Memory of Chirality

An Emerging Strategy for Asymmetric Synthesis
The **concept** of memory of chirality describes a phenomenon in which the "the chirality of a starting material having a chiral sp3 carbon is preserved in the reaction product even though the reaction proceeds at the chiral carbon as a reaction center through reactive intermediates such as carbanions, singlet monoradicals, biradicals, or carbenium ions".

OL, **2002**, 4, 1875.

Memory of chirality describes a phenomenon in which the information on chirality in the original system is kept in a reactive intermediate for a limited time.

1) From static, central chirality to transient, conformational chirality;
2) Then back again
A ‘memory of chirality’ reaction can be defined as a formal substitution at an sp³ stereogenic center that proceeds stereospecifically, even though the reaction proceeds by trigonalization of that center, and despite the fact that no other permanently chiral elements are present in the system.
‘central chirality at a carbon alpha to a carbonyl group is preserved as transient axial chirality of the intermediate enolate and is then regenerated as central chirality in the reaction product (memory of chirality)’;¹

‘the chirality of the starting material is preserved in a reactive intermediate for a limited time’;³

‘the chirality of a starting material having a chiral sp³-carbon is preserved in the reaction product even though the reaction proceeds at the chiral carbon as a reaction center through reactive intermediates such as carbanion, singlet monoradicals, biradicals, or carbenium ions’;⁴
Dynamic Chirality

what kind of lifetime is needed for the conformationally chiral reactive intermediate?

<table>
<thead>
<tr>
<th>Racemization barrier $\Delta G^\ddagger$ (kcal/mol)</th>
<th>Racemization $t_{1/2}$ at $-78 , ^{\circ}C^a$</th>
<th>Racemization $t_{1/2}$ at $25 , ^{\circ}C^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>2.4 s</td>
<td>$3.5 \times 10^{-5}$ s</td>
</tr>
<tr>
<td>14</td>
<td>7 min</td>
<td>$1.0 \times 10^{-3}$ s</td>
</tr>
<tr>
<td>16</td>
<td>20 h</td>
<td>$3.0 \times 10^{-2}$ s</td>
</tr>
<tr>
<td>18</td>
<td>148 d</td>
<td>0.9 s</td>
</tr>
<tr>
<td>20</td>
<td>70 years</td>
<td>26 s</td>
</tr>
</tbody>
</table>

$^a$ Racemization $t_{1/2} = \ln 2/k_{\text{rac}}$, where $k_{\text{rac}} = 2^*(kT/h)*\exp(-\Delta G^\ddagger/RT)$.

sp3-sp3 bond, since such bonds typically have barriers to rotation of less than 7 kcal/mol. In contrast, sp2-sp2 bonds have been used extensively as a source of conformational chirality in intermolecular reactions, since barriers in excess of 16 kcal/mol are easily achieved.
Memory of Chirality in Enolate Chemistry

Seebach

Firstly, reaction could proceed through a mixed aggregate of chiral enolate 7 and achiral enolate 8.

Second possibility is that enolate 8 possessed axial chirality, due to a non-co-planar orientation of the enolate and imine moieties.
Fuji was the first to intentionally design a reaction that would capitalize on the MOC phenomenon.
Reagents and conditions: (i) KH, 18-crown-6, THF, −78 °C to −20 °C

18 was found to racemize with a half-life of 53 minutes, corresponding to a barrier of 22.6 kcal/mol.
Enantioselective $\alpha$-Alkylation of Amino Acid Esters without External Chiral Sources
Two non-identical nitrogen protecting groups that differ widely in steric bulk.

Table 2  Asymmetric Methylation of (S)-22

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base (equiv)</th>
<th>Yield (%)</th>
<th>ee (% , configuration)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LiTMP (1.0)</td>
<td>40</td>
<td>82 (S)</td>
</tr>
<tr>
<td>2</td>
<td>LDA (1.2)</td>
<td>57</td>
<td>22 (S)</td>
</tr>
<tr>
<td>3</td>
<td>KHMDS (1.2)</td>
<td>79</td>
<td>20 (R)</td>
</tr>
</tbody>
</table>

Table 3  Asymmetric α-Methylation of N-MOM-N-Boc α-Amino Acid Derivatives

<table>
<thead>
<tr>
<th>Substrate</th>
<th>R</th>
<th>Yield (%)</th>
<th>ee (% , configuration)</th>
</tr>
</thead>
<tbody>
<tr>
<td>24a</td>
<td>PhCH₂</td>
<td>96</td>
<td>81 (S)</td>
</tr>
<tr>
<td>24b</td>
<td></td>
<td>83</td>
<td>93</td>
</tr>
<tr>
<td>24c</td>
<td></td>
<td>94</td>
<td>79 (S)</td>
</tr>
<tr>
<td>24d</td>
<td></td>
<td>95</td>
<td>80 (S)</td>
</tr>
<tr>
<td>24e</td>
<td></td>
<td>88</td>
<td>76</td>
</tr>
<tr>
<td>24f</td>
<td>Me₂CH</td>
<td>81</td>
<td>87 (S)</td>
</tr>
<tr>
<td>24g</td>
<td>Me₂CHCH₂</td>
<td>78</td>
<td>78 (S)</td>
</tr>
</tbody>
</table>

Table 1  Influence of the temperature on the ee in the α-methylation of (S)-11.

<table>
<thead>
<tr>
<th>Run</th>
<th>Conditions for enolate formation</th>
<th>Yield (%)</th>
<th>% ee&lt;sup&gt;[b]&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>−78°C, 0 min</td>
<td>9</td>
<td>74</td>
</tr>
<tr>
<td>2</td>
<td>−78°C, 15 min</td>
<td>40</td>
<td>82</td>
</tr>
<tr>
<td>3</td>
<td>−78°C, 60 min</td>
<td>28</td>
<td>81</td>
</tr>
<tr>
<td>4</td>
<td>−78°C, 15 min, then −40°C, 15 min</td>
<td>39</td>
<td>10</td>
</tr>
<tr>
<td>5</td>
<td>−78°C, 15 min, then RT, 45 min</td>
<td>26</td>
<td>≈0</td>
</tr>
</tbody>
</table>

[a] The enolate was quenched with methyl iodide at −78°C.  [b] Determined as an N-benzoyl derivative.
Can the structural features that contribute to MOC successfully compete against the influence of a nearby chiral center?
Enantioselective Synthesis of Azacyclic Amino Acids

Cyclic amino acids with a quaternary stereocenter constitute a valuable class of nonnatural amino acids with highly constrained conformations.

N-Boc group was critical to the intermolecular enantioselective a methylation of a amino acid esters via memory of chirality.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>n</th>
<th>R</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>32a</td>
<td>3</td>
<td>PhCH₂</td>
<td>94</td>
<td>98 (S)</td>
</tr>
<tr>
<td>32b</td>
<td>3</td>
<td>4-EtO-C₆H₄-CH₂</td>
<td>95</td>
<td>97</td>
</tr>
<tr>
<td>32c</td>
<td>3</td>
<td>MeSCH₂CH₂</td>
<td>92</td>
<td>97</td>
</tr>
<tr>
<td>32d</td>
<td>3</td>
<td>Me₂CH</td>
<td>78</td>
<td>94</td>
</tr>
<tr>
<td>32e</td>
<td>3</td>
<td>CH₃</td>
<td>91</td>
<td>95 (R)</td>
</tr>
<tr>
<td>32f</td>
<td>2</td>
<td>PhCH₂</td>
<td>61</td>
<td>95</td>
</tr>
<tr>
<td>32g</td>
<td>4</td>
<td>PhCH₂</td>
<td>84</td>
<td>97</td>
</tr>
<tr>
<td>32h</td>
<td>5</td>
<td>PhCH₂</td>
<td>31</td>
<td>83 (S)</td>
</tr>
</tbody>
</table>
Proposed Mechanism of Asymmetric Induction in the Deprotonation/Alkylation of Amino Acid Esters

Mechanistic studies:

* Possible sources of asymmetric induction:

- **SM/enolate aggregates**
- **Chiral enolate with central chirality**
- **Chiral enolate with axial chirality**
A 1:1 mixture of (S)-22 and (±)-37 were subjected to deprotonation with LiTMP at −78 °C followed by addition of methyl iodide, to afford optically active 23 (74% ee, 26% yield) and racemic 38 (30% yield). The same treatment of a 1:1 mixture of racemic 22 and optically active 37 (96% ee) afforded the racemic 23 (17% yield) and optically active 38 (71% ee, 24% yield). These results clearly demonstrate that transfer of chirality between the enolates derived from 22 and 37 does not occur.
The methylene protons of the MOM groups are diastereotopic in both isomers of 39, indicating restricted rotation of the C(2)–N bond. The rotational barrier of the C(2)–N bond in the major Z-isomer of 39 was determined to be 16.8 kcal/mol by variable temperature $^1$H NMR measurements in toluene-$d_8$. This barrier corresponds to a racemization half-life of seven days at $-78 \, ^\circ\text{C}$. Thus, the formation of a slowly racemizing axially chiral potassium enolate appears feasible. The racemization barrier of the potassium enolate was then directly measured by periodic quenching of the enolate intermediate generated from 24a at $-78 \, ^\circ\text{C}$ with methyl iodide. The plot of the relative ee value of 25a (ln ee$_0$/ee$_\text{eq}$) versus deprotonation time ($t$) was linear, and the racemization rate was calculated from the slope ($2k = 5.34 \times 10^{-4}$ min$^{-1}$, corresponding to a racemization half-life of 22 h at $-78 \, ^\circ\text{C}$). Application of the Eyring–Arrhenius equation yields a barrier of 16.8 kcal/mol.
In support of the proposal that axially chiral enolates such as 36 underly the MOC deprotonation/alkylation of amino acid esters, Fuji and Kawabata reported isolation of the \((Z)\)- and \((E)\)-TBS ketene acetals 39 (Figure 3).\(^\text{13}\)
Deprotonation/methylation of enantiopure (S)-40 and (S)-41 gave racemic 42 and racemic 43 respectively. These racemic results are consistent with the intermediacy of achiral enolates. For 40, the presence of two identical Boc protecting groups removes the possibility of chirality on the N–C(2) axis. In the case of 41, the five-membered ring prevents the N substituents from rotating out of the enolate plane to attain axial dissymmetry.
* To explain the retained stereochemistry of the product:

![Chemical structure diagram]

most stable conformer (S)  
(chiral enolate)  
product (S)  
\[ \Delta G_{\text{rot(C-N bond)}} = 16 \text{ kcal/mol (at -78 °C)} \]

* To certify the implication of an axially chiral enolate:

![Chemical structure diagram]

Synthesis, 2005, 1368  
racemic mixtures

AGIE 2000, 39, 2155
Other Cyclization Reactions Involving Axially Chiral Enolate Intermediates

\[
\begin{align*}
\text{48} & \xrightarrow{\text{NaOMe, MeOH}} \text{49 (37\% yield)} + \text{50 (35\% yield)} \\
\text{51} & \xrightarrow{\text{racemization}} \text{ent-51} \\
\text{52 (major conformer of 48)} & \xrightarrow{\text{racemization}} \text{53 (minor conformer of 48)}
\end{align*}
\]
\[
\text{54} \xrightarrow{\text{Et}_3\text{N, MeOH, reflux}} \text{55}
\]

\[
\text{PhCH}_2\text{CO}_2\text{t-Bu} \xrightarrow{\text{Cs}_2\text{CO}_3, \text{MeCN}} \text{59} \rightarrow \text{60 (53\% yield)}
\]

\[
\text{56} \xrightarrow{\text{KCN, MeOH}} \begin{array}{c}
\text{57} \text{OH} \\
+ \\
\text{58} \text{OH}
\end{array}
\]

\[
\text{57:58} = 72:28 \text{ (combined yield 68\%)}
\]
Enantioselective Synthesis of Quaternary 1,4-Benzodiazepin-2-ones

\[
\begin{align*}
\text{R}^1 & \quad \text{Me} & \quad \text{(S)-61a} & \quad \text{(R)-62a} & \quad \%\text{ee} & \quad \%\text{yield} \\
\text{R}^1 & \quad \text{i-Pr} & \quad \text{(S)-61b} & \quad \text{(R)-62b} & \quad 97 & \quad 74
\end{align*}
\]

\[
\begin{align*}
\text{R}^2 & \quad \text{E}^b & \quad \text{Product} & \quad \text{Yield} & \quad \text{ee} \\
\text{Me} & \quad \text{Bn} & \quad (+)-62b & \quad 74 & \quad 97 (3R) \\
\text{Me} & \quad 4\text{-MeC}_6\text{H}_4\text{CH}_2 & \quad (+)-64b & \quad 68 & \quad 95 (3R) \\
\text{Me} & \quad 2\text{-PhC}_6\text{H}_4\text{CH}_2 & \quad (+)-65b & \quad 70 & \quad 99 \\
\text{Me} & \quad \text{allyl} & \quad (+)-66b & \quad 76 & \quad 94 \\
\text{Me} & \quad \text{D} & \quad (+)-67b & \quad 85^c & \quad 99 (3S) \\
\text{Bn} & \quad \text{Me} & \quad (-)-62b & \quad 64 & \quad 95 (3S) \\
\text{Bn} & \quad \text{allyl} & \quad (+)-68b & \quad 57 & \quad 86
\end{align*}
\]
\[
\begin{array}{|c|c|}
\hline
R^1 & \Delta G^\ddagger (\text{kcal/mol})^a \\
\hline
69a & H & 12.3^b \\
69b & Me & 18.0^c \\
69c & i-Pr & 21.1^c \\
69d & t-Bu & >24^d \\
\hline
\end{array}
\]
Memory of Chirality in Radical Chemistry

As such, 72 would have a significant barrier to rotation along the benzylic bond; DFT calculations indicated a barrier of 13.2 kcal/mol for the racemization of 72, corresponding to a half-life of about one minute at −78 °C (Scheme 20).
<table>
<thead>
<tr>
<th>Entry</th>
<th>RX</th>
<th>Product</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TMSCl</td>
<td>74a</td>
<td>72</td>
<td>87</td>
</tr>
<tr>
<td>2</td>
<td>PhCH$_2$Br</td>
<td>74b</td>
<td>37</td>
<td>87</td>
</tr>
<tr>
<td>3</td>
<td>MeOC(O)Cl</td>
<td>74c</td>
<td>67</td>
<td>86</td>
</tr>
<tr>
<td>4</td>
<td>Me$_2$NC(O)Cl</td>
<td>74d</td>
<td>57</td>
<td>84</td>
</tr>
</tbody>
</table>
Retentive Radical Trapping Controlled by a Slow Ring Inversion
Memory of Chirality in Radical Cyclization

[Chemical structures and reactions depicted graphically]
Memory of Chirality in the Cyclization of Photochemically Generated Diradicals

\[
\begin{align*}
(M)-84 & \quad 97\% \text{ ee} \\
(P)-84 & \quad 95\% \text{ ee} \\
(M)-85 & \quad \text{cyclization to pro-S face} \\
(P)-85 & \quad \text{cyclization to pro-R face} \\
(R)-86 & \quad 84\% \text{ ee} \\
(S)-86 & \quad 82\% \text{ ee}
\end{align*}
\]

Bu$_3$SnH
Et$_3$B/O$_2$
25 $^\circ$C, C$_6$H$_6$
100 $^\circ$C
Unrestricted Hartree–Fock calculations on 90 indicated that rotation of the β-single bond would be the slow step of racemization, and would feature a barrier of 5 kcal/mol. This barrier, though quite low, is higher than the expected 2 kcal/mol barrier for cyclization of the singlet diradical.
Memory of Chirality Involving Carbocation Intermediates

[Chemical structures and reactions are depicted here, illustrating the transformation and yield details.]
Memory of Chirality in Total Synthesis

Scheme 1. A key reaction for the synthesis of (−)-penibruguieramine (1).²

