Fourth International Electronic Conference on Synthetic Organic Chemistry (ECSOC-4), www.mdpi.org/ecsoc-4.htm, September 1-30, 2000

[A0091]

Memory of Chirality in Alkylation of a-Amino Acid Derivatives

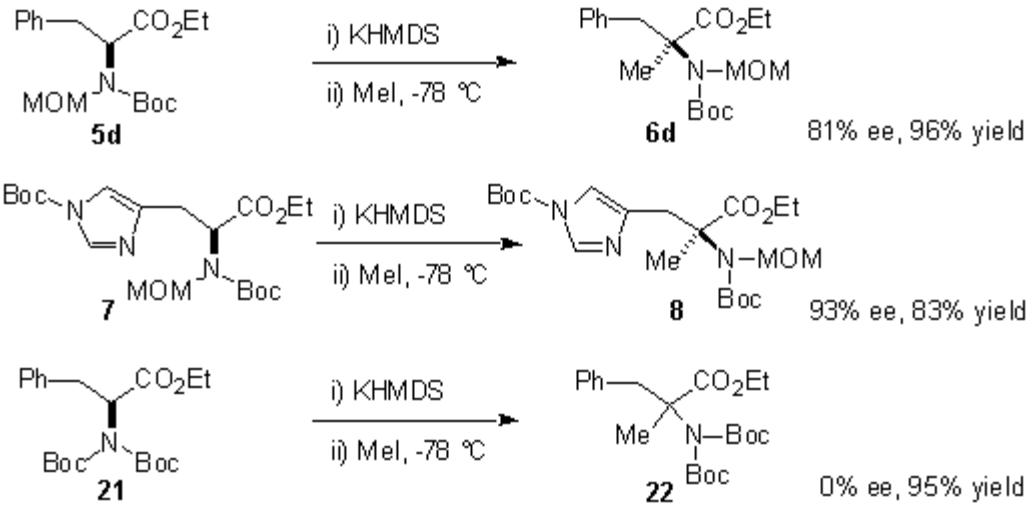
Takeo Kawabata,* Hideo Suzuki, Yoshikazu Nagae, Thomas Wirth, Kiyoshi Yahiro, and Kaoru Fuji

Institute for Chemical Research, Kyoto University, Uji, Kyoto 611-0011, Japan
E-mail: kawabata@scl.kyoto-u.ac.jp

Received: 15 August 2000 / Uploaded: 20 August

ABSTRACT

Treatment of *N*-MOM-*N*-Boc-α−amino acid derivatives **5d** and **7** with potassium hexamethyldisilazide (KHMDS) (1.1 mol eq) followed by methyl iodide at -78 °C gave α−methylated products **6d** and **8** in 81% and 93% ee, respectively. The corresponding *N,N*-di-Boc derivative **21** gave racemic product **22**. A novel mechanism for the asymmetric induction is proposed.
Boc = CO_2tBu, MOM = CH_2OMe

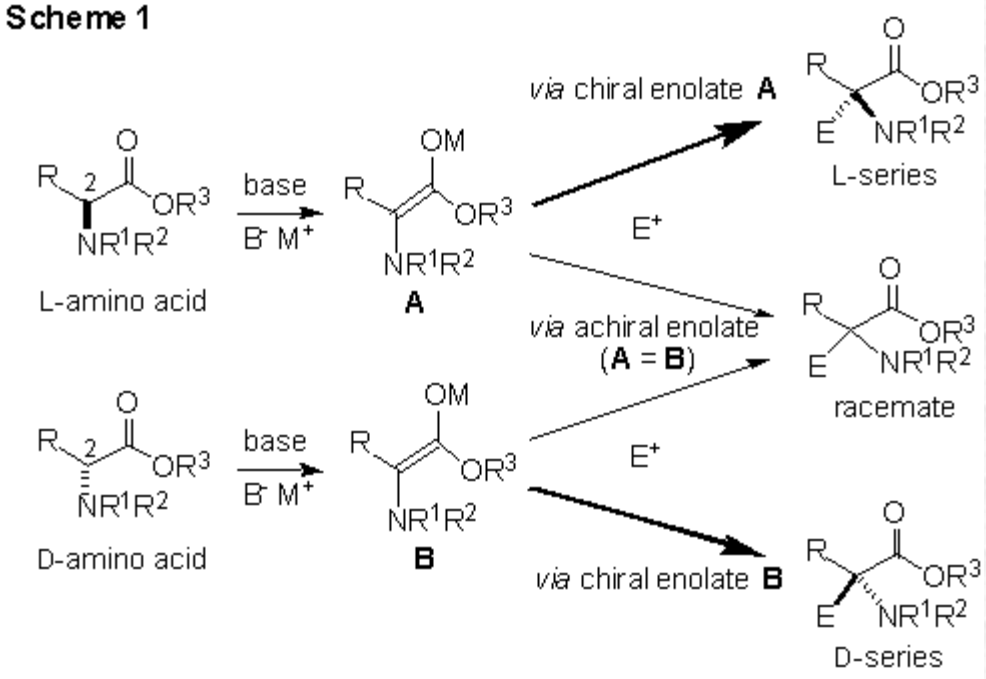


1. Introduction: Memory of Chirality

Nonproteinogenic a,a-disubstituted-a-amino acids have attracted considerable attention because of their utility as conformational modifiers of biologically active peptides and as enzyme inhibitors. Typical methods for asymmetric synthesis of them involve chiral auxiliary-based enolate chemistry (ref. 1). However, the most straightforward strategy for the synthesis would involve direct asymmetric a-alkylation of parent a-amino acids in the absence of additional chiral sources such as chiral auxiliaries, chiral ligands, or even chiral catalysts. Since both L- and D-a-amino acids are readily commercially available, the synthetic route shown in Scheme 1 seems most attractive for the purpose. However, this process usually gives racemic a-alkylated products from either L- or D-a-amino acid because the enolate formation eliminates the chiral information of C(2) and an *achiral enolate* common to both L- and D-series is formed (**A** = **B**). If enolate intermediates enable to *memorize* the chiral information at C(2) of the starting materials, L- and D-a-amino

acids would give optically active L- and D- (or D- and L-) a,a-disubsituted a-amino acids *via* intrinsically chiral enolate intermediates **A** and **B**, respectively. In this paper, we describe asymmetric a-alkylation of a-amino acid derivatives *via* the synthetic route shown in Scheme 1.

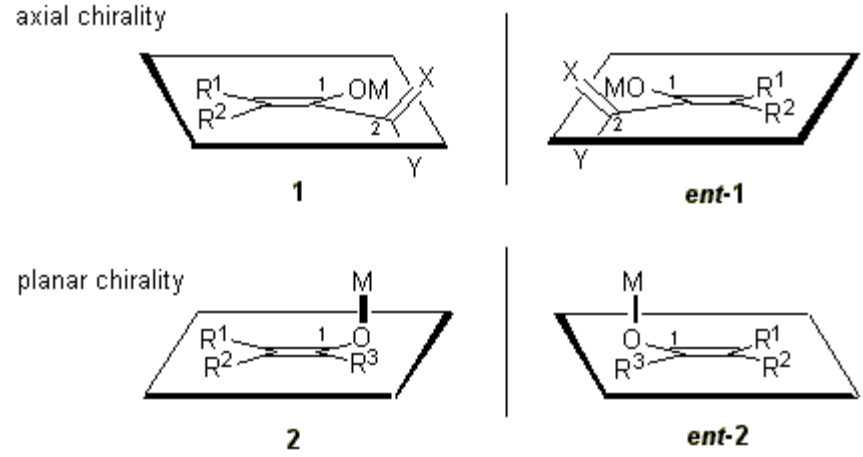
Scheme 1



2. Dynamic Chirality of Enolate Structure

The structure of enolates was long believed to be achiral because all four substituents are on the same plane as the enolate double bond. However, we had proposed intrinsic chirality of enolate structures as shown in Figure 1 (ref. 2 and 3). Enolate **1** has axial chirality along the C(1)-C(2) axis and **2** has planar chirality comprising of the enolate plane and a metal cation. Racemization of these chiral enolates readily takes place though simple rotation of the C(1)-C(2) or C(1)-O bond for **1** and **2**, respectively. Only in a limited time at low temperature, these enolates can exist in chiral nonracemic forms. Because chiral properties of these enolates are time- and temperature-dependent, we prefer to call this type of chirality "dynamic chirality" rather than conformational chirality. Based on dynamic chirality of enolate structures, a unique method for asymmetric a-alkylation of a-amino acid derivatives has been developed.

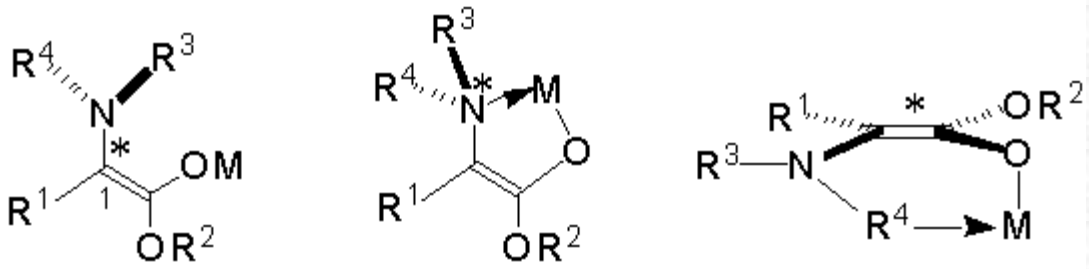
Figure 1



3. Direct Asymmetric a-Alkylation of a-Amino Acids

According to our hypothesis on enolate chirality, enolates derived from a-amino acid derivatives have intrinsic chirality (Figure 2). As shown in **C**, an enolate with axial chirality along the C(1)-N axis is expected when R^3 is different from R^4. An enolate with a chiral nitrogen atom is shown in **D**, where tight coordination of nitrogen to a metal cation creates stereogenic nitrogen atom. An enolate with planar chirality comprising of the enolate plane and a metal cation (**E**) is also possible. We anticipated that the choice of R^3 and R^4 in **C**, **D**, or **E** would have the key role for the generation of a chiral enolate as well as its asymmetric environment, so we examined the effects of the nitrogen substituents of phenylalanine derivatives **3** on asymmetric a-alkylation (Table 1).

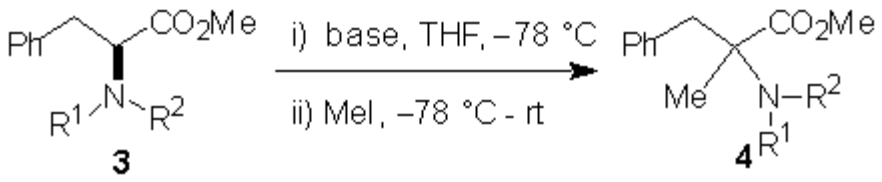
Figure 2



C (chiral C-N axis) **D** (chiral nitrogen) **E** (chiral plane)

Among several phenylalanine derivatives screened, compounds bearing an alkoxycarbonyl group on the nitrogen underwent a-methylation with significant asymmetric induction (entries 5-7). Existence of two substituents on the nitrogen seems essential for the asymmetric induction (entries 1 *vs*. 7). Since *t*-butoxycarbonyl (Boc) group appears critical in the asymmetric induction, we next examined phenylalanine derivatives possessing Boc group and the other subsituent on the nitrogen (Table 2).

Table 1. Screening of Substituents on Nitrogen for Asymmtric α–Methylation of **3**.

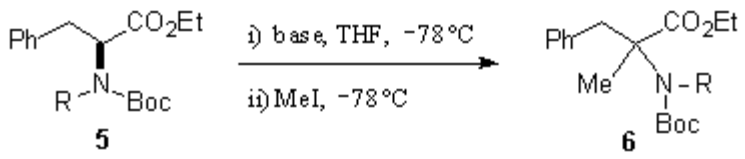


entry	R^1	R^2	base	yield (%)	ee (%)
1	H	CO_2t-Bu	LDA	57	~0
2	Me	CH_2Ph	LDA	45	~0
3	Me	CHO	LHMDS[a]	66	~0
4	Me	COPh	LDA	50	12
5[b]	Me	CO_2CH_2Ph	LHMDS	40	26
6	Me	CO_2Ad[c]	LHMDS	38	35
7	Me	CO_2t-Bu	LHMDS	30	36

a) Lithium hexamethyldisilazide. b) Run in THF-DMF (10:1).
c) 1-Adamantyl ester.

N-Me-*N*-Boc derivative **5a** was found to give the a-methylated product **6a** of 82% ee in 40% yield by the treatment with lithium 2,2,6,6-tetramethylpiperidide (LTMP) followed by methyl iodide (entry 1) (ref. 4). Although *high asymmetric induction was achieved in the absence of external chiral sources*, we were not satisfied with the low chemical yield nor with the property of the *N*-Me group that is hardly removable. We further examined other nitrogen substituents and conditions for asymmetric induction. Some selected results are shown in entries 2-8. The best result was obtained with *N*-methoxymethyl (MOM)-*N*-Boc derivative **5d**. Treatment of **5d** with potassium hexamethyldisilazide (KHMDS) in toluene-THF (4:1) at -78 °C for 30 min followed by addition of methyl iodide afforded **6d** in 96% yield and 81% ee (entry 9). Use of a toluene-THF (4:1) mixture as a solvent is crucial for both high yield and enantioselectivity (entries 7-9).

Table 2. Asymmetric α-Methylation of Phenylalanine Derivatives **5**.



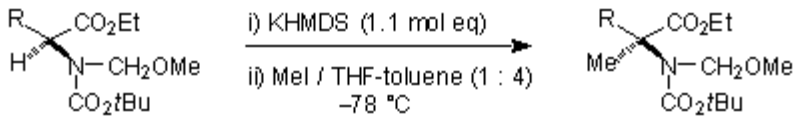
5 **6**

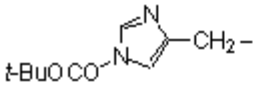
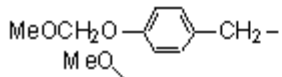
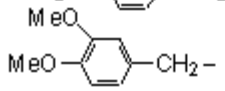
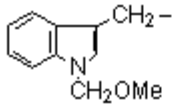
entry	substrate	R	base	product	yield (%)	ee (%)
1	**5a**	Me	LTMP [a]	**6a**	40	82
2	**5a**	Me	KHMDS [b]	**6a**	79	20
3	**5b**	$CH_2CH=CH$	LTMP	**6b**	24	54
4 [c]	**5b**	$CH_2CH=CH$	KHMDS	**6b**	66	31
5	**5c**	$CH_2OCH_2CH_2OMe$	LTMP	**6c**	51	10
6 [c]	**5c**	$CH_2OCH_2CH_2OMe$	KHMDS	**6c**	79	73
7	**5d**	CH_2OMe	KHMDS	**6d**	93	36
8 [d]	**5d**	CH_2OMe	KHMDS	**6d**	47	75
9 [c]	**5d**	CH_2OMe	KHMDS	**6d**	96	81

a) Lithium 2,2,6,6-tetramethylpiperidide. b) Potassium hexamethyldisilazide.
c) Run in toulene-THF (4:1). d) Run in toluene.

a-Methylation of other a-amino acids with *N*-MOM-*N*-Boc subsitutents was carried out under similar conditions (Table 3). a-Amino acid derivatives with aromatic side chains (**5d**, **7**, **9**, **11**, and **13**) as well as aliphatic side chains (**15** and **17**) underwent a-methylation in highly enantioselective manner (76 ~ 93% ee) and in good yields (78 ~ 96%) (ref. 5). Removal of the protective groups of **6d**, **10**, **16**, and **18** was readily accomplished in one step by treatment with 6 M aq HCl to give the corresponding a-methyl a-amino acids in 51 ~ 86% yields (ref. 6). The stereochemical course of a-methylation was retention in each case. The degree of asymmetric induction in a-methylation was comparable among several different amino acids. This implies that MOM and Boc groups at the nitrogen have a decisive effect on the stereochemical course of the reaction.

Table 3. Asymmetric α-Methylation of *N*-MOM-*N*-Boc-α-Amino Acid Derivatives[a]



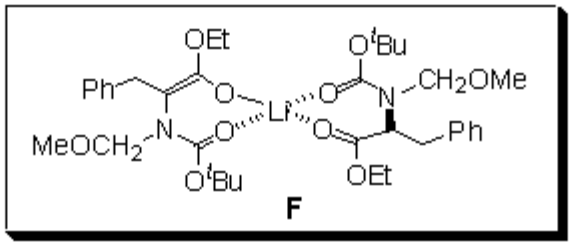
entry	R	substrate[b]	product	yield [%]	*ee* [%]	configuration[c]
1	$PhCH_2-$	**5d**	**6d**	96	81	*S*
2		**7**	**8**	83	93	*a*
3		**9**	**10**	94	79	*S*
4		**11**	**12**	95	80	*S*
5		**13**	**14**	88	76	*a*
6	Me_2CH-	**15**	**16**[e]	81	87	*S*
7	Me_2CHCH_2-	**17**	**18**[e]	78	78	*S*

[a] A substrate was treated with 1.1 mol eq of KHMDS at –78 °C for 30 min (for **5d**, **7**, **9**, **11**, and **13**) or 60 min (for **15** and **17**) followed by 10 mol eq of methyl iodide for 16 - 17 h at –78 °C. [b] *Ee* of each substrate is > 99%. [c] Absolute configuration of the corresponding α-methyl α-amino acid. [d] Not determined. [e] Obtained as an inseparable mixture with the substrate. Yield was determined based on the ratio observed in 400 MHz ^{1}H NMR. Complete separation was achieved with the corresponding *N*-benzoyl derivative.

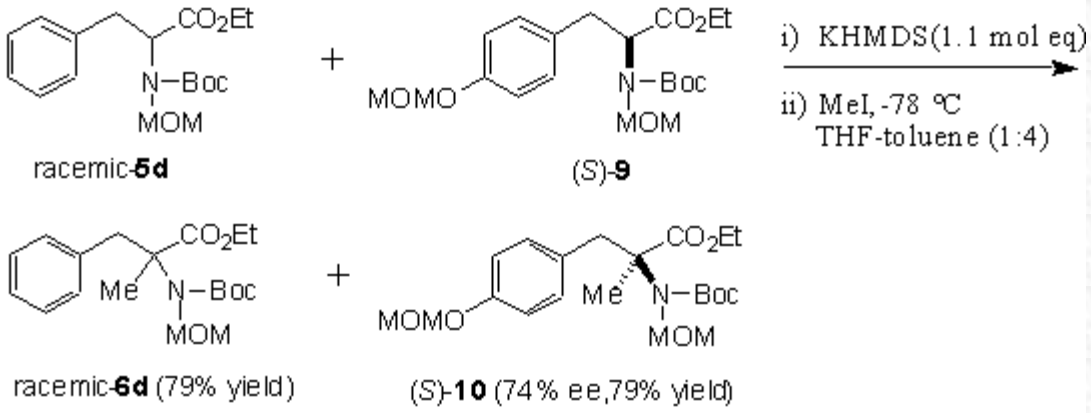
4. Novel Mechanism for Asymmetric Induction

A possible rationale for the present asymmetric induction involves participation of a mixed aggregate **F** (Scheme 2) in which the undeprotonated starting material acts as a chiral ligand of the potassium cation of the *achiral* enolate. To test the feasibility of **F**, a cross over experiments between **5d** and **9** was done (Scheme 2). A 1 : 1 mixture of racemic **5d** and (*S*)-**9** (>99% ee) was treated with KHMDS followed by methyl iodide according to the protocol in Table 3, affording racemic **6d** (79% yield) and (*S*)-**10** (74% ee, 79% yield). This clearly indicates that **F** is not responsible for the present asymmetric induction.

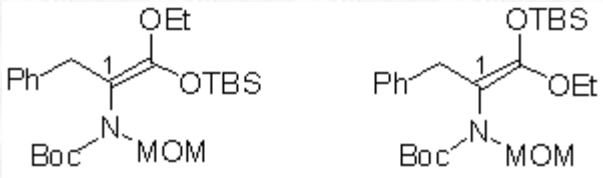
Scheme 2



F



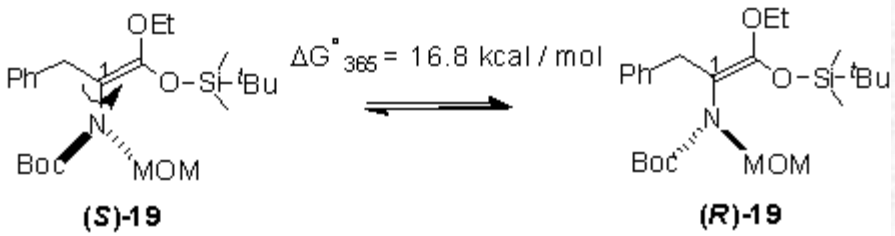
The structure and chiral properties of the intermediate enolate were investigated. Treatment of **5d** with KHMDS (1.1 equiv) in toluene-THF (4:1) at -78 °C for 30 min followed by *t*-butyldimethylsilyl (TBS) triflate gave *Z*-enol silyl ether **19** and its *E*-isomer **20** in a 2 : 1 ratio in combined isolated yields of 83% (**19** and **20** were isolated in 56% and 27% yield, respectively. Each of them exists as a mixture of *N*-Boc *E/Z* isomers; 4:1 for **19** and 5:1 for **20**).



19 **20**

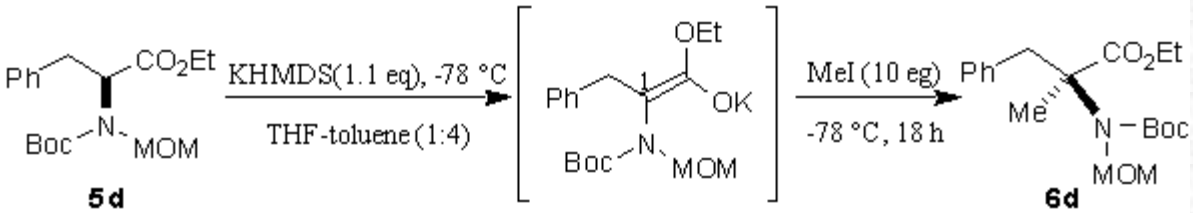
In the ^{1}H NMR spectra of both **19** and **20**, the methylene protons of the MOM groups appeared as AB quartets, which indicates the restricted rotation of the C(1)-N bonds. The rotational barrier of the C(1)-N bond of the major *Z*-isomer **19** was determined to be 16.8 kcal/mol at 365 K by variable-temperature NMR measurements in d_8-toluene (400 MHz ^{1}H NMR, J_{AB} = 9.9 Hz, Dn_{AB} = 228.4 Hz, Tc = 365 K). *The restricted bond rotation brings about axial chirality in* **19** *(chiral C(1)-N axis)* as shown in Scheme 3. The half-life to racemization of **19** was estimated to be 5 x 10^{-4} sec at 92 °C or ca. 7 days at -78 °C from the rotational barrier (ref. 7). This implies that the corresponding potassium enolate could also exist in an axially chiral form with a relatively long half-life to racemization at low temperature.

Scheme 3



We next investigated the behavior of the potassium enolate intermediate toward racemization (Scheme 4). When **5d** was treated with KHMDS for 24 h at -78 °C, the reaction of the resulting enolate with methyl iodide gave **6d** (84% yield) of 36% ee (*cf.* 81% ee by 30-min base treatment). When the enolate was prepared at -78 °C for 30 min then kept at -40 °C for 30 min, its reaction with methyl iodide at -78 °C produced **6d** (88% yield) of 5% ee. These results clearly indicate that racemization of the enolate intermediate took place.

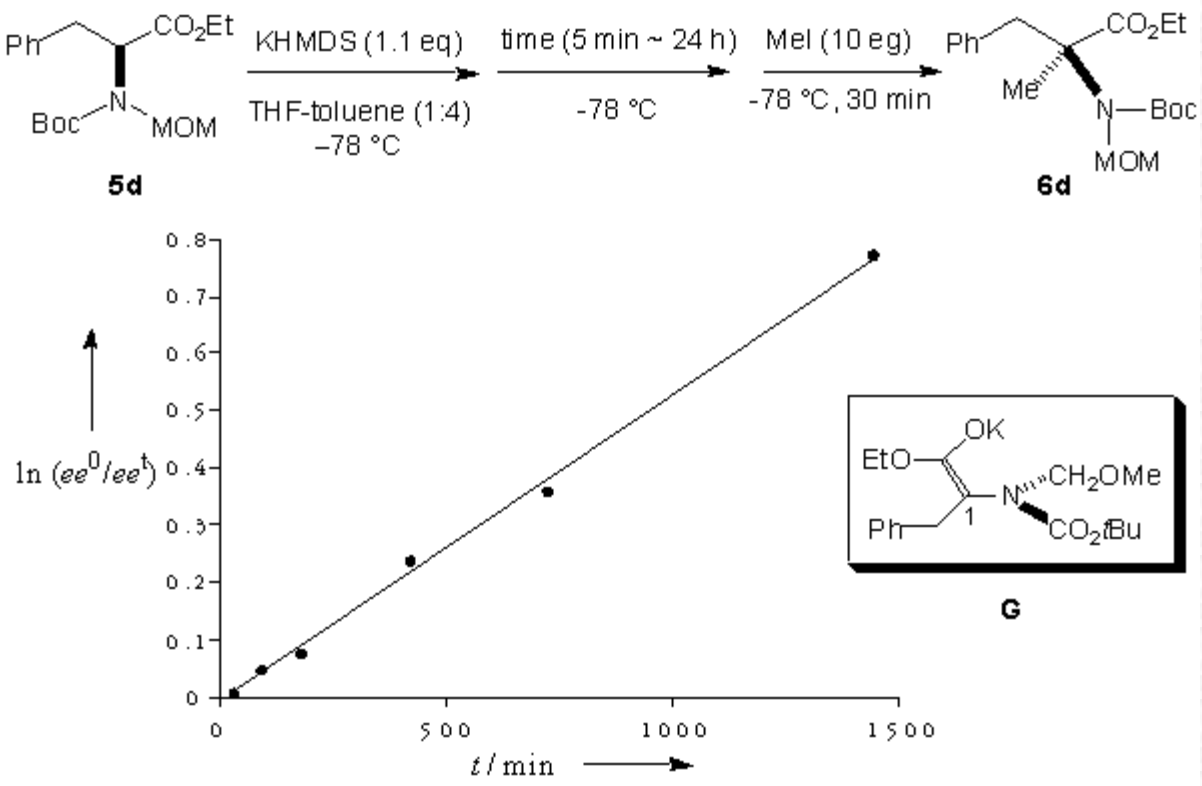
Scheme 4



conditions for enolate-formation	ee of **6d**
-78 °C, 30 min	81% ee
-78 °C, 24 h	36% ee
-78 °C, 30 min then -40 °C, 30 min	5% ee
-78 °C, 30 min then 0° C, 30 min	0% ee

The barrier to racemization was determined through the periodic quench of the enolate intermediate generated at -78 °C with methyl iodide. Figure 3 plots the logarithm of the relative ee's of **6d** as a function of time for base-treatment of **5d** and indicates a very good linear relationship between them (r = 0.999), although the enolate is a 2 : 1 mixture of the *Z*- and *E*-forms. This suggests that the rates of racemization of the *Z*- and *E*-enolates are very close to each other (ref. 8). The barrier was calculated from the slope ($2k = 5.34 \times 10^{-4}$ min^{-1}) to be 16.0 kcal/mol at -78 °C, which matches well with the rotational barrier of the C(1)-N bond of **19**. This suggests that the chirality of the potassium enolate intermediate also originates in the restricted rotation of the C(1)-N bond. We conclude that *a chiral nonracemic enolate with dynamic axial chirality* (**G**) *is the origin for the present asymmetric induction*. The half-life to racemization of the chiral enolate was 22 h at -78 °C, which is long enough for the chiral enolate to undergo asymmetric methylation.

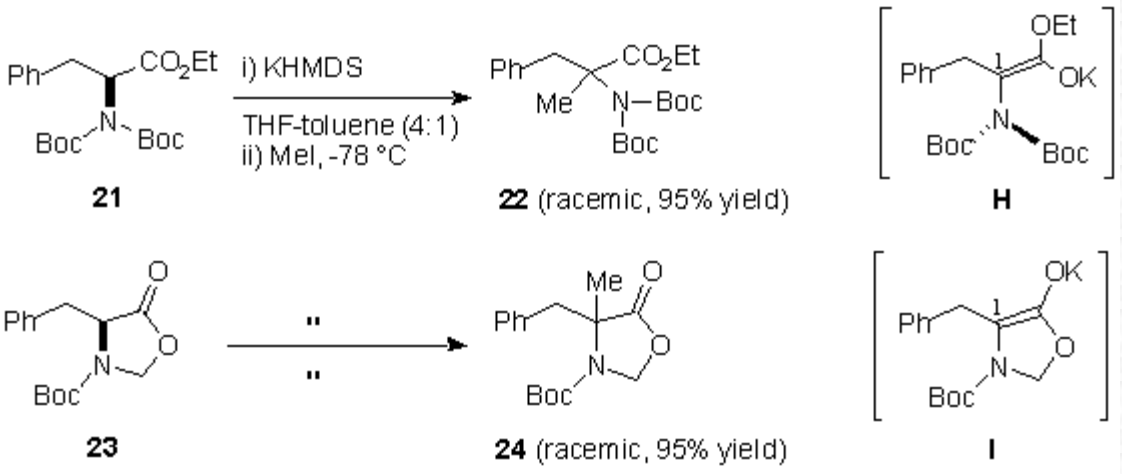
Figure 3



Plot of logarithm of the relative ee of **6d** ($\ln ee^0/ee^t$) versus time for base-treatment of **5d** (t). ee^0 : *Ee* of **6d** obtained by the reaction of the enolate immediately after its generation from **5d** with methyl iodide. ee^t : *Ee* of **6d** obtained by the treatment of **6d** with KHMDS for the time indicated followed by methyl iodide.

Support for this novel mechanism was obtained from the reactions of **21** and **23** (Scheme 5). Upon a-methylation following the protocol in Table 3, the di-Boc derivative **21** (>99% ee) and methylene acetal derivative **23** (>99% ee) gave racemic **22** (95% yield) and **24** (95% yield), respectively. These results are consistent with the conclusions above, since the enolates **H** and **I** generated from **21** and **23**, respectively, are *not* expected to be axially chiral along the C(1)-N axis.

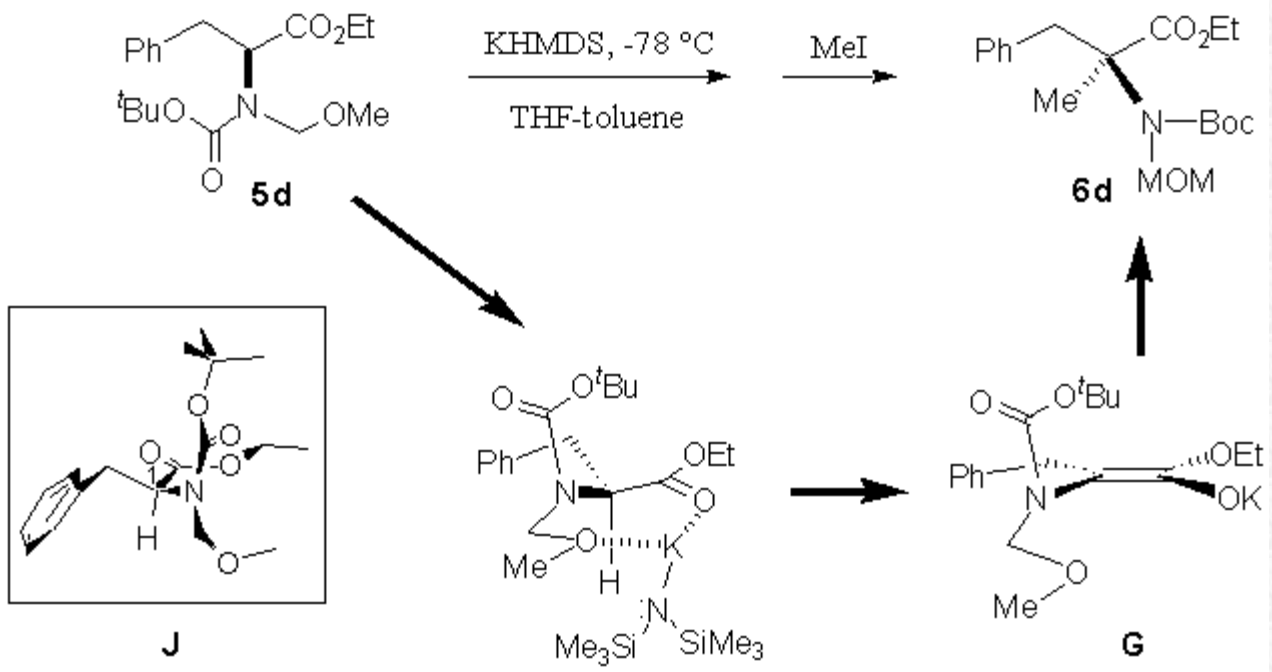
Scheme 5



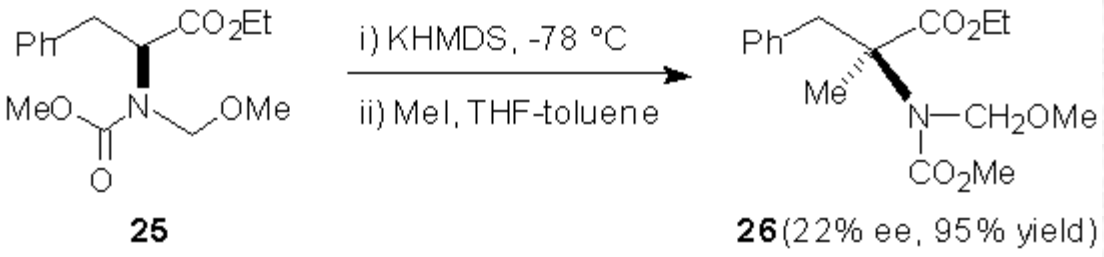
Stereochemical course (retention) of the transformation of **5d** into **6d** may be explained by assuming; 1) deprotonation occurs from the stable conformer **J** (Scheme 6) where the C(1)-H bond is eclipsed with the N-C (MOM) bond (ref. 9)

to produce enantiomerically enriched chiral enolate (**G**), 2) electrophile (methyl iodide) approaches from the sterically less demanding face (MOM) of the enolate double bond of **G**. This is no more than speculation but consistent with the experimental result from **25** that undergoes a-methylation in only 22% ee by the same treatment as that for **5d** (Scheme 7) because of the smaller difference of the steric bulk between MOM and CO_2Me groups than that between MOM and Boc groups in **6d**.

Scheme 6



Scheme 7



5. Conclusion

Asymmetric a-methylation of various *N*-MOM-*N*-Boc-a-amino acid derivatives proceeded in a highly enantioselective manner in the absence of any external chiral source. A chiral nonracemic enolate with dynamic axial chirality (**G**) was shown to be a crucial intermediate for the asymmetric induction. The racemization barrier of the chiral enolate was 16 kcal/mol and the half-life was 22 h at -78°C. The relatively long half-life to racemization of the chiral enolate intermediates is essential for the intermolecular reactions to proceed enantioselectively. On the other hand, intramolecular reactions are expected to occur enantioselectively *via* chiral enolate intermediates with much smaller barriers to racemization (~13 kcal/mol). Because the racemization barrier and the chiral environment of enolates are controllable by introducing substituents or protective groups, asymmetric induction based on the present strategy would have further applicability in enolate chemistry.

Acknowledgment

This work was supported by a Grant-in-Aid for Scientific esearch on Priority Areas (No. 706 : Dynamic Control of Stereochemistry) from the Ministry of Education (Monbusho), Japan.

References and Notes

(1) For examples of *advanced* chiral auxiliaries which utilize chirality of parent a-amino acids, see: a) Seebach, D.; Boes, M.; Naef, R.; Schweizer, W. B. *J. Am. Chem. Soc*. **1983**, *105*, 5390. b) Vedejs, E.; Fields, S. C.; Schrimpf, M. R. *J. Am. Chem. Soc*. **1993**, *115*, 11612. c) Ferey, V.; Toupet, L.; Gall, T. L.; Mioskowski, C. *Angew. Chem. Int. Ed. Engl*. **1996**, *35*, 430.

(2) a) Kawabata, T. *Yakugaku Zasshi*, **1995**, *115*, 700. b) Fuji, K.; Kawabata, T. *Chem. Eur. J*. **1998**, *4*, 373.

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

(4) Kawabata, T.; Wirth, T.; Yahiro, K.; Suzuki, H.; Fuji, K. *J. Am. Chem. Soc*. **1994**, *116*, 10809.

(5) Kawabata, T.; Suzuki, H.; Nagae, Y. Fuji, K. *Angew. Chem. Int. Ed. Engl*. **2000**, *39*, 2155.

(6) Conversion of **12** into a-methyldopa was accomplished in the following three-step sequence, since the treatment of **12** with 6 M HCl gave the corresponding tetrahydroisoquinoline derivative: 1) TMSBr / Me_2S, 2) 1 M NaOH, 3) 47% aq HBr.

(7) The half life at -78 °C was roughly estimated on the assumption that $DS^{\neq}$ of the restricted bond rotation is nearly zero.

(8) The *Z*- and *E*-enolate intermediates should afford a-methylated products of the same absolute configuration, since the 2 : 1 geometric mixture of enolates gave the product of 81% ee in 96% yield (Table 3, entry 1).

(9) The most stable conformation **J** of **5d** was generated by MCMM search with MM3* force field using MacroModel V6.0: a) Chang, G.; Guida, W. C.; Still, W. C. *J. Am Chem. Soc*. **1989**, *111*, 4379. b) Kolossváry, I.; Guida, W. C. *J. Am. Chem. Soc*. **1996**, *118*, 5011.
