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CHIRAL PIPERAZINE AS A NEW CHIRAL CATALYST FOR THE ENANTIOSELECTIVE ADDITION OF DIALKYL ZINCS TO ARYL ALDEHYDES

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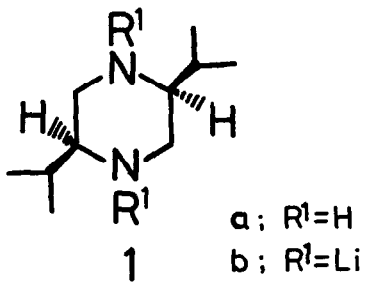
Summary: Optically active sec-alcohols in 90% enantiomeric excess were obtained from the enantioselective addition of dialkyl zincs to aryl aldehydes in the presence of a catalytic amount of dilithium salt of (2S, 5S)-2, 5-diisopropylpiperazine.

Chiral piperazine (cyclic diamine) has rarely been utilized as chiral auxiliary in asymmetric reactions.[1] On the other hand, catalytic asymmetric induction in carbon-carbon bond forming reaction is one of the most important problem in organic synthesis.[2] However, chiral catalyst utilized in enantioselective addition of dialkyl zincs to aldehydes is limited to chiral amino alcohols.[3]

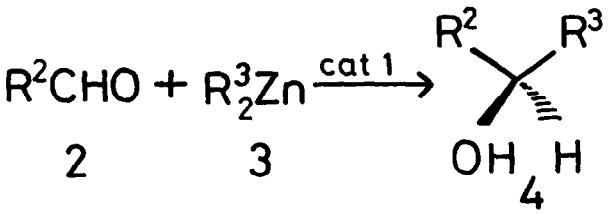
We wish to report that chiral piperazine serves as an effective catalyst for the enantioselective addition of dialkyl zincs to aryl aldehydes.

(2S, 5S)-2, 5-Diisopropylpiperazine (**1a**) [as dihydrochloride, M.p. 265.5-267.0 °C, $[\alpha]_D^{24}$ -24.7° (c 1.0, H_2O)][1] was prepared by the reduction of (2S, 5S)-2, 5-diisopropylpiperazin-3, 6-dione[4] with sodium borohydride - titanium tetrachloride.[5]

Enantioselective addition of diethylzinc to benzaldehyde in the presence of **1a** (6 mol%) afforded (R)-1-phenylpropanol (**4a**) in 81% e.e. It was also found that the presence of dilithium salt of **1a** (**1b**, 6 mol%, prepared in situ from the reaction of **1a** and 2 mol equiv. of n-butyllithium) was more effective to afford (R)-**4a** in 90% e.e. [based on HPLC analysis using chiral column, $[\alpha]_D$ +41.6° (c 5.21, chloroform)]. As shown in Table 1, various aryl aldehydes were alkylated enantioselectively in high e.e.'s with diethyl and dimethyl zincs in the presence of a catalytic amount of **1b**.[6]



1 **a**; R^1=H **b**; R^1=Li



2 **3** **4**

Table 1. Enantioselective Addition of **2** to **3** Catalyzed by **1b**

Entry	R^2	R^3	(R)-4	$[\alpha]_D^{21}$(c, solvent)	Yield(%)	% E.e.
1	C_6H_5	Et	**a**	+41.6° (5.21, $CHCl_3$)	68	92[a] (90)[b]
2	p-MeO-C_6H_4	Et	**b**	+26.6° (5.12, C_6H_6)	65	79[a]
3	p-Cl-C_6H_4	Et	**c**	+23.7° (5.05, C_6H_6)	77	98[a] (90)[b]
4	p-Cl-C_6H_4	Me	**d**	+47.1° (1.64, Et_2O)	23	94[a]

[a]Based on the reported values of $[\alpha]_D$ +45.45° (c 5.15 ,$CHCl_3$) for (R)-**4a**[7]; $[\alpha]_D$ -17.2° (c 5, C_6H_6) for (S)-**4b** in 51% e.e.[8]; $[\alpha]_D$ -10.4° (c 5, C_6H_6) for (S)-**4c** in 43% e.e.[8]; $[\alpha]_D$ +49.9° (c 2, Et_2O) for (R)-**4d**.[9] [b]Based on HPLC analyses using chiral column (Bakerbond DNBPG covalent; 4.6 x 250 mm; 254-nm UV detector); For **4a**, eluent 0.25% 2-propanol in hexane; flow rate 0.44 ml/min; retention time (min), (S)-**4a**, 62.1, (R)-**4a**, 63.7. For **4c**, eluent 0.20% 2-propanol in hexane ; flow rate 0.9 ml/min; retention time (min), (S)-**4c**, 38.5, (R)-**4c**, 39.8.

In a typical procedure, to an ice cooled solution of **1a** (0.0313 g, 0.184 mmol) in toluene (12.3 ml), n-butyllithium (0.368 mmol, 0.245 ml of 1.5 M hexane solution) was added. After 10 min, Et_2Zn (6.2 mmol, 6.2 ml of 1 M hexane solution) was added over a period of 5 min. The mixture was stirred at room temperature for 30 min, and benzaldehyde (0.31 ml, 3.05 mmol) was added at 0 °C. After the reaction mixture was stirred for 20 h at room temperature, 1 M HCl was added to quench the reaction. The mixture was extracted with CH_2Cl_2, and the organic extract was dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The residue was purified by silica gel TLC ($CHCl_3$ as developing solvent).

Thus, chiral piperazine is effective in catalytic asymmetric induction in enantioselective addition of dialkyl zincs to aryl aldehydes.

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