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Chiral Diethanolamines and their Lithium Alcoholates as Catalysts in the Enantioselective Alkylation of Benzaldehyde by Diethylzinc.

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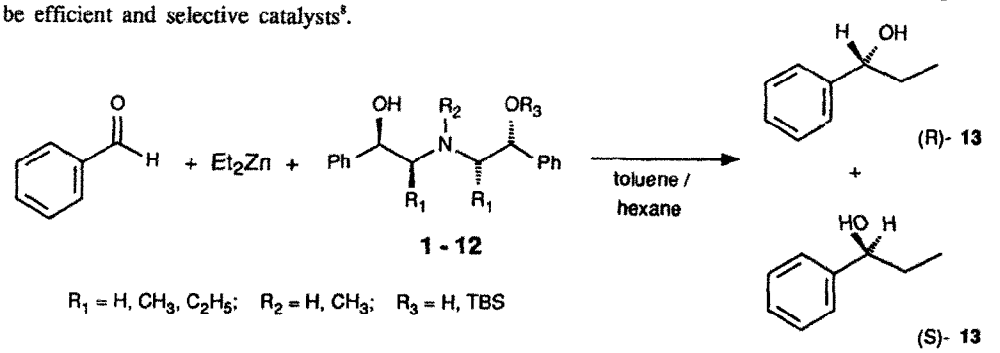
Abstract: The enantioselective alkylation of benzaldehyde by diethylzinc in the presence of catalytic amounts of bis-*erythro* diethanolamines and their lithium alcoholates was studied. The extent of asymmetric induction was found to depend strongly upon subtle changes in the structure of the catalyst used.

Enantioselective synthesis of chiral secondary alcohols, important intermediates in the preparation of many biologically active compounds, has been a topic of major interest in recent years. Optically active secondary alcohols have been synthesized by asymmetric reduction of prochiral ketones[1] and by alkyl addition to aldehydes by organometallic compounds modified with chiral ligands[2]. One of the more attractive methods to prepare these alcohols is the asymmetric addition of a dialkylzinc reagent to an aldehyde, catalyzed by a chiral β-aminoalcohol[3]. Only small amounts of a suitable β-aminoalcohol are required to achieve alkylations with high enantioselectivities, because the uncatalyzed reactions are relatively slow in apolar solvents[4].

Recently, we have reported the synthesis of several optically active bis-*erythro* diethanolamines[5], intermediates in the synthesis of chiral diaza-18-crown-6 ethers, starting from enantiomerically pure O-protected cyanohydrins[6], using a transimination procedure[7]. These diethanolamines (**1-12**) contain the same chiral structural unit as the N,N-dialkylnorephedrine-like β-aminoalcohols which have proved to be efficient and selective catalysts[8].



R_1 = H, CH_3, C_2H_5; R_2 = H, CH_3; R_3 = H, TBS

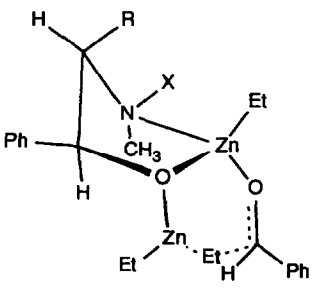
Table 1: *Reaction of Benzaldehyde with Diethylzinc, Catalyzed by Various Diethanolamines*[a].

comp.	catalyst R_1	R_2	R_3	reaction time (h)	product yield (%)[d]	ee (%)[e]	config
1	H	H	TBS[b]	48	84	11	R
2	CH_3	H	TBS	24	92	61	R
3	C_2H_5	H	TBS	24	88	71	R
4	H	CH_3	TBS	72[c]	49	0	-
5	CH_3	CH_3	TBS	24	96	84	R
6	C_2H_5	CH_3	TBS	24	95	85	R
7	H	H	H	48	84	47	R
8	CH_3	H	H	48	90	49	R
9	C_2H_5	H	H	72[c]	52	6	R
10	H	CH_3	H	72	75	10	R
11	CH_3	CH_3	H	72	83	24	S
12	C_2H_5	CH_3	H	72	80	9	S

a) The molar ratio of Et_2Zn : benzaldehyde : catalyst was 2.2 : 1.0 : 0.05. b) TBS = *tert*-butyldimethylsilyl. c) The reaction was still incomplete. d) Isolated yields. e) Determined by HPLC-analysis using a CHIRALCEL OD column; eluent: n-hexane/*iso*-propyl alcohol = 97/3; flow rate 1 mL/min.

Contrary to the latter, diethanolamines have three sites that can potentially coordinate to metal atoms. This may be beneficial to the rigidity of the reactive zinc-complex, which supposedly determines the energy difference in the transition states leading to the (*R*)- and (*S*)-enantiomers. Therefore diethanolamines **1-12** and their lithium alcoholates were tested as to their ability to catalyze the asymmetric addition of diethylzinc to benzaldehyde.

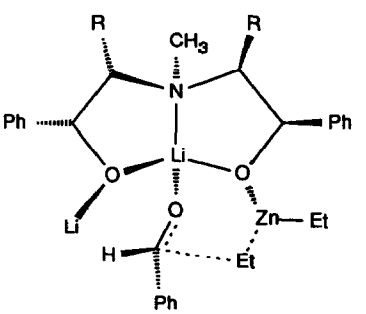
General procedure: To a solution of 0.20 mmol of the diethanolamine in 5 mL of toluene, at 0 °C, 9.7 mL of a 15 wt. % solution (8.8 mmol) of diethylzinc in n-hexane was added. After stirring for 5 min at 0 °C, 420 mg (4.0 mmol) of freshly distilled benzaldehyde, dissolved in 5 mL of toluene, was added. The reaction mixture was allowed to warm to room temperature and stirred for the time indicated in Table 1. After the addition of 50 mL of 1 N HCl, the layers were separated. The water



R = H, CH_3, C_2H_5

X = $CH(CH_3)CH(OTBS)Ph$

Figure 1



R = H, CH_3, C_2H_5

Figure 2

layer was extracted twice with 30 mL of CH_2Cl_2. The combined organic layers were dried on $MgSO_4$ and concentrated. After purification by flash column chromatography (silicagel 60; eluent: ether/petroleum ether 40-60 = 1/1), the optical purity of the product was determined by HPLC-analysis.

As evident from the results obtained for diethanolamines **1-12**, listed in Table 1, the best asymmetric inductions were obtained with catalysts that required only short reaction times. With the exception of compounds **11** and **12** all bis-*erythro* diethanolamines studied favored formation of the (*R*)-enantiomer of **13**. Mono O-TBS protected diethanolamines **1-6** afford enantioselectivities comparable to those displayed by the norephedrine-like catalysts[8]. Apparently, the presence of a *tert*-butyldimethylsilyloxy substituent does not perturb the structure of the reactive zinc-complex to a large extent. Higher asymmetric inductions were obtained when N-substituted diethanolamines (R_2 = CH_3) were used as the catalyst. Enantioselectivities also increased when diethanolamines were used carrying alkyl substituents at the carbon atoms α to nitrogen (entries 5 and 6). The transition states for the reactions catalyzed by diethanolamines **1-6** are expected to be similar to the model proposed by Soai et al., in which two molecules of diethylzinc are involved in the activated complex (Figure 1)[8c].

Diethanolamines **7-12**, on the other hand, having two free hydroxyl groups, were less effective catalysts for the ethylation of benzaldehyde by diethylzinc. Longer reaction times were needed and the asymmetric induction was only moderate. The extra free hydroxyl group in diethanolamines **7-12** may coordinate to zinc in such a way that the reactivity and selectivity of the reactive zinc-complexes are decreased. Alternatively, a number of different reactive complexes are involved, one or more of which lead to formation of one enantiomer of the product, while others favor formation of its mirror image. Surprisingly, in the reactions catalyzed by **11** and **12**, the (*S*)-enantiomer was formed in excess. The only difference with e.g. diethanolamines **8** and **9** consists of the presence of a additional methyl substituent at nitrogen. To the best of our knowledge, reversal of the stereochemical preference as a result of such a subtle difference in catalyst structure has not been observed before.

In table 2 the results are presented for the asymmetric alkylation of benzaldehyde by diethylzinc, when lithium alcoholates of the diethanolamines were applied as the catalysts. Slightly lower stereoselectivities were observed when the lithium salts of diethanolamines **2**, **5**, and **8** were employed, then when their protonated analogues were used. This difference may be due to the fact that lithium

Table 2: *Reaction of Benzaldehyde with Diethylzinc Catalyzed by the Lithium Alcoholates of Various Diethanolamines*[a].

	catalyst			reaction	product		
comp.[b]	R_1	R_2	R_3	time (h)	yield (%)[a]	ee (%)[a]	config
2.Li	CH_3	H	TBS[a]	22	91	44	R
5.Li	CH_3	CH_3	TBS	22	96	75	R
8.2Li	CH_3	H	Li	22	92	40	R
10.2Li	H	CH_3	Li	72	70	44	R
11.2Li	CH_3	CH_3	Li	32	90	79	R
12.2Li	C_2H_5	CH_3	Li	24	94	71	R

a) See Table 1 footnotes a, b, d, and e. b) Prepared *in situ* by treating the diethanolamines at 0 °C with 1 eq (**2** and **5**) or 2 eq of n-butyllithium (**8**, **10**, **11**, and **12**).

has a lower Lewis acid affinity for the benzaldehyde oxygen than zinc(II)[9]. Unexpectedly, the dilithium salts of **10**, **11**, and **12** displayed much better stereoselectivities than their protonated counterparts. Although the reactions catalyzed by diethanolamines **11** and **12** yielded predominantly the (*S*)-enantiomer, their lithium salts favored formation of the (*R*)-enantiomer. This dramatic change in stereoselectivity is most likely due to formation of a different kind of reactive species in the presence of lithium ions. A possible structure of such a species, in which a lithium ion is coordinated to both oxygen atoms and the nitrogen atom, is depicted in Figure 2. In this model one diethylzinc molecule is coordinated to one of the oxygen atoms in such a way, that it is located at the convex side of the two *cis*-fused five-membered rings, oriented *trans* with respect to the α-phenyl substituent. The smaller lithium ion is coordinated to the other oxygen atom at the concave side of the complex. A benzaldehyde molecule is complexed to the central lithium ion, pointing its large phenyl group away from the diethanolamine moiety.

In conclusion, optically active diethanolamines can be rather efficient and selective catalysts for the asymmetric addition of diethylzinc to benzaldehyde. The observed asymmetric induction can not be explained by a single transition state model. The efficiency and selectivity were found to depend strongly upon the detailed structure of the catalyst.

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