The Enantioface-differentiating Methylation of the *N*-Benzylidene-DL-phenylalanine Methyl Ester in the Presence of Chiral Lithium Amides

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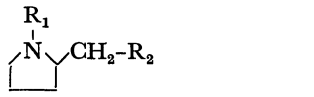
Synopsis. The asymmetric methylation of the *N*-benzylidene-DL-phenylalanine methyl ester was carried out in the presence of lithium salts of secondary amines derived from (*S*)-proline. The lithium amides of poly(imino-1-isobutylethylene) and its corresponding low-molecular-weight model compound, derived from (*S*)-leucine, were similarly used in order to examine the polymer effects with regard to the stereoselectivity.

Several workers[1-3] have recently used Schiff-base derivatives of α-amino acids in order to prepare the higher amino acids by alkylation routes. Yamada *et al.*[2] have furthermore carried out the diastereoface-differentiating alkylation of Schiff bases derived from chiral ketones and achiral α-amino acid esters in the presence of lithium diisopropylamide, thus obtaining optically active α-amino acids. Duhamel *et al.*[4] have also reported that optically active α-amino acid esters were obtained from the corresponding Schiff bases lithiated with chiral lithium amides, followed by protonation with tartaric acid derivatives.

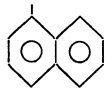
This paper will describe the enantioface-differentiating methylation of Schiff bases lithiated by the use of chiral lithium salts of secondary amines derived from (*S*)-proline and (*S*)-leucine. The Schiff base (*N*-benzylidene-DL-phenylalanine methyl ester) (**A**) was prepared according to the method of Stork.[1]

The chiral lithium amides used in this experiment are as follows:

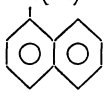


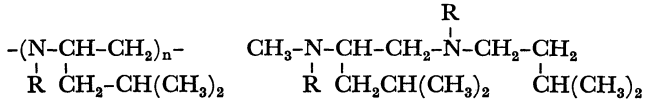
1a R_1=H, R_2=H
1b R_1=Li, R_2=H
2a R_1=H, R_2=N
2c R_1=Li, R_2=N

3a R_1=CH_3, R_2=NHPh
3b R_1=CH_3, R_2=N(Li)Ph
4a R_1=CH_3, R_2=NH



4b R_1=CH_3, R_2=N(Li)

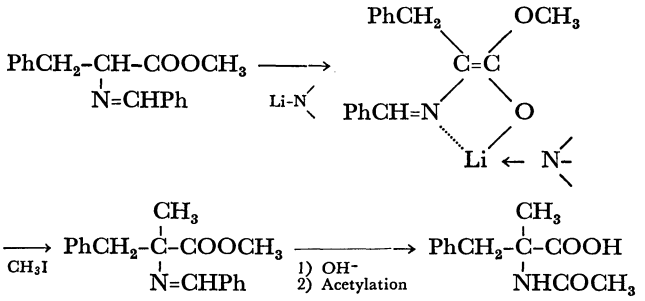




5a R=H **5b** R=Li

6a R=H **6b** R=Li

The methylation of **A** with methyl iodide in the presence of chiral lithium amides at 0 and −78 °C, followed by hydrolysis and successive acetylation, yielded *N*-acetyl-α-methyl-phenylalanine,[2c] whose optical yields (%) and configurations are shown in Table 1.



The product for **3b** showed the highest optical yield (31%) at −78 °C. All the amides except **2c** gave the product of the *S*-configuration. In order to examine the polymer effects with respect to the stereoselectivity, polymeric amide (**5b**) and its corresponding low-molecular-weight model compound (**6b**) were similarly used. At −78 °C, the optical yield of the product for **5b** was, albeit low, about six times as high as that for **6b**.

TABLE 1. THE OPTICAL YIELDS AND CONFIGURATIONS OF *N*-ACETYL-α-METHYLPHENYLALANINE OBTAINED WITH CHIRAL AMIDES

Chiral agents	0 °C	−78 °C
1b	1.0(*S*)	1.8(*S*)
2c	1.0(*R*)	2.1(*R*)
3b	6.2(*S*)	31.0(*S*)
4b	1.3(*S*)	1.9(*S*)
5b	6.0(*S*)	13.5(*S*)
6b	1.5(*S*)	2.2(*S*)

Experimental

The Preparation of Chiral Secondary Amines. (*S*)-2-Methylpyrrolidine (**1a**) was prepared by the method of Kostyanovsky.[5] (*S*)-1-(2-Pyrrolidinylmethyl)pyrrolidine (**2a**) (bp 75—80 °C at 4 mmHg,† $[\alpha]_D^{15}$ +9.6° in C_2H_5OH) was obtained by the reduction (sodium in liquid ammonia) of (*S*)-1-[1-tosyl(2-pyrrolidinyl)methyl]pyrrolidine, which had itself been derived from 1-tosyl(2-pyrrolidinyl)methyl iodide (**2b**) and pyrrolidine; **2b** was made by the reaction of (*N,O*-ditosyl) pyrrolidinylmethanol[5] with sodium iodide. (*S*)-1-Methyl-2-(anilinomethyl)pyrrolidine[6] (**3a**) (bp 123—124 °C at 4 mmHg, $[\alpha]_D^{15}$ −59.3° in C_2H_5OH) was obtained by the reduction (lithium aluminium hydride) of *N*(*N*-benzyloxycarbonylprolyl)aniline, which had itself been prepared from *N*-benzyloxycarbonylproline and aniline by the use of 1-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline; (*S*)-1-methyl-2-(1-naphthylaminomethyl)pyrrolidine (**4a**) (bp 180—190 °C at 4 mmHg, $[\alpha]_D^{20}$ −5.6° in $CHCl_3$) was obtained

† 1 mmHg≈133.322 Pa.

using *N*-benzyloxycarbonylproline and 1-naphthylamine as starting materials in a manner similar to that described in **3a**. Poly(imino-1-isobutylethylene) (**5a**) and N^1-isopentyl-N^2-methyl-4-methyl-1,2-pentanediamine (**6a**) were derived from (*S*)-leucine according to the procedure reported earlier.[7,8]

The Asymmetric Methylation of ***A*** *with Chiral Lithium Amides.* The methylation with **3b** will be given as an example. To a solution of **3a** (2 mmol) in dry THF (5 ml), we added butyllithium (2 mmol) in hexane at −78 °C under argon. A solution of **A** (2 mmol) in dry THF (1 ml) was then added to the reaction mixture. The color of the solution gradually changed from red-orange to yellow, showing the formation of a lithium ester enolate.[2,3] After 15 min, methyl iodide (2 mmol) was added to the solution at −78 °C, and the mixture was stirred for 1 h. After the subsequent removal of the solvent, ether and water were added to the residue. The organic layer separated out was washed with water, dried, and evaporated to dryness. The methylated Schiff base thus obtained was subjected to hydrolysis without purification. The hydrolysis was carried out in 15 ml of 1 mol dm^{-3} sodium hydroxide solution under reflux for 2 h. The reaction mixture was washed thoroughly with ether and neutralized with 6 mol dm^{-3} hydrochloric acid. On cooling, α-methylphenylalanine precipitated as a white powder; it was then filtered off. Yield, 50%. In order to determine the optical yield and configuration, the amino acid was acetylated with acetic anhydride in pyridine. The rotation of the acetamide was $[\alpha]_D^{15}$ −25° (*c* 2, CH_3OH) (Lit,[2c] optically pure (*R*)-*N*-acetyl-α-methylphenylalanine, $[\alpha]_D^{19}$ +80.3° in CH_3OH). The other lithium amides were similarly used for the methylation of **A**. The amount of polymeric agent (**5b**) was calculated on the basis of that of the monomer used in the polymerization (*e.g.*, 10 mg of **5a** corresponds to 10 mg of (*S*)-2-isobutylaziridine).

The methylation of the *N*-benzylideneglycine ethyl ester (**B**) was also attempted with the chiral amides used for the methylation of **A**. However, all the reagents except (**2c**) yielded a mixture which consisted of mono- and dimethylated **B** and unreacted **B**. The monomethylated **B** obtained with **2c** was hydrolyzed in 1 mol dm^{-3} hydrochloric acid to give (*S*)-alanine in a 13% (10%) optical yield at −78 °C (0 °C).

In this experiment, a JASCO DIP-4 automatic polarimeter was used for the measurement of the optical rotation.

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