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Base-Induced Heterochiral Dimerization of an Oxiranyl Carbaldimine: Stereoselective Synthesis of a Highly Functionalized Aziridine

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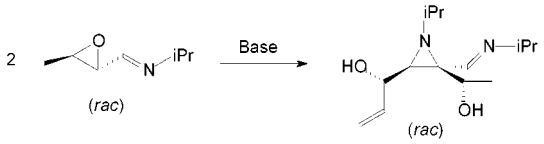
ABSTRACT



Treatment of the oxiranyl carbaldimine with base (LDA or LDA/KO*t*Bu) leads in an one-step procedure to the polyfunctionalized aziridine. This highly diastereoselective reaction is explained by a new type of an Aza-Darzens reaction, in which one enantiomer of the starting material is deprotonated to form an oxiranyl anion, which attacks the imine carbon atom of the other enantiomer (mutual kinetic resolution by double diastereofacial selection).

Similar to oxiranes, aziridines are reactive, valuable building blocks for selective organic transformations by ring-opening processes. In recent years chiral aziridines have found many interesting applications for the stereoselective synthesis of challenging molecules.[1] Among several synthetic routes to chiral aziridines, which start from amino alcohols, epoxides, alkenes, azirines, and imines,[2,3] the Aza-Darzens reaction presents an attractive but as yet seldom used access to substituted aziridines. This approach involves the nucleophilic attack of a leaving group containing carbanion species on imine-type molecules.[4−10]

In this report we present a new, unexpected example of a highly diastereoselective Aza-Darzens reaction, where an oxiranyl carbaldimine dimerizes to form an aziridine with seven neighboring functionalized carbon centers and four stereogenic centers in one step. This reaction was observed while attempting to synthesize the imino allyl alcohol 3-hydroxy-1-azapenta-1,4-diene **(5)** from the (*rac*)-*trans*-oxiranyl carbaldimine **(*rac*)-3** by base-induced ring opening using a lithium diisopropylamide (LDA) and potassium *tert*-butylate (KO*t*Bu) mixture.[11] The imine **(*rac*)-3** was produced in 65% yield as a *trans/cis* mixture (92:8) from the corresponding epoxy aldehyde **(*rac*)-2**. Compound **2** (*trans/cis* ratio 92:8) was obtained in 18% yield from crotonaldehyde **1**,[12] using hydroperoxide (30%) in buffered aqueous solution (pH = 8) as oxidant (Scheme 1).

For the intended base-induced oxirane opening process of **(*rac*)-3** a superbase[11] consisting of LDA/KO*t*Bu was used. However, treatment of **(*rac*)-3** with an equimolar amount of this base at −78 °C, warming to room temperature, and subsequent aqueous workup does not give the expected 3-hydroxy-1-azapenta-1,4-diene **5** but yields the functional-

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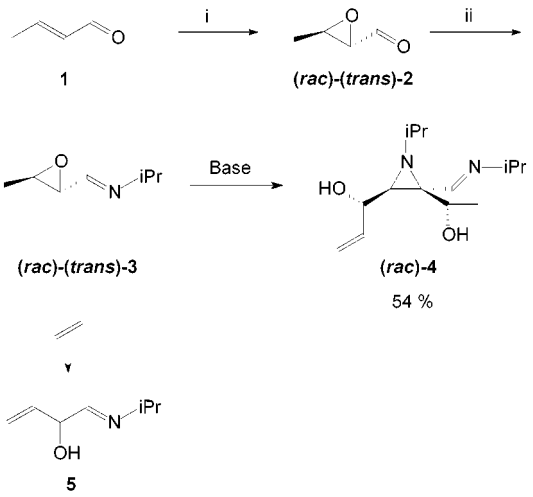
Scheme 1[a]



[a] (i) 30% H_2O_2. (ii) *i*Pr NH_2/molecular sieves.

ized aziridine **(*rac*)-4** in 53.4% yield as colorless crystals. NMR spectra of the crude mixture indicate the formation of 65−70% of **(*rac*)-4** without other products with comparable signals. ^{1}H and ^{13}C NMR spectra show the presence of a single diastereomer, indicating a highly stereoselective reaction pathway. Later experiments showed that LDA also leads to **(*rac*)-4** in similar yield and selectivity.

The unexpected structure of **(*rac*)-4** was elucidated by ^{1}H NMR NOE experiments and by X-ray crystallography (Figure 1). Figure 1 clearly shows the constitution and the

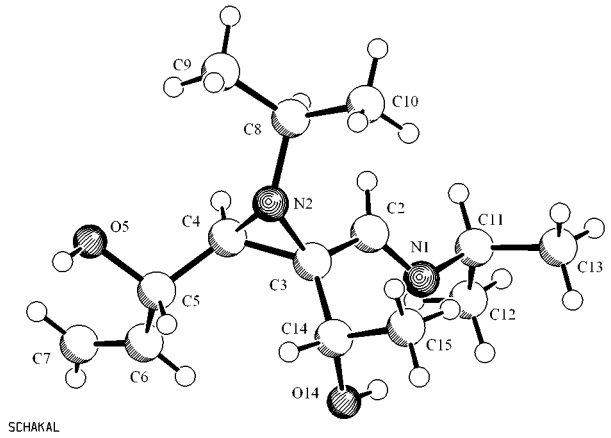
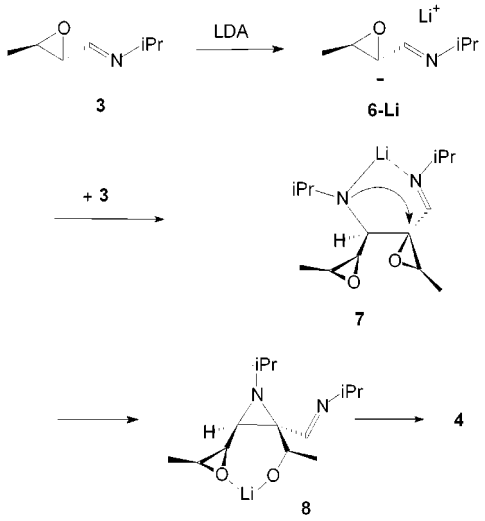


Figure 1. Molecular structure of **(*rac*)-4**.

substitution pattern of **(*rac*)-4** in the crystalline state. **(*rac*)-4** crystallizes in the triclinic space group $P\bar{1}$ (No. 2) with two enantiomeric molecules in the unit cell. The most interesting fact concerns the relative stereochemistry of the newly formed stereogenic aziridine carbon centers; as Figure 1 shows the "dimer" **(*rac*)-4** is formed from each one of the two possible enantiomers of **(*rac*)-3** (heterochiral combination; notice the reversal of the stereochemical descriptor at C1 of the 1-hydroxy-2-propenyl substituent upon oxirane opening!). The substitution pattern of the aziridine ring is *cis*, with the two hydroxy functions on the same side. The isopropyl substituent at the aziridine nitrogen atom N2 points to the less substituted face of the three-membered ring. The imino group shows (*E*)-configuration. The C−N−C bond angle of the aziridine is slightly larger than 60° (61.48°). An intramolecular hydrogen bridge from O14 to N1 (2.086 Å) and an intermolecular hydrogen bridge from O5 to N2′ (2.147 Å) are present in the solid state.

The unexpected formation of **(*rac*)-4** may be explained by a new type of Aza-Darzens reaction that is induced by deprotonation of the starting imine **(*rac*)-3** at the α-carbon atom (Scheme 2). This position is obviously more acidic

Scheme 2



compared to the terminal methyl group, which is usually attacked by strong bases in ring-opening processes of oxiranes to form allyl alkoxides. The structural and electronic properties of the resulting anion, which might be regarded as an unusual aza-enolate type anion (**6**)[13−15] involving an oxirane ring,[16] have been investigated by use of quantum chemical calculations. According to DFT calculations on the B3LYP/6-31+G** level[17] the preferred structure of the isolated anion is characterized by a pyramidal carbanionic center (sum of angles, 311.5°), despite the possible delocalization of charge toward the imine group (aza-enolate), which would however increase the angle (Baeyer) strain in the three-membered ring (Figure 2).

However, the calculated barrier toward inversion at the carbanionic center involving a planar three-coordinate center is very low (4.4 kcal/mol), indicating the possibility of reactions as nucleophile either by retention or inversion at this center. The calculated structure (B3LYP/6-31+G**) of

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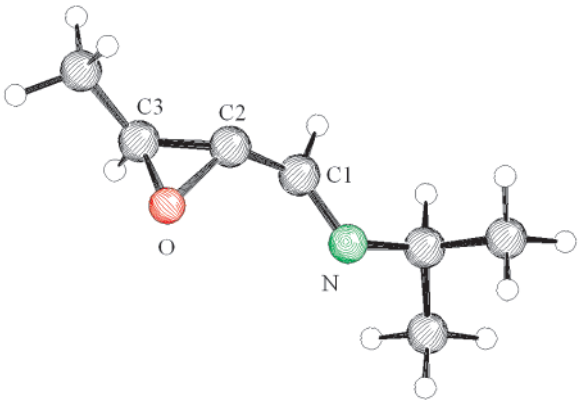

Figure 2. DFT optimized structure of anion **6**. Selected bond lengths [Å]: N−C1 1.313, C1−C2 1.411, C2−O 1.476, C2−C3 1.456, C3−O 1.446; selected bond angles [deg]: N−C1−C2 129.5, C1−C2−O 123.4, C3−C2−O 59.1 (B3LYP/6-31+G**//B3LYP/6-31+G**).

the corresponding lithium compound **6-Li** (Figure 3) is quite similar to that of **6**; in monomeric **6-Li** lithium is four-coordinate, bridging carbon, oxygen, and nitrogen. The bond lengths indicate a little more aza-enolate character (lengthening of N−C1 and shortening of the C1−C2 bond). The C2−O bond is considerably longer in comparison to that of **6**, as a result of the very strong Li−O interaction. Again, the most interesting feature of this structure is the highly pyramidalized four-coordinate carbanionic center (sum of angles, 309.2°). The product of an inversion at C2 is calculated to be 0.99 kcal/mol higher in energy than **6-Li**. With regard to the low inversion barrier its concentration in the reaction mixture is expected to be low.

We assume that this species **6-Li** (or aggregates of it) attacks as a nucleophile a second, enantiomeric molecule of **3** at the imino carbon atom in a highly stereoselective manner, forming intermediate **7** (Scheme 2) (heterochiral combination). We describe this type of diastereoselectivity as mutual kinetic resolution by double diastereofacial selection, which may well be supported by a bridging lithium

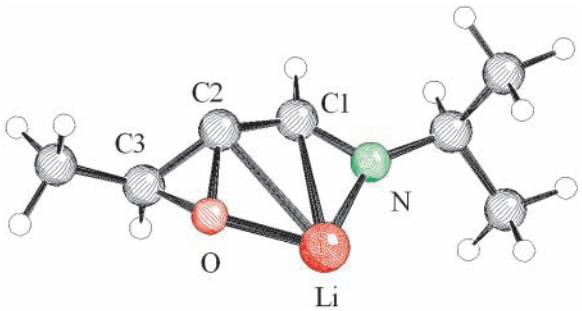

Figure 3. DFT optimized structure of lithium compound **6-Li**. Selected bond lengths [Å]: Li−N 1.884, Li−C1 2.456, Li−C2 2.504, Li−O 1.811, N−C1 1.331, C1−C2 1.397, C2−O 1.529, C2−C3 1.452, C3−O 1.467 (B3LYP/6-31+G**//B3LYP/6-31+G**).

ion keeping the two reacting enantiomers together in a well-defined six-membered transition complex (Scheme 2; see also below). Now regioselective nucleophilic ring opening of the oxirane ring originating from the carbanion leads to the indicated aziridine intermediate **8**. Finally, base-induced ring opening of the other oxirane ring and aqueous work up produces the aziridine ***(rac)*-4**.

The exclusive formation of the *cis* configurated aziridine ring may shed some light on the stereochemical pathway of the reaction. According to semiempirical PM3[18] and DFT calculations (B3LYP/6-31G*), the stereochemistry of the product observed is in agreement with a six-membered transition state of the Zimmerman-Traxler type involving a bridging lithium cation between the two nitrogen atoms. However, because of the special substitution pattern, a clear prediction of the resulting stereochemistry after bond formation on the basis of the distinction of steric demands for equatorial and axial positions is difficult. To explain the high heterochiral diastereoselectivity of the reaction, we postulate an additional chelating by a second lithium cation between the two oxirane rings, keeping them on the same side of the developing aziridine ring (Figures 4 and 5). The DFT

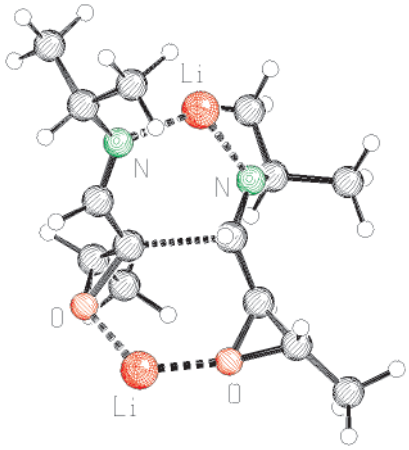

Figure 4. DFT optimized transition structure of the heterochiral combination, assuming retention of configuration and a second lithium ion chelating the oxirane rings. Length of the developing C−C bond: 2.116 Å. (B3LYP/6-31G*//B3LYP/6-31G*).

calculations of such cationic bislithium transition complexes, starting from the energetically more favorable oxiranyllithium compound with retention of configuration, reveal an energy

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difference of 6.8 kcal/mol in favor of the heterochiral combination (Figure 4), despite the manifold lithium chelation of the homochiral combination (Figure 5).

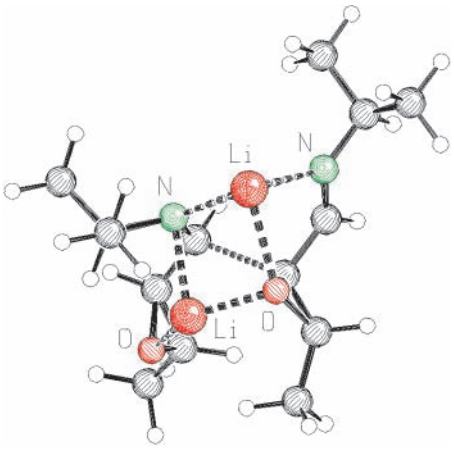

Figure 5. DFT optimized transition structure of the homochiral combination, assuming retention of configuration and a second lithium ion chelating the oxirane rings. Length of the developing C−C bond: 2.069 Å (B3LYP/6-31G*//B3LYP/6-31G*).

On the basis of this postulated mechanism the reaction may be classified as a new type of Aza-Darzens reaction, in which the three-membered heterocyclic ring (here aziridine) is set up by formal addition of an oxiranyl anion to a C=N double bond.

The surprisingly high diastereoselectivity is further supported by unsuccessful experiments to run the same reaction enantioselectively starting from (**2S-*trans***)-**3** (86% ee) as obtained from Sharpless epoxidation of crotyl alcohol. ^{1}H NMR spectra and GC indicate the formation of about 10 products, among them one (<10%) with the NMR signals of **4**. Obviously, the lack of the corresponding enantiomer precludes this reaction from taking place and side reactions dominate. The formation of the small amount of **4** may be explained by the presence of the minor enantiomer in the starting material.

This Aza-Darzens-type reaction is to our knowledge noteworthy because of three new features: (a) For the first time, a 1-aza allylanion bearing an oxirane moiety at the β-carbon atom acts as nucleophile. (b) The leaving group for the formation of the aziridine ring is the oxirane oxygen atom, thus making no use of halogenide-type leaving groups as in conventional Darzens reactions. (c) Both nucleophile and electrophile originate from enantiomers of the same precursor molecule, allowing a highly diastereoselective formal dimerization accompanied by substantial molecular reorganization. All these features provide new, interesting synthetic potential for further synthetic applications in small ring heterocyclic chemistry.

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Supporting Information Available: Experimental procedures, spectroscopic data of the new compounds obtained, and computational details (GAUSSIAN 98 archive entries). This material is available free of charge via the Internet at http://pubs.acs.org.

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