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C_2-Symmetric Chiral Zinc Alkoxides as Catalysts for the Enantioselective Addition of Diethylzinc to Aryl Aldehydes

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Abstract: Various dialkoxides of zinc, magnesium and boron were examined for the enantioselective addition of diethylzinc to aryl aldehydes. Only zinc based reagent catalysed the reaction effectively providing up to 89% *ee* of the product.

Asymmetric catalysis is now recognised as one of the most important and challenging problems in organic synthesis.[1] Ligand accelerated enantioselective addition of diethylzinc to aldehydes has emerged as a prominent reaction in recent times.[2] The majority of the catalysts employed for the reaction are based on amino alcohols. In its simplest form, the mechanism of the reaction involves an assembly of the tricoordinated zinc alkoxide, the aldehyde and the diethylzinc as shown in fig.1. It is presumed that diethylzinc coordinates to the oxygen atom of the catalyst. We reasoned that if this is indeed true, then the catalyst need not be based on an amino alcohol. In fact a C_2- symmetric dialkoxide should function as an effective catalyst. Also, it would be of interest to know the effect of other metals as the Lewis acidic center in the catalyst. We therefore examined some structurally well defined alkoxides of zinc, magnesium and boron derived from certain C_2-symmetric diols.

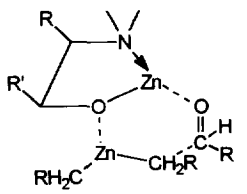
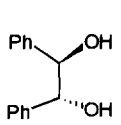
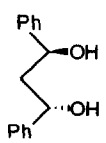


Fig - 1

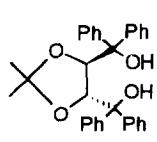
The chiral auxiliaries selected for the present study are representative 1,2-, 1,3- and 1,4- diols which are synthesized by known methods.[3] Some of these diols (**1a -d**) have served as ligands for transition metal based catalyst.[4] Their general synthetic utility however remains underexplored.



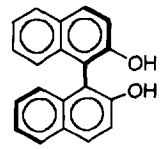
1a



1b

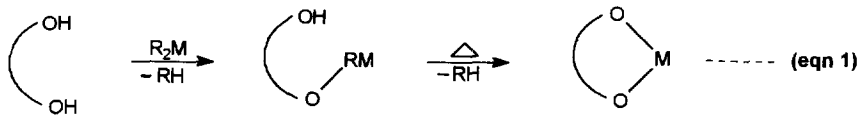


1c

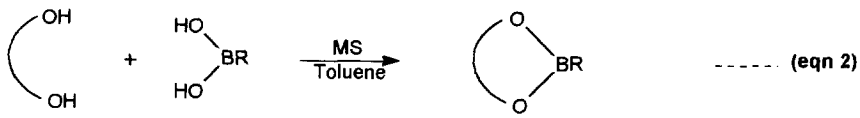


1d

It is known that diethylzinc reacts rapidly with primary, secondary and tertiary alcohols to give the corresponding monoalkoxide. Further reaction of the monoalkoxide with alcohols is very slow.[5] We envisioned that equimolar quantities of diol and diethylzinc or dibutylmagnesium would produce first the monoalkoxide and on heating should form the well defined alkoxide. Indeed, diethylzinc and dibutylmagnesium reacted cleanly with diols to give monoalkoxide which on heating (80 °C, 30 min) gave the desired dialkoxide (eqn.1). The boron analogues were prepared[6] by stirring phenyl/ butylboronic acid with the diol **1a** in the presence of molecular sieves using toluene as the solvent (eqn.2).



M = Zn, Mg



R = Bu, Ph

It has been shown that 1,2-diphenyl ethanediol catalyses the addition of diethylzinc to benzaldehyde.[7] But the reported procedure involves long reaction times and a large excess of diethylzinc. In fact we found that the reaction after 24 h at room temperature gives a mixture of benzylalcohol (19 %), unreacted benzaldehyde (36 %), and the product alcohol (45 %). We believe that the reported reaction proceeds through the corresponding zinc monoalkoxide which is not likely to be a good catalyst. On the other hand, the dialkoxide as prepared in our study using **1a** as the auxialiary, smoothly catalyses the reaction. The reaction was clean (98 % GC yield) and provided the alcohol in 89 % *ee*. It is surprising that the corresponding alkoxides derived from the 1,3- diol **1b** and 1,4- diol **1d** failed to catalyse the reaction. The alkoxide derived from 1,4- diol **1c** catalyses the reaction with moderate enantiomeric excess (44 %). As evident from the Table 1, the alkoxide derived from diol **1a** and diethylzinc was the most successful.

Finally we used the zinc dialkoxide from **1a** as a catalyst for the enantioselective addition of diethylzinc to a variety of aryl aldehydes. The results are summarised in Table 2. As expected, substituents at the *ortho* position on aryl aldehydes rendered the reaction sluggish. In fact, *o*-tolualdehyde and *o*-anisaldehyde gave <50% yield of the product even after 48 h.

Table 1. Diethylzinc addition to benzaldehyde catalysed by C_2-symmetric metal dialkoxides

Entry	Diol	M	Time, h[a]	% Yield	% ee[b]
1	1a	B	48	67	15
2	1a	Zn	18	98	89
3	1a	Mg	24	*c*	-
4	1b	Zn	48	*c*	-
5	1b	Mg	48	*c*	-
6	1c	Zn	48	65	44
7	1d	Zn	24	*c*	-

[a]All the reactions were conducted at room temperature. [b]By comparison with the literature rotation, see reference 8. [c]No appreciable reaction after 24h.

Table 2. Enantioselective addition of diethylzinc to aryl aldehydes catalysed by zinc dialkoxide from **1a**

Entry	Aldehyde	Time, h[a]	% Yield[b]	% ee[c]	config[d]
1	benzaldehyde[e]	24	89	87	R
2	benzaldehyde	18	98	89	R
3	*p*- fluoro benzaldehyde	9	95	70	R
4	*p*- methyl benzaldehyde	14	98	82	R
5	*p*- chlorobenzaldehyde	24	85	69	R
6	β- naphthaldehyde	20	94	84	R

[a]All the reactions were performed using 1: 2: 0.1 molar equivalents of aldehyde: Et_2Zn: catalyst. [b]Yields refer to GC yields, the remainder being benzyl alcohol and unreacted benzaldehyde. [c]Estimated by comparing with the reported maximum rotations, see experimental section. [d]Based on the sign of rotation for the known compound. [e]1.2 Equivalent of Et_2Zn was used.

In conclusion, we have shown that zinc dialkoxide derived from 1,2-diphenylethane diol catalyses the addition of diethylzinc to aldehydes. As for the catalysts based on other metals, neither boron nor magnesium could be useful. In the case of cyclic boronates, although boron provides a good Lewis acidic center, the oxygen atoms are not basic enough for the coordination of diethylzinc. Similarly one can conclude that magnesium alkoxides are not effective Lewis acids. The present study thus not only confirms the mechanism of the reaction, but offers suitably substituted zinc dialkoxides as a new class of chiral Lewis acids.

Experimental

Materials: Diethylzinc was purchased from Aldrich Chemical Company and diluted to 2M solution in toluene. Chiral 1,2-diphenyl ethane diol **1a** was prepared by asymmetric reduction of benzil.[3b] Other chiral auxialiaries were synthesised by known pocedures.[3] All the aldehydes were purified prior to the use by standard procedures. The NMR spectra were recorded on a Bruker 200 in $CDCl_3$ as the solvent with TMS as an internal standard. The optical rotations were measured on a JASCO DIP 181 digital polarimeter. GC analysis was carried out on a HP 5890 series II chromatograph using 10m X 0.5 mm PhMe silicone column.

Preparation of the zinc dialkoxide from 1a.

(*S,S*) (-) 1, 2- Diphenylethanediol (0.107 g, 0.5 mM) in 2 ml of toluene was heated to 80 °C to dissolve the diol completely. Diethylzinc (0.25 ml of 2M solution in toluene, 0.5 mM) was added to the solution at the same temperature. Immediate evolution of ethane was observed. The reaction mixture was kept at 80 °C for 0.5 h during which it turns to a gel indicating the formation of the dialkoxide. The resulting suspension forms a clear yellow solution upon the addition of aldehyde and diethylzinc

Addition of diethylzinc to aryl aldehydes.

The following procedure for benzaldehyde is representative:

The zinc alkoxide prepared as described above was cooled to 0 °C and treated with diehtylzinc (5 ml of 2M solution in toluene, 10mM) and benzaldehyde (0.53 g, 5mM). The reaction mixture was gradually allowed to come to room temperature and stirred at the ambient temperature till TLC indicated the disappearance of benzaldehyde. Thereafter it was quenched with MeOH (0.5 ml) followed by 1N HCl. The reaction mixture was extracted with ether. The extract was washed with brine, dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography followed by kugelrohr distillation to obtain pure (*R*)-(+)-1-phenyl-1-propanol. Yield 0.46 g (68%); ^{1}HNMR: 1.00 (t, J=6.9, 3H), 1.85 (m, 2H), 2.9 (bs, OH), 4.6 (t, J=6.9, 3H), 7.2-7.5 (Ar, 5H); $[\alpha]_D$ +40.46 (c= 5.2, $CHCl_3$), lit.[8] - 45.45 (c= 5.15, $CHCl_3$).

(*R*)-(+)-1-(p-Tolyl)-1-propanol: ^{1}H NMR: 0.9 (t, J=6.8, 3H), 1.75 (m, 2H), 2.05 (bs, OH), 2.35 (s, 3H), 4.55 (t, J=6.8, 1H), 7.1-7.3 (Ar, 4H); $[\alpha]_D$ +35.65 (c= 5.06, benzene), lit.[9] $[\alpha]_D$ +39.3 (c= 5, benzene).

(*R*)-(+)-1-(p-Fluorophenyl)-1-propanol: ^{1}H NMR: 0.9 (t, J=7.1, 3H), 1.75 (m, 2H), 2.2 (bs, OH), 4.55 (t, J=7.1, 1H), 6.95-7.1 (Ar, 2H), 7.2-7.4(Ar, 2H); $[\alpha]_D$ +35.78 (c= 2.44, $CHCl_3$), lit.[10] +51.2 (c= 2.5, $CHCl_3$).

(*R*)-(+)-1-(p-Chlorophenyl)-1-propanol: ^{1}H NMR: 0.9 (t, J=6.8, 3H), 1.75 (m, 2H), 2.25 (bs, OH), 4.55 (t, J=6.8, 1H), 7.2-7.3(Ar, 4H); $[\alpha]_D$ +19.32 (c= 5, benzene), lit.[10] +28 (c= 5, benzene).

(*R*)-(+)-1-(β-Naphthyl)-1-propanol: ^{1}H NMR: 0.9 (t, J=7.3, 3H), 1.85 (m, 2H), 2.2 (bs, OH), 4.75 (t, J=6.6, 1H), 7.4-7.6 (Ar, 3H), 7.7-8.0 (Ar, 2H); $[\alpha]_D$ +25.31 (c= 4.64, benzene), lit.[10] +29.8 (c= 4.7, benzene).

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