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NEW THIOETHER DERIVATIVES AS CATALYSTS FOR THE ENANTIOSELECTIVE ADDITION OF DIETHYLZINC TO BENZALDEHYDE

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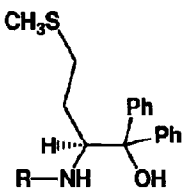
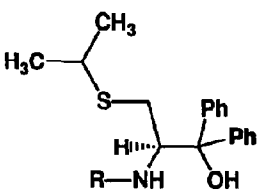
Summary : Different sulfur-containing β-amino alcohols have been synthesized and tested in the catalytic enantioselective addition of diethylzinc to benzaldehyde as chiral auxiliaries. The resulting 1-phenyl-1-propanol was obtained in good chemical yield and high optical purity up to 94 % *ee* under mild reaction conditions.

The enantioselective alkylation of prochiral carbonyl compounds such as aldehydes[1] using e.g. optically active β-amino alcohols[2], piperazines[3], pyridine-based ligands[4] or ferrocenyl amino alcohols[5] as chiral catalysts achieved great interest during the last decade. Only a few papers report the application of sulfur-containing compounds as chiral precursor, namely β-hydroxysulfoxides[6], dialkyl thiophosphoramidates[7] and sulfonamide-titanate complexes[8] in this fundamental carbon-carbon bond-forming reaction.



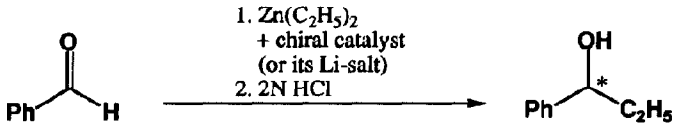
1 (R = H)
2 (R = C_2H_5)
3 (R = *n*-C_3H_7)



4 (R = H)
5 (R = *n*-C_3H_7)

We wish to report herein the synthesis and application of the new L-methionine derivatives **2**, **3** and the L-cysteine-based auxiliary **5** derived from the amino alcohols **1** respectively **4**. (*S*)-2-amino-1,1-diphenyl-4-(methylthio)-1-butanol[9] **1** and (*R*)-2-amino-1,1-diphenyl-3-(isopropyl-

thio)-1-propanol[10] **4** were first acylated with the corresponding acyl chlorides in dichloromethane in the presence of aqueous sodium bicarbonate. The *N*-alkylated products (*S*)-1,1-diphenyl-2-ethylamino-4-(methylthio)-1-butanol **2**[11], (*S*)-1,1-diphenyl-4-(methylthio)-2-propylamino-1-butanol **3**[12] and (*R*)-1,1-diphenyl-3-(isopropylthio)-2-propylamino-1-propanol **5**[13] were obtained after reduction of the corresponding amides with lithium aluminium hydride and short path destillation (Kugelrohr) under vacuum in 60-75 % overall yield.



benzaldehyde chiral 1-phenyl-1-propanol

The reaction of diethylzinc and benzaldehyde was examined in the presence of optically active ligands **1-5** respectively their Li-salts. The influence of the nitrogen substituents (R = H or alkyl) on the enantioselectivity was also investigated.

Table 1: Enantioselective addition of diethylzinc to benzaldehyde in the presence of a catalytic amount of chiral thioethers **1-5** at room temperature.

			1-pheny-1-propanol[a]	
entry	catalyst	concentration [mol %]	optical yield[b] [%]	configuration
1	**1**	10	5	*R*
2	**2**	5	62	*S*
3	**2**	10	76	*S*
4	**3**	5	93	*S*
5	**3**	10	91	*S*
6	**4**	10	45	*R*
7	**5**	5	60	*S*
8	**5**	10	79	*S*

a) Chemical yield 70-90%. b) The optical yield was calculated from the maximum rotation $[\alpha]_D^{20} = -45.45$ (c = 5.15, chloroform) for (*S*)-1-phenyl-1-propanol[14].

In a typical experiment 10 mmol of a 1.1 M solution of diethylzinc in abs. toluene was added to a solution of the respective amount of catalyst **1-5** in dry toluene at –20 °C under argon atmosphere. The mixture was allowed to reach room temperature and treated with 10 mmol benzaldehyde in dry toluene, then the resulting yellow mixture was stirred for 16 h at room temperature. 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 sodiumhydrogen sulfite solution, sodiumhydrogen carbonate solution and water, before drying ($MgSO_4$). The solvent was evaporated under reduced pressure and the residue distilled under vacuum to afford 1-phenyl-1-propanol.The optical yield was determined by optical rotation analysis. The application of the Li-salts of the auxiliaries of **1-5** were carried out according to the literature.[2c]

As can be seen from table 1, the optical purity of the obtained chiral secondary alcohol increases with the bulkiness of the *N*-substituent R (H > C_2H_5 > *n*-C_3H_7) of the catalyst (e.g. entries 2 and 4). When benzaldehyde was reacted with diethylzinc using β-primary amino alcohols **1** and **4** (*R*)-1-phenyl-1-propanol in 5 respectively 45% *op* was obtained (entries 1 and 6). If benzaldehyde was treated with diethylzinc in the presence of β-secondary amino alcolhols **2, 3** and **5** the sence of the asymmetric induction was reversed and the (*S*)-configurated alcohol in up to 93% *op* was produced.

Table 2: Enantioselective addition of diethylzinc to benzaldehyde in the presence of the catalysts Li-**1** to Li-**5** at room temperature.

			1-pheny-1-propanol[a]	
entry	catalyst	concentration [mol %]	optical yield[b] [%]	configuration
9	Li-**1**	10	48	*S*
10	Li-2	5	85	*S*
11	Li-2	10	79	*S*
12	Li-3	5	51	*S*
13	Li-3	10	89	*S*
14	Li-4	10	62	*S*
15	Li-5	5	94	*S*
16	Li-5	10	68	*S*

[a] Chemical yield 70-90%. [b] The optical yield was calculated from the maximum rotation $[\alpha]_D^{20} = -45.45$ (c = 5.15, chloroform) for (*S*)-1-phenyl-1-propanol[14].

The application of lithium alkoxides of **1-5** leads to better enantioselectivities (see table 2). For example, when lithium alkoxide of **5** (5 mol%) is used in the reaction of benzaldehyde with diethylzinc (*S*)-1-phenyl-1-propanol was obtained in 94% *op* (entry 15), whereas the enantioselectivity decreases without preparation of the Li-salt of **5** (60% *op*, entry 7). The higher enantioselectivity of Li-**5** than that of the zinc alkoxide can be attributed to the stronger hard acid character of the lithium cation than zinc. The lithium cation may more easily coordinate with the oxygen atom (hard base) of the approaching aldehyde than zinc does. Thus, this coordination may restrict the number of possible stereochemical courses of the reaction to afford high *op*'s.

It has been shown that the new thioether derivatives **2, 3** and **5** respectively their Li-salts serve as highly efficient homogeneous catalysts in the enantioselective addtion of diethylzinc to benzaldehyde.

Further studies in preparation and application of new auxiliaries from natural sulfur-containing α-amino acids (including cyclic derivatives) are in progress.

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11 (*S*)-1,1-Diphenyl-2-ethylamino-4-(methylthio)-1-butanol **2**: bp.: 200°C/5·10^{-3} mbar (bath temperature); $[\alpha]_D^{20} = -15.4$ (*c*=0.43, MeOH); ^{1}H-NMR ($CDCl_3$): δ in ppm = 0.96 (t, *J*=7.1 Hz, 3H, 3xH2'), 1.46-1.56 (m, 1H, H4), 1.87-1.98 (m, 4H, H4, CH_3S), 2.27-2.61 (m, 4H, 2xH3, 2xH1'), 3.75-3.78 (m, 1H, H2), 7.17-7.66 (m, 10H, Ar-H); ^{13}C-NMR ($CDCl_3$): δ in ppm = 15.21 (C3), 15.60 (C2'), 30.16 (C4), 31.80 (CH_3S), 43.25 (C1'), 63.13 (C2), 78.76 (C1), 125.45-146.95 (Ar-C).

12 (*S*)-1,1-Diphenyl-4-(methylthio)-2-propylamino-1-butanol **3**: bp.: 190-200°C/5·10^{-3} mbar (bath temperature); $[\alpha]_D^{20} = -15.7$ (*c*=0.66, MeOH); ^{1}H-NMR ($CDCl_3$): δ in ppm = 0.76 (t, *J*=5.5 Hz, 3H, 3xH3'), 1.28-1.53 (m, 4H, 2xH4, 2xH2'), 1.87-1.96 (m, 4H, H3, CH_3S), 2.17-2.23 (m, 1H, H3), 2.39-2.55 (m, 3H, 2xH1', N*H*), 3.72-3.76 (m, 1H, H2), 7.17-7.64 (m, 10H, Ar-H); ^{13}C-NMR ($CDCl_3$): δ in ppm = 11.54 (C3'), 15.30 (C3), 23.53 (C2'), 30.25 (C4), 31.80 (CH_3S), 50.85 (C1'), 63.31 (C2), 78.90 (C1), 125.82-146.94 (Ar-C).

13 (*R*)-1,1-Diphenyl-3-(isopropylthio)-2-propylamino-1-propanol **5**: bp.: 170-175°C/ 5·10^{-3} mbar (bath temperature); $[\alpha]_D^{20} = -63.0$ (*c*=0.58, MeOH); ^{1}H-NMR ($CDCl_3$): δ in ppm = 0.76 (t, *J*=7.6 Hz, 3H, 3xH3'), 1.17-1.40 [m, 9H, H3, OH, $(CH_3)_2CH$, $(CH_3)_2CH$], 1.95-2.06 (m, 1H, H3), 2.16 (s, 1H, N*H*), 2.28-2.45 (m, 2H, 2xH2'), 2.73-2.90 (m, 2H, 2xH1'), 3.68-3.74 (m, 1H, H2) (m, 10H, Ar-H); ^{13}C-NMR ($CDCl_3$): δ in ppm = 11.47 (C3'), 23.21 [$(CH_3)_2CH$], 23.34 [$(CH_3)_2CH$], 32.86 (C3), 35.17 (C2'), 51.56 (C1'), 63.83 (C2), 78.05 (C1), 125.48-147.18 (Ar-C).

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