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Stereoselective Synthesis of Novel β,γ-Epoxyhydroxylamines and 4-Hydroxyalkyl-1,2-oxazetidines

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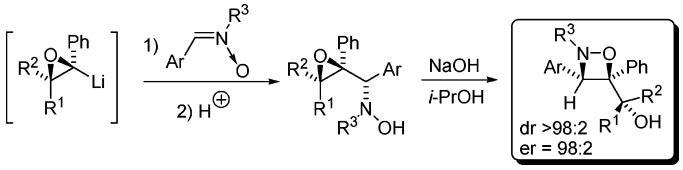
ABSTRACT



A simple and efficient stereoselective synthesis of polysubstituted β,γ-epoxyhydroxylamines and 4-hydroxyalkyl-1,2-oxazetidines, based on the addition of α-lithiated aryloxiranes to nitrones and subsequent cyclization of the corresponding intermediates in a 4-*exo*-tet mode, is described.

Nitrones are compounds extremely important in synthetic organic chemistry. They mainly undergo two fundamental reactions: 1,3-dipolar cycloadditions[1] and nucleophilic additions.[2] Nucleophilic addition reactions have been thoroughly investigated, including alkylation, arylation, alkenylation, cyanation, acylalkylation,[2,3] allylation,[4] allenylation,[5] and alkynylation[6−8] for the preparation of a large variety of substances.

The addition reaction of heterosubstituted organolithiums to nitrones has been successfully used for the preparation of optically active 5-isoxazolidinones and β-amino acids,[9a] optically active oxazolinyl[1,2]oxazetidines,[9b] α-epoxy-β-amino acids,[9c] alkenyloxazolines,[9d] carbon-linked glycoglycines,[9e] lipoxygenase inhibitors,[9f] and imino-C-nucleosides.[9g]

By way of contrast, the addition of α-lithiated aryloxiranes, successfully used for the synthesis of structurally complex

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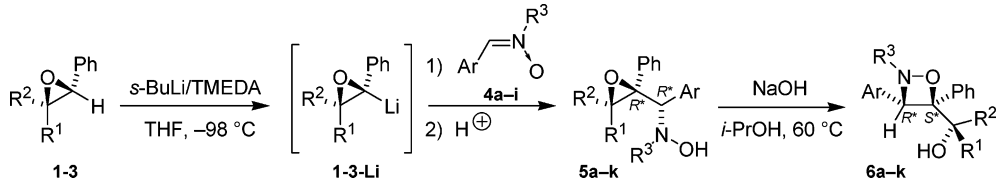
Table 1. Preparation of β,γ-Epoxyhydroxylamines **5a**−**k** and 1,2-Oxazetidines **6a**−**k**



oxirane	R^1	R^2	R^3	Ar	nitrone **4**	hydroxylamine **5** (yield, %)[a]	1,2-oxazetidine **6** (yield, %)[a]	dr[b]
1	H	H	cumyl	Ph	**4a**	**5a** (60)	**6a** (50)	>98/2
1	H	H	cumyl	4-MeC_6H_4	**4b**	**5b** (42)	**6b** (70)	>98/2
1	H	H	cumyl	4-ClC_6H_4	**4c**	**5c** (50)	**6c** (70)	>98/2
1	H	H	cumyl	2-furyl	**4d**	**5d** (82)	**6d** (62)	>98/2
1	H	H	cumyl	4-$MeOC_6H_4$	**4e**	**5e** (54)	**6e** (40)	>98/2
1	H	H	cumyl	5-(3-$CF_3C_6H_4$)−2-furyl	**4f**	**5f** (82)	**6f** (65)	>98/2
2	Me	H	cumyl	4-ClC_6H_4	**4c**	**5g** (60)	**6g** (80)	>98/2
3[c]	H	Ph	cumyl	4-ClC_6H_4	**4c**	**5h** (65)	**6h** (75)	>98/2
1	H	H	*t*-Bu	4-$CF_3C_6H_4$	**4g**	**5i** (60)	**6i** (50)[d]	90/10[e]
1	H	H	*t*-Bu	Ph	**4h**	**5j** (63)	**6j** (85)[d]	>98/2
1	H	H	*t*-Bu	4-ClC_6H_4	**4i**	**5k** (78)	**6k** (95)[d]	>98/2

[a] Isolated yields after column chromatography on silica gel. [b] Diastereomeric ratio (dr) calculated by ^{1}H NMR analysis of the crude reaction mixture. [c] Lithiation reaction performed with *n*-BuLi (see the Supporting Information). [d] Cyclization reaction performed at room temperature. [e] Separable mixture of diastereoisomers (see the Supporting Information).

epoxides and derivatives,[10] has never been investigated. In the present paper, we report the stereoselective preparation of novel β,γ-epoxyhydroxylamines and 4-hydroxyalkyl-1,2-oxazetidines based on the addition of α-lithiated aryloxiranes to nitrones.

α-Lithiated styrene oxide **1-Li** was prepared by treating commercially available styrene oxide **1** with *s*-BuLi in THF and TMEDA at −98 °C, as reported.[11] Addition of *N*-cumylphenyl nitrone **4a** to the dark red solution of **1-Li** furnished the epoxyhydroxylamine **5a**, after quenching with aqueous NH_4Cl, with an excellent diastereoselectivity (Table 1).

Subsequent treatment of **5a** with NaOH/*i*-PrOH led to the diastereoselective formation of 4-hydroxymethyl-1,2-oxazetidine **6a** (dr > 98/2), which is the result of an oxirane ring-opening-promoted intramolecular cyclization taking place in 4-*exo*-tet mode. In a comparable manner **1-Li** reacted with aryl and heteroaryl cumyl nitrones **4b**−**f** to give epoxyhydroxylamines **5b**−**f** and then hydroxyalkyl-1,2-oxazetidines **6b**−**f** (Table 1).

The substitution effect in the starting oxirane was briefly investigated. Lithiated *trans*-phenylpropylene oxide **2-Li** and *cis*-stilbene oxide **3-Li** reacted with nitrone **4c** giving the expected hydroxylamines **5g** and **5h** and then oxazetidines **6g** and **6h** in comparable chemical yields and diastereoselectivity after treatment with NaOH. In contrast, no addition occurred when lithiated *trans*-stilbene oxide was treated with nitrone **4c**, likely because of steric reasons (see ahead).

Concerning the nitrone *N*-substitution we found that the reaction of **1-Li** with *N*-*tert*-butyl nitrones **4g**−**i** afforded, as expected, the *N*-*tert*-butyl hydroxylamines **5i**−**k** and subsequently oxazetidines **6i**−**k**. In contrast, an acid−base reaction occurred when *N*-benzylnitrone **4l** was added to **1-Li** leading to styrene oxide, *N*-phenylethyl nitrone **4m** and compound **7** upon quenching first with MeI and then with aqueous NH_4Cl (Figure 1).

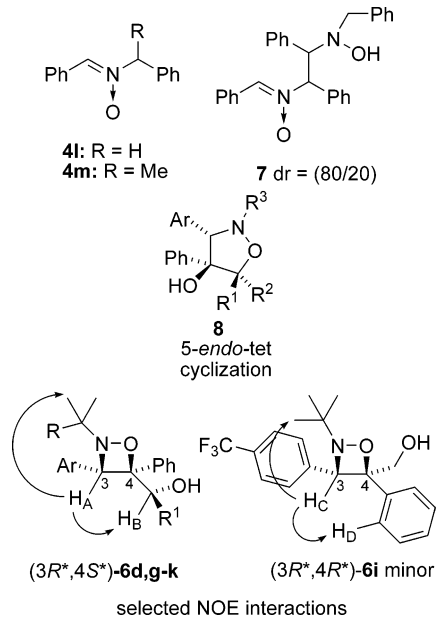


Figure 1.

The configurational assignment of the above epoxyhydroxylamines and oxazetidines gave insights into the reaction

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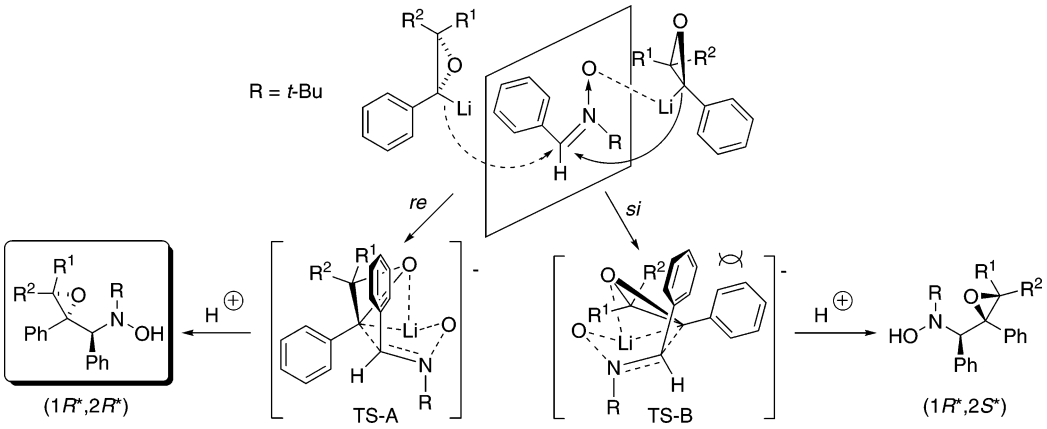

Figure 2. Addition of **1**−**3-Li** to the *re* or *si* face of the nitrone **4h**.

mechanism as well as the observed stereochemistry. The configuration of the epoxyhydroxylamines was assigned by ^{1}H and ^{13}C NMR spectroscopy and, in some cases, the assignment was also confirmed by an X-ray analysis.

The relative configuration of the two stereocenters (3*R**,4*S**) of 1,2-oxazetidines **6d**,**g**−**k** was established by detecting positive NOE effects, diagnostic of the spatially close hydrogen relationship, after applying selective ^{1}H preirradiations within a double pulsed field gradient spin−echo NOE (DPFGSE-NOE) sequence.[12] In the case of the major isomers of **6d**,**g**−**k**, a preirradiation of H_A enhanced either of the methyl protons of the cumyl and *tert*-butyl group linked at the oxazetidine nitrogen or the carbinol proton H_B, as depicted in Figure 1.

Only in the case of the reaction of **1-Li** with **4g** was it possible to isolate the minor diastereomeric oxazetidine (3*R**,4*R**)-**6i**: for this isomer, the NOE enhancement of H_D was observed after selective preirradiation of H_C. This type of assignment was unambiguously confirmed by the X-ray analysis in the case of 1,2-oxazetidine **6j**. The relative configuration of oxazetidine **6c** was confirmed by the X-ray analysis of its precursor **5c** considering that, in the oxazetidine cyclization reaction, there is inversion of configuration at the benzylic carbon attacked by the sodium alkoxide and retention at the other oxirane ring carbon atom. The relative configuration of the other 4-hydroxyalkyl-3-aryl-substituted 1,2-oxazetidines **6a**,**b**,**e**,**f** could be determined by analogy. Indeed, the chemical shift of the proton at the C-3 ring carbon atom for all the major isomers was always found to fall into the range 5.4−5.7 ppm, whereas that for (3*R**,4*R**)-1,2-oxazetidine **6i** was 5.22 ppm.

To explain the observed diastereoselectivity we envisage a preliminary coordination of the lithiated oxirane on the nitrone oxygen followed by the addition to the nitrone going through two different five-membered cyclic transition states: the one leading to the observed (1*R**,2*R**) diastereoisomer (**TS-A**), after the addition of **1-Li** to the *re* face of the nitrone, would not experience the steric interaction between the two aryl groups, which instead is important in the transition state **TS-B** leading to the (1*R**,2*S**) diastereomer (not observed, except in the case of the reaction of **1-Li** with nitrone **4g**, Figure 2).[13]

Supporting such a mechanistic hypothesis is the experimental evidence that lithiated *trans*-stilbene oxide does not add to nitrone **4c**, probably because of the unfavorable additional steric interaction between the aryl groups belonging to the nitrone and the oxirane (R^1 = Ph) in a transition state of the **TS-A** type. It is worth noting that the ring closure of hydroxylamines **5** to isoxazolidines **8** (Figure 1) does not occur probably because it is less thermodynamically favored under these conditions.

The possibility of making optically active hydroxylamines and oxazetidines of the type of **5** and **6** was next evaluated. Indeed, we found that (*R*)-**1-Li** adds to nitrones **4c** and **4h**

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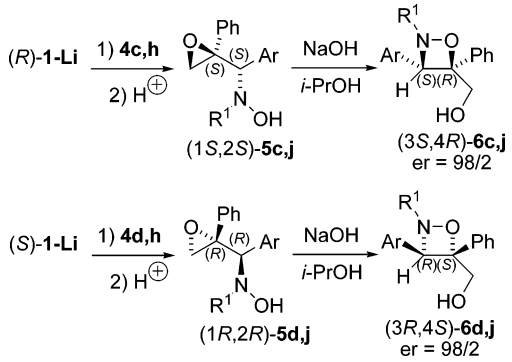
(13) The two competitive mechanistic pathways depicted in Figure 2 refer, in particular, to the addition of **1**−**3-Li** to the *re* or *si* face of the nitrone **4h**.

with an excellent diastereo- and enantioselectivity leading to the formation of hydroxylamines (1*S*,2*S*)-**5c** and (1*S*,2*S*)-**5j** and then to oxazetidines (3*S*,4*R*)-**6c** and (3*S*,4*R*)-**6j** upon treatment with NaOH/*i*-PrOH (Table 2). Similarly, (*S*)-**1-Li** reacted with nitrones **4d** and **4h** to give (1*R*,2*R*)-**5d** and (1*R*,2*R*)-**5j** and subsequently (3*R*,4*S*)-**6d** and (3*R*,4*S*)-**6j**.

Table 2. Preparation of Optically Active β,γ-Epoxyhydroxylamines **5c**,**d**,**j** and 1,2-Oxazetidines **6c**,**d**,**j**



1-Li	nitrone **4**	hydroxylamine **5** (yield, %)[a]	1,2-oxazetidine **6** (yield, %)[a]	er[b]
(*R*)-**1-Li**	**4c**	(1*S*,2*S*)-**5c** (78)	(3*S*,4*R*)-**6c** (78)	98/2
(*S*)-**1-Li**	**4d**	(1*R*,2*R*)-**5d** (60)	(3*R*,4*S*)-**6d** (62)	98/2
(*R*)-**1-Li**	**4h**	(1*S*,2*S*)-**5j** (63)	(3*S*,4*R*)-**6j** (80)	98/2
(*S*)-**1-Li**	**4h**	(1*R*,2*R*)-**5j** (60)	(3*R*,4*S*)-**6j** (75)	98/2

[a] Isolated yields after column chromatography on silica gel. [b] Enantiomeric ratio (er) calculated by HPLC (see the Supporting Information).

The highly diastereoselective formation of hydroxylamines **5** described above is quite intriguing considering that lithiated aryloxiranes have been reported to couple with carbonyl compounds with no or poor diastereoselectivity.[10c,11,14,15] Moreover, considering that the cyclization reaction of **5** to **6** occurs with inversion of configuration at the oxirane ring carbon that is attacked by the oxygen of the hydroxylamino functionality, the above transformation of (*R*)- or (*S*)-**1** to **5** and then to **6** represents a useful stereospecific synthesis of so far undescribed optically active 1,2-oxazetidines **6**.

In conclusion, with this work we have developed a simple and efficient stereoselective method for synthesizing polysubstituted β,γ-epoxyhydroxylamines **5** and hydroxyalkyl-1,2-oxazetidines **6**, simply by adding lithiated aryloxiranes to nitrones. These novel scaffolds, that are accessible in two steps, and which are perfectly stable, seem to be promising for synthetic elaboration to other substances.

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Supporting Information Available: Full experimental details and copies of ^{1}H NMR and ^{13}C NMR spectra for compounds **5a**−**k** and **6a**−**k**. This material is available free of charge via the Internet at http://pubs.acs.org.

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