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

Author(s): Kawabata, Takeo; Suzuki, Hideo; Nagae, Yoshikazu; Chen, Jianyong; Fuji, Kaoru

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Kyoto University
A Chiral Nonracemic Enolate with Dynamic Axial Chirality: Direct Asymmetric Alkylation of α-Amino Acid Derivatives

Takeo Kawabata, Hideo Suzuki, Yoshikazu Nagae, Jianyong Chen and Kaoru Fuji

The structure of enolate was long believed to be achiral. However, a chiral nonracemic enolate with a racemization barrier of 16 kcal/mol at -78 ºC was found to be the crucial intermediate for the asymmetric α-methylation of 1 to give 2 in 81% ee and 96% yield. The asymmetric α-methylation occurs in other amino acid derivatives (Val, Leu, Trp, His, Tyr, Dopa) in 78-93% ee.

Key words: chiral enolate / dynamic chirality / asymmetric synthesis / amino acid / axial chirality

SYNTHETIC ORGANIC CHEMISTRY — Fine Organic Synthesis —

The research interests of the laboratory include the development of new synthetic methodology, molecular recognition, and total synthesis of natural products. Programs are active in the areas of use of chiral leaving groups for an asymmetric induction, asymmetric alkylation of carbonyl compounds based on “memory of chirality”, development of new type of chiral nucleophilic catalysts, utilization of 8,8′-disubstituted 1,1′-binaphthyls as a chiral controller, visualization of molecular length by functionalized phenolphthalein, use of homoaxocalixarene for molecular recognition, syntheses of molecular switch.

Secretary: IZAWA, Yukako
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Guest Research Associate: MARX, Karsten H. (Ph. D); CHEN, Jianyong (Ph. D); STRAGIES Roland (Ph. D)
Students: MOMOSE, Yashima (DC); OHNISHI, Hiroshi (DC); NURUZZAMAN, Mohamamd (DC); OTSUBO, Tadamune (DC); YOSHIIDA, Hiroshi (MC); TANAKA, Hiroyuki (MC); SUZUKI, Ryutaro (MC); MUKOYOSHI, Koichiro (MC); KAWAKAMI, Shinpei (MC); FUKAYA, Takayuki (MC); KUSUMOTO, Tomokazu (MC); MORIMOTO, Tatsuya (MC)

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groups at the nitrogen gave satisfactory results. Treatment of phenylalanine derivative $^{1}$ with potassium hexamethyldisilazide (KHMDS) in toluene-THF (4:1) at $-78 \, ^\circ C$ for 30 min followed by methyl iodide gave $\alpha$-methylated product $^{2}$ in 96% yield and 81% ee.

Intermediate enolate was trapped with $t$-butyldimethylsilyl (TBS) triflate to give $Z$-enol silyl ether $^{3}$ and its $E$-isomer in a 2:1 ratio in combined isolated yields of 85%. The rotational barrier of the C(1)-N bond of $^{3}$ was determined to be 16.8 kcal/mol (365K) by variable-temperature NMR. The restricted bond rotation brings about axial chirality in $^{3}$ along the C(1)-N axis, as shown in D. On the other hand, the rate of racemization of the potassium enolate intermediate was determined to be $5.3 \times 10^{-4}$/min at $-78 \, ^\circ C$ through the periodic quenching of the enolate generated from $^{1}$ and KHMDS with methyl iodide. The barrier of racemization of the enolate was calculated to be 16.0 kcal/mol, which matches the rotational barrier of the C(1)-N bond of $^{3}$. This suggests that the chirality of the potassium enolate also originates in the restricted rotation of the C(1)-N bond. It is concluded that a chiral nonracemic enolate with axial chirality 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 sufficiently long for the chiral enolate to undergo asymmetric methylation $^{[1]}$.

Support for this novel mechanism was obtained from the reactions of di-Boc derivative $^{4}$. Upon $\alpha$-methylation, $^{4}$ gave racemic $^{5}$ in 95% yield. The result is consistent with the conclusions above, since the enolate generated from $^{4}$ can not be axially chiral along the C-N axis.

Asymmetric $\alpha$-methylation also occurred enantioselectively ($78 \sim 93\%$ ee) in various $\alpha$-amino acid derivatives in the absence of any external chiral sources (Table 1). The stereochemical course of $\alpha$-methylation was retention $^{[2]}$.

The protocol for the asymmetric $\alpha$-alkylation was applied to isoleucine and $\textit{allo}$-isoleucine derivatives $^{6}$ and $^{8}$ that possess chiral centers at both C(2) and C(3). $\alpha$-Methylation of $^{6}$ gave $^{7}$ as a major product whereas $^{8}$ gave $^{9}$ predominantly, although both $^{6}$ and $^{8}$ have (S)-chiral center at C(3). This indicates that chirality at C(2) in $^{6}$ and $^{8}$ was preserved in the corresponding enolate intermediates and the induced chirality made a major contribution in the stereochemical course of the reaction, while chirality at the adjacent chiral center C(3) had little effect $^{[3]}$.

In conclusion, a chiral nonracemic enolate with dynamic axial chirality was shown to be the crucial intermediate for direct asymmetric $\alpha$-alkylation of $\alpha$-amino acid derivatives. Some other enolates with a restricted bond rotation should have axial chirality with an intrinsic barrier to racemization. Because 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.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Yield [%]</th>
<th>ee [%]</th>
<th>Configuration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhCH$_2$-</td>
<td>96</td>
<td>81</td>
<td>S</td>
</tr>
<tr>
<td>2</td>
<td>$t$-BuOCO</td>
<td>83</td>
<td>93</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>MeOCH$_2$O-</td>
<td>94</td>
<td>79</td>
<td>S</td>
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<td>4</td>
<td>MeOCH$_2$O-</td>
<td>95</td>
<td>80</td>
<td>S</td>
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<td>76</td>
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<tr>
<td>7</td>
<td>Me$_2$CH$_2$-</td>
<td>78</td>
<td>78</td>
<td>S</td>
</tr>
</tbody>
</table>

a) A substrate (0.5 mmol) was treated with 1.1 mol eq of KHMDS in toluene-THF (4 : 1) at $-78 \, ^\circ C$ for 30 min (for entries 1-5) or 60 min (for entries 6 and 7) followed by 10 mol eq of methyl iodide for 16 - 17 h at $-78 \, ^\circ C$.

References