Memory of Chirality—A New Principle in Enolate Chemistry

Kaoru Fuji* and Takeo Kawabata

Dedicated to Professor Dieter Seebach on the occasion of his 60th birthday

Abstract: We discuss a new principle, memory of chirality, which was recently introduced in the field of asymmetric synthesis. Memory of chirality is a phenomenon in which the chirality of the starting material is preserved in a reactive intermediate for a limited time. Examples are discussed, including the enantioselective alkylation of a ketone and amino acid derivatives.

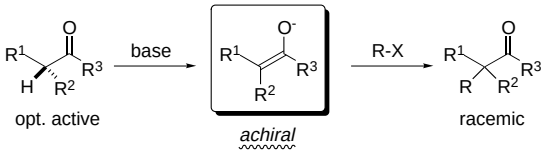
Keywords: alkylation · amino acid · asymmetric alkylation · chirality · enolate

Introduction

Scientific progress is supported by two major pillars. One pillar involves research, carried out following a carefully planned program based on the analysis of a vast number of precedents discovered by scientific pioneers. Projects usually begin from this standpoint. The results obtained in these studies are novel and logical, but understandable from our present knowledge of science, since they were planned to be so and were even anticipated. In the field of synthetic organic chemistry, for example, the fact that a reaction is new does not always mean that it is surprising. However, we know from our experience that some reactions do not always proceed as expected. In most cases, the reaction has simply failed. However, an unexpected result can lead to a wonderful seed waiting to be picked up. If you plant it successfully, you could harvest the unexpected fruit. This process is the birth of a new concept, which is the second and more important pillar which supports scientific progress. In this article, we discuss enantioselective alkylation based on the new principle of memory of chirality.

Discussion

Memory of chirality: A stereogenic center α to a carbonyl group should be lost in the formation of an enolate, since a planar sp^2 carbon center is created from an sp^3 carbon center. Thus, it is impossible to obtain a nonracemic product by quenching the enolate with an electrophile, even though a nonracemic ketone was used as a starting material (Scheme 1). To produce a nonracemic product, a chiral environment, such as the use of chiral electrophiles, chiral ligands, chiral auxiliaries, and sometimes chiral solvents, is required for the reaction conditions.



Scheme 1. The racemic product should be obtained from the alkylation of the optically active ketone when the reaction proceeds via an enolate intermediate.

Or is it? Consider information concerning the chirality of organic molecules to be not simply about the three-dimensional structures but to include the fourth dimension of a timescale. For instance, the *S* and *R* enantiomers of phenylalanine differ by a chiral carbon (Figure la). Conversion of the

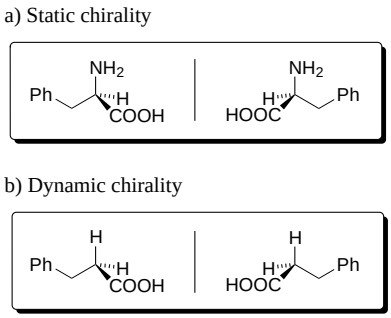


Figure 1. Static chirality and dynamic chirality.

S enantiomer of such a molecule into the *R* enantiomer requires bond scission followed by recombination. This type of chirality may be called static chirality. β-Phenylpropionic acid, formally created by the replacement of the amino group of phenylalanine with a hydrogen, is achiral from the definition of static chirality, because it has no chiral carbon

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center. On a limited timescale, however, β-phenylpropionic acid can take a specific conformation, the enantiomer of which can be drawn as in Figure 1b. Thus, even β-phenylpropionic acid can be considered to exist in an enantiomeric form on a specific timescale. Since one enantiomer can be transformed to the other simply by rotating the bond(s), this has been called conformational chirality. We propose the term dynamic chirality to describe this type of chirality.

If we consider the timescale, an enolate is not always achiral. As shown in Figure 2, an enolate can possess axial or

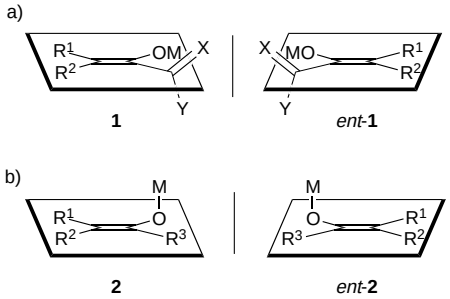
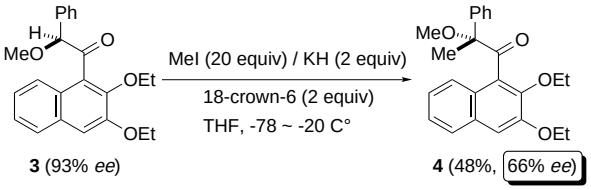


Figure 2. Enantiomeric forms of enolates with a) axial chirality (**1**) and b) planar chirality (**2**).

planar chirality. The enantiomeric forms **1** and *ent*-**1**, and **2** and *ent*-**2**, are not differentiated under normal conditions because of the rapid equilibrium between them. They may be differentiated from each other at an extremely low temperature or by the introduction of specific structural constraints into the molecule, such as changing 2,2′-dihydroxybiphenyl to the corresponding binaphthalene. In such a case, the information on chirality of the starting material can be kept temporarily in the intermediate enolate, to regenerate in turn a central chirality in the product after reaction with an electrophile. Thus, 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.

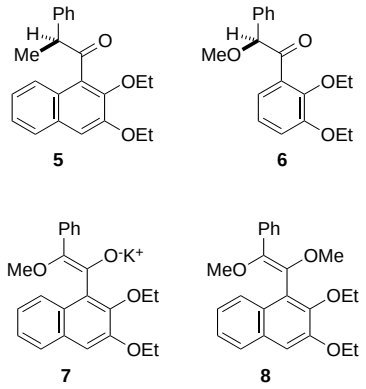
We designed a ketone **3** to allow us to demonstrate this idea. Treatment of a mixture of the ketone (*S*)-**3** (93% *ee*) and methyl iodide with potassium hydride in the presence of 18-crown-6 gave the methylated ketone **4** in optically active form (66% *ee*, Scheme 2).[1] Note that there is no chiral environ-



Scheme 2. Asymmetric methylation of **3** in a nonchiral environment.

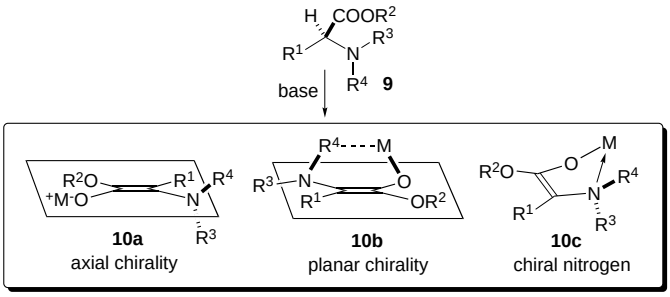
Abstract in Japanese: 本論文では不斉合成の分野に最近導入された「不斉記憶」という新しい現象について解説する。「不斉記憶」とは、本来は反応の進行と共に失われるべき原料系の不斉情報が反応中間体に或る時間内保存される現象である。不斉記憶を発現する例としてケトン及びアミノ酸誘導体のエナンチオ選択的アルキル化について述べる。

ment under these reaction conditions, although we did start from an optically active ketone. This memory of chirality was observed with various electrophiles as long as ketone **3** was used as a starting material. Optically active **5** showed memory of chirality when ethylated, while ketone **6** did not. These findings strongly suggest that the chirality of **3** was preserved as axial chirality in the corresponding enolate **7**. The isolation



of methyl enol ether **8** with 43% *ee* strongly supported our interpretation. In fact an *ee* of 65% was observed for **8** in the reaction mixture directly after work-up. The time-dependent decrease in optical rotation revealed that the half-life of the racemization of **8** was 53 min at 21 °C. The information on chirality held by enolate **7** includes not only the arrangement in three-dimensional space inherent in the original ketone **3**, but also the fourth dimension, the timescale. Whether or not such information on chirality can play an important role in asymmetric synthesis depends upon its lifetime under practical reaction conditions. In the case of ketone **3**, the axial chirality in the corresponding enolate **7** is stable enough at low temperature to give an optically active product.

***α*-Alkylation of phenylalanine derivatives**: An enolate **10**, derived from the optically active amino acid derivative **9**, may exist in an optically active form (Scheme 3). For example,



Scheme 3. The possible forms of dynamic chirality in the enolate **10** generated from an amino acid derivative **9**.

enolates **10a**, which has axial chirality across the carbon–nitrogen bond, **10b**, which has planar chirality consisting of the enolate plane and the metal cation stabilized by coordination with a substituent on the nitrogen, and **10c**, which has a chiral nitrogen atom resulting from the transfer of chirality from the sp^3 carbon center, are all possible according to the

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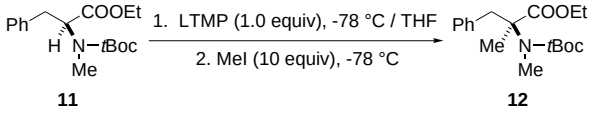
principle of memory of chirality. Although the lifespans of these species are expected to be extremely short, the proper selection of substituents R^1–R^4 may prolong their lifespans. After several fruitless attempts, we found that (*S*)-phenylalanine derivative **11** gave the corresponding (*S*)-α-methyl derivative **12** with 82% *ee* in 40% yield (Scheme 4).[2] Allylation proceeded under similar conditions to give the corresponding α-allyl derivative with 88% *ee* in 15% yield.



11 **12**

Scheme 4. Enantioselective methylation of an (*S*)-phenylalanine derivative **11**. LTMP = lithium 2,2,6,6-tetramethylpiperidide.

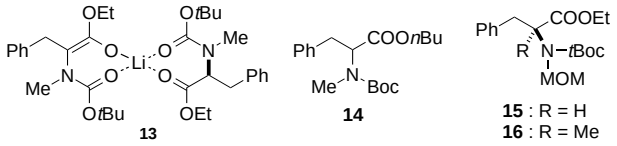
Note again that there is no external chiral environment under these reaction conditions. The origin of this enantioselectivity can be ascribed to preservation of the information on chirality of the starting material in the intermediate anionic species. An alternative interpretation involves a complex **13** consisting of the achiral enolate and remaining optically active starting material. However, a crossover experiment between (*S*)-**11** and the corresponding racemic butyl ester DL-**14** showed that the information on chirality in (*S*)-**11** was not transmitted to the product from DL-**14**; this finding clearly refutes the involvement of complex **13** as the origin of asymmetric induction.

To determine the lifetime of the chiral enolate, (*S*)-**11** was treated with LTMP to generate the corresponding enolate under various conditions. The enolate was then quenched with methyl iodide to give **12** (Table 1). Not surprisingly, configurational stability was shown to be markedly labile to temperature. Although the enolate was configurationally stable for at least an hour at $-78\,^{\circ}C$ (runs 1–3), it was completely lost after stirring at room temperature for 45 min (run 5). This indicates that the enolate derived from (*S*)-**11** adopts a specific structure that maintains the original configuration at a low temperature, but collapses rapidly with an increase in temperature to lose its chirality. The ^{13}C NMR spectra of the anion derived from DL-**11** enriched at the α- and ester carbons revealed that the structure at $-78\,^{\circ}C$ is totally different from that at room temperature. Once these changes had been observed in the spectrum, they persisted even after recooling to $-78\,^{\circ}C$. These findings correspond with the results in Table 1.

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

Run	Conditions for enolate formation[a]	Yield (%)	% *ee*[b]
1	$-78\,^{\circ}C$, 0 min	9	74
2	$-78\,^{\circ}C$, 15 min	40	82
3	$-78\,^{\circ}C$, 60 min	28	81
4	$-78\,^{\circ}C$, 15 min, then $-40\,^{\circ}C$, 15 min	39	10
5	$-78\,^{\circ}C$, 15 min, then RT, 45 min	26	≈ 0

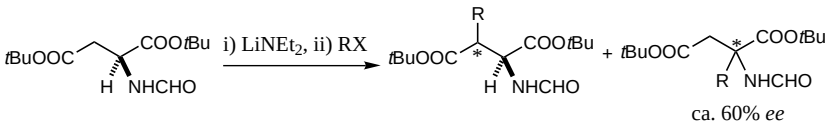
[a] The enolate was quenched with methyl iodide at $-78\,^{\circ}C$. [b] Determined as an *N*-benzoyl derivative.



Development into common chemistry: The efficiency of the present reaction, such as a high yield, high enantioselectivity, and wide applicability, is not a matter of concern at this stage. It is more important to present a novel strategy for asymmetric induction. However, it will be necessary in the second stage of the research to generalize these unprecedented findings. Utility, including a high yield, high enantioselectivity, and a wide range of applications is required for further development. We focused our attention on improving the yield and enantiomeric excess (*ee*) of the alkylation of amino acids, since nonracemic α,α-disubstituted amino acids are important compounds in the fields of medicinal chemistry and biochemistry. Their synthesis by the principle of memory of chirality should be very useful, since the use of nonracemic amino acids as a starting material is the only requirement for the preparation of nonracemic α,α-disubstituted amino acids. The *ee* in the alkylation of (*S*)-**11** was acceptable, but the yield was too low. After extensive investigation of the substituents on the amino group, solvent systems, and bases using (*S*)-phenylalanine as a standard substrate, we found that (*S*)-**15**, the nitrogen atom of which is protected with the *tert*-butoxycarbonyl and the methoxymethyl groups, gave the corresponding α-methyl derivative **16** in 88% yield and 84% *ee* with potassium hexamethyldisilazide (KHMDS) as a base.[3] Our preliminary experimental results indicate that this method can be applied to derivatives of other amino acids.

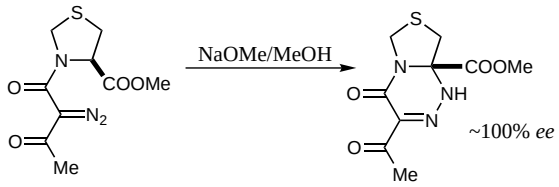
Closing Remarks

Before our first paper on the memory of chirality,[1] Seebach et al.[4] reported a reaction based on the memory of chirality (Scheme 5). Di-*tert*-butyl (*S*)-*N*-formylaspartate gave not only the β-alkylated product but also the α-alkylated product in ca. 15% yield with ca. 60% *ee*. More recently, the examples illustrated in Scheme 6 were reported.[5,6] A crucial difference between the reaction in Schemes 5 and those in Scheme 6 is that the former is an intermolecular reaction, while the latter are intramolecular reactions. Further back, a reaction involving the memory of chirality under acidic conditions was reported by Marquet et al. more than 30 years ago (Scheme 7).[7] Obviously, the information on chirality of the

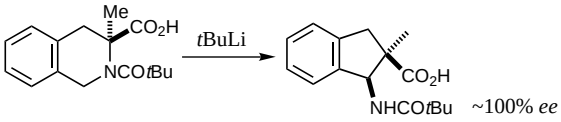


Scheme 5. Memory of chirality in the alkylation of an aspartic acid derivative (Seebach et al., ref. [4]).

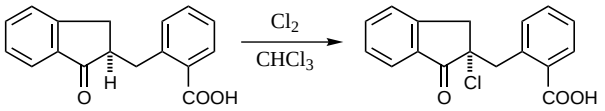
a)



b)



Scheme 6. Intramolecular trapping of chiral enolates. a) Stoodley et al., ref. [5]; b) Seebach et al., ref. [6].



Scheme 7. Memory of chirality under acidic conditions (Marquet et al., ref. [7]).

original ketone is retained in the intermediate enol in this reaction.

Another interesting strategy for asymmetric synthesis, in which the original stereogenic center present in the starting material is lost but then recreated in the final product, involves the principle of self-regeneration of stereocenters (SRS) developed by Seebach et al.[8] Asymmetric reactions based on the SRS principle open new avenues to the synthesis of various types of nonracemic compounds. On the other hand, it is still too early for asymmetric reactions based on the memory of chirality to be of practical use. However, we believe that the memory of chirality represents a new perspective on enolate chemistry and asymmetry itself.

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