Memory of Chirality: Alkylation of α-Amino Acid Derivatives

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Abstract: N-Boc-N-MOM-α-amino acid derivatives (Phe, Val, Leu, His, Trp, Tyr, Dopa) underwent asymmetric α-methylation in 76–93% ee by treatment with KHMDS followed by methyl iodide in the absence of any external chiral source. A chiral nonracemic enolate with dynamic axial chirality is proposed as the crucial intermediate whose racemization barrier is 16.0 kcal/mol and the corresponding half-life is 22h at −78 °C.

1. Introduction: Memory of Chirality

Nonproteinogenic α,α-disubstituted-α-amino acids have attracted considerable attention as synthetic targets because of their utility as conformational modifiers of biologically active peptides and as enzyme inhibitors. Typical methods for their asymmetric synthesis involve chiral auxiliary-based enolate chemistry. However, the most straightforward strategy for the synthesis would involve asymmetric α-alkylation of the parent α-amino acids in the absence of additional chiral sources such as chiral auxiliaries, chiral ligands, chiral electrophiles, or even chiral catalysts. Since both L- and D-α-amino acids are readily commercially available, the synthetic route shown in Scheme 1 seems most attractive for the purpose. This process, however, usually gives racemic α-alkylated products from either L- or D-α-amino acid because the enolate formation eliminates the chiral information at C(2) and an achiral enolate common to both L- and D-series is formed (A=B). If the chirality of the starting materials is preserved in the enolate intermediate (i.e., memory of chirality), L- and D-α-amino acids should give optically active L- and D- (or D- and L-) α,α-disubstituted α-amino acids via intrinsically chiral enolate intermediates A and B, respectively. In this article, we describe the design and development of the novel chirality-transfer process. Dynamic chirality of the enolate structure is the key for designing and understanding this asymmetric process.

Scheme 1. Memory of chirality in alkylation of α-amino acid derivatives

2. Dynamic Chirality of the 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 the intrinsic chirality of enolate structures as shown in Figure 1. Enolate 1 has axial chirality along the C(1)-C(2) axis and 2 has planar chirality comprising the enolate plane and a metal cation. Racemization of these chiral enolates readily takes place through rotation of the C(1)-C(2) or C(1)-O bond for 1 and 2, respectively. Only for a limited time at low temperature, these enolates can exist in chiral nonracemic forms. Because the chiral properties of these enolates are time- and temperature-dependent, we prefer to call this type of chirality "dynamic chirality" rather than conformational chirality. Asymmetric transformations based on dynamic chirality of the enolate structure are shown below.

Figure 1. Dynamic chirality of enolate structure.

3. The First Example of Designed "Memory of Chirality"5

Although chiral nonracemic enolates of type 1 and 2 are expected to exist under particular conditions, their half-lives to racemization are usually too short to effect the actual asymmetric reactions. In order to realize an asymmetric transformation via the chiral enolate of type 1, we designed a chiral ketone 3 that would generate an axially chiral enolate 5 with relatively long half-life to racemization due to the restricted rotation of the C(1)-C(2) bond (Scheme 2). Treatment of 3 with potassium hydride in the presence of alkyl halide and 18-crown-6 gave optically active 4 in 48–67% ee. Intervention of the chiral enolate intermediate with the chiral C
(1)-C(2) axis (5) was suggested by an isolation of chiral non-
racemic enol ether 6 (43% ee by HPLC analysis; Daicel
Chiralpak AD, i-PrOH/haxane=3:97, $\delta \alpha_2^{20}$+21 (c 0.15,
CHCl$_3$)). The enantiomeric purity of 6 decreased gradually
at ambient temperature ($t_{1/2}=53$ min, $\Delta G^\circ_{298}$$=22.6$ kcal/mol).
Direct HPLC analysis of the reaction mixture showed that ee
of 6 was at least 65% in the reaction medium below $-$20 °C.
Thus, the chiral information of 3 appears to be memorized
in the enolate intermediate 5 as dynamic axial chirality and then
regenerated as central chirality in the product 4.

Table 1. Screening of substituents on nitrogen for asymmetric
$\alpha$-methylation of 7

<table>
<thead>
<tr>
<th>Entry</th>
<th>$R^2$</th>
<th>Base</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>LDA</td>
<td>57</td>
<td>$-$0</td>
</tr>
<tr>
<td>2</td>
<td>Me</td>
<td>LDA</td>
<td>45</td>
<td>$-$0</td>
</tr>
<tr>
<td>3</td>
<td>CHO</td>
<td>LHMDS$^a$</td>
<td>66</td>
<td>$-$0</td>
</tr>
<tr>
<td>4</td>
<td>COPh</td>
<td>LDA</td>
<td>50</td>
<td>12</td>
</tr>
<tr>
<td>5$^b$</td>
<td>CO$_2$CH$_2$Ph</td>
<td>LHMDS</td>
<td>40</td>
<td>26</td>
</tr>
<tr>
<td>6$^c$</td>
<td>CO$_2$Ad$^c$</td>
<td>LHMDS</td>
<td>38</td>
<td>35</td>
</tr>
<tr>
<td>7$^c$</td>
<td>CO$_2$Bu</td>
<td>LHMDS</td>
<td>30</td>
<td>36</td>
</tr>
</tbody>
</table>

1) Lithium hexamethyldisilazide. 2) Run in THF-DMF (10:1).

Table 2. Asymmetric $\alpha$-methylation of N-Boc-phenylalanine deriva-
tives 9

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>$R^2$</th>
<th>Base</th>
<th>Product Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9a</td>
<td>Me</td>
<td>LTMP$^a$</td>
<td>10a</td>
<td>40</td>
</tr>
<tr>
<td>2</td>
<td>9a</td>
<td>Me</td>
<td>KHMD$^b$</td>
<td>10a</td>
<td>79</td>
</tr>
<tr>
<td>3</td>
<td>9b</td>
<td>CH$_2$CH$_2$-CH</td>
<td>LTMP</td>
<td>10b</td>
<td>24</td>
</tr>
<tr>
<td>4$^c$</td>
<td>9b</td>
<td>CH$_2$CH$_2$-CH</td>
<td>KHMD$^b$</td>
<td>10b</td>
<td>66</td>
</tr>
<tr>
<td>5$^c$</td>
<td>9c</td>
<td>CH$_2$OHCH$_2$OMe</td>
<td>LTMP</td>
<td>10c</td>
<td>51</td>
</tr>
<tr>
<td>6$^c$</td>
<td>9c</td>
<td>CH$_2$OHCH$_2$OMe</td>
<td>KHMD$^b$</td>
<td>10c</td>
<td>79</td>
</tr>
<tr>
<td>7</td>
<td>9d</td>
<td>CH$_2$OMe</td>
<td>KHMD$^b$</td>
<td>10d</td>
<td>93</td>
</tr>
<tr>
<td>8$^c$</td>
<td>9d</td>
<td>CH$_2$OMe</td>
<td>KHMD$^b$</td>
<td>10d</td>
<td>47</td>
</tr>
<tr>
<td>9$^c$</td>
<td>9d</td>
<td>CH$_2$OMe</td>
<td>KHMD$^b$</td>
<td>10d</td>
<td>96</td>
</tr>
</tbody>
</table>

1) Lithium 2,2,6,6-tetramethylpiperidide. 2) Potassium hexamethyldisilazide.
3) Run in toluene-THF (4:1). 4) Run in toluene.

4. Direct Asymmetric $\alpha$-Alkylation of $\alpha$-Amino Acids

According to our hypothesis on enolate chirality, enolates
derived from $\alpha$-amino acid derivatives also have intrinsic chi-
rality (Figure 2). As shown in A, an enolate with axial chir-
ality along the C(1)-N axis is expected if $R^1$ is different
from $R^2$. An enolate with a chiral nitrogen atom is shown in
B, where tight coordination of nitrogen to a metal cation cre-
ates a stereogenic nitrogen atom.$^5$ An enolate with planar
chirality comprising the enolate plane and a metal cation (C)
is also possible. We anticipated that the choice of $R^1$ and $R^2$
in A, B, or C 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 phenyl-
alanine derivatives 7 on $\alpha$-methylation (Table 1).

Figure 2. Dynamic chirality of the enolates derived from $\alpha$-amino
acids.

Among several phenylalanine derivatives screened, com-
bounds bearing a alkoxycarbonyl group on the nitrogen
underwent $\alpha$-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 a $r$-butoxy carbonyl (Boc) group appears critical
in the asymmetric induction, we next examined phenylala-
nine derivatives possessing a Boc group and the other sub-
stituent on the nitrogen (Table 2). $N$–Me–$N$–Boc derivative
9a was found to give the corresponding $\alpha$-methylated prod-
uct 10a of 82% ee in 40% yield by treatment with lithium 2,
2, 6, 6-tetramethylpiperidide (LTMP) followed by methyl
iodide (entry 1). Although high asymmetric induction was
achieved in the absence of external chiral sources,$^7$ we were not
satisfied with the low chemical yield nor with the property of
the $N$–Me group that is hardly removable. We further exam-
ined other nitrogen substituents and conditions for asymmet-
ric induction. Some selected results are shown in entries 3–
8. The best result was obtained with $N$-methoxymethyl
(MOM)–$N$–Boc derivative 9d. Treatment of 9d with potassium
hexamethyldisilazide (KHMD$^b$) in toluene-THF (4:1) at
$-$78 °C for 30 min followed by the addition of methyl iodide
afforded 10d 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). $\alpha$-Methyla-
tion of other $\alpha$-amino acids with $N$–MOM–$N$–Boc substi-
tuents was carried out under the similar conditions (Table 3).
$\alpha$-Amino acid derivatives with aromatic side chains (9d, 11,
13, 15, and 17) as well as aliphatic side chains (19 and 21)
underwent $\alpha$-methylation in a highly enantioselective manner
(76–93% ee) and in good yields (78–96%). Removal of the
protective groups of 10d, 14, 20, and 22 was readily accom-

\[ \text{Scheme 2. Memory of chirality in alkylation of a ketone 3} \]

\[ \text{Figure 2. Dynamic chirality of the enolates derived from $\alpha$-amino
acids.} \]
plished in one step by treatment with 6 M aq HCl to give the corresponding ω-methyl ω-amino acids in 51–86% yields. The stereochemical course of the ω-methylation was retention in each case. The degree of asymmetric induction in the ω-methylation was comparable among several different amino acids. This implies that the MOM and Boc groups at the nitrogen have a decisive effect on the stereochemical course of the reaction.

5. Novel Mechanism for Asymmetric Induction

A possible rationale for the present asymmetric induction involves participation of a mixed aggregate D in which the undeprotonated starting material acts as a chiral ligand of the potassium cation of the achiral enolate. To test the feasibility of D, a cross over experiment between 9d and 13 was done. A 1:1 mixture of racemic 9d and (S)-13 (>99% ee) was treated 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 23 and its E-isomer 24 in a 2:1 ratio in a combined isolated yields of 83%. (23 and 24 were isolated in 56% and 27% yield, respectively. Each of them exists as a mixture of N-Boc E/Z isomers; 4:1 for 23 and 5:1 for 24). In the 1H NMR spectra of both 23 and 24, 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 23 was determined to be 16.8 kcal/mol at 365 K by variable-temperature NMR measurements in d8-toluene (400 MHz 1H NMR, JAB=9.9 Hz, AvAB=228.4 Hz, Tc=365 K). The restricted bond rotation brings about axial chirality in 23 (chiral C(1)-N axis) as shown in Scheme 3. The half-life to racemization of 23 was estimated to be $5 \times 10^{-14}$ sec at 92 °C or ca. 7 days at −78 °C from the rotational barrier. This implies responsible for the present asymmetric induction.

Then, the structure and chiral properties of the intermediate enolate were investigated. Treatment of 9d 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 23 and its E-isomer 24 in a 2:1 ratio in a combined isolated yields of 83%. (23 and 24 were isolated in 56% and 27% yield, respectively. Each of them exists as a mixture of N-Boc E/Z isomers; 4:1 for 23 and 5:1 for 24). In the 1H NMR spectra of both 23 and 24, 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 23 was determined to be 16.8 kcal/mol at 365 K by variable-temperature NMR measurements in d8-toluene (400 MHz 1H NMR, JAB=9.9 Hz, AvAB=228.4 Hz, Tc=365 K). The restricted bond rotation brings about axial chirality in 23 (chiral C(1)-N axis) as shown in Scheme 3. The half-life to racemization of 23 was estimated to be $5 \times 10^{-14}$ sec at 92 °C or ca. 7 days at −78 °C from the rotational barrier. This implies

### Table 3. Asymmetric ω-methylation of N-MOM–N-Boc-ω-amino acid derivatives

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield [%]</th>
<th>ee [%]²</th>
<th>[α]D³⁰ (conc, CHCl₃)</th>
<th>Configuration²</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhCH₂-</td>
<td>9d</td>
<td>10d</td>
<td>96</td>
<td>81</td>
<td>−89 (c=1.2)</td>
<td>S</td>
</tr>
<tr>
<td>2</td>
<td>t-BuOCO</td>
<td>11</td>
<td>12</td>
<td>83</td>
<td>93</td>
<td>−43 (c=1.1)</td>
<td>−</td>
</tr>
<tr>
<td>3</td>
<td>MeOCH₂O-</td>
<td>13</td>
<td>14</td>
<td>94</td>
<td>79</td>
<td>−81 (c=1.0)</td>
<td>S</td>
</tr>
<tr>
<td>4</td>
<td>MeO</td>
<td>15</td>
<td>16</td>
<td>95</td>
<td>80</td>
<td>−96 (c=1.0)</td>
<td>S</td>
</tr>
<tr>
<td>5</td>
<td>H₂C₂O₉Me⁻</td>
<td>17</td>
<td>18</td>
<td>88</td>
<td>76</td>
<td>−64 (c=0.9)</td>
<td>−</td>
</tr>
<tr>
<td>6</td>
<td>Me₂CH₂-</td>
<td>19</td>
<td>20</td>
<td>81</td>
<td>87</td>
<td>+8.5 (c=1.2)²</td>
<td>S</td>
</tr>
<tr>
<td>7</td>
<td>Me₂CH₂-</td>
<td>21</td>
<td>22</td>
<td>78</td>
<td>78</td>
<td>+20 (c=0.5)²</td>
<td>S</td>
</tr>
</tbody>
</table>

a) A substrate (0.5 mmol) was treated with 1.1 mol eq of KHMDS at −78 °C for 30 min (for 9d, 11, 13, 15, and 17) or 60 min (for 19 and 21) followed by 10 mol eq of methyl iodide for 16 - 17 h at −78 °C. b) Enantiomeric excess (ee) was determined by HPLC analysis with chiral columns: 10d: Chiralpak AD, 2% iPrOH/hexane, 12, 14: Chiralpak AD, 5% iPrOH/hexane, 16, 18: Chiralpak AD, 5% iPrOH/hexane, 20 (benzotate): Chiralpak AS, 3% iPrOH/hexane, 22 (benzotate): Chiralpak AD, 1% iPrOH/hexane. d) Absolute configuration of the corresponding ω-methyl ω-amino acid. e) Not determined. f) Obtained as an inseparable mixture with the substrate. Yield was determined based on the ratio of signals observed in 400 MHz 1H NMR. Complete separation was achieved with the corresponding N-benzyl derivative. g) Optical rotation of the corresponding N-benzyl derivative.
that the corresponding potassium enolate could also exist in an axially chiral form with a relatively long half-life to racemization at low temperatures.

We next investigated the behavior of the potassium enolate intermediate toward racemization. When 9d was treated with KHMDH for 24 h at \(-78^\circ C\), the reaction of the resulting enolate with methyl iodide gave 10d (84% yield) of 36% ee (cf. 81% ee by 30-min base treatment; see Table 3, entry 1). When the enolate was prepared at \(-78^\circ C\) for 30 min, then kept at \(-40^\circ C\) for 30 min, its reaction with methyl iodide at \(-78^\circ C\) produced 10d (88% yield) of 5% ee. These results clearly indicate that racemization of the enolate intermediate took place. The barrier to racemization was determined through the periodic quench of the enolate intermediate generated at \(-78^\circ C\) with methyl iodide. Figure 3 plots the logarithm of the relative ee's of 10d as a function of time for base-treatment of 9d 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.11 The barrier was calculated from the slope (2k=5.34 \times 10^{-4} \text{ min}^{-1}) to be 16.0 kcal/mol at \(-78^\circ C\), which matches well the rotational barrier (16.8 kcal/mol) of the C(1)-N bond of 23. This suggests that the chirality of the potassium enolate also originates in the restricted rotation of the C(1)-N bond. We conclude that a chiral non-racemic enolate with dynamic axial chirality (E) is the origin for the present asymmetric induction. The half-life to racemization of the chiral enolate was 22 h at \(-78^\circ C\), which is long enough for the chiral enolate to undergo asymmetric methylation.

Support for this novel mechanism was obtained from the reactions of 25 and 27. Upon \(\alpha\)-methylation following the protocol in Table 3, the di-Boc derivative 25 (>99% ee) and methylene acetal derivative 27 (>99% ee) gave racemic 26 (95% yield) and 28 (95% yield), respectively. These results are consistent with the conclusions above, since the enolates F and G generated from 25 and 27, respectively, are not expected to be axially chiral along the C(1)-N axis.12

The stereochemical course (retention) of the transformation of 9d into 10d may be explained by assuming (Scheme 4): 1) deprotonation occurs from the stable conformer H where the C(1)-H bond is eclipsed with the N-C (MOM) bond13 to produce enantiomerically enriched chiral enolate (E), 2) an electrophile (methyl iodide) approaches from the sterically less demanding face (MOM) of the enolate double bond of E. This is no more than speculation but is consistent with the experimental result from 29 that undergoes \(\alpha\)-methylation in only 22% ee by the same treatment as that for 9d because of the smaller difference in the steric bulk between the MOM and CO\(_2\)Me groups than that between the two.

![Scheme 3. Dynamic axial chirality in 23](image)

![Figure 3. Plot of logarithm of the relative ee value of 10d (ln ee'/ ee) versus time (t) for base treatment of 9d. ee': The ee value of 10d obtained by the reaction of the enolate immediately after its generation from 9d with methyl iodide. ee: The ee value of 10d obtained by the treatment of 9d with KHMDH for the time indicated followed by addition of methyl iodide. 0.25 mmol of 9d was employed for each run. Reactions were quenched 30-min after the addition of methyl iodide to minimize racemization of the enolate intermediate during alkylation: ee'=80% (t=5 min), ee=10 min=79%, ee=30 min=76%, ee=180 min=74%, ee=420 min=63%, ee=1440 min=56%, ee=1680 min=37%.](image)

6. Memory of Chirality in Literature

More than 30 years ago, Marquet reported a surprising example of \(\alpha\)-chlorination of a chiral ketone 30 that gave optically active 31 in the absence of additional chiral sources.14 In 1981, Seebach reported that alkylation of aspartic acid derivative 32 gave a \(\beta\)-alkylated product (ca. 55%) as well as an \(\alpha\)-alkylated product 33 (ca. 15%) of ca. 60% ee.15 Recently, Koning reported that electron transfer-mediated benzyl substitution of 34 proceeded with retention of enantimeric purity.16 "Memory of chirality" has been also found in intramolecular reactions by Stoodly, Seebach, and Giese.17
The memory effect of chirality has been reported in host-guest interaction by Aida\textsuperscript{18} and also in macromolecular helicity by Yashima.\textsuperscript{19}

**Conclusion**

Asymmetric α-methylation of various N-MOM-N-Boc-α-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 (E) 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 in a moderate manner in the absence of any external chiral source. A chiral nonracemic enolate with dynamic axial chirality (E) 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).

The 2,3-dihydroxyazole ring in the potassium enolate G is supposed to be nearly planar.


**PROFILE**

Takeo Kawabata is an Associate Professor of Kyoto University. He was born in Osaka in 1955. He received his Ph.D degree in 1983 from Kyoto University under the guidance of Professor Eiichi Fujita. After working as a postdoctoral fellow (1983-1985) at Indiana University with Professor Paul A. Grieco, he joined Sagami Chemical Research Center as a researcher (1985-1989). He was appointed Assistant Professor of Institute for Chemical Research, Kyoto University, in 1989 and promoted to Associate Professor in 1998. He received the Pharmaceutical Society of Japan Award for Young Scientists in 1995. His research interests include asymmetric synthesis, enolate chemistry, and nucleophilic catalysis.

Kaoru Fuji received both his B.A. and Ph. D. degrees from Kyoto University. He was appointed Assistant Professor of the Institute for Chemical Research, Kyoto University in 1967. After a postdoctoral stay with James P. Kutney at the University of Texas at Austin (1971-1973), he was promoted to Associate Professor in 1973, and Professor in 1983. During that time, he joined Prof. P. Gassman's group at the University of Minnesota as a research fellow (1981-1982). Dr. Fuji has been the recipient of Pharmaceutical Society of Japan Award for Young Scientists (1980) and of Pharmaceutical Society of Japan Award (1998), and held a visiting position at Université Louis Pasteur de Strasbourg, France (1991 and 1994) and at Université Paris-Sud (1996).

Research interests include asymmetric synthesis, natural product synthesis, and design and synthesis of artificial receptors.

References and Notes


3) Recently, excellent catalytic methods for asymmetric synthesis of α,α-disubstituted α-amino acid derivatives have been developed; for examples, see: (a) Kuwano, R. Ito, Y. J. Am. Chem. Soc. 1999, 121, 3236. (b) Ooi, T.; Takeuchi, M.; Kameda, M.; Maruoka, K. J. Am. Chem. Soc. 2000, 122, 5228.


8) Conversion of 16 into α-methylidopa was accomplished in the following three-step sequence, since the treatment of 16 with 6 M HCl gave the conversion tetrhydroxysquinoline derivative: 1) TMSBr / Me2S, 2) 1 M NaOH, 3) 47%aq HBr.


10) The half-life at −78 °C was roughly estimated on the assumption that ΔS° of the restricted bond rotation is nearly zero.