Memory of Chirality: An Emerging Strategy for Asymmetric Synthesis

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Abstract: ‘Memory of chirality’ (MOC) is an intriguing strategy for asymmetric synthesis because it appears to do the impossible: the sole chiral center of a molecule directs the stereochemical course of a reaction even though that center is destroyed in the key reactive intermediate. This review describes the critical role of transient conformational chirality in these processes, and defines the three essential requirements for success in an MOC method. The growing application of MOC to asymmetric synthesis methodology is discussed, with extensive coverage of enolate, radical, photochemical and carbocation reactions.

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Keywords: asymmetric synthesis, dynamic chirality, enolates, memory of chirality, stereoselectivity

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1 Introduction
The term 'memory of chirality' (MOC) was coined by Fuji, who was the first to successfully design a reaction to capitalize on this principle.1 The proposal that MOC could underly reaction enantioselectivity was actually first offered by Seebach (vide infra).2 MOC has attracted attention in part because it appears to do the impossible: how can the memory of the sole chiral center of a substrate be retained in a process that destroys that center? MOC has been described as a phenomenon in which:

- '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',2
- '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

Although all these definitions capture the key concept of MOC, the last definition by Matsumura5 best illustrates the scope of intermediates to which it has been applied. Yet for the purpose of this review, we would offer our own definition:

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.

As Fuji’s 1991 definition1 illustrates, the key to this phenomenon is the preservation of the static central chirality of the starting material in the form of transient (or ‘dynamic’) conformational chirality of the reactive intermediate. Thus, MOC methods offer a conceptually different approach to stereocontrol than Seebach’s Self Regeneration of Sterocenters (SRS) strategy,3 which relies upon the influence of a permanent chiral center in the reactive intermediate. The concept of dynamic chirality will be discussed below, as will additional requirements for successful MOC transformations. Fuji and Kawabata have published two excellent reviews on MOC,3,6 the latter of which appeared during the writing of this review. Whereas these reviews focus principally on enolate chemistry, in this review we attempt a broader review of work in this area.

1.1 Requirements for Memory of Chirality

Beginning students of organic chemistry learn that if an enantiopure sp3-hybridized stereogenic center is trigonalized, any chiral products resulting from that intermediate will be racemic (Scheme 1).
Can circumstances be imagined that would allow this axiom to be violated? In the absence of any other chiral controllers, a non-racemic outcome would only be possible if the intermediate possesses some form of conformational chirality.\(^1\)\(^2\) By its very nature, this conformational chirality will be short-lived; Fuji and Kawabata have termed this phenomenon ‘dynamic chirality’,\(^3\) since the enantio purity of the intermediate is dependent on time and temperature. To illustrate this concept, these authors contrast the chirality present in phenylalanine 1 and phenylpropionic acid 2 (Figure 1).

Phenylalanine 1 possesses static, central chirality. Phenylpropionic acid 2, however, is normally considered to be achiral. Closer consideration leads to the realization that in addition to the achiral anti-conformation 2-a typically drawn for phenylpropionic acid, two chiral, enantiomeric gauche conformations 2-g\(^{+}\) and 2-g\(^{-}\) exist. Of course, under normal conditions, these enantiomeric conformations interconvert rapidly by single bond rotation. Nevertheless, under appropriate circumstances, conformational chirality could influence the stereochemical fate of a reactive intermediate.

Biographical Sketches

Hongwu Zhao was born in China (1968). He received his B.Sc. (1992) and M.Sc. (1995) degrees in Chemistry in China at Northeast Normal University, and then served as a lecturer at Dalian Technology University. In 2000, he received his Ph.D. in Chemistry from Peking University under the supervision of Professor Wenting Hua, and then did postdoctoral research at the University of Hong Kong with Professor Dan Yang. From 2001 to 2004, he performed postdoctoral research in Professor Carlier’s lab at Virginia Tech on memory of chirality routes to quaternary 1,4-benzodiazepin-2-ones. His research interests include molecular recognition, asymmetric synthesis methodology and synthesis of biologically active molecules.

Danny Hsu was born in Hong Kong (1980). He received his B.Sc. (First Class Honor) degree in Chemistry from the Hong Kong University of Science and Technology in 2002, where he did undergraduate research with Professors L. L. Yeung and C. K. Chang. He is now a Ph.D. candidate at Virginia Tech under the guidance of Professor Carlier. He is currently working on memory of chirality methods for the enantioselective synthesis of quaternary benzodiazepine derivatives.

Paul R. Carlier was born in the United States (1961). He received his B.A. (1983) in Chemistry from Hamilton College, where he undertook undergraduate research with Professor Robin B. Kinnel. In 1988, he received his Ph.D. from the Massachusetts Institute of Technology, working with Professor K. Barry Sharpless on asymmetric epoxidation and epoxide ring-opening reactions. After three years in industry (Polaroid Corporation), he took his first academic position at the Hong Kong University of Science and Technology in 1991. In 2000, he accepted his current position as Associate Professor in the Department of Chemistry at Virginia Tech (USA). His research interests include stereoselective and asymmetric synthesis, medicinal chemistry, and structural investigations of organolithiums.
However, formation of a conformationally chiral intermediate is not a sufficient condition for MOC: this intermediate must be formed enantioselectively. The essential requirements for a MOC reaction are illustrated for a hypothetical deprotonation/methylation in Scheme 2.

Scheme 2

Firstly, deprotonation of the stereogenic center in the enantiopure reactant (S)-A-H must generate a conformationally chiral reactive intermediate (M)-A- with high enantioselectivity. We use the helical descriptors (M)- and (P)- to describe the chirality of the intermediates; the choice of (M)-helicity in this example is arbitrary. Secondly, this conformationally chiral intermediate (M)-A- must not readily racemize, at least not on the time scale of the desired subsequent reaction. Finally, the conformationally chiral intermediate must react with MeI with high stereospecificity to produce (S)-A-Me (again, the choice of (S)-configuration is arbitrary). Failure to meet all three of these requirements will result in little or no enantioselectivity. Note that both steps of the MOC process involve transfer of chirality: from static, central chirality to transient, conformational chirality (1), and then back again (2). How to ensure efficient chirality transfer in both steps is not immediately clear, and represents the essential challenge of the MOC strategy.

1.2 Dynamic Chirality

Since conformational chirality is by definition transient, one question arises immediately: what kind of lifetime is needed for the conformationally chiral reactive intermediate? Assuming that racemization of this intermediate is a unimolecular process, the Eyring equation provides a physical chemical foundation upon which to design MOC methods (Table 1).

Table 1  Dependence of Racemization t_{1/2} on Barrier and Temperature

<table>
<thead>
<tr>
<th>Racemization barrier</th>
<th>Racemization t_{1/2} at −78 °C</th>
<th>Racemization t_{1/2} at 25 °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>∆G‡ (kcal/mol)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>2.4 s</td>
<td>3.5 × 10⁻⁵ s</td>
</tr>
<tr>
<td>14</td>
<td>7 min</td>
<td>1.0 × 10⁻³ s</td>
</tr>
<tr>
<td>16</td>
<td>20 h</td>
<td>3.0 × 10⁻² s</td>
</tr>
<tr>
<td>18</td>
<td>148 h</td>
<td>0.9 s</td>
</tr>
<tr>
<td>20</td>
<td>70 years</td>
<td>26 s</td>
</tr>
</tbody>
</table>

* Racemization t_{1/2} = ln 2/k_{rac}, where k_{rac} = 2*(kT/h)*exp(−∆G‡/RT).

As shown in Table 1, at −78 °C, a barrier of 16 kcal/mol would provide a reactive intermediate sufficient time to undergo a slow intermolecular reaction without significant racemization. However, at room temperature, racemization would proceed two million times faster, and intramolecular reaction or solvent trapping would appear to provide the only way to achieve enantioselective reaction of such an intermediate. From a design standpoint, therefore, successful intermolecular MOC reactions rarely depend upon hindered rotation around an sp²–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.

2 Memory of Chirality in Enolate Chemistry

The MOC phenomenon was first demonstrated in the field of enolate chemistry, and to date, enolates have proven the most fertile ground for the application of the MOC principle.

2.1 α-Alkylation of an Aspartic Acid Ester Enolate

In the course of studying β-alkylation of diethyl malate via its dilithiated derivative, Seebach and Wasmuth turned their attention to the N-formyl aspartic acid ester analog (Scheme 3).

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In addition to obtaining the expected β-alkylation product 9, they obtained a 15% yield of the α-alkylation product 10. Unexpectedly, 10 was isolated in 60% ee. To account for how 10 was obtained in enantiomerically enriched form from an intermediate 8 that possessed no chiral center, Seebach proposed two explanations. Firstly, reaction could proceed through a mixed aggregate of chiral enolate 7 and achiral enolate 8. In this way, chiral enolate 7 would act as a chiral controller for alkylation of the achiral enolate 8. A second possibility is that enolate 8 possessed axial chirality, due to a non-co-planar orientation of the enolate and imine moieties (as depicted in Scheme 3). Although the original paper did not record any experiments to discriminate between these two mechanistic scenarios, Seebach later suggested that the mixed aggregate scenario was operative. Thus, MOC (as defined in Section 1 above) may not be responsible for asymmetric induction in 10. Nevertheless, as will become clear in the course of this review, amino acid derivatives have proven very fertile ground for MOC methods, and axial chirality along the N–C(2) bond of amino acid ester enolates has been shown to play a major role in many of these reactions.

2.2 Designed Asymmetric Alkylation of a Naphthyl Ketone

Fuji was the first to intentionally design a reaction that would capitalize on the MOC phenomenon. His key insight was that deprotonation of a stereogenic center α to a carbonyl in 11 need not always lead to an achiral enolate intermediate 12 (Scheme 4).

![Scheme 4](image)

Under the appropriate circumstances, conformationally chiral enolates might be formed, such as axially chiral 13 or planar chiral 14. Of course, for a successful MOC reaction, these chiral enolates would need to be formed enantioselectively, and not racemize quickly on the alkylation reaction time scale.

To achieve a slowly racemizing, axially chiral enolate intermediate, Fuji and Kawabata chose to explore deprotonation of chiral 1-naphthylketone 15. Deprotonation of 15 with KH/18-crown-6, followed by trapping with MeI gave the desired product 17 in 66% ee (Scheme 5).

![Scheme 5](image)

This stunning result clearly indicates the formation of a nonracemic chiral enolate intermediate. The authors proposed that the reaction occurs via the axially chiral enolate 16, whose structure is reminiscent of the atropisomeric 1,1-binaphthyls. Support for an axially chiral enolate such as 16 came from two other observations. First, O-alkylation product 18 was also detected in the reaction mixture, and HPLC analysis immediately following the reaction indicated 65% ee. At room temperature (21 °C), 18 was found to racemize with a half-life of 53 minutes, corresponding to a barrier of 22.6 kcal/mol. Secondly, compound 19, the phenyl analog of 15, was subjected to the same reaction conditions but gave racemic 20. This result is consistent with the expectation that the enolate derived from 19 would possess a lower barrier for rotation along the 1,1' bond than would the 1-naphthyl analog 16.

2.3 Enantioselective α-Alkylation of Amino Acid Esters without External Chiral Sources

Asymmetric synthesis of α-substituted α-amino acids has attracted considerable attention because of the biological and medicinal importance of these compounds. Fuji and Kawabata realized that these compounds could poten-
Memory of Chirality

Three types of enolate chirality can be envisioned: axial (A), planar (B), and central (C). A key design feature of the authors is the use of two non-identical nitrogen protecting groups that differ widely in steric bulk. The authors’ first published report relied upon N-Me, N-Boc amino acid esters (Table 2).12

As hoped, non-racemic products were obtained, the best % ee being realized with LiTMP as base (entry 1). Interestingly, both lithium bases gave retention, but KHMDS gave a predominance of inversion (20% ee). Although this work represents a major achievement, the yield under the most enantioselective conditions is clearly not acceptable, and the products are not easily demethylated. Six years later, Kawabata and Fuji reported a greatly superior protocol that relies upon N-MOM, N-Boc amino acid esters (Table 3).13

As can be seen in Table 3, the N-MOM,N-Boc amino acid esters are alkylated in 76–93% ee and 78–96% yield. In addition to providing superior yields and enantioselection, the two protecting groups are easily removed during acidic ester hydrolysis (6 M aq HCl), affording the corresponding α-Me-α-amino acids in 51–86% yields. In each case where correlation was performed, the α-methylation was shown to proceed with retention of configuration.

Table 2

<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>

Substrate R Yield (%) ee (% configuration)

Table 3

<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>
2.4 Enantioselective Synthesis of Azacyclic Ami-no Acids

Cyclic amino acids with a quaternary stereocenter constitute a valuable class of nonnatural amino acids with highly constrained conformations. The importance of these compounds has motivated the development of efficient methods for their asymmetric synthesis.\textsuperscript{14} Kawabata et al. reported a simple and efficient protocol for asymmetric intramolecular cyclization of $\alpha$-amino acid derivatives to afford a variety of quaternary azacyclic amino acids of high enantiomeric purity.\textsuperscript{15} Knowing that the $N$-Boc group was critical to the intermolecular enantioselective $\alpha$-methylation of $\alpha$-amino acid esters via memory of chirality, Kawabata et al. designed a series of $N$-Boc-$N$-$\omega$-bromoalkyl-$\alpha$-amino acid derivatives $32a$–$h$ as substrates for asymmetric intramolecular cyclization (Table 4).

Treatment of $32a$–$h$ with KHMDS in THF at $-60$ °C gave the corresponding optically active azacyclic amino acid derivatives $33a$–$h$ in 31–95% yields and 83–98% ee (Table 4). Thus, by this protocol the enantioselective construction of four-, five-, six-, and seven-membered azacyclic amino acids was achieved. The chirality of the parent amino acids was almost completely preserved during enolate formation and subsequent cyclization, giving enantiotomerically enriched azacyclic quaternary amino acids with retention of configuration.

2.5 Proposed Mechanism of Asymmetric Induction in the Deprotonation/Alkylation of Ami-no Acid Esters

Fuji and Kawabata have carried out a number of mechanistic investigations that support the role of MOC in stereochemical control. As discussed in section 2.2 above, in the alkylation of naphthyl ketone 15, axially chiral enol ether 18 was isolated (Scheme 5). For the enantioselective deprotonation/alkylation of $N$-Boc,$N$-Me amino acid esters 22, the authors considered several mechanistic scenarios (Figure 2).

Asymmetric induction could arise from a chiral enolate/starting material aggregate 34, a species 35 with a chiral $N$ atom, or an axially chiral enolate 36. To rule out the intermediacy of a chiral enolate/starting material aggregate such as 34, the authors conducted a crossover experiment (Scheme 8).\textsuperscript{12}

<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>PhCH$_2$</td>
<td>94</td>
<td>98 (S)</td>
</tr>
<tr>
<td>32b</td>
<td>3</td>
<td>4-EtO-C$_6$H$_4$-CH$_2$</td>
<td>95</td>
<td>97</td>
</tr>
<tr>
<td>32c</td>
<td>3</td>
<td>MeSCH$_2$CH$_2$</td>
<td>92</td>
<td>97</td>
</tr>
<tr>
<td>32d</td>
<td>3</td>
<td>Me$_2$CH</td>
<td>78</td>
<td>94</td>
</tr>
<tr>
<td>32e</td>
<td>3</td>
<td>CH$_3$</td>
<td>91</td>
<td>95(R)</td>
</tr>
<tr>
<td>32f</td>
<td>2</td>
<td>PhCH$_2$</td>
<td>61</td>
<td>95</td>
</tr>
<tr>
<td>32g</td>
<td>4</td>
<td>PhCH$_2$</td>
<td>84</td>
<td>97</td>
</tr>
<tr>
<td>32h</td>
<td>5</td>
<td>PhCH$_2$</td>
<td>31</td>
<td>83 (S)</td>
</tr>
</tbody>
</table>
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. Thus, asymmetric induction in these reactions is not due to formation of a chiral enolate starting material aggregate such as 34. Interestingly, however, in a subsequent study on deprotonation/methylation of O-methyl mandelic acid amides, Fuji and Kawabata did find support for a mixed aggregate mechanism for asymmetric induction.16

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 acetics 39 (Figure 3).13

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 1H NMR measurements in toluene-d8. This barrier corresponds to a racemization half-life of seven days at −78 °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 °C with methyl iodide. The plot of the relative ee value of 25a (in ee0/ee) versus deprotonation time (t) was linear, and the racemization rate was calculated from the slope (2k = 5.34 × 10−4 min−1, corresponding to a racemization half-life of 22 h at −78 °C). Application of the Ey-slope (2k = 5.34 × 10−4 min−1, corresponding to a racemization half-life of 22 h at −78 °C). Application of the Ey-slope (2k = 5.34 × 10−4 min−1, corresponding to a racemization half-life of 22 h at −78 °C). Application of the Ey-

Scheme 8: Reagents and conditions: i) LiTMP, THF, −78 °C; ii) MeI.
Deprotonation yields the axially chiral nonracemic enolate 45. Steric control of the alkylation then leads to retentive methylation and formation of (S)-25a. Fuji and Kawabata proposed a similar mechanism to account for the retentive cyclization of (S)-32a (Scheme 10).

Scheme 10

In this case, a conformational search identified two stable conformers, 46a,b, of similar energy. The authors proposed that deprotonation of 46b is disfavored due to a steric interaction between KHMDS and the N-Boc group. Thus, deprotonation of 46a is favored, to give axially chiral nonracemic enolate 47 which then cyclizes to give (S)-33a.

The mechanistic rationale offered by Fuji and Kawabata for retentive deprotonation/alkylation of amino acid esters 22, 24, and 32 is powerful in its simplicity. One experimental detail that is not accommodated by the model as laid out thus far is the lower enantioselectivity obtained with electrophiles other than MeI. To account for this variation, Fuji and Kawabata proposed that enolate aggregates exist in solution and possess differential reactivities and selectivities toward individual electrophiles. In support of this idea, the authors demonstrated superior allylation % ee with homo- and heterodimeric substrates designed to form intramolecular aggregates.17,18

2.6 Other Cyclization Reactions Involving Axially Chiral Enolate Intermediates

Concurrent with Fuji’s early studies on MOC, Stoodley and co-workers isolated the bicyclic side product 50 with complete retention of configuration as they attempted to transform 48 into 49 (Scheme 11).19

Scheme 11

The best conditions devised for the preparation of bicyclic compound 50 involved the addition of triethylamine to a boiling solution of 48 in methanol (65% yield). To account for the stereochemistry of 50, Stoodley et al. postulated the intermediacy of axially chiral enolate 51 with a sizeable energy barrier to racemization (Scheme 12).

Scheme 12

Restricted rotation about the amide bond of 48 was evidenced by 1H NMR spectroscopy at −60 °C in CDCl3, which demonstrated the presence of three rotamers in the ratio of 50:32:18.20 The kinetic preference for the deprotonation of 48 to give chiral enolate 51 rather than its enantiomer ent-51 is attributable to the stability of conformation 52 relative to conformation 53 (Scheme 13).

Although both 52 and 53 adopt the (Z)-amide geometry and an anti-relationship between the keto and diazonium groups, significant A1,3 interaction exists between the N-acyl substituent and the CO2Me group in geometry 53. Thus, deprotonation of major conformer 52 gives enolate 51 in preference to ent-51, which then cyclizes to 50.

Stoodley and co-workers found that this reaction could be extended to thiazolidine dioxides 54, giving the bicyclic sulfone 55 with complete retention of configuration and in 86% yield (Scheme 14).21
Finally, Stoodley and co-workers found that intramolecular aldol reaction of $56$ gave two enantiopure, diastereomeric products $57$ and $58$ in a 72:28 ratio (Scheme 15).22

After Fuji and Kawabata reported their first studies of deprotonation/alkylation reactions of protected amino acid esters, González-Muñiz published a MOC route to conformationally constrained quaternary 4-alkyl-4-carboxy-2-azetidinones (Scheme 16).24,25

The asymmetric induction proved sensitive to the identity of the nitrogen protecting group, the ester alkyl group, and the amino acid side chain. The optimum substrate $59$ cyclized to $60$ in 56% ee. The authors attributed this asymmetric induction to the formation of an axially chiral enolate, a proposal that is strengthened by the structural similarity of $59$ to Fuji and Kawabata’s substrate $32$.

In closing this section on enantioselective enolate cyclizations, we must note a study by Seebach and co-workers on the retentive rearrangement of a lithiated $N$-acyl-tetrahydroisoquinoline.26 Although the mechanism of this reaction has not been firmly established, the authors proposed an opening of the tetrahydroisoquinoline ring to give an axially chiral enolate, followed by enantioselective ring closure.

2.7 Enantioselective Synthesis of Quaternary 1,4-Benzodiazepin-2-ones

1,4-Benzodiazepin-2-ones are among the most important scaffolds in medicinal chemistry, representing the prototypical ‘privileged structure’.27,28 However, 1,4-benzodiazepin-2-ones possessing a quaternary center at C(3) have received very little attention from synthetic or medicinal chemists, possibly due to the limited commercial availability of the most obvious starting materials (enantiopure quaternary amino acids). Recently, Carlier and co-workers reported a MOC route to such ‘quaternary’ 1,4-benzodiazepin-2-ones (Scheme 17).29

Whereas sequential deprotonation/benzylation of enantiopure alanine derivative (S)-$61a$ gave racemic $62a$, application of the same protocol to the $N$-i-Pr analog $61b$ gave the desired product $62b$ in 97% ee. These divergent results were attributed to the formation of a conformationally chiral enolate intermediate, whose racemization rate critically depends on the size of the N(1) substituent $R^1$. High levels of enantioselectivity for the alkylation of $61b$ were attained with other active electrophiles (Table 5). Enantioselectivities ranged from 94 to 99%, and are independent of the size of the electrophile. Methylation and al-
lylation reactions of the N-i-Pr phenylalanine analog (S)-63b are also highly enantioselective (95 and 86% ee respectively). Retentive stereochemistry was established by hydrolyzing quaternary 1,4-benzodiazepin-2-one 62b and 64b to the known quaternary amino acids (8 M HCl, 140 °C, 3 days, 50–62% yield), and by chiral stationary phase HPLC of deuterium product 67b.

As mentioned previously, enantioselectivity in these reactions is attributed to the formation of nonracemic, conformationally chiral enolates. To understand how these enolates are chiral, and how they are formed enantioselectively, one must appreciate the non-planar nature of the benzodiazepine ring. Despite the absence of a stereogenic center, glycine-derived 1,4-benzodiazepin-2-ones 69a–d are chiral, existing as conformational enantiomers (Table 6).30,31

The helical descriptors (M)- and (P)- are used to describe the sense of ring chirality, based on the sign of the R1–N(1)–C(7)–C(8) dihedral angle. As demonstrated in Table 6, the barrier to inversion in these compounds depends strongly upon the size of the N(1) substituent.29,30,32 It is also well known that when a single substituent is present at C(3), as in 61b, it strongly prefers to be pseudoaxial.33 Thus, the chirality at C(3) controls the helicity of the diazepine ring of 61b. As shown in Scheme 18, a (3S)-center will induce the diazepine ring to adopt the (M)-conformation.

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### Table 5 Enantioselective Synthesis of Quaternary 1,4-Benzodiazepin-2-ones via Memory of Chirality

<table>
<thead>
<tr>
<th>R2</th>
<th>E²</th>
<th>Product</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me Bn</td>
<td>+</td>
<td>(+)-62b</td>
<td>74</td>
<td>97 (3R)</td>
</tr>
<tr>
<td>Me 4-MeC₂H₅CH₂</td>
<td>+</td>
<td>(+)-64b</td>
<td>68</td>
<td>95 (3R)</td>
</tr>
<tr>
<td>Me 2-PhC₂H₅CH₂</td>
<td>+</td>
<td>(+)-65b</td>
<td>70</td>
<td>99</td>
</tr>
<tr>
<td>Me allyl</td>
<td>+</td>
<td>(+)-66b</td>
<td>76</td>
<td>94</td>
</tr>
<tr>
<td>Me D</td>
<td>+</td>
<td>(+)-67b</td>
<td>85</td>
<td>99 (3S)</td>
</tr>
<tr>
<td>Bn Me</td>
<td>–</td>
<td>(+)-62b</td>
<td>64</td>
<td>95 (3S)</td>
</tr>
<tr>
<td>Bn allyl</td>
<td>+</td>
<td>(+)-68b</td>
<td>57</td>
<td>86</td>
</tr>
</tbody>
</table>

Reagents and conditions: i) 1.2 equiv LDA, 6 equiv HMPA, 1.2 equiv n-BuLi, –78 °C; ii) 10 equiv electrophile; iii) aq NH₄Cl.

Electrophiles used: BnBr, 4-MeC₂H₅CH₂Br, 2-PhC₂H₅CH₂Br, allyl bromide, D-OTFA, MeI.

### Table 6 Dynamic Chirality of 69a–d

<table>
<thead>
<tr>
<th>R1</th>
<th>ΔG² (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>69a</td>
<td>12.3</td>
</tr>
<tr>
<td>69b</td>
<td>18.0</td>
</tr>
<tr>
<td>69c</td>
<td>21.1</td>
</tr>
<tr>
<td>69d</td>
<td>&gt;24</td>
</tr>
</tbody>
</table>

a Determined by ¹H NMR spectroscopy (coalescence).

b Ref. 30.
c Ref. 29.
d Ref. 32.

Scheme 18

Therefore, although deprotonation of (3S)-61b destroys the stereogenic center at C(3), the resulting enolate would remain chiral by virtue of the non-planar diazepine ring. Since the major (M)-conformer of (3S)-61b is stereoelectronically better disposed for deprotonation than is the minor (P)-conformer, deprotonation should preferentially yield the (M)-enolate.
To address the issues of enolate structure and racemization, DFT calculations were carried out on 70b, the enolate ion derived from des-chloro analog of 61b (Figure 5).

Identical calculations were carried out on 70a, the N-Me analog. The equilibrium geometries of enolates 70a,b are chiral, and feature essentially flat C(3) carbons (sum of angles 358.5°, 359.0°). Thus, the retentive stereochemistry cannot be attributed to pyramidalization of C(3).

The calculated ring inversion transition structures of 70a,b indicate near eclipsing of the N(1) substituent (R 1) and C(8) (dihedral angles 13.4°, 12.8°). B3LYP/6-31+G*/B3LYP/6-31G* activation free energies for ring inversion at –78 °C of 70a (N-Me) and 70b (N-i-Pr) are 12.4 and 17.5 kcal/mol, which correspond to racemization t1/2 (–78 °C) values of 0.11 minutes and 970 hours respectively. Thus, the racemizing benzylation of 61a and the enantioselective benzylation of 61b (Scheme 17) may be rationalized. Finally, if the model proposed thus far is correct, retentive alkylation necessitates approach of the electrophile to the concave face of enolate. The factors that would favor this contra-steric alkylation are as of yet unclear.

3 Memory of Chirality in Radical Chemistry

3.1 Retentive Benzylic Substitution Induced by Dynamic Planar Chirality

Recently, Koning and co-workers developed a method for the stereospecific umpolung of arene-tricarbonylchromium complexes 71 derived from readily available chiral 1-arylalkanols. Calculations indicated that the benzylic radical 72 resulting from 1 electron reduction and fragmentation of 71 is actually better described as a 17-valence electron complex with an exocyclic C–C double bond (Scheme 19).34

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).

Koning et al. envisaged that if radical 72 could be generated enantioselectively from 71, and rapidly reduced to the configurationally stable anion 73, enantioselective alkylation at the benzylic carbon should be possible. Starting from readily available (R)-1-phenylethanol (91% ee), complex 71 was obtained (91% ee). Treatment of 71 with 2.1 equivalents of lithium 4,4¢-di-tert-butylbiphenyl (LiDBB) in THF at –78 °C afforded a solution of the anion 73, which was treated with a variety of electrophiles to give rise to the desired products 74 in fair yields (37–72%) and with a high degree of retention (84–87% ee, Table 7).

As no external chiral sources are present in these reactions, the origin of the stereoselectivity could only be ascribed to preservation of the starting material chirality in both radical and anionic intermediates. In this case, it appears that the central chirality of the starting materials is
3.2 Retentive Radical Trapping Controlled by a Slow Ring Inversion

It is well known that acyclic radicals invert rapidly, and the barrier to inversion has been estimated at less than 0.5 kcal/mol. However, for a cyclic radical, the racemization and ring inversion processes would be coupled, possibly increasing the barrier. Since the barrier to chair-chair ring inversion in the tetrahydropyranyl radical $75$ is likely in the range of 5–10 kcal/mol, Rychnovsky and co-workers envisioned that if $75$ could be generated in nonracemic form, stereoselective trapping might be possible (Scheme 21).

Scheme 21

Carboxylic acid $76$ was prepared in optically pure form and converted to its $N$-hydroxypyridine-2-thione ester. Photolysis of the ester in toluene at $-78 \ ^\circ\mathrm{C}$ with 1 M PhSH as a hydrogen atom donor led to the expected product $77$ in 86% ee with retention of configuration (Scheme 22).

Scheme 22

The enantiomeric excess of $77$ was found to depend strongly upon the concentration of the PhSH quench, evi
dencing competition between ring inversion and intermolecular trapping. A similar conformational memory effect was also observed when the enantiopure memory effect $75$ was generated reductively (Scheme 23).

Scheme 23

The enantiomeric purity of the product $77$ in these reactions was highly dependent upon the concentration of the reducing agent, suggesting competition between reduction and racemization of radical $75$. In both the photolysis and reductive cleavage reactions, memory of the original chiral centers of $76$ and $78$ is proposed to be retained by the conformation of the tetrahydropyranyl ring (and not simply by the pyramidalization of a sp$^3$-hybridized radical). Therefore, these reactions constitute examples of memory of chirality.

3.3 Memory of Chirality in Radical Cyclization

Rychnovsky and co-workers have also exploited conformational chirality in the transannular cyclization of medium ring radicals (Scheme 24).

Scheme 24

EnantiomERICally enriched $N$-hydroxypyridine-2-thione mixed oxalate $80$ was prepared in situ from the corresponding cyclodecenyl alcohol and photolysed in toluene.
at –35 °C; bicyclic product **81** was obtained in 68% ee. The authors proposed that photolysis of **80** generates cyclooctadienyl radical **82** (Scheme 25).

**Radical 82 possesses conformational chirality and is generated in nonracemic form from the enantioenriched starting material. If transannular cyclization of 82 can compete effectively with inversion of the medium ring conformation to ent-82, bicyclic radical 83 will be formed in nonracemic form. Finally, transfer of the 2-thiopyridyl moiety from the starting material 80 would generate optically enriched product 81 and propagate the radical chain.**

Curran and co-workers have developed a series of highly enantioselective radical cyclization reactions that convert atropisomeric starting materials to centrally chiral products. Although these reactions may best be considered as examples of ‘transfer of chirality’, their success also depends upon the transient conformational chirality of a reactive intermediate. In this sense, these reactions can also be considered as examples of MOC. o-Iodoacylanilides **84** are atropisomeric and the (M)- and (P)-enantiomers were prepared via a chiral pool route from lactic acid. The barrier for interconversion of the enantiomers of **84** was estimated to be 30.8 kcal/mol. However, upon radical deiodination, a much more readily racemized radical **85** would be formed. Since oxindoles (R)-**86** and (S)-**86** were obtained in high enantiomeric excess from the antipodal starting materials, the authors concluded that cyclization of aryl radical **85** was much faster than racemization.

Note that the absolute configuration of the products indicates that radical cyclization of (M)-**85** occurs on the pro-S (i.e. β)-face of the alkene. Curran has described this process in terms of the alkene twisting toward the aryl radical.

3.4 Memory of Chirality in the Cyclization of Photochemically Generated Diradicals

In 1999, Giese and co-workers reported that alanine derivative **87** underwent asymmetric photocyclization in the presence of naphthalene, a triplet quencher. Two diastereomeric products, **88** and **89**, were formed in high enantiomeric excess (Scheme 27).

Note that **88** and **89** have identical configurations at C(2). The authors proposed that the asymmetric reaction occurred via a singlet diradical intermediate. In the absence of a triplet quencher, the photochemical reaction gave significantly lower asymmetric induction, suggesting intervention of the longer lived (and thus racemizable) triplet diradical. The formation of major product **88** was rationalized to occur via formation of the helically chiral singlet diradical (M)-**90** (Scheme 28).
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.

The enantiospecific formation of 90 in the (M)-conformation can be rationalized in terms of the (S)-configuration of starting material 87 and the intramolecular nature of the hydrogen atom abstraction. Finally, the formation of minor diastereomer 89 can be rationalized in terms of a singlet diradical intermediate that differs from (M)-90 only in the orientation of the α-sigma bond.

An asymmetric cyclization of a diradical generated by photodecarboxylation was reported by Griesbeck and co-workers. Upon irradiation, L-proline derivative 91 formed benzodiazepine derivative 92 in 86% ee and greater than 98% de (Scheme 29).

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The high enantioselectivity was initially unexpected, because 92 results from the recombination of a 1,7-triplet diradical. As described above, the intervention of triplet diradicals proved deleterious to the enantioselectivity of the reaction of alanine ester 87, since it possesses only low rotation barrier single bonds. However, the authors proposed that the conformationally chiral 1,7-triplet diradical formed by photodecarboxylation of 91 exhibits a high barrier to rotation around the sp²–sp² C–N(prolyl) bond. In support of this proposal, molecular mechanics calculations on 91 indicated a barrier of 13 kcal/mol about this bond. The authors did not speculate as to how the diradical intermediate was formed in enantiopure form, but a strong conformational preference in the starting material 91 is likely responsible.

Matsumura and co-workers found the N-benzylolethylamine derivative 93 was electrochemically oxidized to give 94 with inversion of configuration in 69% yield and 39% ee (Scheme 30). To increase the enantioselectivity, analog 95, bearing a bulky o-phenylbenzoyl as the N-protecting group, was synthesized. Interestingly, electrolysis of 95 proceeded in retentive fashion, giving o-methoxylated serine derivative 96 in 80% ee (Scheme 31).

To account for the retentive stereochemistry, the authors proposed that the reaction occurred via conformationally chiral iminium ion 97. Since the o-phenyl group shields the bottom face of the iminium ion, methanol attacks from above, yielding 96 (Scheme 32). Formation of the conformationally chiral iminium ion 97 in the indicated enantiomeric form was rationalized in terms of oxidation of the most stable conformer (AM1) of the enantiopure starting material 95. Racemization of 97 would be slowed by hindered rotation of the sp²–sp² amide single bond, and thus capture by MeOH leads to 96 in high enantiomeric purity.

4 Memory of Chirality Involving Carbocation Intermediates
as starting materials. Therefore, in certain cases, MOC methods may prove competitive with catalytic asymmetric synthesis for the preparation of enantiomerically pure compounds.

References


Scheme 32  Reagents and conditions: 2F/mol NaOMe/MeOH, –30 °C, Pt cathode, graphite anode.

5 Conclusion

Memory of chirality is an emerging strategy for enantioselective synthesis. In general, MOC methods involve destruction of the sole original stereogenic center of a starting material, enantioselective generation of a conformationally chiral intermediate, and subsequent enantioselective transformation into a centrally chiral product. For intramolecular or solvent-capture reactions, low barrier sp3–sp3 or sp2–sp3 bonds in the conformationally chiral intermediate can provide a sufficient barrier to racemization to permit enantioselective reaction. However, for intermolecular reactions, higher barrier sp2–sp3 bonds typically must be present to guarantee a sufficient racemization half-life for the reactive intermediate.

Successful MOC reactions must fulfill three conditions. First, the enantiopure centrally chiral starting materials must be enantioselectively transformed into a conformationally chiral intermediate. Second, this chiral intermediate must not racemize during the timescale of the reaction. Third, transformation of the conformationally chiral intermediate back to a centrally chiral product must occur with excellent enantioselectivity.

To date, MOC has found predominant application in enolate chemistry, but the MOC principle has also been successfully applied in reactions involving radical, diradical, and carbocation intermediates. As chemists grow in their understanding of how to generate enantiopure, conformationally chiral reactive intermediates, further applications of the MOC principle will follow. Like the ‘self-regeneration of stereocenters’ strategy, successful MOC methods will use cheap, abundant members of the chiral pool