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Memory of Chirality in Cascade Rearrangements of Enediynes

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Abstract: The cascade rearrangement of chiral enediynes **1c**−**e**, involving successively 1,3-proton shift, Saito−Myers cyclization, 1,5-hydrogen atom transfer, and intramolecular coupling of the resulting biradical, proceeded at 80 °C to form tri- and tetracyclic heterocycles possessing a quaternary stereogenic center with a very high level of memory of chirality.

Since the discovery of the mighty anticancer properties of natural products containing enediynes moieties, mechanistic studies, syntheses, and evaluation of new compounds in this family have stimulated the creativity of multidisciplinary researchers.[1] The biological activity of these compounds is related to their aptitude to rearrange according to Bergman[2] or Saito−Myers cyclizations.[3] These processes lead to highly reactive (σ,σ) and (σ,π) biradicals,[4] respectively, capable to abstract hydrogen atoms from DNA strands and, as a consequence, to induce DNA cleavage and apoptosis. In spite of the impressive number of publications that can be listed in this field,[5] there are still some trails left unexplored in the reactivity of these compounds.

We disclose in this Communication a polar-radical crossover cascade rearrangement that proceeds with memory of chirality at 80 °C. Memory of chirality (MOC) is intended here as defined by Fuji and Kawabata,[6,7] i.e., "an asymmetric transformation in which the chirality of the starting material is preserved in the conformationally labile intermediate during the transformation".

Elegant examples of biradicals rearrangements via 5-exo ring closure or intramolecular hydrogen shift subsequent to Bergman or Saito−Myers cyclization have already been explored, mainly by Grissom[8] and by Wang.[9] The choice of substrates of type **1** should open routes to dihydrobenzoisochromenes or tetrahydrobenzoisoquinolines.[10]

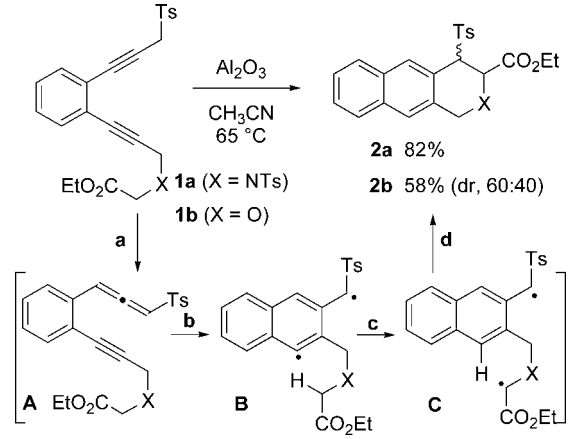
The efficiency of the planned rearrangement was first tested on achiral substrates **1a** and **1b**. The mechanism of the reaction and the experimental results are given in Scheme 1.

Optimization of the reaction conditions was achieved on the glycine derivative **1a**. This led to select acetonitrile as the solvent—for the sake of a faster reaction rate—and Al_2O_3 as the base to form the intermediate enynallene.[11] Under these conditions, the rearrangement of **1a** was completed within 5 h at 65 °C (99% conversion according to ^{1}H NMR using pentamethylbenzene as internal standard) and led to **2a** as a unique stereoisomer that was isolated in 82% yield.[12]

Under the same experimental conditions, ester **1b** led to **2b** as a 60:40 mixture of diastereomers after 24 h at 65 °C. The two isomers of **2b** were isolated in 34 and 24% yield, respectively. Up to 23% of the starting material was recovered.

In the cascade, the first elementary step (step **a**) leads to enynallene **A**, which spontaneously undergoes Saito−Myers cyclization to give biradical **B** (step **b**). The following 1,5-hydrogen shift gives rise to biradical **C** (step **c**), which eventually forms product **2** through intramolecular coupling of the two reactive centers (step **d**). We thought that hydrogen abstraction from a captodative position should offer several advantages, such as enhancing the rate of step **c**.[13]

Scheme 1



Investigation of the MOC in the reaction was by far the most exciting purpose.[6,7,14] Most examples of application of the concept of MOC involve carbanionic species.[15] A limited number of articles are concerned with cationic[16] or radical intermediates.[17,18] Among the latter, four reports refer to intramolecular coupling of biradicals resulting from Norrish type II photochemical processes.[17a,b,i,j] It must be emphasized that, in their seminal articles, Giese and co-workers[17a,b] demonstrated that biradicals generated from a photochemically excited ketone could lead to high enantiomeric excess (ee), provided that the triplet state was quenched.

Therefore, the reactivity of both racemic **1c** and optically active substrate (*S*)-**1c** (97.5% ee) was investigated in order to measure the ee in the cyclization products (Scheme 2).

Reasonable chances to observe MOC in the process could be anticipated from the following statements:

• Only one conformation of the side chain enables the transfer of the hydrogen atom from the stereogenic center. Therefore, intermediate **Cc** should be generated in a chiral conformation at the captodative center (Figure 1, DFT B3LYP/6-31G(d)[19]).

• The captodative radical center in **Cc** should be planar, and what is more, owing to the rotational barrier around bond α,[20] it should retain its initial conformation during the recombination step (**d**).

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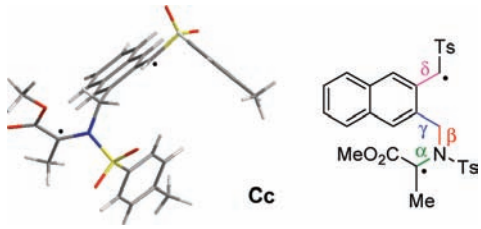
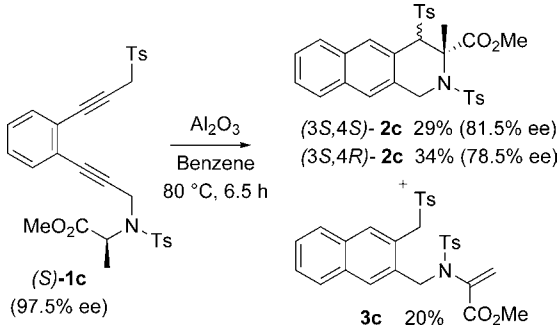


Figure 1. Conformation of "native" biradical **Cc**.

• Racemization of the captodative center can also result from rotation around bond β. Therefore, in order to observe MOC, an additional condition has to be fulfilled. Not only does rotation around the sp^2C-N bond (α) have to be impeded, but also rotation around the sp^3C-N bond (β), controlled by the bulk of the two substituents at nitrogen, must be slow compared to rotation around the sp^2C-sp^3C bond (γ).

All these requirements being satisfied, ideally, only two clockwise and two counterclockwise rotation modes around σ bonds γ and δ should be allowed. They should control the lifetime of biradical **Cc**. Two diastereoisomers should result. One should expect the tricyclic product to be formed in a stereospecific way, with retention of configuration at the initial stereogenic carbon.

Scheme 2



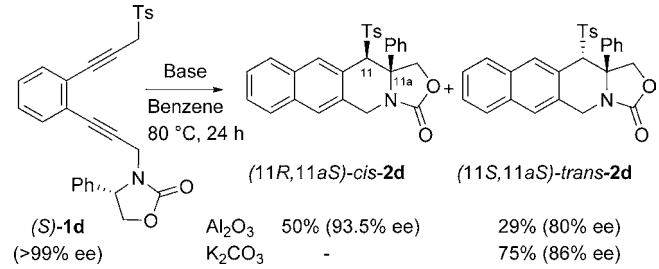
As summarized in Scheme 2, introducing a methyl group at the stereogenic center had two consequences. First, (3*S*,4*S*) and (3*S*,4*R*) diastereomers of the cyclized product **2c** were formed in 29 and 34% isolated yield,[21] with 81.5 and 78.5% ee, respectively.[22] Even though the reaction was slower in benzene, the latter was used to replace acetonitrile, which led to lower ee's. Second, a new product (**3c**), resulting from a regiospecific dismutation between the two radical centers instead of recombination, was isolated in 20% yield.

We assumed that the reaction proceeded with retention of configuration at the stereogenic center, which was demonstrated in further studies performed with **1d** (*vide infra*). We tentatively ascribe the limitation of the ee to the fact that the rates of rotation around σ bonds are not independent of each other. In particular, rotation around bond β becomes easier as the nitrogen atom moves out of the plane of the aromatic system. This probably explains the difference in ee's observed for cis and trans isomers.

The formation of **3c** results from hydrogen abstraction at the methyl group by the benzylic radical center. It is likely to occur at a stage where benzylic stabilization is significantly lowered by rotation around bond δ. This "dismutation" process is a limitation that no longer interfered in the cyclization of substrates **1d** and **1e** (Schemes 3 and 4).

As shown in Scheme 3, the rearrangement of (*S*)-**1d** led to a mixture of cis and trans diastereomers, isolated in 50 and 29% yield, respectively. The ee of *cis*-**2d** was 93.5%, whereas the ee of *trans*-**2d** was only 80%. The reaction was also achieved on the (*R*)-enantiomer. It was possible to demonstrate that the reaction proceeded with retention of configuration at the stereogenic center. The assignment of the absolute configurations resulted from the X-ray analyses of (11*R*,11a*S*)-**2d**, i.e., the major cis enantiomer isolated from (*S*)-**1d**, and of (11*R*,11a*R*)-**2d**, i.e., the major trans enantiomer isolated from (*R*)-**1d**.

Scheme 3



In this case, owing to the restriction of the number of degrees of freedom in the intermediate biradical **Cd**, the cyclic structure advantageously compensates the loss of the captodative character of the intermediate radical. However, a longer time of reaction was needed to reach completion. The preferential formation of the cis diastereomer is likely to be the consequence of π-stacking interactions between the aryl groups of two adjacent susbtituents, as shown in the solid-state structure (Figure 2).

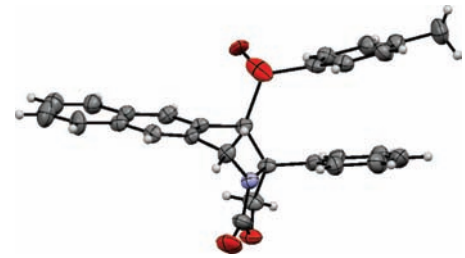
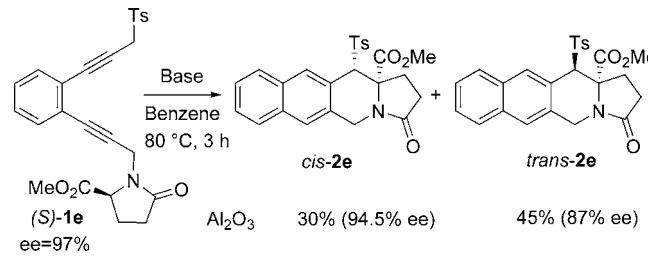


Figure 2. ORTEP structure of (11*R*,11a*S*)-*cis*-**2d**.

When the reaction was carried out with K_2CO_3, only *trans*-**2d** was formed in 86% ee and 75% yield. Contrary to Al_2O_3 (pK_a 8−9), K_2CO_3 (pK_a 10.2) induced a fast epimerization of the stereogenic center in position α with respect to the tosyl group in *cis*-**2d**.[23] This was confirmed by treating isolated *cis*-**2d** with K_2CO_3.

The rearrangement of **1e** led similarly to a mixture of cis and trans diastereomers that were isolated in 30 and 45% yield, respectively.[24] In all likelihood, the reaction also proceeded with retention of configuration. The ee of *cis*-**2e** was 94.5%, whereas the ee of *trans*-**2e** was 87% (Scheme 4). As compared to **1d**, little epimerization of the cis isomer occurred when K_2CO_3 was used as the base. According to chiral HPLC analysis, cis and trans isomers were formed in a 33:67 ratio, with 91 and 89.5% ee, respectively.

Scheme 4



The observation of a higher ee for the cis diastereomers than for the trans ones probably reflects the variation of steric crowding all along the pathways (either conrotatory or disrotatory) leading to these isomers.

In conclusion, the four-step cascade rearrangement of enediynes of type **1**, involving successively 1,3-proton shift, Saito−Myers cyclization, 1,5-hydrogen atom transfer, and intramolecular coupling of the resulting biradical, was shown to occur with memory of chirality, which opens routes to the asymmetric synthesis of heterocyclic α-aminoester derivatives with a quaternary stereogenic center. It is remarkable that, in this process, the phenomenon of MOC led to high ee's at a temperature as high as 80 °C. Mechanistic studies, including theoretical approach and introduction of structural diversity, are currently under investigation. New results will be reported in due course.

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Supporting Information Available: Experimental procedures, characterization data, HPLC analyses, NMR spectra for all new compounds, computational details, and X-ray data for (3*S**,4*R**)-**2c**, *trans*-**2d**, and *cis*-**2d** (PDF, CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) The structures' assignment was based both on the chemical shift of the proton in position α relative to the tosyl group, which is more deshielded when it is cis with respect to the carbethoxy group (δ = 4.74 ppm in (3*S*,4*R*)-**2c**; δ = 4.50 ppm in (3*S*,4*S*)-**2c**), and on the chemical shift of the carbon of the methyl group attached to the quaternary center that is more shielded in (3*S*,4*R*)-**2c** (δ = 23.4 ppm), than in (3*S*,4*S*)-**2c** (δ = 29.5 ppm). The crystal structure obtained for racemic (3*S**,4*R**)-**2c** confirmed this assignment.

(22) The temperature was increased to 80 °C for the rearrangement to be completed in an acceptable time. At 65 °C, the starting material was not totally consumed after 24 h and the ee's of the products were not significantly modified.

(23) In the case of **1c**, the use of potassium carbonate resulted in the formation of a mixture of rearranged products that could not be identified.

(24) The cis and trans structures were assigned from dihedral angles determined from Chem3D models. In the cis isomer, one dihedral angle in the CH_2−CH_2 moiety of the γ-lactam ring is very close to 90°. This explains why one vicinal coupling constant in the four-spin system is zero. This leads to dd splitting patterns for the related protons. Conversely more complex ddd patterns are observed in the spectrum of the trans isomer.

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