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Diastereoselective One-Step Synthesis of Functionalized *cis*-Aziridinyl Alcohols from Oxiranyl Carbaldimines

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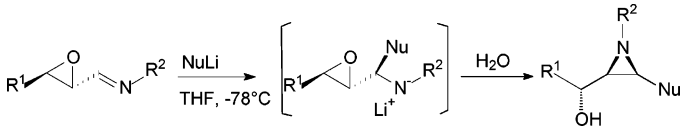
ABSTRACT



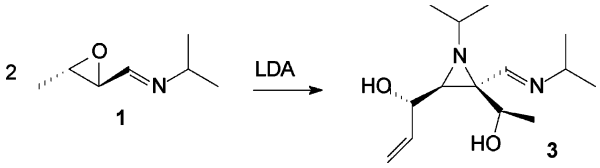
Upon treatment with lithiumorganic nucleophiles, trans-configured oxiranyl carbaldimines are transformed into anti-configured *cis*-aziridinyl alcohols with excellent diastereoselectivity. This conversion may be explained by a new type of the *aza*-Payne rearrangement, including first a nucleophilic attack on the imine carbon atom with diastereofacial differentiation followed by an intramolecular nucleophilic opening of the oxiranyl ring with simultaneous formation of the aziridine ring.

Similar to oxiranes, aziridines are valuable building blocks in modern synthetic organic chemistry. Besides the application of aziridines in the stereoselective synthesis of important, biologically active compounds such as alkaloids, β-lactam antibiotics, and amino acids, they have found use as chiral auxiliaries or ligands in transition-metal-catalyzed reactions.[1,2]

Among several synthetic routes starting from 1,2-amino alcohols, hydroxycarboxylic acids, epoxides, alkenes, dioles, azirines, and imines, the *aza*-Payne reaction provides an attractive but rarely used access to the heterocycle.[3,4]

In this report, we present a new type of the *aza*-Payne reaction, in which oxiranyl carbaldimines **1** are transformed into aziridinyl alcohols **2** with excellent regio- and diastereoselectivity upon treatment with lithiumorganic nucleophiles. This work is based on our earlier discovery that oxiranyl carbaldimines **1** dimerize in a highly diastereoselective process to yield aziridine derivatives **3** with up to four stereogenic centers and up to seven functionalized carbon centers in one step, which is described best as an *aza*-Darzens reaction (Scheme 1).[5]

Scheme 1



Thus, dropwise addition of a THF solution of oxiranyl carbaldimines **1a**−**k** to a solution of the lithium reagent in dry THF at −78 °C, warming to room temperature, and subsequent aqueous workup gave the aziridinyl alcohols **2aa**−**kc** in good yields and excellent diastereoselectivity[6,7] (Scheme 2, Table 1, see Figure 1 for the X-ray structure of **2hc**).[8]

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(3) Tanner, D. *Angew. Chem.* **1994**, *106*, 625−646; *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 599−616.
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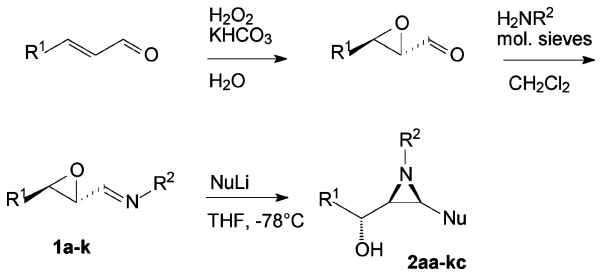
Scheme 2



The corresponding starting materials **1a**−**k** were synthesized in a straightforward manner starting from α,β-unsaturated aldehydes by epoxidation with hydrogen peroxide in buffered aqueous solution as an oxidant (30% yield), followed by condensation with aliphatic amines (75% yield) as cis/trans mixtures (average cis/trans ratio of 8:92).[9,10] The corresponding diastereomeric ratio of the *cis*-aziridinyl alcohols **2aa**−**kc** was determined to be 92:8 (anti/syn). The diastereomers can be separated by flash chromatography.[11,12]

The transformation of aminomethyloxiranes into aziridinyl alcohols is known as the *aza*-Payne rearrangement.[13] However, in most cases, external nucleophiles are used for the ring opening of the oxirane. Vaultier et al.[14] have induced this rearrangement by deprotonation of aminomethyloxiranes, thus generating an internal nucleophile for ring conversion. Here, we report on the first case wherein an amine anion is generated as an intermediate by attack of a nucleophile on an imine functionality. This approach broadens the scope of the reaction considerably.

Table 1. Synthesis of Oxiranyl Carbaldimines **1** and Formation of Aziridinyl Alcohols **2** by Nucleophilic Attack

1	R^1	R^2	Nu	**2**	yield [%]
1a	Me	*i*-Pr	MeLi	**2aa**	42
	Me	*i*-Pr	BuLi	**2ab**	60
	Me	*i*-Pr	PhLi	**2ac**	63
1b	Me	*t*-Bu	MeLi	**2ba**	35
	Me	*t*-Bu	BuLi	**2bb**	47
	Me	*t*-Bu	PhLi	**2bc**	65
	Me	*t*-Bu	PhCCLi	**2bd**	33
1c	Me	Pr	MeLi	**2ca**	54
	Me	Pr	BuLi	**2cb**	47
	Me	Pr	PhLi	**2cd**	70
1d	Me	*c*-Hex	PhLi	**2d**	69
1e	Me	*c*-Pr	BuLi	**2ea**	35
	Me	*c*-Pr	PhLi	**2eb**	67
1f	Me	1-Adam[a]	PhLi	**2fa**	65
	Me	1-Adam[a]	2-furanyl-Li	**2fb**	60
1g	*i*-Pr	*i*-Pr	MeLi	**2ga**	53
	i-Pr	*i*-Pr	BuLi	**2gb**	59
	i-Pr	*i*-Pr	PhLi	**2gc**	74
1h	*i*-Pr	*t*-Bu	MeLi	**2ha**	56
	i-Pr	*t*-Bu	BuLi	**2hb**	76
	i-Pr	*t*-Bu	PhLi	**2hc**	92
1i	*i*-Pr	Pr	BuLi	**2ia**	41
	i-Pr	Pr	PhLi	**2ib**	60
	i-Pr	Pr	PhCCLi	**2ic**	49
1j	Pr	*i*-Pr	BuLi	**2ja**	59
	Pr	*i*-Pr	PhLi	**2jb**	64
1k	Pr	*t*-Bu	MeLi	**2ka**	32
	Pr	*t*-Bu	BuLi	**2kb**	56
	Pr	*t*-Bu	PhLi	**2kc**	65

[a] 1-Adam: 1-adamantyl.

To explain this unprecedented transformation we suggest a highly diastereoselective *aza*-Payne rearrangement reaction,

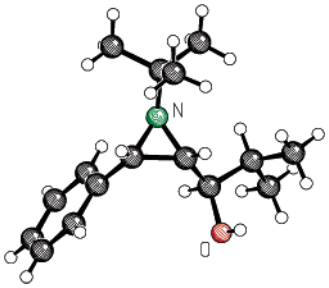


Figure 1. Molecular structure of **2hc** in the crystalline state.

which is fully supported by quantum chemical calculations of structural and electronical properties of the lithiated intermediates and transition states on the SCS-MP2/6-31+G*//RHF/6-31+G* level (Figure 2).[15,16] As a first step, we postulate the formation of a five-membered chelate ring with the lithium cation being coordinated by nitrogen and oxygen of the oxiranyl carbaldimine **1-Li** (E_{rel} = 0.00 kcal

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(8) **Typical Experimental Procedure for the Preparation of 2hc.** Under an argon atmosphere, phenyllithium (1.10 mL, 2.20 mmol, 2.0 M in dibutyl ether) was dissolved in anhydrous THF (15 mL) at −78 °C. A solution of **1h** (339 mg, 2.00 mmol) in dry THF was added dropwise over 30 min, and the mixture was allowed to warm to room temperature over 16 h. After addition of water (20 mL), the aqueous phase was extracted with dichloromethane (4 × 20 mL), and the combined organic layers were dried over magnesium sulfate. The solvent was evaporated, and the organic residue was purified by flash chromatography to give *anti*,*cis*-**2hc** (0.469 g, 1.86 mmol, 93.0%) as a colorless solid. Mp: 56 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (d, ^3J = 6.8 Hz, 3H, $(CH_3)_2CHCH$), 0.95 (d, ^3J = 6.8 Hz, 3H, $(CH_3)_2CHCH$), 1.07 (s, 9H, $(CH_3)_3C$), 1.74 (dsept, $^3J_1$ = 6.8 Hz, $^3J_2$ = 4.0 Hz, 1H, $(CH_3)_2CHCH$), 2.15 (dd, $^3J_1$ = 7.6 Hz, $^3J_2$ = 6.4 Hz, 1H, $CHCHPh$), 2.93 (d, ^3J = 6.4 Hz, 1H, $CHPh$), 3.24 (dd, $^3J_1$ = 7.6 Hz, $^3J_2$ = 4.0 Hz, 1H, $CHCH(OH)$), 7.20 (br t, ^3J = 7.1 Hz, 1H, CH_{arom}), 7.27−7.31 (m, 2H, CH_{arom}), 7.40−7.42 ppm (m, 2H, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.1, 19.5 ($(CH_3)_2CHCH(OH)$), 26.9 ($(CH_3)_3C$), 31.2 ($(CH_3)_2CH$), 37.0 ($CHPh$), 42.1 ($PhCHCH$), 53.1 ($(CH_3)_3C$), 74.0 ($CH(OH)$), 126.7, 127.7, 128.1 (CH_{arom}), 138.2 ppm (C_{ipso}). MS (EI, *m*/*z*) = 247 [M^+], 232, 230, 216, 190, 160, 148, 118, 106, 91, 70, 57. IR (KBr): $\tilde{\nu}$ = 3350 cm^{-1} (s, OH), 3086 (m, CH_{arom}), 3062 (m, CH_{arom}), 3028 (m, CH_{arom}), 2968 (vs, CH_{aliph}), 2929 (vs, CH_{aliph}), 2906 (s, CH_{aliph}), 2873 (s, CH_{aliph}), 1952 (w), 1878 (w), 1815 (w), 1604 (m), 1495 (m), 1468 (s, CH_{aliph}). Anal. Calcd for $C_{16}H_{25}NO$ (247.38): C, 77.68; H, 10.19; N, 5.66. Found: C, 77.70; H, 10.15; N, 5.49.

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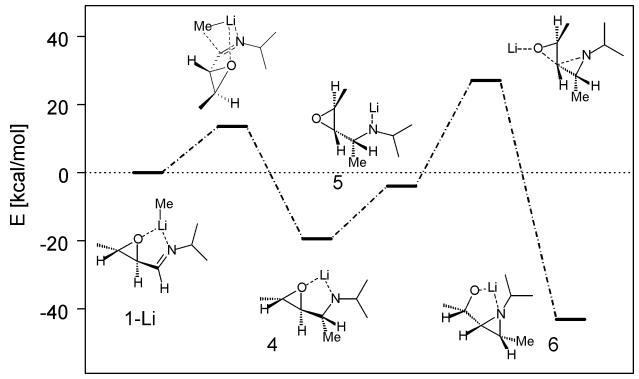


Figure 2. Calculated energies for the interconversion of **1-Li** to **6** (methyllithium as a nucleophile) (SCS-MP2/6-31+G*) [kcal/mol].

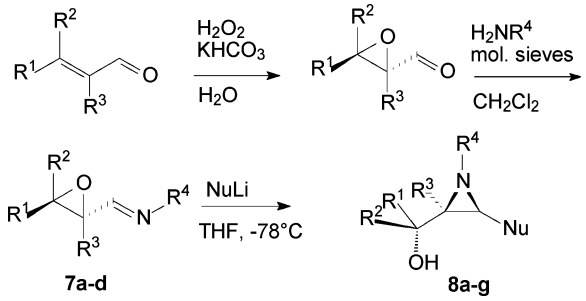
mol^{-1}, trans diastereomer). This fixed conformation of the electrophile offers the diastereotopic faces of the imine double bond. The attack of the negatively charged carbon nucleophile proceeds from the sterically less hindered, oxirane ring remote face, forming an amine anion **4**. **4** Is predicted to be more than 19 kcal mol^{-1} lower in energy compared to the starting structure with the lithium ion still being coordinated to the nitrogen and oxygen atoms. The calculated activation barrier amounts to ca. 13.5 kcal mol^{-1}. As the aziridine ring-forming step, we assume an S_N2-type attack of the negatively charged nitrogen atom on carbon atom C2 of the oxirane ring. This attack requires a 180° turn of the oxirane moiety to form **5**, enabling a proper S_N2 trajectory with inversion at the stereogenic carbon C2. This is accompanied by the breakdown of the lithium chelate, with the lithium counterion still being coordinated to the nitrogen atom. Due to the incomplete coordination sphere of the metal center, we calculate a relatively high energy of about 15.5 kcal mol^{-1}, compared to the first intermediate **4**, for this second intermediate **5** in the gas phase. Since solvent-stabilizing effects will be active in solution, this value is probably too large.

In the third reaction step the aziridine ring **6** is formed after an S_N2-type attack at the C2 of the epoxide, accompanied by simultaneous ring opening of the oxirane to form an *anti*-alcoholate with respect to the cis-configured heterocycle. In this step, the configuration at carbon atom C2 is inverted, while that of carbon atom C3 remains predefined by the epoxide configuration. We calculate a high activation barrier (27.1 kcal mol^{-1}) for this gas-phase process due to coordinational unsaturation of the lithium ion. For the reaction in solution, however, one can assume that other metal ions, stemming from the reaction mixture, coordinate to the developing oxygen anion and will contribute to lower the barrier.

The final intermediate, the aziridinyl alcoholate **6**, is by far the energetically most stable isomer within this set of structures (−43.1 kcal mol^{-1}) and demonstrates the exothermicity of the proposed reaction mechanism. In **6**, the five-membered lithium chelate ring is regenerated, now with an sp^3 instead of an sp^2 carbon center next to the three-membered ring. The higher stability of the aziridine moiety **6** compared to the oxirane structure **1-Li** is obvious. Experimentally, hydrolysis of the O−Li bond with water yields the observed anti,cis-configured aziridinyl alcohol **2**.

Even tris-substituted aliphatic α,β-unsaturated aldehydes such as 2-methyl-2-pentenal and 3-methylcrotonaldehyde can be transformed by the same reaction sequence via oxidation with hydrogen peroxide[17] and condensation with primary aliphatic amines[18] to give **7a**−**d** (**7a**, *E*:*Z* = 3:2), which yield the three-membered N-heterocycles **8** after nucleophilic attack. Depending on the position of the substituents at C2 or C3 of the epoxide moiety, either aziridinyl alcohols with three substituents at the aziridine ring **8a** or tertiary alcohols **8b**−**g** are the reaction products (Scheme 3, Table 2).

Scheme 3



A slightly different reaction sequence and conditions are required for the synthesis of and nucleophilic attack on oxiranyl carbaldimines with an aromatic substitution pattern. Because of the insufficient nucleophilicity of aniline, 4-meth-

Table 2. Synthesis of *cis*-Aziridines **8a**−**g** From the Oxiranyl Carbaldimines **7a**−**d**

	R^1	R^2	R^3	R^4	Nu	yield [%]
7a, **8a**	Et	H	Me	*t*-Bu	PhLi	36
7b, **8b**	Me	Me	H	*i*-Pr	BuLi	25
7b, **8c**	Me	Me	H	*i*-Pr	PhLi	52
7c, **8d**	Me	Me	H	*t*-Bu	BuLi	38
7c, **8e**	Me	Me	H	*t*-Bu	PhLi	37
7c, **8f**	Me	Me	H	*t*-Bu	PhCCLi	37
7d, **8g**	Me	Me	H	*c*-Hex	PhLi	43

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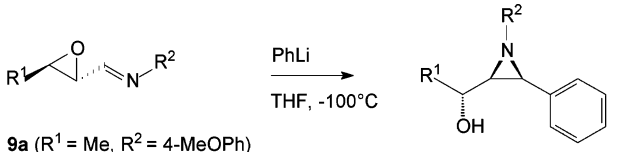
oxyaniline was reacted instead with 2,3-epoxybutanal to demonstrate the chemistry of an N-aromatic-substituted oxiranyl carbaldimine **9a**.

Competing reactions such as oxidation giving the corresponding acid limit the direct epoxidation of cinnamaldehyde. A two-step reaction pathway starting with the epoxidation of cinnamyl alcohol by MCPBA followed by selective oxidation of the alcohol functionality using the Dess−Martin periodinane provides a good alternative strategy, yielding the phenyl-substituted oxiranyl carbaldehyde.[19,20] Condensation reaction with *tert*-butylamine (30% yield) gives compound **9b**, which decomposes upon standing within a few days.[6]

Scheme 4



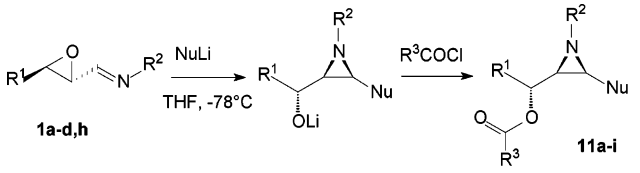
9a (R^1 = Me, R^2 = 4-MeOPh)
9b (R^1 = Ph, R^2 = t-Bu)

10a (R^1 = Me, R^2 = 4-MeOPh)(47%)
10b (R^1 = Ph, R^2 = t-Bu)(53%)

To prevent possible lithiation of the aromatic rings, the lithium nucleophiles were dissolved in dry THF and cooled to −100 °C. Very slow dropwise addition of the aryl-substituted oxiranyl carbaldimines **9a**,**b** as a very dilute THF solution (2−3 mmol/10−15 mL of THF), warming to room temperature, and aqueous workup gave the aziridinyl alcohols **10a**,**b** in similar yield and diastereoselectivity compared to compounds **2** and **8** with an aliphatic substitution pattern (Scheme 4).

Trapping of the lithium alcoholates with acid chlorides as a third reaction component is also possible in a one-pot procedure. After formation of the aziridinyl intermediates within a reaction time of 1 h at −78 °C and another 30 min at −20 °C to complete the conversion, addition of a solution of the acid chlorides and slow warming to room temperature gave the corresponding aziridinyl esters **11a**−**h** in good yields. Even the formation of a bis-aziridine **11i** by reaction with phthaloyl chloride is possible (Scheme 5).

Scheme 5



1a-d,h

11a-i

R^3 = 4-Br-Ph-CO, 4-NO_2-Ph-CO, t-Bu-CO, Ph-CH=CH-CO, CH_3-CO, 1,2-$(OC)_2$-Ph (17-62%)

These results indicate that the attack of the lithium nucleophile and the oxirane−aziridine rearrangement proceed rapidly, as the process is complete within less than 2 h. Considering the smooth synthesis of different oxiranyl carbaldimines, the easy access to functionalized lithium organics via deprotonation with lithium bases (including carbonyl compounds), or the possibility of transmetalation of appropriate organo halides or tin compounds, an even wider scope of this reaction is to be expected.

In conclusion, we have developed a new and experimentally easy synthesis of *cis*-aziridinyl alcohols and their corresponding esters by nucleophilic attack on oxiranyl carbaldimines. The chelate-controlled S_N2-type ring opening of the epoxides results in the formation of cis-configured aziridines. The anti/syn ratio of the alcohol moieties depends on the trans/cis ratio of the epoxides. The starting materials are simply accessible via epoxidation of α,β-unsaturated aldehydes and subsequent condensation with primary amines. The postulated reaction mechanism, which is supported by ab initio calculations, is described best as a variant of the *aza*-Payne reaction, proceeding with excellent diastereofacial differentiation. It includes the nucleophilic attack of an organolithium reagent on an aldimine from the sterically less hindered face, an S_N2-type ring opening of the oxirane by the intermediately formed amine anion with simultaneous formation of a *cis*-aziridine ring, and trapping of the aziridinyl alcoholate with water or various acid chlorides.

Acknowledgment. Support by the Deutsche Forschungsgemeinschaft (DFG, SFB 424) and by the Fonds der Chemischen Industrie is gratefully acknowledged.

Supporting Information Available: Summary of theoretical data (total energies, relative energies) and crystallographic data (CIF) for compounds **2hc**, **8e**, and **10b**, as well as NMR spectroscopic data of selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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