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CATALYTIC ENANTIOSELECTIVE ADDITION OF DIETHYLZINC TO ALDEHYDES: SYNTHESIS AND APPLICATION OF A NEW CYCLIC CATALYST

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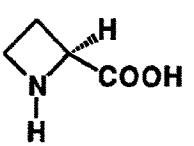
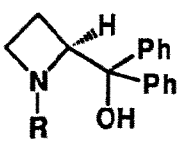
Abstract: The new optically active b-amino alcohol (*S*)-1-methyl-2-(diphenylhydroxymethyl)azetidine (*S*)-**4** derived from (*S*)-azetidinecarboxylic acid (*S*)-**1** catalyzes the enantioselective addition of diethylzinc to various aldehydes. The resulting chiral secondary alcohols **5a-h** are obtained in high optical yields up to 100 % under mild reaction conditions.

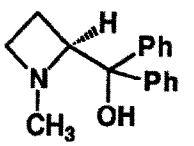
Chiral auxiliaries prepared from cyclic amino acids have attracted much attention over the last decade[1]. In particular (*S*)-proline derivatives often lead to very high asymmetric inductions in organic syntheses[2]. Less is known on chiral auxiliaries prepared from the nonproteinogenic amino acids (*S*)-azetidinecarboxylic acid[3] (*S*)-**1**, (*S*)-pipecolinic acid[4] (1*R*,3*R*,5*R*)-2-azabicyclo[3.3.0]octane carboxylic acid[5], (*S*)-porretine[6] and (*S*)-2-indoline carboxylic acid[7].



(*S*)-**1**



(*S*)-**2** (R=H)
(*S*)-**3** (R=CHO)



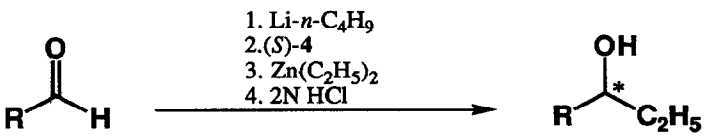
(*S*)-**4**

In this paper we report on the synthesis and application of an optically active amino alcohol (*S*)-**4** derived from (*S*)-**1**, a constituent of the natural mugineic acid[8]. (*S*)-2-(diphenylhydroxymethyl)azetidine (*S*)-**2** was prepared from the amino acid (*S*)-**1** according to the literature[3a]. The chiral catalyst (*S*)-1-methyl-2-(diphenylhydroxymethyl)azetidine (*S*)-**4** was

obtained from (*S*)-2-(diphenylhydroxymethyl)azetidine (*S*)-**2** in two steps. Thus, the alcohol (*S*)-**2** is first formylated to give (*S*)-1-formyl-2-(diphenylhydroxymethyl)azetidine (*S*)-**3** in 91% yield[9]. The *N*-methyl derivative (*S*)-**4** is obtained from (*S*)-**3** by reduction with lithium aluminium hydride in 89% yield[10].

Enantioselective addition of organozinc reagents to aldehydes affords optically active secondary alcohols. The reaction is one of the most important asymmetric reactions. The clean nucleophilic addition of diethylzinc to benzaldehyde in the presence of an optically active diamino alcohol was first reported by *Mukaiyama et al.*[11,12]. *Oguni* and *Omi* found that optically active β-amino alcohols as ligands in such reactions not only accelerate but also direct the stereochemical outcome in the absolute sense[13].

In order to examine the effect of the new catalyst (*S*)-**4** the reaction of diethylzinc with various aldehydes was investigated.



5 a - h

In a typical procedure *n*-butyllithium (1.35 mmol = 0.85 ml of 1.6M hexane solution) was added to a solution of the catalyst (*S*)-**4** (0.65 mmol) in dry toluene at – 40° C. After 10 min diethylzinc (26.7 mmol, 24.3 ml of 1.1 M toluene solution) was added over a period of 5 min. The mixture is allowed to reach the room temperature and treated within 10 min. with 13 mmol aldehyde, then the resulting mixture was stirred for 40 h at the 22° C. The reaction was quenched with 2N hydrochloric acid, the organic layer was separated, and the aqueous layer was extracted with diethyl ether. The combined organic layers were extracted with sodium-hydrogen sulfite solution, sodiumhydrogen carbonate solution and water, before drying. The solvent is evaporated under reduced pressure and the residue distilled under vacuum to afford the corresponding *sec.* alcohols **5a-h** (see Table 1).

As can be seen from Table 1 when the lithium alkoxide of the new chiral β-amino alcohol (*S*)-**4** is used as a catalyst in the reaction of diethylzinc with various aromatic aldehydes, enantioselectivities up to 100% ee are observed. Using the corresponding proline auxiliary (*S*)-1-methyl-2-(diphenylhydroxymethyl)pyrrolidine (*S*)-**6** *Soai* obtained **5f** with 73% ee. On the other hand, we obtained **5f** with an optical purity of 80% employing 5 mol% Li-(*S*)-**4**.

The aliphatic alcohol **5h** is formed in 67% ee from nonanal and $ZnEt_2$ in the presence of 5 mol% Li-(*S*)-**4**.

Table 1: Enantioselective addition of diethylzinc to aldehydes in the presence of catalyst (*S*)-**4** and (for comparison) the proline-derived amino alcohol (*S*)-1-methyl-2-(diphenylhydroxymethyl)pyrrolidine (*S*)-**6**.

			secondary alcohol **5a-h** [a]	
entry	R	catalyst [concentration mol%]		optical yield[b] [%] (configuration)
1	Ph	(*S*)-**4** [5]	**5a**	98 (*S*)[c]
2	4-Cl-C_6H_4	(*S*)-**4** [5]	**5b**	100 (*S*)[d]
3	2-MeO-C_6H_4	(*S*)-**4** [5]	**5c**	94 (*S*)[e]
4	4-MeO-C_6H_4	(*S*)-**4** [5]	**5d**	100 (*S*)[f]
5	4-Me-C_6H_4	(*S*)-**4** [5]	**5e**	99 (*S*)[g]
6	*E*-Ph-CH=CH	(*S*)-**4** [5]	**5f**	80 (*S*)[h]
7	*E*-Ph-CH=CH	(*S*)-**6** [2]	**5f**	73 (*S*)[14]
8	2-furyl	(*S*)-**4** [5]	**5g**	94 (*S*)[i]
9	1-octyl	(*S*)-**4** [5]	**5h**	67 (*S*)[j]

[a] Chemical yield 70-90%. [b] The optical yield was calculated from the maximum rotation. [c] $[\alpha]_D^{20} = -45.45$ (c = 5.15, chloroform) for (*S*)-1-phenyl-1-propanol[15]. [d] $[\alpha]_D^{20} = -23.5$ (c = 0.82, benzene) for (*S*)-1-(4-chlorophenyl)propan-1-ol in 93 % ee[16]. [e] $[\alpha]_D^{20} = -53.6$ (c = 3, toluene) for (*S*)-1-(2-methoxyphenyl)propan-1-ol[17]. [f] $[\alpha]_D^{20} = -17.2$ (c = 5, benzene) for (*S*)-1-(4-methoxyphenyl)propan-1-ol[18]. [g] $[\alpha]_D^{20} = -39.2$ (c = 5.1, benzene) for (*S*)-1-(4-methylphenyl)propan-1-ol[19]. [h] $[\alpha]_D^{20} = -6.6$ (c = 3.2, chloroform) for (*S*,*E*)-1-phenyl-1-penten-3-ol in 75% ee[20]. [i] $[\alpha]_D^{20} = +12.6$ (c = 2.09, chloroform) for (*R*)-1-(2-furyl)propan-1-ol in 95 % ee[21]. [j] $[\alpha]_D^{20} = +7.79$ (c = 8.7, ethanol) for (*S*)-3-undecanol in 87 % ee[22].

Further studies to compare the catalytic activity and the enantioselectivity of (*S*)-**4** with other chiral β-amino alcohols are under developement.

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9 (*S*)-1-formyl-2-(diphenylhydroxymethyl)-azetidine (*S*)-**3**: m.p.: 202-203.5 °C; ^{1}H-NMR (DMSO): δ in ppm = 2.13-2.23 (2m, 2H, H3), 3.48-3.57, 3.67-3.75 (2m, 2H, H4), 5.55-5.60 (dd, 1H, H2), 6.10 (s, 1H, CHO), 7.19-7.53 (m, 10H, 2xC_6H_5); ^{13}C-NMR (DMSO): δ in ppm = 19.0 (C3), 44.8 (C4), 67.6 (C2), 77.8 (CPh_2OH), 126.2-145.9 (ArC), 161.8 (C=O); MS (CI, *i*-Butane): 268 (MH^+, 58%).

10 (*S*)-1-methyl-2-(diphenylhydroxymethyl)-azetidine (*S*)-**4**: m.p.: 55-56 °C; $[\alpha]_D^{20}$ = +39.3 (*c*=5.0, $CHCl_3$) ; ^{1}H-NMR ($CDCl_3$): δ in ppm = 1.73 (s, 3H, CH_3), 1.77-1.86 (m, 1H, H3), 1.97-2.10 (m, 1H, H3), 2.68-2.76 (m, 1H, H4), 3.20-3.26 (m, 1H, H4), 4.01, 4.04 (dd, J^3 = 7.8 Hz, 1H, H2),4.76 (s, 1H, OH), 7.02-7.49 (m, 10H, 2xC_6H_5); ^{13}C-NMR ($CDCl_3$): δ in ppm = 19.3 (C3), 44.2 (CH_3), 52.2 (C4), 74.0 (C2), 75.6 (CPh_2OH), 125.6-146.7 (ArC); MS (CI, *i*-Butane): 254 (MH^+, 100%).

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