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EFFECTS OF SOLVENTS ON THE ENANTIOFACE-DIFFERENTIATING (ASYMMETRIC) ADDITION OF BUTYLLITHIUM TO BENZALDEHYDE USING (2S, 2'S)-2-HYDROXYMETHYL-1-[(1-METHYLPYRROLIDIN-2-YL)METHYL]-PYRROLIDINE AS A CHIRAL LIGAND

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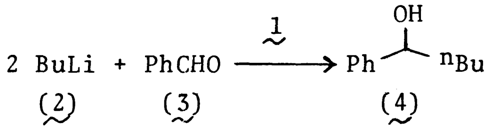
Effects of solvents were examined on the enantioface-differentiating addition of butyllithium to benzaldehyde using (2S, 2'S)-2-hydroxymethyl-1-[(1-methylpyrrolidin-2-yl)methyl]-pyrrolidine as a chiral ligand. Very high optical purity (95%) was attained when the addition was carried out in a 1:1 mixture of dimethoxymethane and dimethyl ether at -123°C.

In our previous paper,[1)] we reported that considerably high optical purity was achieved in the enantioface-differentiating addition reaction of alkyllithium to aldehydes using (2S, 2'S)-2-hydroxymethyl-1-[(1-methylpyrrolidin-2-yl)methyl]-pyrrolidine (**1**) as a chiral ligand.

In this communication, we wish to report the significant effect of solvents on the optical purity of alcohols obtained in the above mentioned reaction. Effects of solvents were examined in the addition of butyllithium (**2**) to benzaldehyde (**3**) using **1** as the chiral ligand. The addition reaction was carried out according to the procedure described in the previous paper,[1)] and the results are summarized in the table.



$$\underset{(2)}{2\ \mathrm{BuLi}} + \underset{(3)}{\mathrm{PhCHO}} \xrightarrow{1} \underset{(4)}{\mathrm{Ph}\overset{\mathrm{OH}}{\mathrm{CH}}{}^{n}\mathrm{Bu}} \qquad (S)\text{-}(-)$$

Of various solvents screened at a temperature of -78°C for comparison, the best result was obtained when the addition reaction was carried out in dimethoxymethane (Exp. 9, 72% O.P.). It is generally observed that the optical purity of the product in the asymmetric syntheses increases with a decrease in temperature (Exp. 1, 2, 9, and 10). Then in order to carry out the reaction at -123°C, we employed mixed solvents of dimethoxymethane with solvents of low melting points (dimethyl ether or pentane, Exp. 11 and 12).

The following experimental procedure is illustrative; immediately after evaporation of a hexane (4.66 ml) solution of butyllithium (6.75 mmol) in vacuo at 0°C, dry dimethoxymethane (10 ml) and **1** (0.803 g, 4.05 mmol) in 2.5 ml of dimethoxymethane were added successively at -78°C under an argon atmosphere. The reaction mixture was stirred for 30 minutes, and 13 ml of dry dimethyl ether was introduced into it. Then the reaction mixture was cooled to -123°C (liq N_2-diethyl ether bath), and a dimethoxymethane (0.5 ml) solution of benzaldehyde (0.106 g, 1 mmol) was added.

Table Effects of Solvents on the Optical Purity of 4

Exp.	Solvent	Temp (°C)	Yield (%)[a]	Optical Purity (%)[b]
1	Me_2O	-78	80	53
2	Me_2O	-123	80	82
3	Et_2O	-78	70	48
4	i-Pr_2O	-78	73	4
5	Pr_2O	-78	83	31
6	DME[c]	-78	94	53
7	Hexane	-78	49	20
8	THF	-78	80	48
9	$CH_2(OMe)_2$	-78	67	72
10	$CH_2(OMe)_2$	-100	77	87
11	$CH_2(OMe)_2$-pentane (1:1)	-123	57	77
12	$CH_2(OMe)_2$-Me_2O (1:1)	-123	77	95

a) Isolated yield. b) The alcohol obtained has S configuration. See ref. 2). c) 1,2-Dimethoxyethane.

The stirring was continued for 1 hr and the reaction was quenched with water (5 ml). After evaporation of dimethyl ether, the reaction mixture was acidified with 6N hydrochloric acid and extracted with diethyl ether. The organic layer was dried over anhydrous sodium sulfate. After removal of the solvent, the residue was chromatographed on silica gel TLC. The isolated product was further purified by short path vacuum distillation, and 1-phenyl-1-pentanol (4, 0.127 g, 77% S.Y., 95% O.P., $[\alpha]_D^{22}$ -29.8° (c=3, benzene)) was obtained as a colorless oil.

It was also found that even in the case of the reaction of butyllithium with aliphatic aldehyde (isobutyraldehyde), the corresponding alcohol, 2-methyl-3-heptanol, was obtained in much higher optical purity (80%) in comparison with the previously reported result.[1]

It is noted that very high optical purity was achieved in the enantioface-differentiating addition of butyllithium to benzaldehyde by using the 1:1 mixture of dimethoxymethane and dimethyl ether as the solvent.

Further investigation is now in progress.

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