

Catalytic Enantioselective Addition of Diethylzinc to Aldehydes by Chiral Secondary γ -Aminoalcohols¹

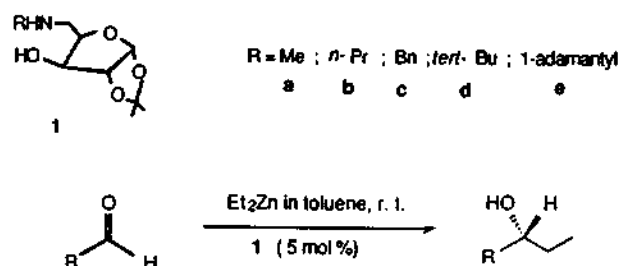
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Received August 8, 1994

The catalytic enantioselective alkylation of carbonyl compounds is a potentially important method for the preparation of optically active alcohols. Considerable attention has been focused on the addition of diorganozinc reagents to aldehydes mediated by a wide range of chiral catalysts affording the product alcohols with high optical purities.² Among them, it has been found that sterically congested β -tertiary aminoalcohols able to form a five membered ring are essential for high enantioselectivities. On the other hand, it has been realized that the actual catalysts of these reactions are not the aminoalcohols themselves, but zinc chelates formed *in situ* from the zinc reagents and aminoalcohols. Consequently, the catalysts containing other metals in place of zinc have been developed. For example, an oxazaborolidine derived from a secondary amine, *l*-ephedrine, and borane afforded higher enantioselectivities than the original zinc chelated from of the same ligand.³ However, the use of γ -secondary aminoalcohols for such reaction has not been reported, although they have a strong possibility as chiral ligands to

form metallated complexes with a variety of metals. Very recently, we reported that γ -tertiary aminoalcohols derived from α -D-xylose were highly effective catalysts for the reaction to give optically active secondary alcohols with high enantioselectivities.⁴ Therefore, we decided to undertake the study of catalytic enantioselective addition of diethylzinc to aldehydes using γ -secondary aminoalcohols, 1,2-*O*-isopropylidene-5-deoxy-5-*N*-alkylamino- α -D-xylofuranose derivatives (**1a-e**) as new chiral ligands.



The new chiral ligands **1a-e** were prepared from 1,2-*O*-isopropylidene-5-*O*-*p*-toluenesulfonyl- α -D-xylofuranose **2**⁵ and the corresponding primary amines in 45-88% yields.⁶ We initially compared the enantioselectivities of the catalysts for benzaldehyde chosen as representative. Thus, the aldehyde was reacted with diethylzinc in the presence of 5 mol% of each of **1a-e** in toluene at room temperature (*ca.* 20 °C). With one exception (**1a**), all the reaction examined proceeded smoothly to give 1-phenyl-1-propanol in good yields. Catalytic effect for enantioselectivities of the product alcohol exhibited the increase by the variation of the steric size of R in the

Table 1. Catalytic Enantioselective Addition of Diethylzinc to Aldehydes in the Presence of 5 mol% of **1a-e** in Toluene at Room Temperature^a

Entry	Aldehydes	Ligands (1)	Time (h)	Products alcohols		
				Yield (%) ^b	% <i>ee</i> ^c	Abs. config. ^d
1	Benzaldehyde	1a	48	50	7	S
2	Benzaldehyde	1b	10	78	69	R
3	Benzaldehyde	1c	10	71	69	R
4	Benzaldehyde	1d	10	83	77	R
5	Benzaldehyde	1e	10	95	82	R
6	<i>o</i> -tolualdehyde	1e	10	99	77	R
7	<i>p</i> -tolualdehyde	1e	10	98	78	R
8	1-naphthaldehyde	1e	10	95	84 ^e	R
9	heptanal	1e	10	97	68	R
10	Cyclohexanecarboxaldehyde	1e	10	96	80	R
11	Hydrocinnamaldehyde	1e	10	93	69	R
12	Cinnamaldehyde	1e	20	68	55 ^f	R
13	Benzaldehyde	1e'	10	98	70	R
14	Benzaldehyde	1e''	10	94	68	R
15	Benzaldehyde	1e'''	10	87	41	R
16	Benzaldehyde	1e''''	10	83	67	R

^a[aldehyde] : [ligands] : [Et₂Zn] = 1 : 0.05 : 2.0, unless otherwise indicated. ^bGC yields. ^cDetermined by capillary GC analyses using a Chiraldex GTA column (Astec Inc.). ^dBased on elution orders in GC or HPLC analyses. ^eDetermined by HPLC analyses by a Chiralcel OD column (Daicel Co.). ^f[aldehyde] : [**1e**] : [*n*-BuLi] : [Et₂Zn] = 1 : 0.05 : 0.05 : 2.0. ^g[aldehyde] : [**1e**] : [BH₃] : [Et₂Zn] = 1 : 0.05 : 0.05 : 2.0. ^h[aldehyde] : [**1e**] : [AlMe₃] : [Et₂Zn] = 1 : 0.05 : 0.05 : 2.0. ⁱ[aldehyde] : [**1e**] : [Ti(O*i*-Pr)₄] : [Et₂Zn] = 1 : 0.05 : 0.05 : 2.0.

chiral ligands **1** from Me→*n*-Pr→Bn→*tert*-Bu→1-adamantyl, such as 7% *ee* with **1a**, 69% *ee* with **1b**, 69% *ee* with **1c**, 77% *ee* with **1d** and 82% *ee* with **1e**. The results led us to investigate the catalytic enantioselective addition of diethylzinc to other aldehydes with **1e**. The optical inductions were good for both aromatic and aliphatic aldehydes while the α,β -unsaturated aldehyde tested provided the corresponding alcohol of only moderate enantiomeric excess.⁷ On the other hand, we also prepared catalysts based on Li, B, Al and Ti by reacting the ligand **1** with *n*-BuLi, BH₃, AlMe₃ and Ti(O*i*-Pr)₄, respectively and compared their enantioselectivities for benzaldehyde. The enantiomeric excesses of the product alcohol obtained with these metallated oxaza ring system⁸ are clearly inferior to that obtained with Zn (82% *ee*), such as Li (70% *ee*), B (68% *ee*), Al (41% *ee*), and Ti (67% *ee*). The results are summarized in Table 1.

Acknowledgment. The present study was supported by a grant from the Basic Science Research Institute Program (BSRI-94-3412), Ministry of Education, Korea, 1994.

References and Notes

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6. For the structures of **1a-1e**, satisfactory results were obtained from IR, NMR (¹H and ¹³C) spectroscopic and elemental analyses data.
7. The following procedure is representative. Under a nitrogen atmosphere, a toluene solution (3.6 ml) of diethylzinc (4 mmol) was added to **1e** (343 mg, 0.1 mmol) in toluene (0.4 ml) and stirred at room temperature for 30 min. After benzaldehyde (212 mg, 2 mmol) was added to this, the mixture was stirred at the same temperature for 10 h and then diluted with ether (15 ml). The excess diethylzinc was destroyed by addition of 1.5 N HCl (10 ml). The mixture was then extracted with ether (3×15 ml). GC analysis indicated the formation of 1-phenyl-1-propanol in a 95% yield. The extract was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The product alcohol was isolated by bulb-to-bulb distillation and further purified with silica gel column chromatography. Enantiomeric excess was measured by GC analysis of trifluoroacetate of the product alcohol using a 20 m Chiraldex GTA capillary column. GC analysis showed a composition of 91 (R) and 9 (S) (*i.e.*, 82% *ee*).
8. Presumably, these catalysts contain Li, B, Al, or Ti. However, the exact structure of these catalysts in solution are not known.