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Communications

Catalytic Enantioselective Reactions. Part 6.⁺ A New Chiral Catalyst for Highly Enantioselective Addition of Diethylzinc to Aliphatic Aldehydes

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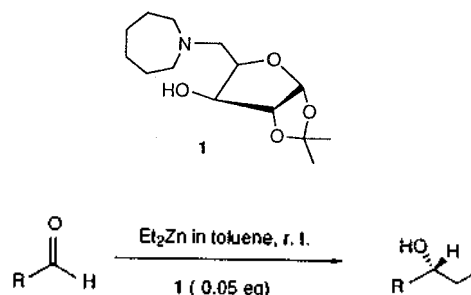
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In recent years, a wide range of chiral catalysts for the enantioselective addition of dialkylzincs to aldehydes to give optically active secondary alcohols has been extensively studied.¹ Of the catalysts reported, it has been realized that most of them are highly effective for aromatic aldehydes in such reaction, whereas only a few catalysts to be successful in providing high asymmetric induction for aliphatic aldehydes have been appeared in the literature.² Therefore, it is a formidable challenge to develop highly enantioselective chiral catalysts for the addition of dialkylzincs to aliphatic aldehydes.

Recently, we reported the enantioselective addition of diethylzinc to aldehydes using γ -amino alcohols as chiral catalysts.³ Among the chiral catalysts examined, a γ -aminoalcohol, 1,2-*O*-isopropylidene-5-deoxy-5-morpholino- α -D-xylofuranose bearing a heterocyclic amine moiety in the structure, provided the best results for the ethylation of both aromatic and hindered aliphatic aldehydes leading to optically active secondary alcohols with high enantioselectivities.^{3a} In continuation of our efforts to gain a better understanding of the catalytic effects and to develop the efficient chiral catalysts for such reaction, we prepared a series of new 1,2-*O*-isopropylidene-5-deoxy-5-heterocyclicamino- α -D-xylofuranose derivatives possessing a variety of heterocyclic amino substituents at the 5-position of the xylofuranose ring moiety and compared their enantioselectivities as chiral catalysts. In the course of this study, we found that 1,2-*O*-isopropylidene-5-deoxy-5-hexamethyleneimino- α -D-xylofuranose **1** induces high enantioselectivity for the addition of diethylzinc to aliphatic aldehydes. Hereby we wish to report the results for such catalytic

enantioselective ethylation to aldehydes.



The catalyst could be easily prepared by the reaction of 1,2-*O*-isopropylidene-5-*p*-toluenesulfonyl- α -D-xylofuranose⁴ with excess hexamethyleneimine in 64% yields.⁵

The reactions were carried out by the treatment of aldehydes with 2 eq diethylzinc in the presence of 5 mole% of **1** in toluene at *ca* 20 °C. The reactions proceeded smoothly to the corresponding alcohols in good yields. For relatively unhindered aliphatic aldehydes, **1** provided high asymmetric induction, such as 78% ee for hexanal, 83% ee for heptanal, 92% ee for 3-methylbutanal and 83% ee for hydrocinnamaldehyde. The catalyst also provide high enantioselectivity with 92% ee for a relatively hindered, 2-methylpropanal. However, the asymmetric induction for a more hindered aliphatic aldehyde, 2,2-dimethylpropanal, decreased significantly, showing 76% ee. In the case of aromatic aldehydes, the catalyst afforded lower asymmetric induction than those for aliphatic aldehydes, such as 71% ee for benzaldehyde and 61% ee for 1-naphthaldehyde. For an α,β -unsaturated aldehyde, cinnamaldehyde, very low asymmetric induction (18% ee) was observed. In this reaction, all the alcohols obtained were consistently enriched in the (*R*)-enantiomers. The results were summarized in Table 1. The following procedure is representative. Under a nitrogen atmosphere, a toluene solution (3.6 mL) of diethylzinc (4 mmol) was added to **1** (25.1 mg, 0.1 mmol) in toluene (0.4 mL) and stirred at room temperature (*ca.* 20 °C) for 30 min. After 3-methylbutanal (172 mg, 2 mmol) was added to this, the mixture was stirred at the same temperature for 16 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

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

Aldehydes	Time (h)	Product alcohols		
		Yield (%) ^b	% ee ^c	Abs. Config. ^d
Hexanal	16	90	78	R
Heptanal	16	88	83	R
3-Methylbutanal	18	92	92	R
Hydrocinnamaldehyde	16	87	83 ^e	R
2-Methylpropanal	16	94	92	R
2,2-Dimethylpropanal	16	85	76	R
Cinnamaldehyde	20	75	18 ^f	R
Benzaldehyde	20	98	76 ^g	R
1-Naphthaldehyde	20	98	61 ^f	R

^a[aldehyde] : [**1**] : [Et₂Zn] = 1 : 0.05 : 72. ^bGC yields. ^cDetermined by capillary GC analyses of (+)-MTPA esters, unless otherwise indicated. ^dBased on the sign of optical rotations and elution orders of peaks in GC or HPLC analyses. ^eDetermined by capillary GC analysis of (-)-menthyl carbonate. ^fDetermined by HPLC analysis using a Chiralcel OD column. ^gDetermined by capillary GC analyses using a Chiraldex GTA column (Astec Inc.)

ether (3×15 mL). GC analysis indicated the formation of 5-methyl-3-hexanol in a 92% yield. The extract was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The alcohol product was isolated by bulb-to-bulb distillation and further purified with silica gel column chromatography. Enantiomeric excess was measured by GC analysis of (R)-MTPA ester of the alcohol product using a 50 m methylsilicon capillary column. GC analysis showed a composition of 96 (R) and 4 (S) (*i.e.*, 92% ee).

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 - 1**: mp 40-41 °C; [α]_D²⁴-13.6 (c 1, CHCl₃); IR (KBr, cm⁻¹), 3458, 2978, 2814, 1453, 1380; ¹H NMR (300 MHz, CDCl₃, TMS) δ 1.32 (s, 3H, CH₃), 1.47 (s, 3H, CH₃), 1.40-1.80 (m, 8H, NCH₂CH₂CH₂CH₂CH₂CH₂), 2.64-2.73 (m, 2H, NCH₂CH₂CH₂CH₂CH₂CH₂), 2.86-2.96 (m, 3H, H-5a and NCH₂CH₂CH₂CH₂CH₂CH₂), 3.29 (dd, 1H, J=2.8

and 14.6 Hz, H-5b), 4.05-4.07 (m, 1H, H-4), 4.31 (d, 1H, J=2.26 Hz, H-3), 4.49 (d, 1H, J=3.57 Hz, H-2), 5.97 (d, 1H, J=3.6 Hz, H-1); ¹³C NMR (75.46 Hz, CDCl₃, TMS) δ 111.7 (CMe₂), 105.5 (C-1), 86.1 (C-2), 78.4 (C-3), 77.3 (C-4), 57.8 and 57.7 (C-5 and NCH₂CH₂CH₂CH₂CH₂CH₂), 27.9, 26.9, 26.8 and 26.3 (H₃CCCH₃ and NCH₂CH₂CH₂CH₂CH₂CH₂); Anal. Calcd for C₁₄H₂₅NO₄: C, 61.96; H, 9.29; N 5.16. Found: C, 62.33; H, 9.64; N, 5.10.

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A Useful Method for the Selective Reduction of Isoxazoline Nuclei in the Presence of Double Bonds by the Use of Lindlar Catalyst

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In the past two decades, the nitrile oxide cycloaddition reaction has attracted much attention in synthetic organic chemistry.¹ The value of this cycloaddition reaction is ascribed mainly to the utility of the cycloaddition products as latent synthetic equivalents. One can cleave isoxazolines to produce the β-hydroxy carbonyl unit, which occurs in a large number of important natural products. In this type of cleavage the N-O bond of isoxazolines is first reduced and the resultant β-hydroxy imines are then rapidly hydrolyzed in the presence of water to give β-hydroxy ketones. Generally, metal (Ra-Ni or supported metal catalyst) catalyzed hydrogenolysis methods² have been used for the conversion of isoxazolines to β-hydroxy ketones. Unfortunately, olefins, especially mono- and disubstituted olefins, are not compatible with these cleavage methods, although tri- and tetrasubstituted double bonds are known to be generally retained. Hindered disubstituted olefins may also be retained in some instances.^{2c} From the point of selectivity, the Torrsell's TiCl₃ reductive cleavage procedure is known to be far better. Double bonds can survive the conditions of this procedure without difficulty.³ However, the yields which attend such procedure are not often satisfactory and the requisite reagent TiCl₃ difficult to handle. Thus, the development of a more practical and selective procedure for the reduction of isoxazoline nuclei in the presence of double bonds is of value.

Recently, we have observed that the Lindlar catalyst (Pd/CaCO₃, poisoned with lead) has enough catalytic power to unmask the isoxazoline ring to afford the β-hydroxy ketone unit under the atmosphere of hydrogen.⁴ Encouraged by these observations, we examined the Lindlar catalyst reduction of isoxazolines containing variously substituted alkyl groups (Scheme 1). We now wish to report a mild