Study of cyclic derivatives of 1,2- and 1,3-aminoalcohols as chiral catalysts in additions of diethylzinc to benzaldehyde.

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The enantioselectivity of the addition reactions of diethylzinc to benzaldehyde in the presence of cyclic derivatives of 1,2- and 1,3-aminoalcohols as catalysts has been studied.

Keywords: 1,2- and 1,3-aminoalcohols, chiral catalysts, diethylzinc, benzaldehyde

The reaction of diethylzinc with benzaldehyde has been used as a standard procedure for testing the efficiency of different molecules[1] as chiral catalysts.

The search of new catalysts which could be easy to prepare and exhibit high reactivity and enantioselectivity is a field of continuous interest. Enantiopure β-amino alcohols have been extensively used and their activity was explained by the formation of alkylzinc aminoalkoxide species which induce enantioselectivity.[2]

In the design of new catalysts, the search of new functional groups which mimic the amino alcohol ligands and their incorporation in structurally rigid skeletons for an improvement in enantioselectivity is a challenge in organic synthesis. Some of these improvements have been reported by the incorporation of the amine function as a part of ring, morpholine or oxazolidine,[3,4] and also the substitution of the alcohol moiety of a β-amino alcohol with an amide.[5]

Results and discussion

With this objective we have studied the addition reaction of diethylzinc to benzaldehyde using as catalysts the compounds **1**–**6** obtained[6-8] from 3-phenyloxiran-2-ylmethanol, ephedrine and pseudoephedrine.

Compounds **1** and **2** are amino alcohols with an additional ether or amide function in a six membered ring. Compounds **3** and **4**, also with three coordination centres, are oxazolidines with a N-methylcarboxamide substituent. Compounds **5** and **6** are oxazolidine derivatives from ephedrine and pseudoephedrine.

The best enantiomeric results were obtained in experiments carried out in toluene or toluene-dichloromethane at room temperature and molar concentrations of the chiral ligand of 0.08%. The chemical yields and the extent of the enantiofacial discrimination depend on the catalyst. In the case of compounds **1**, **2**, **3**, **4** and **5**, the (*S*)-1-phenyl-1-propanol was obtained with poor enantiomeric excess. However, with compound **6** as catalyst the reaction afforded (*R*)-1-phenyl-1-propanol with 65% e.e. The yields and enantiomeric excess are summarised in Table 1.

As a result of our work it is worth mentioning that in the reaction of addition of diethylzinc to benzaldehyde in the presence of the oxazolidine **6**, we have obtained a 65% e.e., a similar enantioselectivity to the reported in literature for the same reaction with the amino alcohol ephedrine.[9] The oxazolidine **6**, has no a secondary alcohol function and it is not able to afford the corresponding zinc alkoxide chiral intermediate derivative which induce the enantioselectivity in reactions of aminoalcohols.

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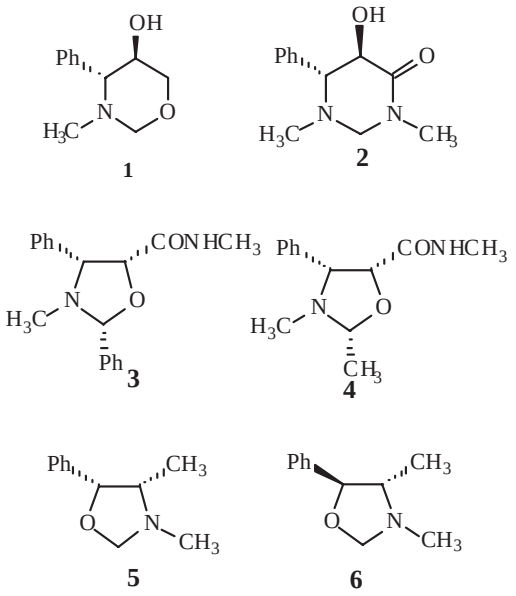

Fig. 1 (4*R*,5*R*)-3-Methyl-4-phenyl-1,3-oxazin-5-ol **1**;[6] (5*S*, 6*S*)-6-phenyl-5-hydroxy-1,3-dimethylhexahydro-4-pyrimidinone **2**;[8] (2*S*, 4*S*, 5*S*)-2,4-diphenyl-N5-3-dimethyl -1,3-oxazolane-5-carboxamide **3**;[8] (2*S*, 4*S*, 5*S*)-4-phenyl-N5-2,3-trimethyl-1,3-oxazolane-5-carboxamide **4**;[8] (4*S*,5*R*)-3,4-dimethyl-5-phenyl-1,3-oxazolidine **5**;[7] (4*S*,5*S*)-3,4-dimethyl-5-phenyl-1, 3-oxazolidine **6**.[7]

Table 1 Enantioselective addition of Et_2Zn to benzaldehyde catalysed by ligand **1–6**

Ligand	Solvent	Yield/%	e.e.[a]/%	Config.[b]
1	Toluene/CH_2Cl_2	82	30	*S*
2	Toluene	79	10	*S*
3	Toluene	71	1	*S*
4	Toluene	73	9	*S*
5	Toluene	86	22	*S*
6	Toluene	79	65	*R*

[a]Enantiomeric excess was determined by GC chiral column Supelco β-dex 120 30×0.25×0.25, temperature injector and detector 200°C, temperature program: 40°C for 1 min then 5°C/min to 120°C isomer (*S*) R_f = 34.5 min, (*R*) R_f = 36.1 min.
[b]Determined by polarimetry, based on the maximum values described for the specific rotation of (*S*)-1-phenyl-1-propanol $[\alpha]_D^{20}$ = –47 (*c* 2.2, hexane) 98% e.e.

Experimental

General procedure for asymmetric addition of diethylzinc to benzaldehyde

The catalyst **1**–**6** (0.1 mmol) was dissolved in freshly distilled toluene (6 ml) under nitrogen atmosphere at 20 °C. Diethylzinc (1M solution in hexane, 2.5 ml, 2.5 mmol) was added dropwise and the mixture was stirred for 1 h. The benzaldehyde (0.127 ml, 1.25 mmol) in toluene dry (3 ml) was added dropwise, the reaction mixture was stirred for 48 h. The reaction was quenched with aqueous

hydrochloric acid solution 10% (8 ml). The layers were separated and the aqueous solution extracted with diethyl ether (3 × 6 ml). The combined organic extracts were washed with brine (15 ml), dried (Na_2SO_4), filtered and concentrated under reduced pressure to give an oil that was purified by column chromatography (hexane/ethyl acetate) to give (*S*) or (*R*)-1-phenyl-1-propanol.

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