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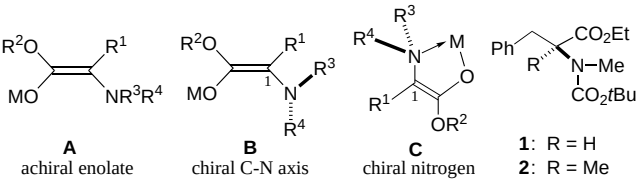
A Chiral Nonracemic Enolate with Dynamic Axial Chirality: Direct Asymmetric α-Methylation of α-Amino Acid Derivatives**

Takeo Kawabata,* Hideo Suzuki, Yosikazu Nagae, and Kaoru Fuji

The structure of enolates was long believed to be achiral because all four substituents are on the same plane as the enolate double bond. For example, enolates generated from α-amino acid derivatives are seemingly achiral when substituents $R^1 - R^4$ are achiral (**A**). However, we proposed that some enolate structures are intrinsically chiral.[1–3] As shown in **B** an enolate with axial chirality along the C1-N axis is expected if R^3 is different from R^4. An enolate with a chiral nitrogen atom is shown in **C**, where tight coordination of the



A achiral enolate | **B** chiral C-N axis | **C** chiral nitrogen

nitrogen atom to a metal cation creates a stereogenic nitrogen atom.[4] Racemization of these chiral enolates takes place so readily through simple C1–N bond rotation that the chirality is not static, but dynamic. These enolates can exist in chiral nonracemic forms for a limited time at low temperatures. We describe here experimental evidence for a chiral nonracemic enolate with dynamic axial chirality, as exemplified in **B**. Asymmetric α-methylation of various α-amino acid derivatives can occur in a highly enantioselective manner through the intrinsically chiral enolate intermediate.[5–7]

We have previously reported that phenylalanine derivative **1** undergoes asymmetric α-methylation by treatment with lithium 2,2,6,6-tetramethylpiperidide followed by methyl iodide to give **2** in 82% *ee* and 40% yield.[2] This is the second example of the retention of chiral information of optically active α-amino acid derivatives during their α-alkylation. The first one was reported by Seebach and Wasmuth.[6a] Although the transformation of **1** into **2** was noteworthy in that asymmetric induction was realized without using any external chiral sources, such as chiral auxiliaries or chiral ligands, there were significant drawbacks: 1) low chemical yield, 2) low generality of asymmetric induction among α-amino acids, and 3) difficulty in removing the *N*-methyl protective group. The mechanism of the novel asymmetric induction was ambiguous. We further examined the present strategy in order to develop a more efficient process and to elucidate the mechanism. We anticipated that the choice of R^3 and R^4 in **B** or **C** would have the key role for the asymmetric induction, so we screened the substituents at the nitrogen atom of phenylalanine. We found that substrates possessing *t*-butoxycarbonyl (Boc) and methoxymethyl (MOM) groups at the nitrogen atom gave satisfactory results. Treatment of *N*-Boc-*N*-MOM-phenylalanine derivative **3** with potassium hexamethyldisilazide (KHMDS) in toluene:THF (4:1) at −78 °C for 30 min followed by methyl iodide afforded α-methylated product **4** in 96% yield and 81% *ee* (Table 1, entry 1).[8] Similarly, α-methylation of histidine derivative **5** gave **6** in 83% yield and 93% *ee* (entry 2). The α-amino acid derivatives **7**, **9**, and **11** with aromatic side chains, as well as those with aliphatic side chains, **13** and **15**, gave α-methylated products **8**, **10**, **12**, **14**, and **16**, respectively, in 78 – 95% yields and *ee* values of 76 – 87% by a similar treatment (entries 3 – 7). Removal of the protective groups of **4**, **8**, **14**, and **16** was readily accomplished in one step by treatment with 6 M

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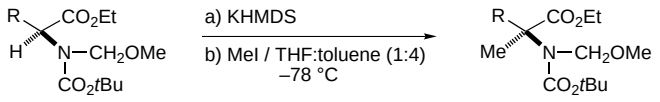
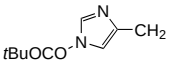
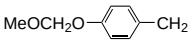
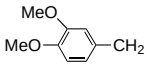
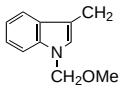
Table 1. Asymmetric α-methylation of α-amino acid derivatives.[a]

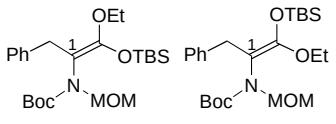


Entry	R	Substrate[b]	Product	Yield [%]	*ee* [%][c]	$[\alpha]_D^{20}$ (*c* in $CHCl_3$)	Configuration[d]
1	$PhCH_2$	**3**	**4**	96	81	−89 (1.2)	*S*
2		**5**	**6**	83	93	−43 (1.1)	[e]
3		**7**	**8**	94	79	−81 (1.0)	*S*
4		**9**	**10**	95	80	−96 (1.0)	*S*
5		**11**	**12**	88	76	−64 (0.9)	[e]
6	Me_2CH	**13**	**14**[f]	81	87	+8.5 (1.2)[g]	*S*
7	Me_2CHCH_2	**15**	**16**[f]	78	78	+20 (0.5)[g]	*S*

[a] The substrate was treated with 1.1 equiv of KHMDS at −78 °C for 30 min (for **3**, **5**, **7**, **9**, and **11**) or 60 min (for **13** and **15**) followed by 10 equiv of methyl iodide for 16–17 h at −78 °C. See the Supporting Information for the experimental procedure and physical data. [b] The *ee* value of each substrate is >99 %. [c] Determined by HPLC using columns with chiral stationary phases: **4**: Chiralpack AD, 2 % *i*PrOH in hexane; **6**, **8**: Chiralpack AD, 5 % EtOH in hexane; **10**, **12**: Chiralpack AD, 5 % *i*PrOH in hexane; **14** (benzoate): Chiralpack AS, 3 % *i*PrOH in hexane; **16** (benzoate): Chiralpack AD, 1 % *i*PrOH in hexane. [d] Absolute configuration of the corresponding α-methyl-α-amino acid. [e] Not determined. [f] Obtained as an inseparable mixture with the substrate. The yield was determined on the basis of the ratio of signals observed in the 400 MHz ^{1}H NMR spectra. Complete separation was achieved with the corresponding *N*-benzoyl derivative. [g] Optical rotation of the corresponding *N*-benzoyl derivative.

aqueous HCl to give the corresponding α-methyl-α-amino acids in 51–86 % yields.[9] The α-methylation was shown to proceed with retention of stereochemistry. The degree of asymmetric induction in the α-methylation was comparable among several amino acids. This observation implies that MOM and Boc groups at the nitrogen atom have a decisive effect on the stereochemical course of the reaction.

The structure and chiral properties of the intermediate enolate were investigated to clarify the mechanism of the present asymmetric induction. Treatment of **3** with KHMDS (1.1 equiv) in toluene:THF (4:1) at −78 °C for 30 min followed by addition of *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBS triflate) gave the *Z* enol silyl ether **17** and its *E* isomer **18** in a 2:1 ratio in combined yields of 83 %.[10] The methylene protons of the MOM groups appeared as AB quartets in the ^{1}H NMR spectra of both **17** and **18**, which indicates the restricted rotation of the C1–N bonds. The rotational barrier of the C1–N bond in the major *Z* isomer (**17**) was determined to be 16.8 kcal mol^{-1} (365 K) by variable-temperature NMR measurements in [D_8]toluene (400 MHz ^{1}H NMR, $J_{AB}=9.9$ Hz, $\Delta\tilde{\nu}_{AB}=228.4$ Hz, $T=365$ K). The restricted bond rotation brings about axial chirality in **17** (chiral C1–N axis), as shown in **D**.[11] The half-life of racemization in **17** was estimated from the rotational barrier to be 5×10^{-4} s at 92 °C or approximately 7 days at −78 °C.[12] This value implies that the corresponding potassium enolate could also exist in an axially chiral form with a relatively long half-life to racemization at low temperatures.



17 **18**

We then investigated the behavior of the enolate intermediate toward racemization. When **3** was treated with KHMDS for 24 h at −78 °C, the reaction of the resulting enolate with methyl iodide gave **4** (84 % yield) with 36 % *ee* (81 % *ee* after 30 min base treatment, Table 1, entry 1). When the enolate was prepared and maintained at −78 °C for 30 min then kept at −40 °C for 30 min, its reaction with methyl iodide at −78 °C produced **4** (88 % yield) with 5 % *ee*. These results clearly indicate that racemization of the enolate intermediate occurs. The barrier to racemization was determined through the periodic quenching of the enolate intermediate generated at −78 °C with methyl iodide. A graph of the logarithm of the relative *ee* values of **4** as a function of time for base-treatment of **3** (Figure 1) indicates a very good

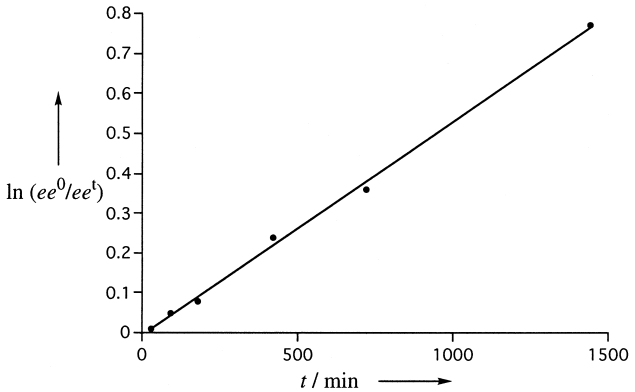


Figure 1. Plot of the logarithm of the relative *ee* value of **4** ($\ln ee^0/ee^t$) versus time (*t*) for base treatment of **3**. ee^0 = the *ee* value of **4** obtained by the reaction of the enolate immediately after its generation from **3** with methyl iodide. ee^t = the *ee* value of **4** obtained by the treatment of **3** with KHMDS for the time indicated followed by addition of methyl iodide. See Supporting Information for experimental details.

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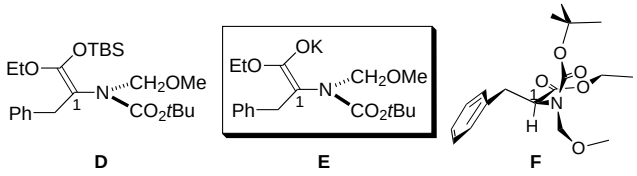
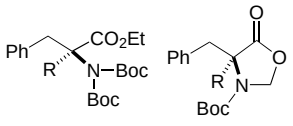
linear relationship exists ($r = 0.999$), although the enolate is a 2:1 mixture of the *Z* and *E* forms. This observation suggests that the rates of racemization of the *Z* and *E* enolates are very close to each other.[13] The barrier was calculated from the slope ($2k = 5.34 \times 10^{-4}\,\mathrm{min}^{-1}$) to be 16.0 kcal mol^{-1} at $-78\,^{\circ}$C, which matches well with the rotational barrier of the C1–N bond of **17**. This result suggests that the chirality of the potassium enolate intermediate also originates in the restricted rotation of the C1–N bond. We conclude that a chiral nonracemic enolate with dynamic axial chirality (**E**) is the



origin for the present asymmetric induction. The half-life of racemization of the chiral enolate was 22 h at $-78\,^{\circ}$C, which is long enough for the chiral enolate to undergo asymmetric methylation. The stereochemical course (retention) of α-methylation of **3** may be explained by assuming: 1) deprotonation occurs from the stable conformer **F**[14] where the C1–H bond is eclipsed by the N–C(MOM) bond to produce enantiomerically enriched chiral enolate (**E**)[15] and 2) the electrophile (methyl iodide) approaches from the sterically less demanding face (MOM) of the enolate double bond of **E**.

Support for this novel mechanism was obtained from the reactions of **19** and **21**. The di-Boc derivative **19** (>99% *ee*) and methylene acetal derivative **21** (>99% *ee*) gave racemic **20** (95% yield) and **22** (95% yield), respectively, upon α-methylation. These results are consistent with the conclusions above, since the enolates generated from **19** and **21** are not expected to be axially chiral along the C–N axis.[16, 17]



19: R = H
20: R = Me

21: R = H
22: R = Me

In conclusion, a chiral nonracemic enolate with dynamic axial chirality was shown to be a crucial intermediate for direct asymmetric α-methylation of α-amino acid derivatives. The racemization barrier of the chiral enolate was 16 kcal mol^{-1} and the half-life was 22 h at $-78\,^{\circ}$C. Likewise, some enolates with a restricted bond rotation should have axial chirality with an intrinsic barrier to racemization. Since the rotational barrier is controllable by introducing substituents or protective groups, asymmetric induction based on the present strategy would have further applicability in enolate chemistry.

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[8] A reaction of **3** is briefly described in reference [3].
[9] Conversion of **10** into α-methyl-3-(3,4-dihydroxyphenyl)alanine (α-methyldopa) was accomplished in the following three-step sequence, since the treatment of **10** with 6M HCl gave the corresponding tetrahydroisoquinoline derivative: 1) TMSBr/Me_2S, 2) 1M NaOH, 3) 47% aq HBr.
[10] **17** and **18** were separately isolated in 56% and 27% yield, respectively. Each of them exists as a mixture of *N*-Boc *E*/*Z* isomers (4:1 for **17** and 5:1 for **18**).
[11] The absolute configuration of **D** and **E** is shown provisionally.
[12] The half-life at $-78\,^{\circ}$C was roughly estimated on the assumption that ΔS^{+} of the restricted bond rotation is nearly zero.
[13] The *Z* and *E* enolate intermediates should afford α-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 1, entry 1).
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[15] The difference in the potential energies between **F** and a conformer where the C1–H bond is eclipsed by the N–C(Boc) bond, which will give the enantiomer of **E**, is estimated to be 1.0 kcal mol^{-1}. The difference may increase at the transition state for deprotonation as a result of the enhanced steric interactions in the presence of a base.
[16] The 2,3-dihydroxazole ring in the potassium enolate generated from **21** and KHMDS is supposed to be nearly planar.
[17] A mixed aggregate of an achiral enolate with an undeprotonated starting material was considered as another possible intermediate for asymmetric induction. This was eliminated by a crossover experiment between **3** and **7**: A 1:1 mixture of racemic **3** and (*S*)-**7** (>99% *ee*) was α-methylated according to the procedure in Table 1 and afforded racemic **4** (79% yield) and (*S*)-**8** (74% *ee*, 79% yield), respectively.

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