Fructose derived pyridyl alcohol ligands: synthesis and application in the asymmetric diethylzinc addition to aldehydes

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Easily available chiral ketones were employed for the synthesis of optically active pyridyl alcohols, which were applied in the asymmetric diethylzinc addition to aldehydes, up to 89.4% *e.e.* was obtained using *D*-fructose-derived pyridyl alcohol.

Keywords Pyridyl alcohols, diethylzinc, asymmetric addition

Catalytic enantioselective reactions have received much attention in recent years and significant progress has been made in the carbon-carbon bond forming reactions using chiral-modified metal complexes.[1] Enantioselective addition of organometallic reagents toward carbonyl compounds in the presence of chiral ligands[2] plays an increasingly important role in the synthesis of chiral secondary alcohols which are found in the structures of many natural products and synthetic pharmaceuticals. Since the first report on the reaction using a catalytic amount of certain β-amino alcohols by Oguni and Omi in 1984,[3] numerous efforts have been made to search for new effective ligands in the reaction and to prove the reaction mechanism by many organic chemists.[2,4] Afterwards, a variety of chiral β-amino alcohols have been used as effective ligands. As analogs of β-amino alcohols, pyridyl alcohols should be also effective ligands for this reaction.[5] Although the chrial pyridyl alcohols obtained by resolution as ligands have been reported by Bolm, Chan *etc.*,[5] preparation of these pyridyl alcohol ligands is difficult. In this paper, we will report a convenient method to prepare chiral pyridyl alcohols using easily available chiral ketones as starting materials and the application of chiral pyridyl alcohols in asymmetric diethylzinc addition to aldehydes.

Chiral pyridyl alcohols (**1**—**6**) were synthesized as follows. Pyridyl alcohols (**1**—**5**) can be synthesized by the reaction of 2,6-lutidine with corresponding chiral ketones in the presence of *n*-BuLi.[6] For *D*-fenchone, almost equal amount of *exo* and *endo* attacked products **1** and **2** was obtained and separated by flash chromatography. For *D*-camphor, only a single diastereomer **3** was isolated. *D*-Fructose-derived chiral ketones[7] can also react with 2,6-lutidine in the presence of *n*-BuLi to give single equatorial attacked products (**4** and **5**) in high yields. The structure of **5** has been determined by X-ray analysis.[8] The monoadduct **3** was further functionalized by theaddition of *n*-BuLi (2.2 equiv.) to a solution of the monoadduct **3** in Et_2O, followed by the addition of 1.1 equiv. of *D*-camphor, led to the diol adduct **6** in moderate yield. Similar attempt to synthesize the condensation product of monoadduct **5** and *D*-fructose-derived chiral ketone failed, probably due to steric hindrance (Scheme).

In order to examine the catalytic ability of the ligands, the addition of diethylzinc to aldehyde was carried out at 0℃ in the presence of a catalytic amount (5 mol%) of various chiral pyridyl alcohols (**1**—**6**) in toluene. The enantiomeric excess of the obtained alcohols with catalysts are shown in Table 1 (Entries 1—6). All catalysts gave optically active 1-phenyl-1-propanol. Among them *D*-fenchone-derived pyridyl alcohol **2** shows highly effective activity to give good asymmetric induction (Entry 2), while **1** shows low activity and asymmetric induction (Entry **1**). Ligand **3** from camphor has high activity, but the asymmetric induction is moderate.

Received June 29, 1999; accepted September 20, 1999.
Project (Nos. 29790127 and 29872045) supported by the National Natural Science Foundation of China.

Scheme

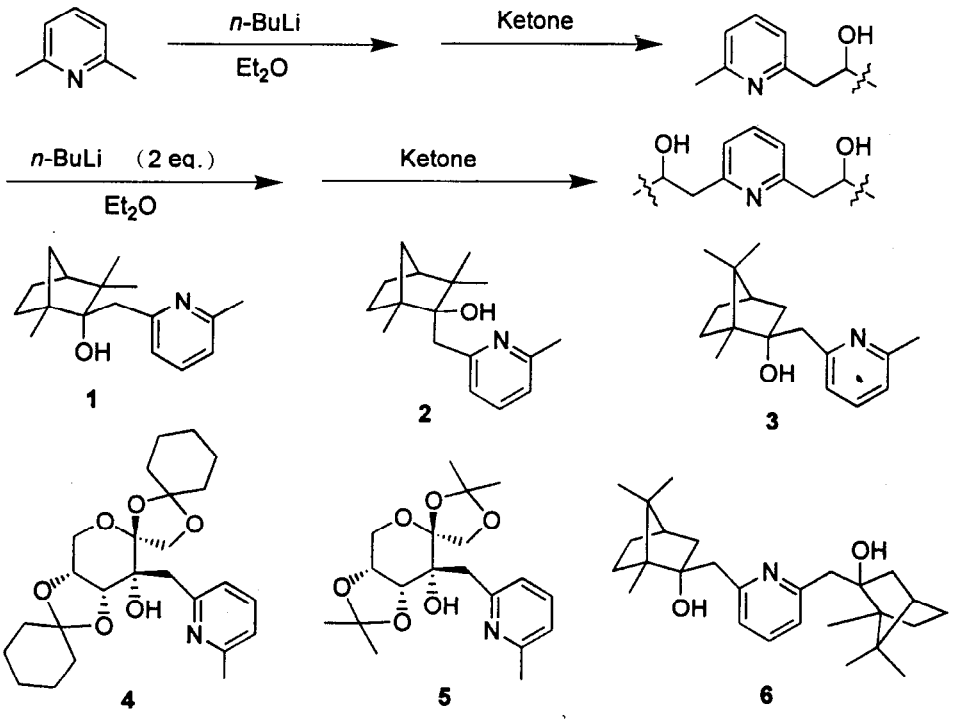
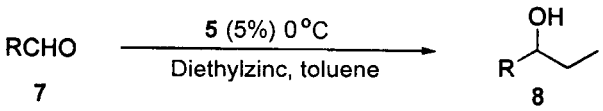


Table 1 Enantioselective addition of diethylzinc to aldehydes using **1**—**6** as a catalyst[a]



Entry	R	Ligands	Yield (%)[b]	*e.e.* (%)[c]	Config.[d]
1	Ph (**7a**)	**1**	43	15.4	*S*
2	Ph (**7a**)	**2**	98	72.9	*S*
3	Ph (**7a**)	**3**	94	59.5	*R*
4	Ph (**7a**)	**4**	88	83.5	*R*
5	Ph (**7a**)	**5**	93	88.5	*R*
6	Ph (**7a**)	**6**	82	47.1	*R*
7	*p*-ClC_6H_4 (**7b**)	**5**	92	87.6	*R*
8	*p*-$MeOC_6H_4$ (**7c**)	**5**	83	89.4	*R*
9	*p*-$NMe_2C_6H_4$ (**7d**)	**5**	85	82.9	*R*
10	*p*-BrC_6H_4 (**7e**)	**5**	97	86.4	*R*
11	*o*-$OMeC_6H_4$ (**7f**)	**5**	98	88.8	*R*
12	Biphenyl (**7g**)	**5**	96	89.2	*R*
13	Ferocenyl (**7h**)	**5**	82	88.0	*R*
14	2-Naphthyl (**7i**)	**5**	95	80.2	*R*
15	1-Naphthyl (**7j**)	**5**	84	85.4	*R*
16	PhCH = CH (**7k**)	**5**	84	41.0	*R*
17	Cyclohexyl (**7m**)	**5**	75	71.1	*R*

[a] The reaction was carried out in hexane-toluene (1:1) with 5 mol% of catalysts **1**—**6** 2.0 equiv of diethylzinc to aldehydes. [b] Isolated yield based on aldehydes. [c] Determined by HPLC analysis using Chiralcel OD. [d] Configurations were assigned by comparison with the sign of optical rotation and known elution order from a Chiralcel OD column.

Sugar-derived ligands **4** and **5** can effectively catalyze this reaction, in which acetone-protected ligand 5 has slight higher enantioselectivity and reaction rate than cyclohexanone-protected 4. In view of yield and enantioselectivity, the best chiral ligand is *D*-fructose-derived chiral pyridyl alcohol 5. Using the optimized conditions, a variety of substrates were examined,[9] and the results are listed in Table 1 (Entries 7—17).

As can be seen from Table 1, under the same reaction conditions, several aromatic aldehydes were examined by using the ligand **5**, and afforded the corresponding secondary alcohols (Entries 5—15) in high chemical yields and good enantioselectivity (80.2—89.4% *e.e.*). For aliphatic aldehyde (Table 1, Entry 17), the enantioselectivity of the reaction was moderate (71.1%). For α,β unsaturated cinnamyl aldehyde **7k**, the asymmetric induction is low (Entry 16).

It has been shown that the new pyridyl alcohols serve as efficient homogenerous catalysts in the enantioselective addition of diethylzinc to aldehydes, and synthesis of these effective ligands from cheap sugar was simple. Further studies in preparation and application of new pyridyl alcohols from natural sugar are in progress.

References and notes

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8. Selective data for compound **5**: $[\alpha]_D^{20} = -20.1^\circ$ (*c*, 1.65, $CHCl_3$). δ_H(300 MHz, $CDCl_3$): 1.18(s, 3H), 1.42(s, 3H), 1.46(s, 3H), 1.51(s, 3H), 2.50(s, 3H), 2.91 (d, J = 14.3Hz, 1H), 3.05(d, J = 14.3Hz, 1H), 4.00—4.12(m, 5H), 4.36(d, J = 9.6Hz, 1H), 6.94—6.95(m, 2H), 7.41—7.46(m, 1H): *m/z*(%): 365 ($M^+ + 1$, 42.33), 349 (15), 165 (33), 134 (56), 107 (100). ν_{max} 3279, 2993, 1597, 1216, 1081, 1002, 865. Anal. $C_{19}H_{27}NO_6$. Calcd: C, 62.45; H, 7.45; N, 3.83. Found: C, 62.16; H, 7.42; N, 3.54.
9. *General procedure for catalytic asymmetric addition of various aldehydes with diethylzinc in the presence of chiral pyridyl alcohols* To a suspension of **1**—**6** (0.05 mmol) in toluene (2.5 mL) was added Et_2Zn (2.2 mL, 2.2 mmol, 1 mol/L in hexane), after 30 min, the reaction system was cooled to 0℃, the aldehyde (1.0 mmol) was added under argon atmosphere, After being stirred for appropriate time, the reaction was quenched with 3 mol/L HCl. The mixture was extracted with ether. The organic layer was washed with brine, dried, and evaporated under reduced pressure to give an oily residue. Purification of the residue by preparative TLC gave optically active alcohol.

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