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Enantioselective addition of diethylzinc to aldehydes catalyzed by a β-amino alcohol derived from (+)-3-carene

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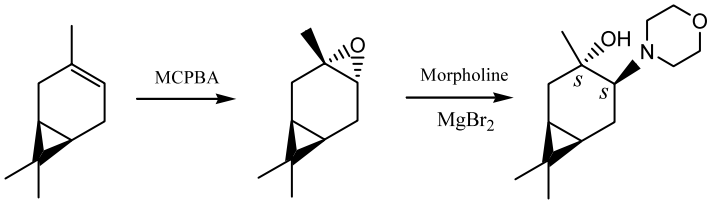
Dedicated to Professor Robert L. Augustine on his 70th birthday

Abstract—A (+)-3-carene derived aminoalcohol was successfully used as a chiral ligand in the catalytic enantioselective diethylzinc addition to various aldehydes. Very high enantiomeric excess (up 98% in 1-(2-methoxyphenyl)-1-propanol) was obtained. A plausible mechanism has been suggested for the observed enantioselectivity. © 2003 Elsevier Science Ltd. All rights reserved.

The enantioselective C–C bond formation is among the most fundamental and important synthetic constructions in chemistry.[1] Catalytic asymmetric addition reactions[2d] have attracted major attention in this regard and today it is one of most active areas of research in organic chemistry. The enantioselective addition of diethylzinc to aldehydes in the presence of catalytic amounts of chiral aminoalcohols as effective chiral ligand for this reaction was first discovered by Oguni et al.[3] However, the first report of very high enantioselectivity in the catalytic addition of Et_2Zn was reported by Noyori et al.,[4] who achieved 98% ee using DAIB (*N*,*N*-dimethylamino isoborneol), a terpene based chiral ligand. Since then various catalysts derived from terpene based chiral amino alcohols have been used to catalyze this type of reaction with varied asymmetric inductions.[5]

With our earlier work on the synthesis of terpene based compounds,[6a,b] and in particular the success seen in the application of isopinocampheyl based ligands in catalytic asymmetric deprotonation,[6c] we were inspired by the recent reports by Nugent et al.[7] A (+)-3-carene derived amino alcohol was successfully used as a chiral auxiliary in the addition of lithium cyclopropyl acetylide to an unprotected *N*-acylketimine in very high enantiomeric excess. While there are reports on the successful use of pinene,[8] nopinone,[9] fenchone-camphor[10] and very recently limonene[11] derived amino alcohols in the enantioselective addition of diethylzinc, to the best of our knowledge there is no report on (+)-3-carene derived amino alcohols. Herein we report the first study on the use of (1*S*,3*R*,4*S*,6*R*)-4-amino-3-caranol, a (+)-3-carene derived aminoalcohol as chiral catalyst in the enantioselective addition of diethylzinc to aldehydes.



(+)-3-Carene **1** **2**

Scheme 1.

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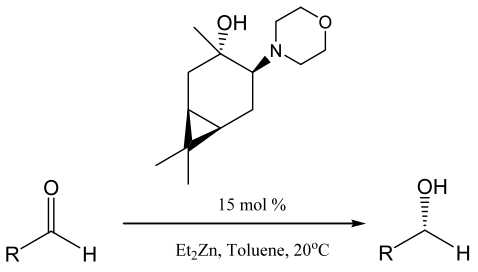

Scheme 2.

The β-amino alcohol was synthesized in two simple steps following the literature procedure.[7a] (+)-3-Carene on epoxidation with MCPBA yielded the corresponding carane epoxide **1** in 80% yield (Scheme 1). Epoxide **1**, on $MgBr_2$ induced, diastereoselective, nucleophilic ring opening with morpholine was converted to the corresponding β-amino alcohol derivative **2** in 60% yield.

This amino alcohol **2**, (1*S*,3*S*,4*S*,6*R*)-3,7,7-trimethyl-4-morpholino-4-yl-bicyclo(4.1.0)heptano-3-ol, was used as a chiral auxiliary for the enantioselective addition of diethylzinc to aldehydes (Scheme 2). Initial studies with the catalyst loading suggested that maximum ee was obtained with 15% catalyst (Table 1).

Also, in our preliminary experiments it was noted that temperature has a detrimental effect on the ee. A high ee and yield was obtained at room temperature. Interestingly, however, low conversion and low ee were observed at lower temperature, which is advantageous from the practical viewpoint. To generalize the reaction, various aldehydes were reacted with diethylzinc under optimum reaction conditions, i.e. toluene as a solvent, 20°C, 15% chiral catalyst.[12] The results are summarized in Table 2.

The efficiency of the chiral catalyst to activate the diethylzinc was reasonably high, as the GC analysis showed conversion >98% within 4 h. The results show (Table 2) that overall moderate to good yields (55–77%) were obtained. Also, for most of the aldehydes studied a moderate to excellent enantioselectivity (72–98%) was obtained. However, with the exception of *p*-chlorobenzaldehyde where the reaction was extremely sluggish and did not go to completion a low selectivity (entry 3, ee 33%) was seen. A moderate selectivity was obtained with an α,β-unsaturated aldehyde (*E*-cinnamaldehyde, ee 75%) while reaction with an aliphatic aldehyde (cyclohexanecarboxaldehyde, ee 93%) gave product with high ee. In a notable observation very high enantioselectivity (ee >98%) was obtained in the case of *o*-anisaldehyde. While *p*-nitrobenzaldehyde did not react under the experimental conditions and a sluggish reaction was seen with 2-pyridine carboxaldehyde.

Table 2. Enantioselective addition of diethylzinc to aldehydes catalyzed by β-amino alcohol **2**

Entry	Aldehyde	Yield (%)[a]	Ee (%)	Config.[b]
1	Benzaldehyde **3a**	68	81	(*R*)-(+)
2	*o*-Chlorobenzaldehyde **3b**	68	73	(*R*)-(+)
3	*p*-Chlorobenzaldehyde **3c**	66[c]	33	(*R*)-(+)
4	*o*-Methoxybenzaldehyde **3d**	76	98	(*R*)-(+)
5	*p*-Methoxybenzaldehyde **3e**	77	73	(*R*)-(+)
6	*o*-Methylbenzaldehyde **3f**	60	72	(*R*)-(+)
7	(*E*)-Cinnamaldehyde **3g**	69	75	(*R*)-(+)
8	Cyclohexanecarboxaldehyde **3h**	55	93	(*R*)-(+)
9	*p*-Nitrobenzaldehyde **3i**	NR	–	–
10	Pyridine carboxaldehyde **3j**	60[d]	–	–

[a] Isolated yield.
[b] Determined by comparison of specific rotation with literature value.
[c] Based on recovered starting material.
[d] Could not be separated from the catalyst.

In all the examples studied the *R* absolute configuration for the resulting alcohols was noted. Based on our results a plausible mechanism for the diethylzinc addition is proposed (Fig. 1) which can be explained with Noyori type tricyclic transition state model.[2a,13]

The diethylzinc coordinates with tertiary hydroxy group of amino alcohol **2** to form a pentacyclic amino alcohol–zinc complex (Fig. 1). The stereochemical disposition of *gem* dimethyl groups, tertiary methyl group as well as the bulkier amine moiety makes the attachment of the aldehyde from the top β face highly hindered. Among the two diastereomeric *anti* transition states, the *anti* (*R*)-TS, (**4-anti *R***, Fig. 1), where the aldehyde approaches with '*re* face attack' suffers no unfavorable steric interactions with the Ph and the Zn_A–Et group and is energetically more favorable. The steric interaction between Zn_A–Et and the *N*-alkyl substituent[14] is responsible for the further energy difference between the two transition states *anti*-(*R*) and *anti*-(*S*) and is responsible for higher ee with bulkier *N*-alkyl derivatives.

To summarize, we have demonstrated the effective use of a sterically hindered, bicyclic aminoalcohol as a chiral catalyst, in the enantioselective addition of diethylzinc to various aldehydes. The results illustrate the stereochemical efficacy of a conformationally constrained β-amino alcohol with rare *trans* disposed aminoalkyl and alcohol groups significantly deviated from the usual coplanarity. A plausible mechanism has

Table 1. Effect of catalyst loading on the ee in the diethylzinc addition to benzaldehyde

Entry	Catalyst mol (%)	Yield (%)	$[\alpha]_D$	Ee	Configuration
1	5	62	+22.0	46.6	*R*
2	10	65	+37.4	77.9	*R*
3	15	69	+39.0	81.2	*R*

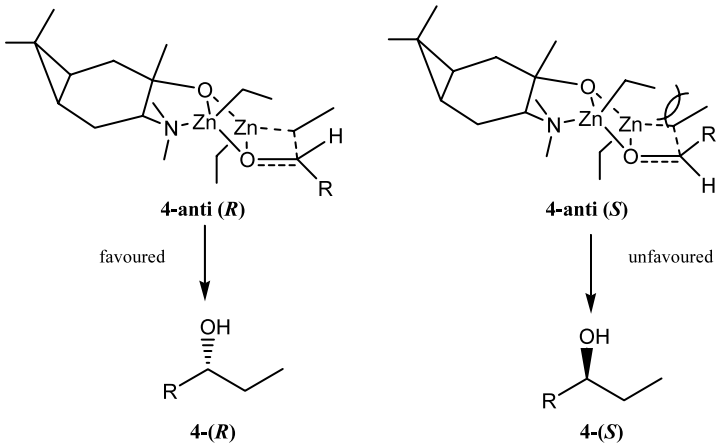

Figure 1. Proposed transition states.

been proposed to account for the effective facial enantioselection in a sterically demanding framework. The studies regarding theoretical calculations for the proposed transition states are currently underway.

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12. *Typical experimental procedure*: To a solution of **2** (36 mg, 0.15 mmol) in toluene (2 mL) was added 2 M Et_2Zn

toluene solution (1.0 mL, 2 mmol) under argon at room temperature. The reaction was allowed to stir for 30 min at room temperature and then benzaldehyde (1 mmol) in toluene (2 mL) was added to it over 2 min. The reaction mixture turned yellow upon addition of aldehyde and was allowed to stir at room temperature for 20 h. Reaction was quenched with 2N HCl (4 mL), the organic layer separated and aqueous layer extracted with diethyl ether (3×5 mL). The combined organic extracts were washed with saturated sodium hydrogen carbonate (5 mL) followed by water (5 mL) and finally brine (5 mL). Drying over Na_2SO_4 and evaporation under reduced pressure yielded a crude alcohol, which was further purified by flash column chromatography (acetone/pet ether 1:25) to give the purified alcohols (yield 68%). The enantiomeric excess and absolute configuration was determined from the specific rotation of the purified product.

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14. To study the effect of bulk of the *N*-alkyl substituent on enantioselectivity, (1*S*,3*R*,4*S*,6*R*)-4-allylamino-3-caranol, a chiral catalyst with less bulkier *N*-allyl group was synthesized. When used as a chiral catalyst in the enantioselective alkylation of benzaldehyde, (*R*)-1-phenyl-1-propanol was obtained with 60% ee which is considerably less for the same reaction with chiral catalyst **2** (ee 81% with benzaldehyde).