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A chiral disulfide derived from (*R*)-cysteine in the enantioselective addition of diethylzinc to aldehydes: loading effect and asymmetric amplification

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Abstract

A chiral disulfide derived from (*R*)-cysteine is described to catalyze the enantioselective addition of diethylzinc to benzaldehyde with high enantioselectivities at different catalyst loadings. Nonlinear effects have also been evaluated and the relationship between the ee of the catalyst and the ee of the product has been found to be strictly linear.

Keywords: Chiral; Nonlinear effects; Enantioselectivities

1. Introduction

The asymmetric addition of organozinc reagents to carbonyl compounds allows the synthesis of chiral alcohols that are ubiquitous in the structures of natural products and drugs. Over the past decades a large number of chiral catalysts have been developed and high enantioselectivities have been achieved [1]. In addition, many of the principles for the design of ligands for metal catalyzed enantioselective synthesis have come from the study of the addition of diethylzinc to aldehydes [2].

Chiral ligands with an amino alcohol scaffold are the most widely studied compounds to promote the asymmetric reaction of organozinc compounds with aldehydes [3]. Besides the success of amino alcohols on this reaction, many other classes of ligands such as diamines [4], diols [5], amino thiols, disulfides [6] and diselenides [7] have been found to induce high enantioselectivities in the formation of the secondary alcohols.

Within the several effective ligands reported, the leading studies of Noyori in the highly enantioselective conversion of aromatic aldehydes to chiral secondary alcohols catalyzed by dimethylaminoisoborneol (DAIB) certainly play a central role in this reaction. With this amino alcohol benzaldehyde could be converted to (*S*)-1-phenylpropanol in 95% ee by using the chiral ligand DAIB in only 15% ee.

To explain such exceptional nonlinearity, extensive experimental and theoretical work has been carried out which has resulted in a proposed mechanism for such effect and has generated an outstanding contribution for the understanding of this process [1a,8]. While nonlinear effects have the advantage to allow the use of enantiomerically impure materials [9], sometimes it requires high loadings of the catalyst, because formation of heterodimer often lowers the reaction rate. Typically, the loading of ligands varies from 5 to 10 mol%, which limits the use of this reaction to high-scale synthesis. Thus, it is of interest that the formation of dimeric complexes of the ligand with diethylzinc is suppressed and lower amounts of

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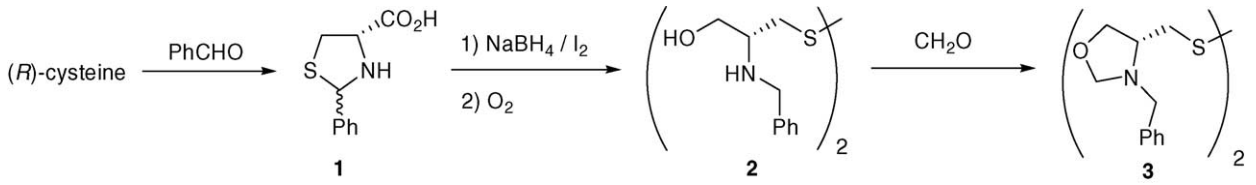


Scheme 1.

catalyst effectively promote the alkylation with high stereoselectivity.

Only a few examples of low loading catalysts have been described to date, and there is still a lack of studies of alkylation at low catalyst concentrations [7d,10]. Wipf has recently published an interesting paper in which he has studied the influence of the ligand loading of the catalyst in the enantioselective addition of diethylzinc to benzaldehyde. He has found that his ligand was still effective at a loading as low as 0.05 mol% [11].

In this context, we developed the synthesis of a chiral disulfide easily obtained in a short, high yielding route starting from the inexpensive and commercially available amino acid (*R*)-cysteine (Scheme 1). This ligand was applied in the addition of diethylzinc to several aromatic and aliphatic aldehydes and enantioselectivities of up to >99% were achieved when 2 mol% of the catalyst were used [12].

In this paper we report about the detailed examination of the effect of ligand loading in aldehyde alkylation in order to obtain information concerning the nonlinearity of this catalyst. If a nonlinear effect is present, the product will be obtained in high ee even with diminished enantiomeric purity of the catalyst. On the other hand, if a strictly linear effect is observed, a dependence of the ee as a function of the ee of the catalyst will become apparent and even low amounts of catalyst should furnish the secondary alcohol in high ee.

2. Results and discussion

The synthesis of chiral disulfide **3** is readily achieved in three synthetic steps. First (*R*)-cysteine is cyclized with benzaldehyde leading to thiazolidine **1** which was further converted to disulfide amino alcohol **2** by reduction of the acid group and reductive cleavage of the C–S bond of the thiazolidine ring with subsequent oxidation to the disulfide. Oxazolidine **3** was obtained by treatment of **2** with paraformaldehyde. The chiral disulfide **3** was obtained with 67% overall yield. It is also worth to mention that this synthetic sequence does not require any chromatographic separation, which makes it easy to perform on a gram scale. Also, under reaction conditions the disulfide bridge is cleaved reductively, and thus dimeric **2** behaves like a monomeric free sulfide.

X-ray structure analysis has been performed and clearly shows that the absolute configuration has not been affected during the synthesis of the **3** (Fig. 1).

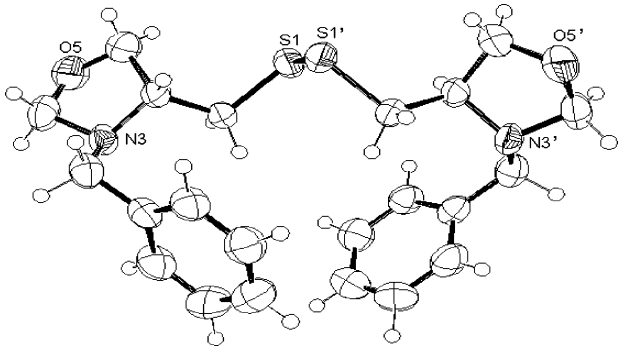


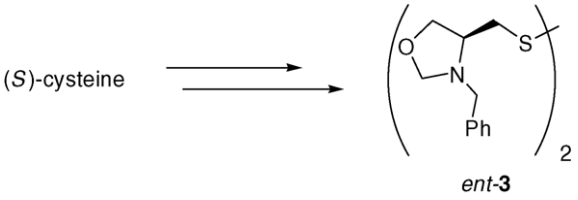
Fig. 1. An ORTEP view of **3** as determined by X-ray crystallography.

In order to evaluate the effects of nonlinearity of this catalyst, its enantiomer preparation was required. So, *ent*-**3** could be obtained with the same protocol and similar overall yield only starting from (*S*)-cysteine (Scheme 2).

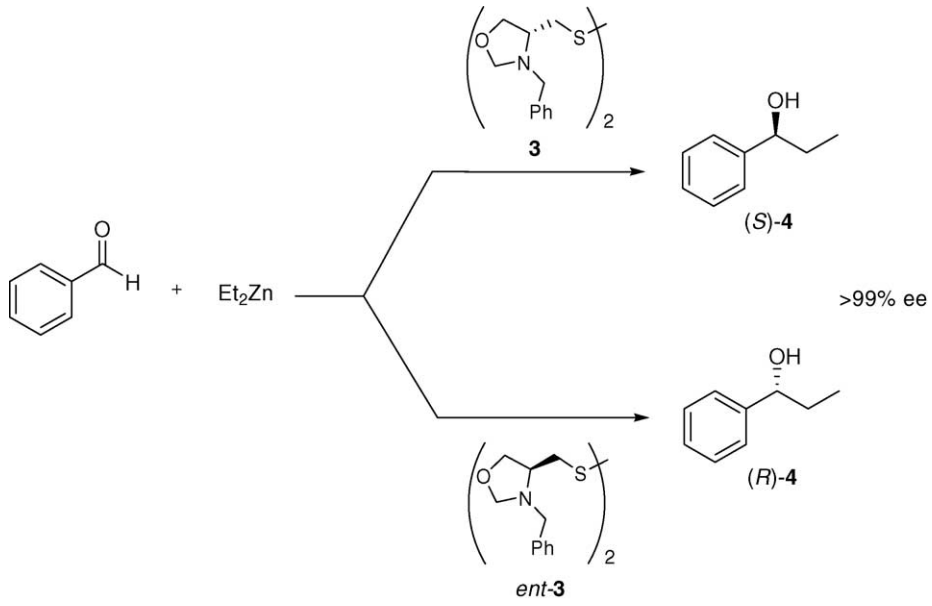
With both enantiomeric ligands in hands, we could effectively study the nonlinearity of our catalytic system. Benzaldehyde was then treated with diethylzinc in toluene at 0 °C for 48 h using different enantiomeric excess of **3** (Scheme 3).

The results depicted in Fig. 2 demonstrate that the relationship between the ee of the catalyst and the ee of the product is essentially linear. The linear correlation coefficient is of 0.995. In all reactions, a loading of 2 mol% of **3** at different ees was employed. An ee of >99% of (*S*)-**4** was achieved when pure **3** was used. When the addition was carried out in the presence of *ent*-**3** only (*R*)-**4** was formed in >99% ee.

The loading effect of the catalyst was also examined. Concentrations varying from 0.1 to 10 mol% were tested and it could be observed that the ee of the alkylated product remained very high in the range of 1–10 mol%. A decrease to 65 and 61% ee was detected when 0.5 and 0.1 mol% of **3** have been used, respectively (Fig. 3). The reactions were carried out under our standard conditions originally optimized for 2 mol% catalyst (toluene, 0 °C, 48 h), quenched with 1 M HCl and the crude mixture was distilled before analysis by chiral HPLC.



Scheme 2.



Scheme 3.

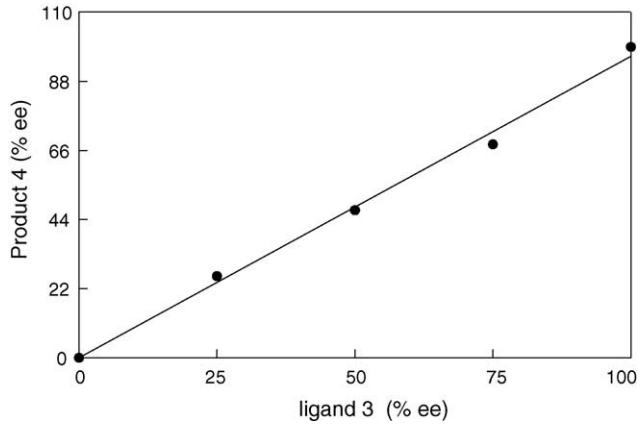


Fig. 2. Linear correlation between ee of 1-phenyl-1-propanol (**4**) and ee of ligand **3**.

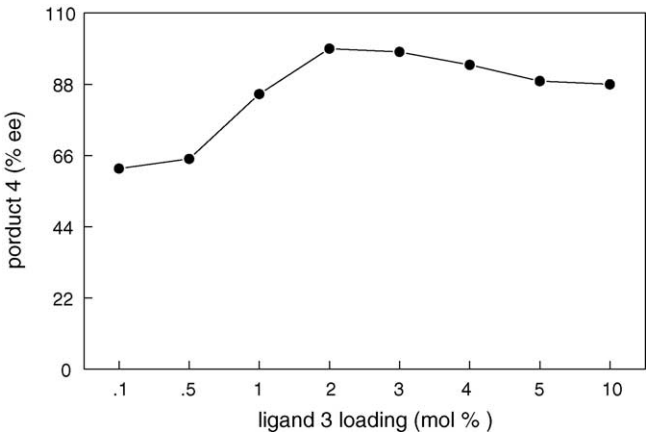
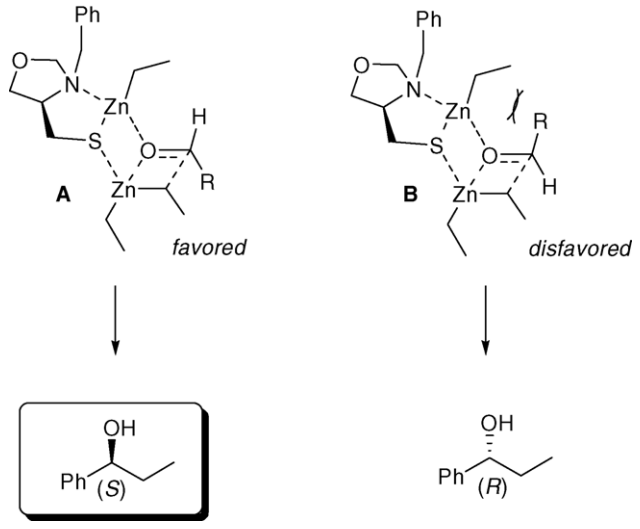


Fig. 3. Relationship between the ee 1-phenyl-1-propanol (**4**) and loading of ligand **3**.

Although the exact active species are still unclear, we assumed that the disulfide bond in **3** is initially broken by diethylzinc, generating the thiolate, which acts effectively as the chiral ligand. The proposed transition states depicted in Scheme 4 are based on the Noyori dinuclear zinc complexes [8,13]. Transition state structure **A**, which leads to the formation of the (*S*) enantiomer, is favored over **B**, because it avoids axial positioning of the aldehyde *R*-group and any destabilizing interaction with the ethyl group attached to the zinc atom.

Obviously, *R*/*S*-heterodimeric Zn-complexes of the sulfide ligand **3** do not have an enhanced stability and thus are not removed from the equilibrium of reactive species. Either such complexes do not form, or they are kinetically sufficiently fast to dissociate that their intermediate forma-



Scheme 4.

tion does not interfere with the catalyzed ethyl addition process.

3. Conclusions

In summary, we have described studies on the linearity effects and investigations of the loading effect on the enantioinduction of a cysteine-derived disulfide as catalyst for the enantioselective addition of diethylzinc to benzaldehyde. We have found a strictly linear correlation between the ee of the chiral catalyst and the ee of the secondary alcohol formed. This effect suggests that the dimer formation is suppressed or kinetically unimportant and allowed us to employ low loadings of the catalyst with still high enantioselectivity (up to 99%).

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