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ENANTIOSELECTIVE ADDITION OF Et_2Zn TO ALDEHYDES PROMOTED BY A CHIRAL SCHIFF BASE METAL COMPLEX

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Abstract: An optically active zinc complex prepared with ligand 1 has been used to promote the enantioselective addition of Et_2Zn to aldehydes. This study represents a new application for these metallo-salen complexes.

Chiral salen complexes are sterically well defined and kinetically non labile metal compounds. In principle, asymmetric induction can be favoured in this type of complexes by the proximity of the stereogenic center to the reactive metal (Fig. 1).

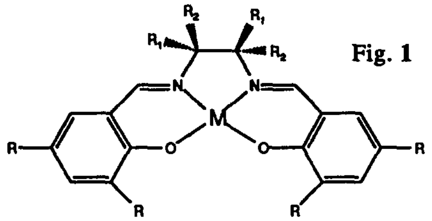


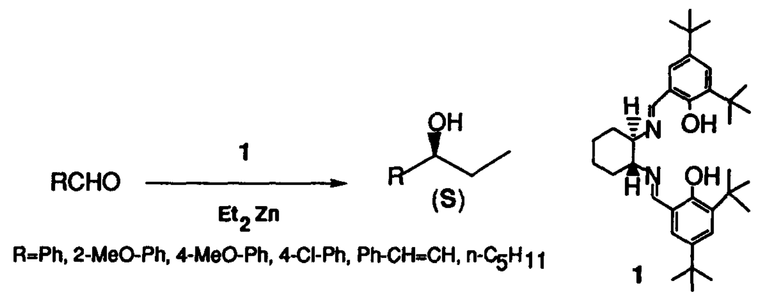
Fig. 1

Optically active metallo salen complexes have been reported to be efficient catalysts for asymmetric oxo transfer reactions such as the epoxidation of alkenes and the oxidation of sulfides.[1]. Recently, the utility of this type of chiral catalysts has been expanded to include their applicaion to new reactions, such as asymmetric cyclopropanation[2], asymmetric Diels-Alder reactions[3] and ring opening of meso-epoxides.[4]

Asymmetric addition of dialkylzinc to aldehydes in the presence of a catalytic amount of β-amino alcohols has been studied extensively and high enantiomeric excesses were obtained for the synthesis of optically active secondary alcohols.[5]

However, the use of salen-based ligands for promoting this kind of reaction has never been reported. Herein, we disclose our preliminary results arising from the development of a new application of metallo-salen complexes which were prepared by the use of inexpensive and widely-available homochiral Schiff base ligands[6], and which are capable of catalyzing the addition of organometallic species to a carbonyl functionality. In our initial study, we used the commercially available (R,R)-(-)-N,N'-bis(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediamine **1**[7] to afford the addition of Et_2Zn to aldehydes. The zinc complex of **1** was generated *in situ* by the addition of one equivalent of Et_2Zn to the chiral Schiff base at room temperature. The resulting complex was then used in a catalytic amount (10 mol.%) to promote the desired addition (Scheme 1).

Scheme 1



Initially, benzaldehyde was used as a model compound in order to evaluate the influence of solvent and temperature on the enantioselectivity of the reaction (Table 1).

Table 1: Addition of Et_2Zn to Benzaldehyde Promoted by the Chiral Schiff Base 1.

Entry[a]	R	Solvent	Temp. C°	Yield%[b]	e.e.%[c,d]
1	Ph	Toluene	0	50	35
2	"	CH_2Cl_2	0	75	30
3	"	Toluene	25	75	60
4	"	Toluene	40	75[e]	60
5	"	CH_2Cl_2	25	88	34
6	"	Hexane	25	64	64
7	"	Hexane	-40 to 25[f]	65	68
8	"	Toluene	-40 to 25[f]	75	70

a) All the reactions were carried out using Et_2Zn (2.1 mmol), 1 (0.1 mmol) and PhCHO (1 mmol). The reaction mixture was stirred for 24 hours at the temperature reported. b) Isolated yields. c) The enantiomeric excess was determined by GC analysis using a chiral β-cyclodextrin column. d) The *S* configuration of the product alcohol was established by an optical rotation measurement: entry 3, $[\alpha]_D^{22}$= -30.0 (c 1.21, $CHCl_3$); (*S*) -1- Phenyl -1-propanol: $[\alpha]_D^{22}$= -47.6 (c 6.11, $CHCl_3$), 98% e.e.[8] e) 10% of benzyl alcohol was isolated as by-product.
f) The aldehyde was added, the reaction was stirred for 1 hour at -40°C, and the mixture was warmed to room temperature and stirred for 24 hours.

The results collected in Table 1 show that the best conditions for obtaining high values of e.e. and good yields were the use of toluene as solvent and the addition of the aldehyde at low temperature. This protocol was applied to other aldehydes and the results are reported in Table 2.

Table 2: Addition of Et_2Zn to Aldehydes Promoted by Chiral Schiff Base 1.

Entry	R[a]	Yield%[b]	e.e.%[c,d]	$[\alpha]_D$
1	2-MeO-Ph	84	45	e
2	4-MeO-Ph	82	45	-13.8 (c 1, C_6H_6)
3	4-Cl-Ph	50	77	-17.6 (c 1.2,C_6H_6)
4	Ph-CH=CH	99	50	-3 (c 1,$CHCl_3$)
5	n-C_5H_{11}	62	25	e

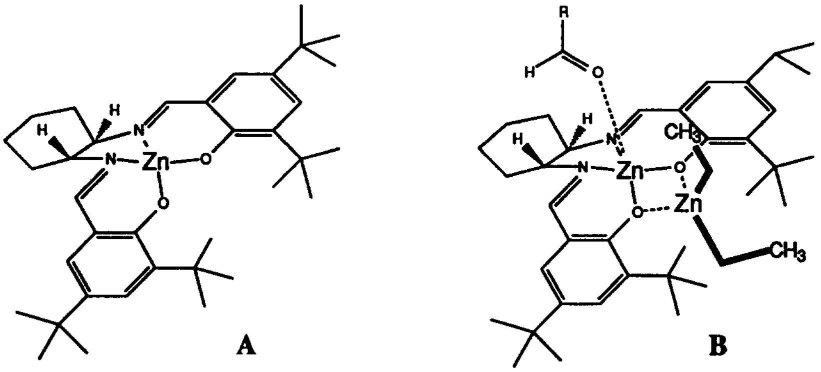
a) The aldehyde was added to the resulting mixture at 0°C, was stirred for 1 hour and then warmed to room temperature. b) Isolated yields. c) Determined by GC analysis using a chiral β-cyclodextrin column. d) The S-configuration of the alcohols obtained was established by optical rotation measurement which were compared with the values reported in the literature: (S)-1-(p-Methoxyphenyl)-1-propanol: $[\alpha]_D^{22}$= - 17.2 (C_6H_6), 43%e.e.[9]; (S)-1-(p-Chlorophenyl)-1-propanol: $[\alpha]_D^{22}$= -10.5 (c 5, C_6H_6)[9] ;(S)-1-Phenylpent-1-en-3-ol: [$[\alpha]_D^{22}$= -5.7 ($CHCl_3$), 96%e.e.[9] e) Not determined.

As may be anticipated, this methodology gives higher e.e. with aromatic aldehydes then with aliphatic ones.

In an attempt to rationalize the results obtained and to investigate the structure of the chiral zinc complex involved, we examined mixtures of the Schiff base 1 with 1, 2, and 5 equivalents of Et_2Zn (1M in hexane) by ^1H NMR spectroscopy. An analysis of the spectrum of the complex obtained with the addition of 1 eq. of Et_2Zn shows the disapparence of the signals due to the phenolic protons and no evidence of an ethyl resonance correponding to Et_2Zn. Based on both of these observations, we propose the structure A shown in Fig 2 for our metallo-salen promoter. This type of structure has been reported for a Schiff base complex of zinc and for those of other metals.[10] The signals due to the protons of the ligand are broadened and indicative of a species of lower symmetry than those of the ligand itself. Of futher interest is the appearance a of broadened resonance due to the Et_2Zn and a change in the appearance of the resonances due to the ligand, upon the addition of a second equivalent of Et_2Zn. We attribute this spectrum to the coordination of the second equivalent of the Et_2Zn to the oxygen atoms of the metallo-Schiff base complex.[11]

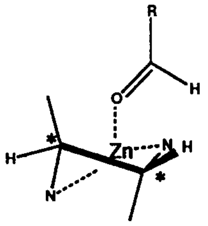
On the basis of this data and that of the enantioselectivities observed for the Et_2Zn addition, we suggest the model shown in Fig 2 (B) to illustrate a plausible interaction between the metallo-Schiff base complex, Et_2Zn, and a representative aldehyde. Bimetallic tin-zinc Schiff base complexes similar to the hypothetical complex B were recently crystallographically characterized.[12]

Fig. 2



As part of this model, we propose that the aldehyde coordinates to the Schiff base complex with its hydrogen atom oriented to give a minimum interaction with the stereocenters (Fig 3)

Fig 3



The two oxygen atoms of the Schiff base can act as a bidentate ligand to complex Et_2Zn and to activate it toward addition to the coordinated aldehyde. The absolute configurations of the isolated alcohols are in agreement with this model.

Typical Experimental Procedure: To a solution of ligand 1 (0.1 mmol) in toluene (4 mL) was added Et_2Zn (0.1 mmol) and the resulting mixture was stirred for 1 hour at room temperature. This solution was cooled to -20°C and Et_2Zn (2 mmol) was added. After 5 minutes, the aldehyde was added (1 mmol) and the solution was warmed to room temperature and then allowed to stir for an additional 24 hours. The reaction mixture was then diluted with Et_2O, quenched with a saturated $NaHCO_3$ solution, and filtered through Celite. After removal of the organic phase, the aqueous phase was extracted with Et_2O (2 x 2 mL) and the organic phases were combined, dried, and concentrated to dryness. The crude reaction residue was then purified by flash chromatography.

In summary, we describe a new approach to the addition of organometallic reagents to organic substrates. Extensions to improve the enantiomeric excesses with the development of other chiral metallo-Schiff base complexes (i. e.- ones capable of forming bimetallic catalysts and coordinating organometallic reagents) are currently in progress in our laboratory.

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