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New δ-aminoalcohol for the enantioselective addition of dialkylzincs to aldehydes

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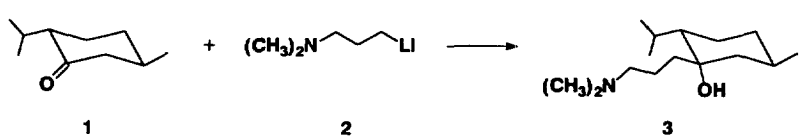
Abstract: A new optically active δ-aminoalcohol has been synthesized diastereoselectively in one step from (−)-menthone and N,N-dimethylaminopropyl lithium. The aminoalcohol catalyzed the addition of diethylzinc and dimethylzinc to aldehydes in high yields and enantioselectivities of up to 89%. © 1997 Elsevier Science Ltd

The enantioselective addition of dialkylzinc compounds to aldehydes has been intensively investigated since Noyori and co-workers demonstrated the high catalytic activity and efficiency of the (−)-3-*exo*-dimethylamino isoborneol (DAIB) as a chiral ligand.[1] The origin of the catalytic activity has been elucidated to be in the formation of alkylzinc aminoalkoxide species acting as catalysts, and an explanation concerning the mechanism, as well as the nonlinear relationship between the enantiomeric purity of some ligands (e.g. DAIB) with those of the alcoholic products formed, has also been suggested.[1–3] In recent years, a wide variety of aminoalcohols, being exclusively β-aminoalcohols, have been prepared and used as catalysts for enantioselective dialkylzinc additions to aldehydes.[2] The application of γ-aminoalcohols has been occasionally reported,[4,5] however we did not find any data concerning simple δ-aminoalcohols in the literature. The highly effective 1,2-substituted ferrocenyl aminoalcohols prepared in recent years, being δ-aminoalcohols, should not be discussed and compared here, because the asymmetric induction seems to result from the metallocene planar chirality, as shown recently.[6,7]

Recently we have reported a simple synthesis of homochiral δ-aminoalcohols via the addition of N,N-dimethylaminopropyl lithium to (+)-camphor and (−)-fenchone.[8] The enantioselectivity using these aminoalcohols as catalysts by the addition of diethylzinc to benzaldehyde was moderate, however the possibility to direct the asymmetric induction has been indicated. In this paper we report on the very simple synthesis of a new homochiral δ-aminoalcohol and its activity as a catalyst for the addition of dialkylzincs to aldehydes.

The addition of N,N-dimethylaminopropyl lithium[9] **2** to (−)-menthone **1** resulted in the preparation (Scheme 1) of (1*S*,2*S*,5*R*)-1-N,N-dimethylaminopropyl-2-isopropyl-5-methylcyclohexan-1-ol **3** in high yield.[8,10]



1 **2** **3**

Scheme 1.

The assistance of $CeCl_3$ was not necessary in this case as described by camphor and fenchone.[8,11] The addition was highly diastereoselective as a result of the favoured equatorial attack of reagent **2** and thus allowed the determination of the absolute configuration of **3** (the presence of the other diastereoisomer could not be detected; the relative position of the substituents in the cyclohexyl moiety

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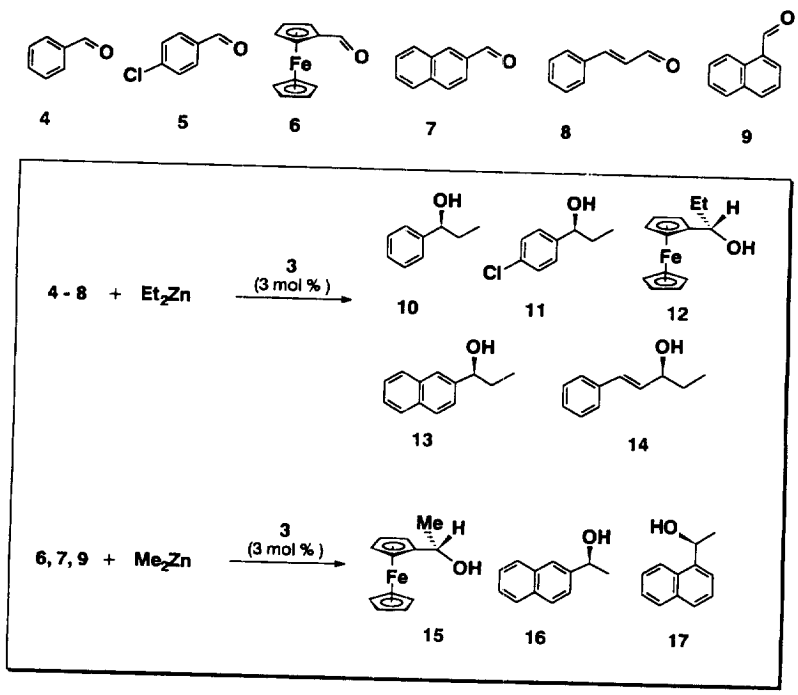
was deduced from NMR experiments[12]). The preference of the equatorial attack during the addition of lithiated acetonitrile to menthone (eq/ax=20:1) has been previously described by Trost.[13]

The δ-aminoalcohol **3** was tested as a catalyst (3 mol %) for the addition of Et_2Zn and Me_2Zn to aldehydes **4–9** (Scheme 2, Table 1). The addition of Et_2Zn to aldehydes **4–8** in toluene/hexane, according to standard procedures,[8] occurred relatively rapidly and quantitatively with very good enantioselectivities, with the exception of aldehyde **8** (entries 1–5).



Scheme 2.

Dimethylzinc was prepared in situ in diethyl ether solution according the procedure described by Seebach.[14] The methylation of aldehydes **6**, **7** and **9** was carried out in diethylether and was much slower than the ethylation which was similar to previous published data,[15] however the yields of the product alcohols were high. The optical purities of the isolated products were also acceptable in these cases (entries 6–8). It is to be pointed out that the synthesis of enantiomerically enriched derivatives **12** and **15** is rather important, because they can serve as precursors for the preparation of optically active ferrocenes possessing planar chirality.[15,16]

The multistep synthesis of an analogous β-aminoalcohol with a (−)-menthone skeleton, however with an additional stereogenic center bearing the amino group has been recently described.[17] The enantioselectivities observed by the addition of diethylzinc to benzaldehyde and some other aldehydes are indeed better than the results reported here, however the difference is not significant, bearing in mind the distance of the amino group from the stereogenic center in the case of the δ-aminoalcohol **3**. Therefore it can be assumed that the chiral center of the menthone moiety attached to the alkoxyzinc group in the catalyst complex plays the major role for the asymmetric induction.

In conclusion, we have demonstrated with the synthesis of **3** the first example, to our knowledge, of a simple δ-aminoalcohol acting as a catalyst for the asymmetric addition of dialkylzinc compounds to aldehydes.

Table 1. Addition of dialkylzincs to aldehydes catalyzed by aminoalcohol **3**

Entry	Aldehyde	R_2Zn[a]	Time [h]	Product	Yield[b] [%]	$[\alpha]_D^{20}$ (c, solvent)	Optical Purity[c] [%]
1	**4**	Et_2Zn	18	**10**	99	-42.0 (c=2.2, hexane)	89 (*S*)[d]
2	**5**	Et_2Zn	46	**11**	99	-21.2 (c=5.0, benzene)	75 (*S*)[e]
3	**6**	Et_2Zn	24	**12**	99	+51.1 (c=1.1, benzene)	89 (*S*)[f]
4	**7**	Et_2Zn	48	**13**	99	-22.3 (c=3.4, benzene)	84 (*S*)[g]
5	**8**	Et_2Zn	4	**14**	99	-1.4 (c=2.7, $CHCl_3$)	22 (*S*)[h]
6	**6**	Me_2Zn	140	**15**	98	+22.2 (c=1.0, benzene)	71 (*S*)[i]
7	**7**	Me_2Zn	160	**16**	86	-32.7 (c=1.0, CH_3OH)	86 (*S*)[j]
8	**9**	Me_2Zn	160	**17**	65	-54.9 (c=1.0, CH_3OH)	70 (*S*)[k]

[a] The addition of Et_2Zn occurred in toluene/hexane 2/1 (v/v) according the procedure described in ref.[8]; diethyl ether solution of Me_2Zn was prepared according the literature procedure[14] and the addition occurred in diethyl ether.

[b] Yields of isolated products (after Kugelrohr distillation or column chromatography). [c] Determined by polarimetry based on the maximum values for the specific rotations of the corresponding enantiomers. [d] For (*S*)-(-)-**10** $[\alpha]_D^{20}$=-47 (c=2.2, hexane) for 98 % ee in Fluka-Catalogue 1995/96, p. 1185. [e] For (*S*)-(-)-**11** $[\alpha]_D^{22}$=-28.2 (c=5.01, benzene) for 100 % ee in ref.[18]. [f] For (*R*)-(-)-**12** $[\alpha]_D^{20}$=-57.5 (c=1.0, benzene) for >96 % ee in ref.[15]. [g] For (*S*)-(-)-**13** $[\alpha]_D^{22}$=-26.6 (c=3.35, benzene) for 97 % ee in ref.[18]. [h] For (*S*)-(-)-**14** $[\alpha]_D^{22}$=-6.3 (c=2.70, $CHCl_3$) for 100 % ee in ref.[18]. [i] For (*R*)-(-)-**15** $[\alpha]_D^{20}$=-31.1 (c=1.0, benzene) for >99 % ee in ref.[15]. [j] For (*S*)-(-)-**16** $[\alpha]_D^{20}$=-38 (c=1, CH_3OH) for >98 % ee in Fluka-Catalogue 1995/96, p. 1069. [k] For (*S*)-(-)-**17** $[\alpha]_D^{20}$=-78 (c=1, CH_3OH) for 98 % ee in Fluka-Catalogue 1995/96, p. 1069.

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10. (−)-Menthone (0.28 g, 1.81 mmol) was added to a cooled solution (−15°C) of N,N-dimethylaminopropyl lithium (0.25 g, 2.69 mmol in 5 ml THF). After warming to room tempera-

ture and stirring for 1.5 h the mixture was hydrolysed with 2 N HCl (12 ml) and then washed with Et_2O (3×10 ml). The acidic aqueous layer was treated with conc. Na_2CO_3 solution, extracted with Et_2O (3×10 ml) and the ether phase was dried (Na_2SO_4). After evaporation of the solvent, the pure aminoalcohol **3** was isolated as a colourless oil (0.37 g, 85%). $[\alpha]_D^{20}=-8.5$ (c 2.0, $CHCl_3$). Anal. calcd for $C_{15}H_{31}NO$ (241.4): C, 74.63; H, 12.94; N, 5.80; found: C, 74.51; H, 12.65; N, 5.69. The new δ-aminoalcohol was characterized by NMR (^1H, ^{13}C, HXCORR, NOESY etc.; Bruker Avance DRX-250).

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