Direct Asymmetric α-Alkylation of Phenylalanine Derivatives Using No External Chiral Sources

Takeo Kawabata, Thomas Wirth, Kiyoshi Yahiro, Hideo Suzuki, and Kaoru Fuji*

Institute for Chemical Research
Kyoto University, Uji, Kyoto 611, Japan

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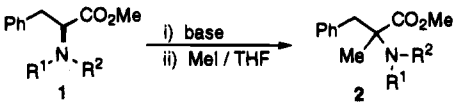
Asymmetric synthesis of α-substituted α-amino acids has attracted considerable attention because of the biological and chemical importance of these compounds.[1] One of the most efficient methods for their synthesis has been *via* enolate chemistry utilizing chiral auxiliaries.[1,2] However, it would 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. In this communication, we describe a solution to this problem. Enolates generated from optically active α-amino acids are not always achiral, according to the concept of *memory of chirality*, which we recently proposed.[3] 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 88% without the addition of any external chiral source.[4-6]

To explore the asymmetric α-alkylation reaction, several (*S*)-phenylalanine methyl esters **1** carrying functionalities on nitrogen were prepared, since we expected that these functionalities would play a crucial role in the asymmetric induction. The results of α-methylation of optically active **1** are summarized in Table 1.

Compounds **1d-f** bearing an alkoxycarbonyl group on the nitrogen were methylated with significant asymmetric induction. After obtaining the results in Table 1, we chose *N*-Boc-phenylalanine ethyl ester **3**[7] for further optimization of the asymmetric alkylation. The preparation of **3** (>96% ee) was accomplished through esterification of L-phenylalanine ($SOCl_2$−EtOH) and *tert*-butoxycarbonylation ($(Boc)_2O$, EtN^iPr_2), followed by *N*-methylation (Ag_2O−MeI). Treatment of **3** with a variety of bases in THF followed by methyl iodide afforded **5**, whose ee was determined as its *N*-benzoyl derivative **6** (Table 2). 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 **5** was determined by chemical correlation with **7**.[8] 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 equiv of LTMP was employed. Increasing the amount of base decreased the efficiency of the asymmetric induction without affecting the yield of **5**. Deuteriation of the enolate generated from **3** and 1.1 equiv of LTMP was carried out by treatment with D_2O. Recovered **3** (76% yield) contained 51% deuterium and had 76% ee with the *S* configuration. If all of the enolate was trapped with deuterium,[9] deuteration would proceed with retention of configuration in 55% ee. Enolate formation was estimated to be complete[10] in entries 7−9 since

Table 1. α-Methylation of **1**[a]



compd	R^1	R^2	base	product	yield, %	% ee[b]
1a	Me	CH_2Ph	LDA	**2a**	45	~0[c]
1b	Me	CHO	LHMDS[d]	**2b**	66	~0
1c	Me	COPh	LDA	**2c**	50	12
1d	Me	CO_2CH_2Ph	LHMDS[e]	**2d**	40[f]	26
1e	Me	CO_2Ad[g]	LHMDS	**2e**	38	35
1f	Me	$CO_2{}^tBu$	LHMDS	**2f**	30[f]	36
1g	H	$CO_2{}^tBu$	LDA[h]	**2g**	57	~0

[a] Substrate **1** of >84% ee was treated with the base (1.1−1.8 equiv) at −78 °C for 30−60 min followed by methyl iodide at −78 °C to room temperature. Reactions were run in THF unless otherwise indicated. [b] Ee was determined by HPLC analysis using Daicel CHIRALCEL OD (5% ^{i}PrOH−hexane) after conversion to **2c** unless otherwise indicated. [c] Determined on **2a** using Daicel CHIRALCEL OJ (1% ^{i}PrOH−hexane). [d] Lithium hexamethyldisilazide. [e] Run in THF−DMF (10:1). [f] Overall yield of **2c**. [g] 1-Adamantyl ester. [h] The amount of base used was 2.4 equiv.

Table 2. Asymmetric α-Methylation of **3**[a]

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

[a] **3** (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. [b] Determined by HPLC analysis using Daicel CHIRALPAK AS (3% EtOH−hexane). The letter in the parentheses indicates the absolute configuration. [c] The absolute configuration was *S* in each entry. Ee was determined by HPLC analysis using Daicel CHIRALPAK AS (3% EtOH−hexane). [d] Not determined. [e] This result was in sharp contrast to that from **1** (Table 1, **1f**). Reproducibility of the results was confirmed by repeated experiments.

(1) For example, 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) Recently, a new type of chiral auxiliary for α-amino acid synthesis was developed based on asymmetric transformation of oxazaborolidinones; see: Vedejs, E.; Fields, S. C.; Schrimpf, M. R. *J. Am. Chem. Soc.* **1993**, *115*, 11612.

(3) Kawabata, T.; Yahiro, K.; Fuji, K. *J. Am. Chem. Soc.* **1991**, *113*, 9694.

(4) Braña has reported that α-methylation of an L-tryptophan derivative furnished optically active product.[4a] The reported optical rotation of the product, $[\alpha]^{30}_D$ −3.8° ($CHCl_3$), corresponds to *ca.* 60% ee based on the reported rotation of the almost optically pure compound (>95% ee).[4b] However, re-examination of this unusual reaction by us and by Schöllkopf *et al.*[4b] gave totally racemized product; see: (a) Braña, M. F.; Garrido, M.; López, M. L.; Sanz, A. M. *J. Heterocycl. Chem.* **1980**, *17*, 829. (b) Schöllkopf, U.; Lonsky, R.; Lehr, P. *Liebigs Ann. Chem.* **1985**, 413.

(5) It is reported that α-alkylation of an aspartic acid derivative proceeded without complete racemization; see: Seebach, D.; Wasmuth, D. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 971.

(6) Intramolecular cyclization of methyl (4*R*)-3-(2-diazo-3-oxobutanoyl)-thiazolidine-4-carboxylate has been reported to proceed with retention of configuration *via* a planar ester enolate possessing axial chirality; see: Beagley, B.; Betts, M. J.; Pritchard, R. G.; Schofield, A.; Stoodley, R. J.; Vohra, S. *J. Chem. Soc., Chem. Commun* **1991**, 924; *J. Chem. Soc., Perkin Trans. 1* **1993**, 1761.

(7) The ethyl ester derivative **3** rather than the methyl ester **1** was selected as substrate because the former often affords better yields in α-methylation reactions than the latter, especially when LTMP is employed as a base.

(8) Corey, E. J.; McCaully, R J.; Sachdev. H. S. *J. Am. Chem. Soc.* **1970**, *92*, 2476.

(9) A ^{13}C-NMR study using the $^{13}C_2$,^{15}N−labeled derivative of **3** also indicated that only 50−60% of the starting material was converted to the anionic species when 1.1 equiv of LTMP was employed at −78 °C.

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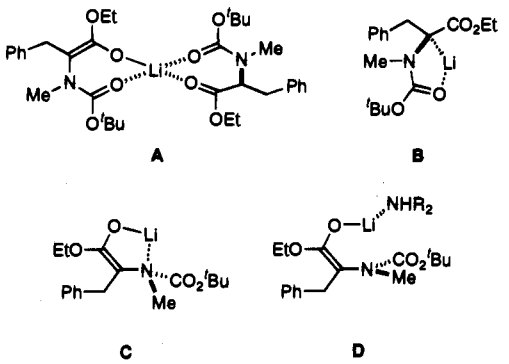
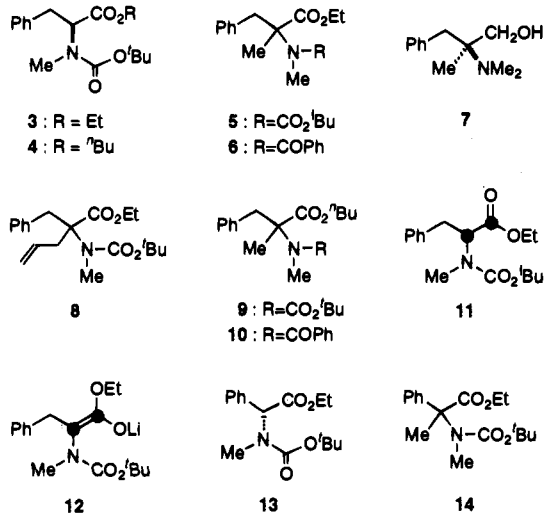
Chart 1



the ee of recovered **3** 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 **3** proceeded with ~40% yield irrespective of the extent of enolate formation.

Asymmetric α-allylation of **3** afforded **8** of 88% ee (15% yield, 62% recovery of **3**) when **3** was treated with LTMP (1.0 equiv) and then with allyl bromide at −78 °C.



Mechanistic aspects of the present asymmetric induction were investigated. Shown in Chart 1 are plausible intermediates: (**A**) mixed aggregates of the *achiral* enolate with the undeprotonated optically active starting material, (**B**) a configurationally stable carbanion stabilized by the adjacent *N*-Boc group,[11] (**C**) an enolate with chiral nitrogen strongly coordinated with lithium, and (**D**) an enolate with C−N chiral axis in which the steric bulk of the OLi group is increased by coordination with the amine originating from LTMP. To estimate the feasibility of **A**, crossover experiments between **3** and the butyl ester **4**[12] were done. A 1:1 mixture of **3** (96% ee) and racemic **4** was treated with LTMP (1.0 equiv to the total amount of **3** and **4**) at −78 °C followed by addition of methyl iodide at the same temperature to afford optically active **5** (74% ee, 26% yield) and racemic **9** (30% yield). The same treatment of a 1:1 mixture of racemic **3** and optically active **4** (96% ee) afforded racemic **5** (17% yield) and optically active **9** (71% ee, 24% yield). The optical purity of **5** and **9** was determined by HPLC analysis of the *N*-benzoyl derivatives, **6** and **10**, respectively. These observations clearly indicate that **A** does *not* make a significant contribution to the asymmetric induction.[13]

The anionic species generated from **3** and LTMP can be expected to contain some chiral information. To examine the structure of the anionic species, we carried out a ^{13}C-NMR study of [1,2-$^{13}C_2$]phenylalanine derivative **11** (racemic) prepared from [1,2-$^{13}C_2$]glycine according to the reported procedure.[14] Racemic **11** was treated with [^{7}Li]LTMP (1.7 equiv) in d_8-THF at −78 °C, and the mixture was immediately transferred to an NMR tube at that temperature. Although the spectrum measured at −78 °C 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 **12**.[15] Recooling the enolate solution to −78 °C did not lead to significant changes in the spectrum, the major signals of **12** remaining unchanged. Next, we investigated the effects of the observed structural changes caused by temperature variation on the asymmetric α-methylation of **3**. Racemic **5** was obtained in 26% yield when **3** (96% ee) was treated with LTMP (1.0 equiv) at −78 °C for 15 min and then at 20 °C for 45 min followed by methyl iodide at −78 °C.[16] Thus, we concluded that the initially formed anionic species at −78 °C could memorize the original chiral information, while the achiral enolate **12**, formed after the temperature was raised, neither possessed chiral information nor could recall it even when recooled to −78 °C. We propose **B** as the initial anionic species, although involvement of aggregates of **C** or **D** cannot be excluded at the present stage. Results from the α-methylation of **13** also support **B**. (*R*)-Phenylglycine derivative **13** (52% ee) gave **14** as a racemate (57% yield) under the standard conditions. The anionic species generated from **13** is expected to possess a normal enolate structure rather than a carbon−lithium bond due to the presence of a phenyl group directly attached to the asymmetric α-carbon.[17]

In conclusion, we have developed a conceptually novel method for asymmetric α-alkylation of α-amino acid derivatives in which no external chiral sources are employed. Studies directed toward structure determination of the intermediary anionic species generated from **3** and LTMP at −78 °C are currently under way using ^{13}C-, ^{15}N-, and ^{6}Li-NMR measurements.

Supplementary Material Available: Spectral data for **1f**, **2f**, **3**−**6**, **8**-**10**, and **14** and synthetic procedures for **3**−**6** (5 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering informatin.

(10) This conclusion is consistent with the results from a ^{13}C-NMR study which showed that more than 90% of the starting material **11** was converted to the anionic species on treatment with 1.7 equiv of LTMP at −78 °C.

(11) Configurationally stable carbanions stabilized by the adjacent *N*-Boc group have been reported.[11a,b] Also, asymmetric synthesis *via* dipole-stabilized carbanion intermediates has been developed:[11c-e] (a) Kerrick, S. T.; Beak, P. *J. Am. Chem. Soc.* **1991**, *113*, 9708. (b) Chong, J. M.; Park, S. B. *J. Org. Chem.* **1992**, *57*, 2220. (c) Meyers, A. I.; Fuentes, L. M. *J. Am. Chem. Soc.* **1983**, *105*, 117. (d) Hoppe, D.; Krämer, T. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 160. (e) Pearson, W. H.; Lindbeck, A. C. *J. Am. Chem. Soc.* **1991**, *113*, 8546.

(12) The reactivity of 4 in asymmetric α-methylation was similar to that of **3**. Thus, treatment of 4 (96% ee) with LTMP (1.0 equiv) followed by methyl iodide at −78 °C afforded (*S*)-**9** of 66% ee.

(13) The possibility of accidental enantiomeric enrichment of **5** and/or **6** during the purification step was excluded; the ee of **6** was constant in entry 7 of Table 2 whether the purification step was included or not: Diter, P.; Taudien, S.; Samuel, O.; Kagan, H. B. *J. Org. Chem.* **1994**, *59*, 370.

(14) De Nicola, A.; Einhorn, J.; Luche, J.-L. *Tetrahedron Lett.* **1992**, *33*, 6461.

(15) For recent studies of ^{13}C-NMR spectra of lithium enolates, see: Kim, Y.-J.; Bernstein, M. P.; Galiano Roth, A. S.; Romesberg, F. E.; Williard, P. G.; Fuller, D. J.; Harrison, A. T.; Collum, D. B. *J. Org. Chem.* **1991**, *56*, 4435.

(16) Production of the racemate is not due to the prolonged deprotonation time since treatment of **3** with LTMP (1.0 equiv) at −78 °C for 60 min followed by methyl iodide afforded **5** of 81% ee.

(17) The configurational stability of a carbanion at the benzylic position is known to be relatively low,[17a-c] although an exception has been reported:[17d] (a) Cram, D. J.; Kingsbury, C. A.; Rickborn, B. *J. Am. Chem. Soc.* **1961**, *83*, 3688. (b) Meyers, A. I.; Guiles, J.; Warmus, J. S.; Gonzalez, M. A. *Tetrahedron Lett.* **1991**, *32*, 5505. (c) Beak, P.; Du, H. *J. Am. .Chem. Soc.* **1993**, *115*, 2516. (d) Hoppe, D.; Carstens, A.; Krämer, T. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1424.