

Memory of Chirality: Direct Asymmetric α -Alkylation of Phenylalanine Derivatives

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The (*S*)-phenylalanine derivative **1** was treated with lithium 2,2,6,6-tetramethylpiperidide and then with methyl iodide at $-78\text{ }^{\circ}\text{C}$ to afford **3** in 82% ee without addition of any external chiral source. The asymmetric methylation reaction proceeded with retention of configuration.

Keywords: Asymmetric synthesis/ Amino acid/ Alkylation

Asymmetric synthesis of α -substituted α -amino acids has attracted considerable attention because of the biological and chemical importance of these compounds.¹ One of the most efficient methods for their synthesis has been *via* enolate chemistry utilizing chiral auxiliaries. However, it would be even more efficient if direct α -alkylation of the enolates generated from optically active α -amino acids could proceed enantioselectively without using any external chiral source. This has not been possible due to the loss of chirality at the α -carbon of α -amino acids in the corresponding enolates due to their achiral nature. However, enolates generated from optically active α -amino acids are not always achiral, according to the concept of *memory of chirality*, which we recently proposed.² In searching for conditions under which enolates are chiral, we discovered that optically active *N*-methyl-*N*-Boc-phenylalanine derivatives can undergo direct asymmetric α -alkylation with ee's as high as 82% without the addition of any external chiral source.

Treatment of **1** (>96% ee) with a variety of bases in THF

followed by methyl iodide afforded **3**, whose ee was determined as its *N*-benzoyl derivative **4** (Table I). Among the bases screened, lithium 2,2,6,6-tetramethylpiperidide (LTMP) proved to be the most effective for the asymmetric induction (entries 1-4). Asymmetric methylation proceeded with retention of configuration when LTMP or lithium diisopropylamide (LDA) was employed, while inversion of configuration was observed with potassium hexamethyldisilazide (KHMDs). The absolute configuration of **3** was determined by chemical correlation with **5**. The degree of asymmetric induction depended on the amount of LTMP employed (entries 5-9). The best results (82% ee, 40% yield) were obtained when 1.0 eq of LTMP was employed. Increasing the amount of base decreased the efficiency of the asymmetric induction without affecting the yield of **3**. Deuteration of the enolate generated from **1** and 1.1 eq of LTMP was carried out by treatment with D_2O . Recovered **1** (76% yield) contained 51% deuterium and had 76% ee with *S* configuration. If all of the enolate was trapped with

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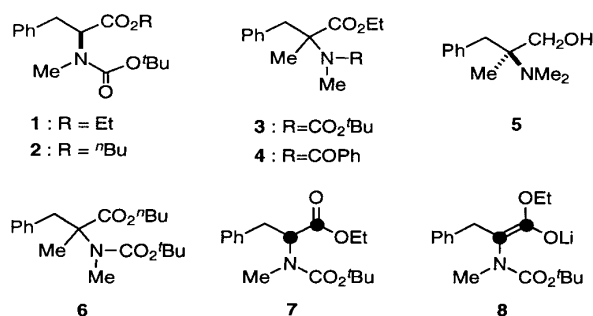
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deuterium, deuteration would proceed with retention of configuration in 55% ee. Enolate formation was estimated to be complete in entries 7-9 since the ee of recovered **1** was ~50%, whereas enolate formation in entries 5 and 6 was found to be incomplete. When the extent of enolate formation was low, a considerable amount of starting material was recovered (entry 5). When it was high, on the other hand, formation of side products increased. As a result, α -methylation of **1** proceeded with ~40% yield, irrespective of the extent of enolate formation.



Mechanistic aspects of the present asymmetric induction were investigated. Shown in Chart I are plausible intermediates: (A) mixed aggregates of the *achiral* enolate with the undepronated optically active starting material, (B) a configurationally stable carbanion stabilized by the adjacent *N*-Boc group, (C) an enolate with chiral nitrogen strongly coordinated with lithium, (D) an enolate with a C-N chiral axis in which the steric bulk of the OLi group is increased by coordination with the amine originating from LTMP, and (E) an enolate with a chiral plane. To estimate the feasibility of A, cross-over experiments between **1** and the butyl ester **2** were done. A 1 : 1 mixture of **1** (96% ee) and racemic **2** was treated with LTMP (1.0 eq to the total amount of **1** and **2**) at -

Table 1. Asymmetric α -Methylation of **1**.^a

entry	base (eq)	yield of 3	ee of 4 ^b	recovered 3	
				yield	% ee ^c
1	LTMP (1.1)	38	79 (<i>S</i>)	23	87
2	LDA (1.2)	57	22 (<i>S</i>)	25	<i>d</i>
3	LHMDS (1.2)	0	-	<i>d</i>	<i>d</i>
4	KHMDS (1.2)	79	20 (<i>R</i>)	0	-
5	LTMP (1.0)	40	82 (<i>S</i>)	36	92
6	LTMP (1.5)	42	77 (<i>S</i>)	17	73
7	LTMP (2.0)	42	73 (<i>S</i>)	13	48
8	LTMP (4.0)	36	66 (<i>S</i>)	13	54
9	LTMP (6.0)	37	55 (<i>S</i>)	22	48

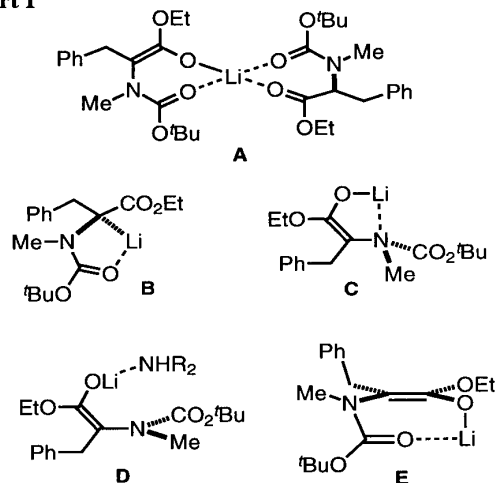
^a**1** (98% ee) was treated with the base in THF at -78 °C for 15 min followed by methyl iodide at -78 °C for 4 h.

^bDetermined by HPLC analysis using Daicel CHIRALPAK AS (3% EtOH/hexane). The letter in the parentheses indicates the absolute configuration. ^cThe absolute configuration was *S* in each entry. Ee was determined by HPLC analysis using Daicel CHIRALPAK AS (3% EtOH/hexane). ^dNot determined.

78 °C followed by addition of methyl iodide at the same temperature to afford optically active **3** (74% ee, 26% yield) and racemic **6** (30% yield). The same treatment of a 1 : 1

mixture of racemic **1** and optically active **2** (96% ee) afforded racemic **3** (17% yield) and optically active **6** (71% ee, 24% yield). These observations clearly indicate that A does *not* make a significant contribution to the asymmetric induction.

Chart I



The anionic species generated from **1** and LTMP can be expected to contain some chiral information. To examine the structure of the anionic species, the ¹³C-NMR spectrum was studied on the anionic species generated from [1,2-¹³C₂]-phenylalanine derivative **7** (racemic) with ⁷Li-LTMP (1.7 eq) in d₈-THF at -78 °C. Although the spectrum measured at this temperature gave complicated and uninterpretable signals, raising the temperature of the solution to 20 °C induced a complete change in the spectrum, in which two doublets now appeared at δ 159.9 ($J = 115$ Hz) and 86.4 ($J = 115$ Hz). These signals could be assigned to a normal enolate structure **8**. Re-cooling the enolate solution to -78 °C did not lead to significant changes in the spectrum, the major signals of **8** remaining unchanged. Next, we investigated the effects of the observed structural changes caused by temperature variation on the asymmetric α -methylation of **1**. Racemic **3** was obtained in 26% yield when **1** (96% ee) was treated with LTMP (1.0 eq) at -78 °C for 15 min, then at 20 °C for 45 min followed by methyl iodide at -78 °C. Thus, it can be concluded that the initially formed anionic species at -78 °C could memorize the original chiral information, while the *achiral* enolate **8**, formed after raising the temperature, neither possessed chiral information nor could recall it even when re-cooled to -78 °C. Studies directed toward structure determination of the intermediary anionic species generated from **1** and LTMP at -78 °C are currently under way.

References and Notes

1. a) For examples, see: a) Seebach, D.; Boes, M.; Naef, R.; Schweizer, W. B. *J. Am. Chem. Soc.* **1983**, *105*, 5390. b) Schöllkopf U. *Tetrahedron* **1983**, *39*, 2085.
2. Kawabata, T.; Yahiro, K.; Fujii, K. *J. Am. Chem. Soc.* **1991**, *113*, 9694.