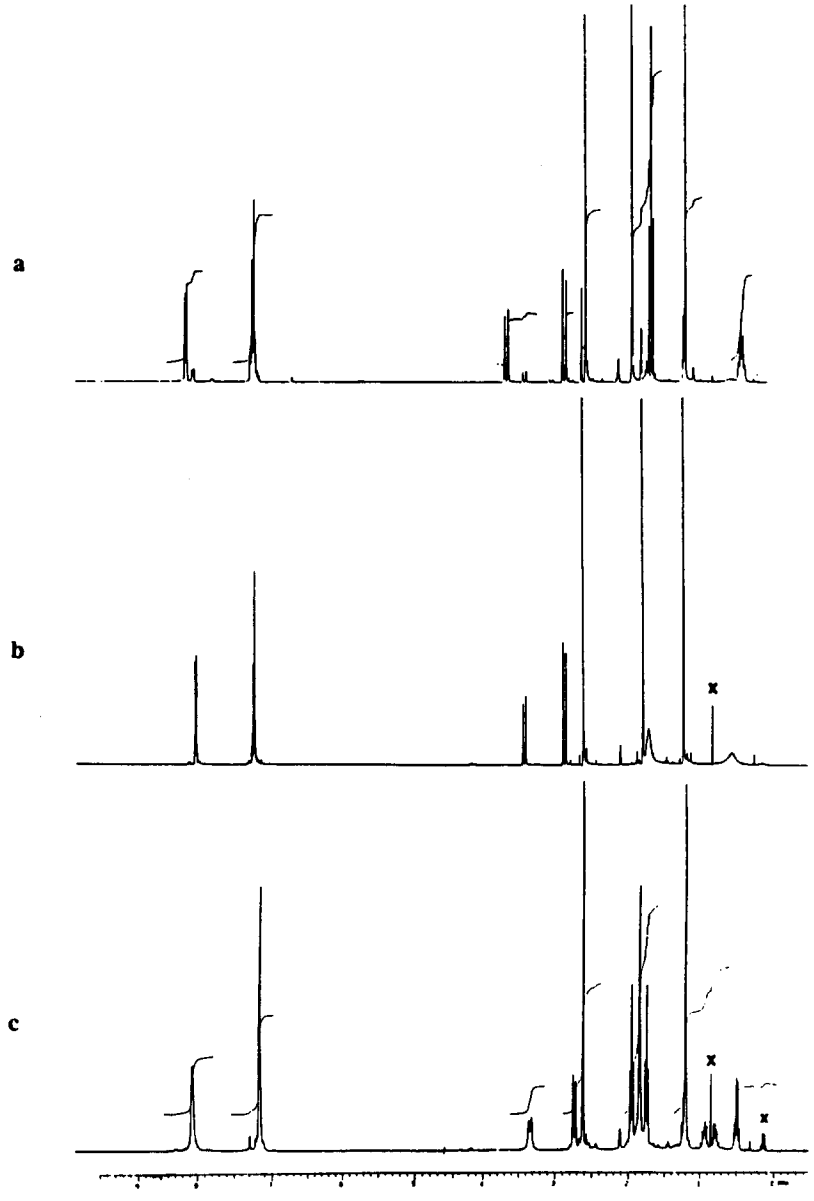


Figure 2. ^{1}H-NMR spectra of **1a** after treatment with $ZnEt_2$ (toluene-d_8; room temp.; x = unknown impurities): a, *rac*-**1a**/$ZnEt_2$; b, (*R*)-**1a**/$ZnEt_2$; c, (*R*)-**1a**/$ZnEt_2$, -40°C.

The chemical shift differences in ^{1}H- and ^{13}C-NMR spectra (see Table 1 and 2) of complexes obtained from *rac*-**1a** and *(R)*-**1a** were attributed to the formation of diastereomeric aggregated structures. The degree of *inter*molecular association of zinc alkoxides varies depending on the steric requirements of the ligand system .[10] In the case of DAIB, enantiopure and racemic amino alcohols give two dinuclear associates which substantially differ in both stability and reactivity.[4] These differences have been also observed with compounds derived from diethylzinc and pyridyl alcohols,[11] and they are believed to be the basis for the strong asymmetric amplification in the alkyl transfer to aldehydes[11a] and enones.[12] In the catalyst system described here, two aggregated species with relatively similar stabilities are formed.[13] This is reflected in the relatively weak asymmetric amplification in alkylation reactions.[7, 14]

Cooling the sample of the zinc compound obtained from reaction of *rac*-**1a** with diethylzinc to -80°C did not significantly influence the ratio of the two zinc alkoxides, but new signals of unknown species (presumably of higher aggregates) were detected. With the exception of the resonance for the methylene protons of the zinc ethyl group, the signals of the major compound were almost temperature independent reflecting its high rigidity in the aggregated structure. The former signal changed from a broad quartet to a complicated multiplet upon lowering the temperature. No appreciable chemical shift difference was observed for any signals. *This behavior was significantly different to that of the optically active zinc alkoxide* [derived from *(R)*-**1a**]. Whereas one broad signal was detected for the methyl group of the zinc-ethyl moiety at room temperature, two well-resolved triplets of equal intensity appeared at 1.67 and 1.88 ppm when the sample was cooled below -20°C (Figure 2c; coalescence at ca. 0°C). The resonances for the methylene protons changed from a broad signal to three quartet-like multiplets. We therefore concluded that at low temperature, the homochiral zinc aggregates loose flexibility resulting in magnetic inequivalency of the zinc ethyls.

Table 1. ^{1}H-NMR data for **1a** and ethylzinc alkoxides derived from *rac*-**1a** and *(R)*-**1a**[a]

Compound	CH_3	CH_3	CH_2	NCH_3	m/p-aromatic H	o-aromatic H	$ZnCH_2$	CH_2CH_3
1a	1.10	1.69	2.55, 3.03	2.52	7.01 - 7.09	7.62 - 7.67	---	---
rac-**1a**/$ZnEt_2$	1.18	1.90	2.84, 3.63	2.56	7.01 - 7.11	7.96 - 8.02	0.42	1.65
(R)-**1a**/$ZnEt_2$	1.21	1.78	2.85, 3.39	2.60	7.05 - 7.15	7.86 - 7.93	0.48 - 0.55	1.64 - 1.72

[a] 300 MHz, room temp., toluene-d_8.

This behavior was also shown by ^{13}C-NMR spectroscopy. Ethylzinc alkoxides derived from *rac*-**1a** and *(R)*-**1a** gave different spectra (Table 2). Upon cooling the optically active zinc complex, magnetically inequivalent ^{13}C-signals were detected for the ethyl groups. Low temperature ^{1}H,^{13}C-COSY experiments allowed a correlation of resonances (at -30°C).

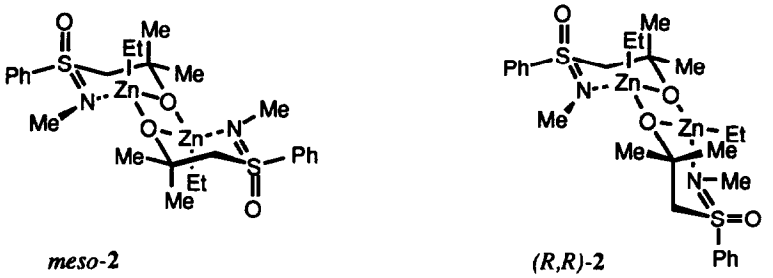
Table 2. ^{13}C-NMR data for **1a** and ethylzinc alkoxides derived from *rac*-**1a** and *(R)*-**1a** upon treatment with diethylzinc (no aromatic carbons included)[a]

Compound	CH_3[b]	CH_3[b]	α-C	β-C	NCH_3[b]	$ZnCH_2$	CH_2CH_3
1a	31.6	31.6	65.8	70.1	28.9	---	---
rac-**1a**/$ZnEt_2$	30.7	35.3	69.0	71.9	30.7	0.8	19.9
(R)-**1a**/$ZnEt_2$	30.6	35.2	68.9	71.7	30.6	6.6	10.3

[a] 75 MHz, room temp., toluene-d_8. [b] In the room temp. spectra the methyl resonances (CH_3/NCH_3) were not assigned with certainty.

Both zinc alkoxides [from *rac*-**1a** and *(R)*-**1**] gave well separated resonances for the diastereotopic methyl group protons at the β-carbon. Their chemical shift differences, of $\Delta\delta$ = 0.72 and 0.57 ppm, were attributed to their relatively fixed equatorial and axial positions in six-membered zinc-containing chelates (compare Figure 1). In β-hydroxysulfoximine **1a**, the difference in chemical shift of the methyl resonances is a result of the cyclic arrangement formed by the hydrogen bond between the hydroxyl proton and the sulfoximine nitrogen.[15]

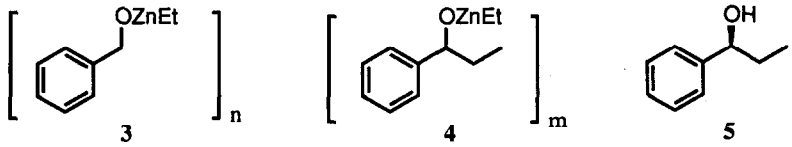
A series of NOE difference experiments on the zinc alkoxides prepared from *rac*-**1a** and *(R)*-**1a** suggested that *in both cases* non-monomeric species were present in solution.[16] However, confirmatory evidence for the hypothetical dimeric associates *meso*-**2** and *(R,R)*-**2** (shown in Figure 3) could not be obtained.[17]



meso-**2** *(R,R)*-**2**

Figure 3. Suggested molecular solution structures of dinuclear zinc alkoxides *meso*-**2** and *(R,R)*-**2** derived from *rac*-**1a** and *(R)*-**1a**, respectively, upon treatment with diethylzinc.

NMR spectroscopy of 1:1 mixtures of zinc alkoxides and benzaldehyde in toluene-d_8 showed that *no* ethyl transfer occurred, regardless of whether *rac*-**1a** or *(R)*-**1a** was used for the preparation of the zinc complex. In the case of the zinc alkoxide obtained from racemic **1a**, the position of the sharp aldehyde proton signal and the resonances for the zinc aggregate remained unchanged. In contrast, the enantiopure zinc alkoxide prepared from *(R)*-**1a** behaved differently, and aldehyde addition gave rise to a new species (in about 40%) which was assumed to be an aldehyde/zinc alkoxide coordination compound. In both samples, slow formation of the reduction product benzyl ethylzinc alkoxide (**3**) was detected. Surprisingly, when diethylzinc was added to the sulfoximine zinc alkoxides, NMR spectroscopy indicated an inverse aggregate stability. Now the signals of the homochiral zinc alkoxide remained unchanged. However, a new ethyl-containing compound was formed in small quantities (< 10%) with the zinc alkoxide derived from *rac*-**1a**. The two new species found in these separate studies were also detected in the NMR spectrum when both reactants, diethylzinc and aldehyde were present in the corresponding reaction mixture. In these experiments, the appearance of the resonance at δ 4.65 indicated the formation of the addition product **4**.[18] Competition experiments showed that the alkyl transfer to give **4** was catalyzed about five time more rapidly by the enantiopure β-sulfoximine zinc alkoxide than by the heterochiral associate.



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During the catalyzed ethyl transfer from diethylzinc to benzaldehyde, the new chiral zinc alkoxide **4** is continuously formed. When *(R)*-**1a** was used as catalyst precursor, **4** was highly enantiomerically enriched and the *(R)*-configurated product was obtained predominantly. Although zinc alkoxides are known to convert to cubic tetramers,[2a,10,19] we wondered about the influence of **4** and its absolute configuration on the reaction pathway and the catalyst structure.[20-24] When 1:1 mixtures of *rac*-**1a** and *(S)*-**5** in toluene-d_8 were treated with diethylzinc at room temperature, the formation of the corresponding zinc alkoxides was exhibited by NMR spectroscopy. No sign of the occurrence of mixed aggregates was detected. The same observation was made for solutions containing alkoxides derived from *(R)*-**1a** and *(S)*-**5**. However, significant broadening of the ^{1}H NMR signals occurred when diethylzinc was added to a 1:1 mixture of *(R)*-**1a** and *(R)*-**5**, indicating the generation of a more dynamic system. Increasing the amount of *(R)*-**5** to two equivalents led to the formation of a new species and gave rise to a very complex ^{1}H-NMR spectrum. From these results we conclude that the constitution of the zinc-containing β-alkoxysulfoximine aggregate *is influenced by the stereochemical effect of the product*. Only the product with the correct absolute configuration leads to an interaction with the catalyst precursor. In the catalysis with zinc alkoxides derived from *(R)*-**1a** only the predominantly formed *(R)*-enantiomer of **4** influences the catalyst aggregate. Because it is not unreasonable to assume that the active catalyst is a monomeric zinc alkoxide,[2a,4b] the cleavage of the higher aggregates could result in an activation of the overall catalyst system. The effect of the product on its own catalyzed formation, and the stereochemical outcome of the reaction *via enhanced catalyst activation* would then be a very special example of an *enantioselective autocatalysis*.[20, 21, 24]

Further investigation directed towards the identification of more intermediates in asymmetric catalyses is currently being pursued in our laboratories.[1]

EXPERIMENTAL SECTION

General ^{1}H-NMR spectra were recorded at 300 or 400 MHz in toluene-d_8 with toluene-d_7 as internal reference (δ 2.09 ppm). ^{13}C-NMR spectra were recorded at 75 MHz in toluene-d_8 with $C_6D_5\underline{C}D_3$ as internal reference (δ 20.4 ppm). Chemical shifts are reported in ppm (δ). β-Hydroxysulfoximine **1a** was prepared by literature methods.[25] *(R)*- and *(S)*-1-Phenyl-1-propanol were obtained commercially (Fluka).

NMR Studies.[26] General Procedure for the Preparation of the Complexes. In a flame-dried Schlenk flask under argon, **1a** was dissolved in toluene-d_8 and the solution was cooled to 0°C. At this temperature, 1 equiv of diethylzinc was added to a give a 0.077 M solution of the resulting zinc alkoxide. After degassing the solidified mixture (cold bath; liquid N_2) under vacuum, 0.8 mL of the solution was transfered into a predried capped NMR tube using a gas-tight syringe. At -95°C (acetone/N_2) the NMR tube was sealed under vacuum. For NMR studies of complexes derived from *rac*-**1a**, a hexane solution of **1a** was treated with diethylzinc to give a white precipitate which was recrystallized from toluene (by heating to 50-60°C). Isolated crystals were used for NMR and X-ray studies.

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