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Nitrogen Dynamics and Reactivity of Chiral Aziridines: Generation of Configurationally Stable Aziridinyllithium Compounds

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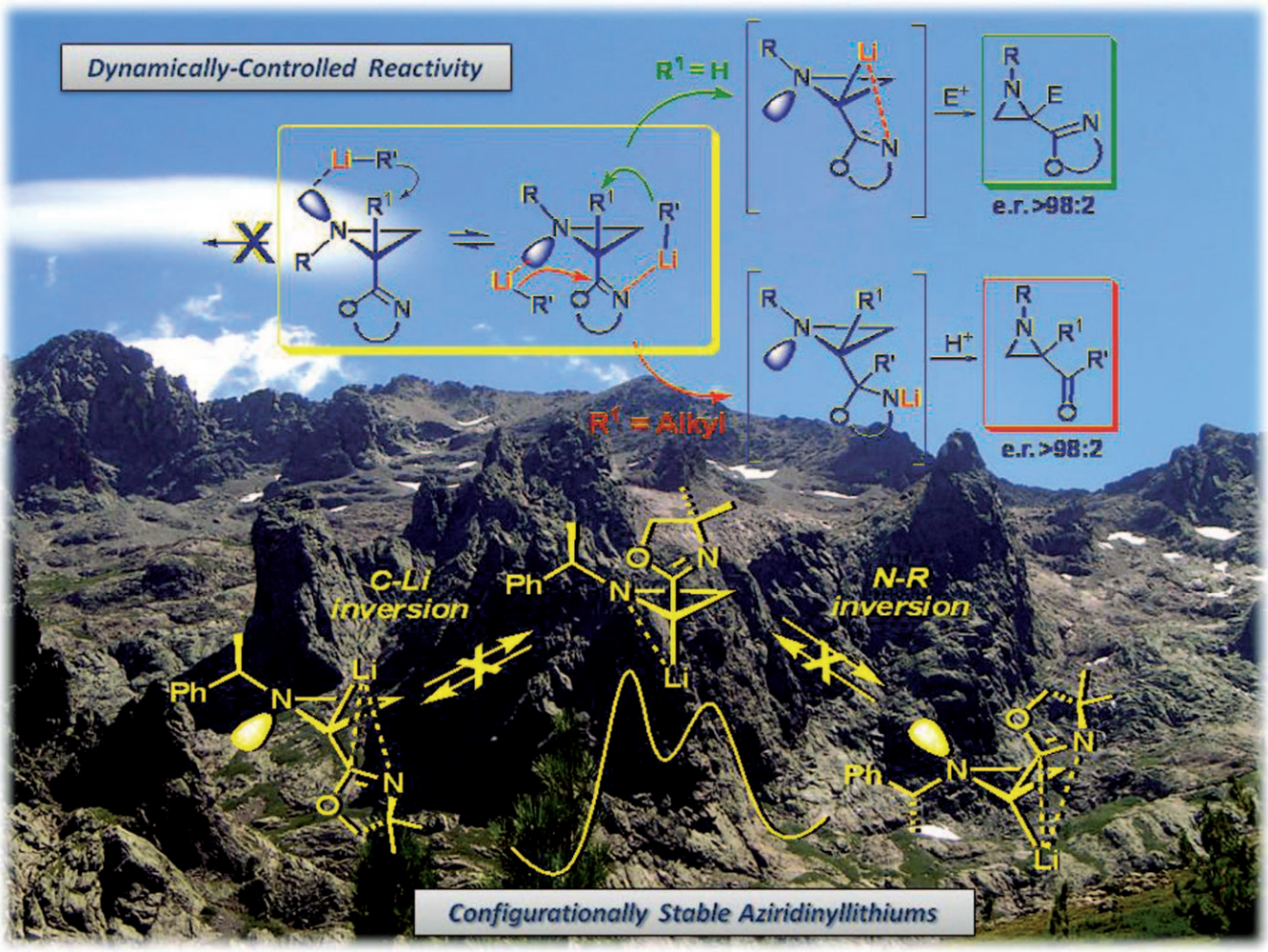

Abstract: Diastereomeric oxazolinylaziridines (*R*,*R*)-**9** and (*R*,*S*)-**9** have been regioselectively lithiated at the α-position with respect to the oxazolinyl ring. The resulting aziridinyllithium compounds proved to be chemically and configurationally stable under the experimental conditions used, thus furnishing, upon trapping with electrophiles, chiral 2,2-disubstituted aziridines, in contrast to the corresponding α-lithiated oxazolinyloxiranes that have been reported to be chemically stable but configurationally unstable. This peculiar behavior of the nitrogen-bearing heterocycle has been rationalized on the basis of DFT calculations and the observed dynamics of the aziridine nitrogen atom. The DFT analysis allowed the disclosure of a solvent-dependent differing stability of diastereomeric lithiated aziridines (*R*,*R*)-**9**-Li and (*R*,*S*)-**9**-Li, suggesting η^3-coordinated oxazolinylaziridinyllithium compounds as likely intermediates. Such intermediates could be the result of a dynamically controlled lithiation that relies on the preliminary formation of a complex between the lithiating agent and the oxazolinyl ring. According to this model, the competing complexation of the lithiating agent by the lone pair of electrons on the aziridine nitrogen would cause addition to the oxazoline C=N bond, thus ending up with the formation of oxazolidines, which are precursors of useful chiral ketoaziridines. The proposed model has been also supported by estimating the nitrogen inversion barrier by dynamic NMR spectroscopic experiments.

Keywords: ketoaziridines · lithium · nitrogen dynamics · NMR spectroscopy · stereoselectivity

Introduction

Aziridines are widely used as versatile building blocks for the synthesis of a variety of biologically and pharmaceutically important molecules.[1] Several methods of synthesis of chiral aziridines have been developed and their use as chiral building blocks has also emerged.[2] The synthesis of functionalized aziridines based on the lithiation/trapping sequence of readily available parent aziridines has become more and more useful over recent years.[3] The generation of lithiated aziridines involved in such a methodology by deprotonation (usually by using an organolithium or a lithioamide) clearly depends on several factors, including the nature of the aziridine-ring substitution and the stereochemistry at the aziridine nitrogen atom.[4] As a matter of fact, when an electron-withdrawing group (EWG) is on one of the aziridine-ring carbon atoms, lithiation takes place normally at the α-position to that group,[5] whereas with alkyl-substituted terminal aziridines (bearing an EWG on the nitrogen atom) lithiation takes place at the β-*trans* position with respect to the alkyl group.[6] Moreover, the lithiation/trapping reactions meet the problem of the configurational stability of the related aziridinyllithium compounds, so far scarcely investigated but of great importance for planning stereoselective synthesis of aziridines and derivatives. Indeed, at least with reference to aziridines bearing an EWG substituent on the lithiated carbon atom, studies on the configurational stability of these compounds and the stereochemistry of trapping them with electrophiles are rather rare. In an early report, Seebach et al.[7] studied lithiated aziridinyl thioesters (*S*,*R*)-**1** and (*S*,*S*)-**1**, thus demonstrating that their configurational stability depends on the configuration of the starting aziridine (Figure 1). Moreover, Housson and co-workers[8] reported that lithiated aziridinyl esters (*R*,*R*)-**2** and (*R*,*S*)-**2** were configurationally stable under different reaction conditions and reacted with electrophiles with retention of configuration (Figure 1).

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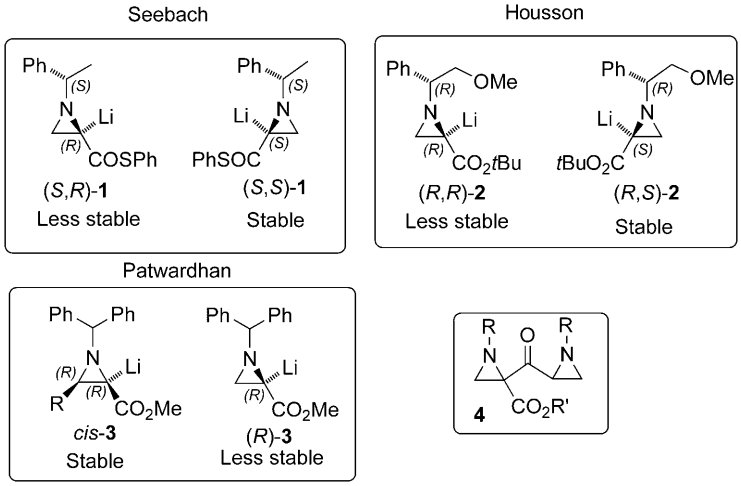
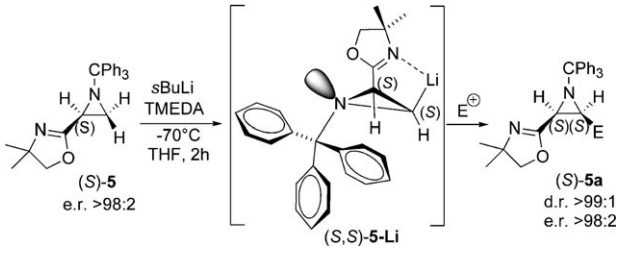


Figure 1. Reported aziridinyl ester compounds.

Finally, Patwardhan et al.[9] investigated the alkylation of lithiated aziridine-2-carboxylate compounds bearing a benzhydryl group on the nitrogen atom and found high diastereoselectivity only with aziridines of the type *cis*-**3**, whereas the lithiated aziridine carboxylate compound (*R*)-**3** underwent racemization. Variable amounts of dimerization products **4**, which decreased the yields of the trapping reactions, were always observed in the reactions of all the studied lithiated aziridine carboxylate compounds.

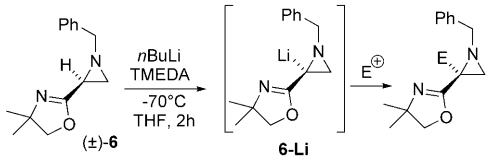
In our recent studies on the lithiation of *N*-alkyl oxazolinylaziridines, we found that the regioselectivity depends on the steric demand of the *N*-substituent. Indeed, chiral 1-trityl-2-oxazolinylaziridine (*S*)-**5** could be regioselectively β-lithiated to give chemically and configurationally stable (*S*,*S*)-**5**-Li, as proved by electrophilic trapping, and yield chiral *cis*-2,3-disubstituted aziridine (*S*)-**5a** (Scheme 1).[10]



Scheme 1. Regioselective β-lithiation of terminal oxazolinylaziridines. TMEDA = tetramethylethylenediamine.

Conversely, oxazolinylaziridines with a less sterically demanding *N*-substituent, such as 1-benzyl-2-oxazolinylaziridine (±)-**6**, underwent exclusive α-lithiation to give **6**-Li and products derived upon its trapping (Scheme 2).

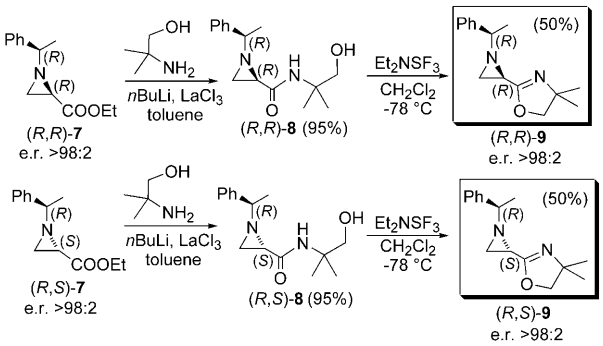
As the configurational stability of α-lithiated oxazolinylaziridines is so far completely unexplored, we decided to undertake a detailed investigation on this topic and were also intrigued by the recent observation that α-lithiated oxazolinyloxiranes generated from optically pure precursors have a pronounced bias to epimerization.[11]



Scheme 2. Regioselective α-lithiation of terminal oxazolinylaziridines.

Results and Discussion

To begin the study, chiral 1-phenylethyl-2-oxazolinylaziridines (*R*,*R*)-**9** and (*R*,*S*)-**9** were prepared starting from diastereomeric esters (*R*,*R*)-**7** and (*R*,*S*)-**7**[7,12] upon treatment with 2-methyl-2-amino-1-propanol and *n*BuLi in toluene and subsequent reaction of the resulting amides (*R*,*R*)-**8** and

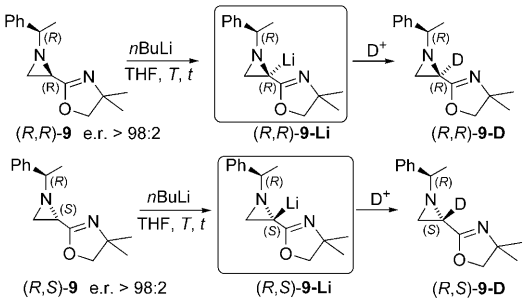


Scheme 3. Preparation of chiral oxazolinylaziridines (*R*,*R*)-**9** and (*R*,*S*)-**9**.

(*R*,*S*)-**8** with diethylamino sulfurtrifluoride (Scheme 3).[13] No epimerization at C2 was observed during all the synthetic steps.

Once prepared, both the diastereomeric aziridines (*R*,*R*)-**9** and (*R*,*S*)-**9** were subjected to the lithiation/deuteration sequence under varied reaction conditions. Both aziridines (*R*,*R*)-**9** and (*R*,*S*)-**9** underwent highly regioselective lithiation at the α-position to give (*R*,*R*)-**9**-Li and (*R*,*S*)-**9**-Li and, in both cases, quenching with a deuterium source within 1 hour from their generation took place with complete retention of configuration (Table 1, entries 1–3 and 6–8). Nevertheless, at a closer look, some differences in the thermal and configurational stability of (*R*,*R*)-**9**-Li and (*R*,*S*)-**9**-Li were observed. In analogy with the work of Seebach and

Table 1. Lithiation/deuteration (MeOD) sequence of aziridines (*R*,*R*)-**9** and (*R*,*S*)-**9**.



Entry	Aziridine	*T* [°C]	*t*	D [%][a]	Yield [%][b]	Ratio (*R*,*R*)/(*R*,*S*)[c]
1	(*R*,*R*)-**9**	−98	15 min	90	80	>98:2
2	(*R*,*R*)-**9**	−98	30 min	90	80	98:2
3	(*R*,*R*)-**9**	−98	1 h	90	80	98:2
4	(*R*,*R*)-**9**	−98	4 h	90	80	98:2
5	(*R*,*R*)-**9**	−78	4 h	80	70	>98:2
6	(*R*,*S*)-**9**	−98	15 min	90	80	5:95
7	(*R*,*S*)-**9**	−98	30 min	90	80	5:95
8	(*R*,*S*)-**9**	−98	1 h	90	80	6:94
9	(*R*,*S*)-**9**	−98	4 h	–[d]	–	25:75
10	(*R*,*S*)-**9**	−78	4 h	–[d]	–	23:77

[a] Deuterium content established by ^{1}H NMR spectroscopic and/or MS-(ESI) analysis. [b] Yield of isolated products. [c] Diastereomeric ratio by ^{1}H NMR spectroscopic and GC-MS analysis of the crude reaction mixture. [d] Degradation occurred under these reaction conditions and only traces of epimerized deuterated compounds were detected by GC-MS analysis.

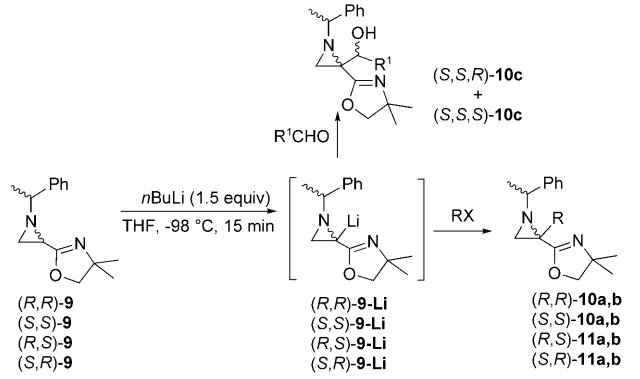
Housson, it was found that in some cases the reactions of the (*R*,*S*)-**9** diastereoisomer were less selective than those of (*R*,*R*)-**9**. The lithiated intermediate (*R*,*S*)-**9**-Li proved to be thermally and configurationally unstable for a longer reaction time and at a higher temperature (Table 1, entries 9 and 10), thus leading to degradation products and appreciable epimerization. Conversely, lithiated intermediate (*R*,*R*)-**9**-Li was thermally and configurationally stable even at a temperature higher than −98 °C and for a long reaction time (Table 1, entry 5).

The same behavior was observed, as expected, also for the enantiomeric aziridines (*S*,*S*)-**9** and (*S*,*R*)-**9**, prepared by using the corresponding aziridinyl esters obtained from (*S*)-phenylethylamine (Scheme 3).

In view of this, the generation of the lithiated aziridines from all the available stereoisomers and the stereoselective trapping with electrophiles was investigated by using −98 °C for 15 minutes as optimal reaction conditions. Under such conditions, trapping with alkyl halides furnished enantiomerically enriched 2,2-disubstituted aziridines (*S*,*S*)-**10a**,**b**, (*R*,*R*)-**10a**,**b**, (*R*,*S*)-**11a**,**b**, and (*S*,*R*)-**11a**,**b** in good yields (Table 2).

Trapping of lithiated aziridine (*S*,*R*)-**9**-Li with *para*-ClC_6H_4CHO occurred with low stereoselectivity with respect to the newly created stereogenic centre, thus furnishing the two diastereomeric aziridines (*S*,*S*,*R*)-**10c** and (*S*,*S*,*S*)-**10c** in a 70:30 ratio and 55% overall yield. Fortunately, the two diastereoisomers could be separated by flash chromatography and the absolute configuration of the *S*,*S*,*R* isomer was ascertained by X-ray analysis.[14] This stereochemical outcome revealed that the aziridine ring in (*S*,*S*,*R*)-**10c** had the same configuration at C2 of the starting aziridine (*S*,*R*)-**9**, thus demonstrating that the transformation (*S*,*R*)-**9**→(*S*,*R*)-**9**-Li→(*S*,*S*,*R*)-**10c** takes place with retention of configuration. Because of the observed retention of configuration in the deuteration and hydroxyalkylation reactions of all the isomeric aziridines **9**, the absolute configuration of alkylated aziridines (*S*,*S*)-**10a**,**b**, (*R*,*R*)-**10a**,**b**, (*R*,*S*)-**11a**,**b**, and (*S*,*R*)-**11a,b** was assigned by analogy.

Table 2. Lithiation/trapping sequence of aziridines **9** with electrophiles.



Aziridine	Electrophile	Product	Yield [%][a]	d.r.[b,c]
(*R*,*R*)-**9**	MeI	(*R*,*R*)-**10a**	90	>99:1
(*R*,*R*)-**9**	EtI	(*R*,*R*)-**10b**	90	>99:1
(*R*,*S*)-**9**	MeI	(*R*,*S*)-**11a**	86	>99:1
(*R*,*S*)-**9**	EtI	(*R*,*S*)-**11b**	60	>99:1
(*S*,*R*)-**9**	MeI	(*S*,*R*)-**11a**	80	>99:1
(*S*,*R*)-**9**	EtI	(*S*,*R*)-**11b**	60	>99:1
(*S*,*S*)-**9**	MeI	(*S*,*S*)-**10a**	85	>99:1
(*S*,*S*)-**9**	EtI	(*S*,*S*)-**10b**	85	>99:1
(*S*,*R*)-**9**	*p*-ClC_6H_4CHO	(*S*,*S*,*R*)-**10c** (*S*,*S*,*S*)-**10c**	55[d]	>99:1[e]

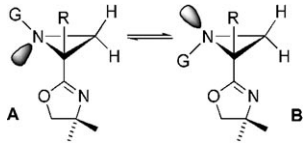
[a] Yield of the isolated products. [b] Epimerization would give a mixture of diastereomers. [c] Diastereomeric ratio established by ^{1}H NMR spectroscopic and/or GC-MS analyses. [d] Overall yield of two separable diastereomers (d.r. = 70:30). [e] Diastereomeric ratio for both (*S*,*S*,*R*)-**10c** and (*S*,*S*,*S*)-**10c**.

Dynamics of the aziridine nitrogen atom: An interesting aspect highlighted by the NMR spectroscopic analysis of α-alkylated products was that they exist as a mixture of two slowly equilibrating invertomers (as a consequence of the nitrogen inversion) in a ratio that depends on the α-substituent and on the configuration of the starting aziridine.[15] Mindful of the importance of such a dynamic phenomenon on the reactivity of aziridines[4,16,17] and on its potential application at the molecular level for the development of molecular switches,[18] we decided to run a dynamic NMR spectroscopic investigation as well with the aim of obtaining insight into the lithiation mechanism and the reasons for the observed configurational stability.

Several aziridines were investigated, including the already reported *N*-benzyl aziridines **12a–c**,[10] and the distribution of the two invertomers was evaluated by NMR spectroscopic analysis by varying the solvent and temperature (Table 3). It is remarkable that the steric demand of the α-substituent very much affects the **A**/**B** ratio. The stereochemistry of each invertomer **A** and **B**, with reference to the configuration of the nitrogen atom, was first ascertained by ^{1}H NMR spectroscopic analysis under slow-exchange conditions by using 1D selective NOESY experiments with the DPFGSE sequence.[19]

Figure 2 reports the results of this stereochemical investigation for oxazolinylaziridines **12b**,**c** and (*R*,*S*)-**11a**,**b** in

Table 3. Distribution of invertomers of terminal oxazolinylaziridines.



Aziridine	G	R	**A**/**B**[a]	**A**/**B**[b]
12a	$PhCH_2$	H	>95:5	>95:5[c]
(*R*,*R*)-**9**	$PhCHCH_3$	H	>95:5	>95:5[c,d]
(*R*,*S*)-**9**	$PhCHCH_3$	H	>95:5	>95:5[c,d]
12b	$PhCH_2$	Me	38:62	30:70[d]
(*R*,*R*)-**10a**	$PhCHCH_3$	Me	15:85	17:83[d]
(*R*,*S*)-**11a**	$PhCHCH_3$	Me	44:56	23:77[d]
12c	$PhCH_2$	Et	15:85	10:90[d]
(*R*,*R*)-**10b**	$PhCHCH_3$	Et	15:85	10:90[d]
(*R*,*S*)-**11b**	$PhCHCH_3$	Et	10:90	10:90[d]

[a] Ratio at 298–233 K in $CDCl_3$. [b] Ratio at 298–203 K in a different solvent. [c] Ratio at 270 K in [D_8]THF. [d] Ratio at 270–203 K in [D_8]toluene.

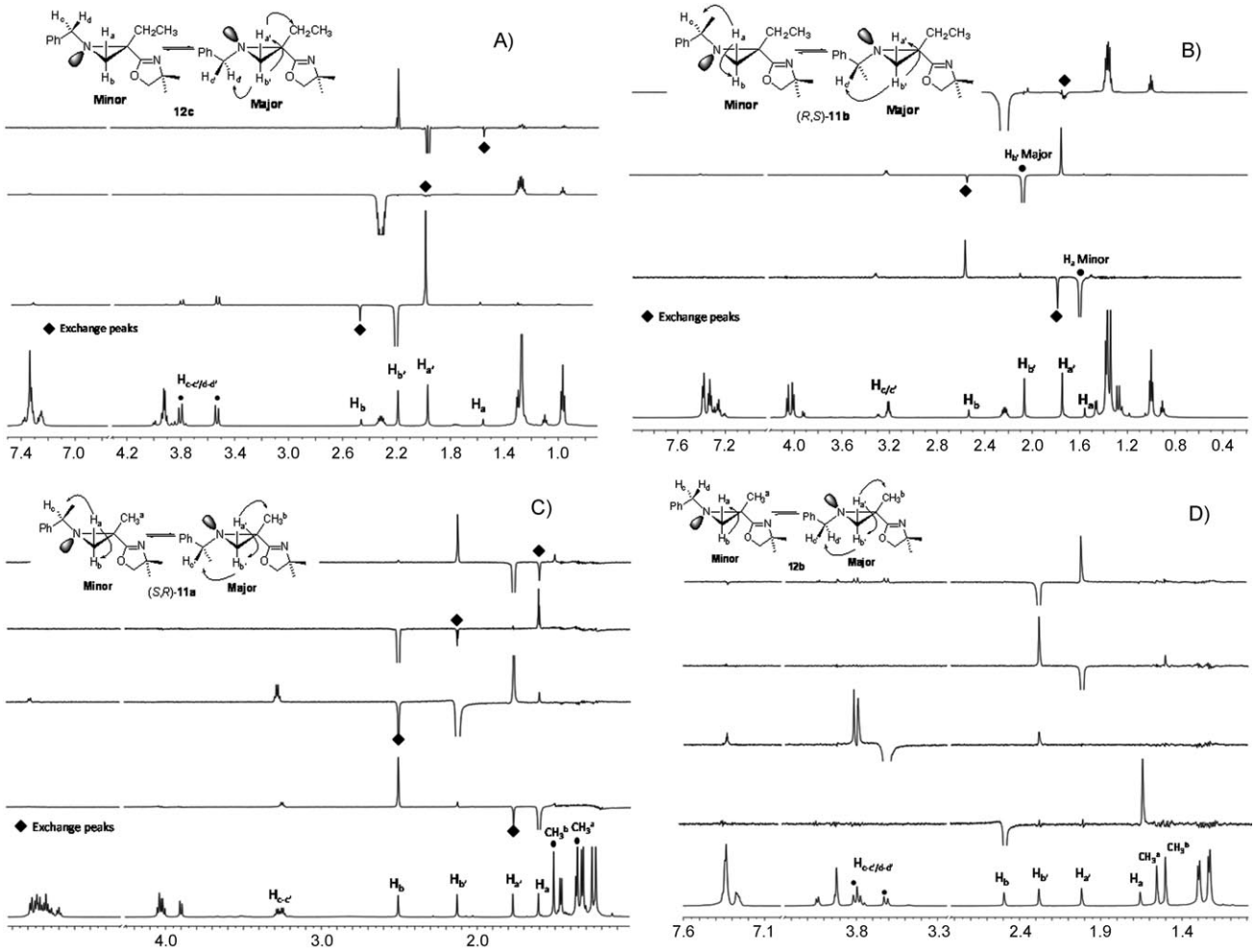


Figure 2. Stereochemical analysis for oxazolinylaziridines **12b**,**c**, (*S*,*R*)-**11a**, and (*R*,*S*)-**11b**: A–C) $CDCl_3$, 270 K; D) $CDCl_3$, 223 K. Main NOE interactions are shown.

$CDCl_3$ under slow-exchange conditions.[20] The aziridine protons $H_{a/a'}$ and $H_{b/b'}$ were used as probes to establish the spatial relationship between the groups.[21] Either *N*-benzyl or *N*-phenylethyl C2-substituted (R≠H) oxazolinylaziridines preferentially set the *N*-substituent on the same side of the oxazolinyl ring regardless of the steric demand of the C2 alkyl substituent. This preferred arrangement of the *N*-substituent was also demonstrated in a different solvent such as [D_8]toluene (see the Supporting Information) in which a more marked imbalance between invertomers was observed with respect to $CDCl_3$ (Table 3).

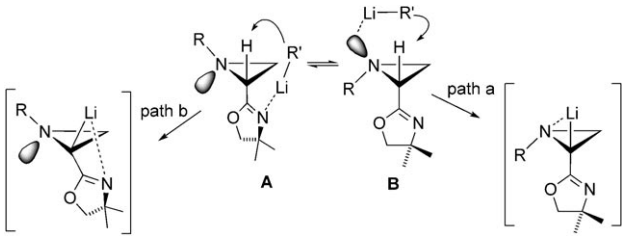
In contrast, the same structural analysis (in $CDCl_3$ or [D_8]toluene solution) performed on C2-unsubstituted (R = H) oxazolinylaziridines **12a**, (*R*,*R*)-**9**, and (*R*,*S*)-**9** disclosed that the almost exclusive invertomers (d.r. > 95:5) set the *N*-substituent in a *trans* relationship with respect to the oxazolinyl group (see the Supporting Information), thus leaving the lone pair of electrons on the opposite side to the proton to be removed. This evidence was also demonstrated by 1D selective NOESY experiments in [D_8]THF, which is the solvent for the lithiation reaction.

Because it has been reported that nitrogen dynamics and the availability of the lone pair of electrons play a pivotal role in determining the regioselectivity of the lithiation in *N*-alkyl-2-phenyl- and 2,3-diphenylaziridines[4b,c,17] and promote the formation of complexes with the lithiating agent,[22] the question is whether the same factors could account for the lithiation of oxazolinylaziridines.

On the basis of the ratio between the two invertomers of aziridines (*R*,*R*)-**9** and (*R*,*S*)-**9** (d.r. **A**/**B** > 95:5), the lone pair of electrons on the aziridine nitrogen atom could come into play only if invertomer **B** is deprotonated much faster than **A** (Scheme 4, path a). However, under the reaction conditions (−98 °C), the inversion process is almost blocked and the reaction of **B** is expected to be very slow. Moreover, the two oxazoline heteroatoms in invertomer **A** could also form complexes with the base competing with the aziridine nitrogen atom (Scheme 4, path b).

With the aim of verifying our hypothesis, we decided to estimate the nitrogen inversion barrier and to perform DFT calculations on neutral and lithiated oxazolinylaziridines.

The nitrogen inversion barrier was first established for aziridines **12b** (d.r. = 70:30 in [D_8]toluene)[23] and (*S*,*S*)-**10a**



Scheme 4. Possible pathways for the regioselective α-lithiation of oxazolinylaziridines.

Table 4. Relative energies [kcal mol^{-1}] for lithiated oxazolinylaziridines (*R*,*R*)-**9**-Li and (*R*,*S*)-**9**-Li.

Molecule	G MP2[a,b]	G M062X[a]
(*R*,*S*)-**9**-*N*-Li-inv	11.81	10.33
(*R*,*S*)-**9**-η^3-*N*-Li	0.00	0.00
(*R*,*S*)-**9**-*O*-Li	4.52	5.89
(*R*,*R*)-**9**-*N*-Li-inv	10.41	11.88
(*R*,*R*)-**9**-η^3-*N*-Li	0.00	0.00
(*R*,*R*)-**9**-*O*-Li	7.15	8.50

[a] Relative energies in kcal mol^{-1}. [b] G MP2//M062X

(d.r. = 83:17 in [D_8]toluene) by dynamic NMR spectroscopic experiments and line-shape analysis[24] (Figure 3) by finding $\Delta G^{\neq}_{(298)}$ values for the conversion of major into minor of $\Delta G^{\neq}_{(298)} = 16.8$ and 16.3 kcal mol^{-1}, respectively. These values were in the range expected for this type of *N*-alkyl-substitued aziridine[25] and were used as a reference for the estimation of the nitrogen inversion barrier of aziridines (*R*,*R*)-**9** and (*R*,*S*)-**9**, in which the very low intensity (<5%) of the ^{1}H NMR signals of the minor invertomers encumbers an accurate analysis of the inversion process by dynamic NMR analysis.[26]

Calculations with the modern M06-2X functional and post HF MP2 method[27] were subsequently performed on neutral and lithiated oxazolinylaziridines (*R*,*R*)-**9**, (*R*,*S*)-**9**, (*R*,*R*)-**9**-Li, and (*R*,*S*)-**9**-Li. The search for the equilibrium geometry was run for both the invertomers of the neutral aziridines (*R*,*R*)-**9** and (*R*,*S*)-**9**. According to 1D selective NOESY experiments in $CDCl_3$, [D_8]THF, and [D_8]toluene, even the calculations demonstrated that for both (*R*,*R*)-**9** and (*R*,*S*)-**9** the most stable invertomer sets the *N*-substituent and the oxazolinyl ring *trans* each other. In fact, it was found that aziridines (*R*,*R*)-**9** and (*R*,*S*)-**9** were more stable than the corresponding nitrogen invertomers (*R*,*R*)-**9**-inv and (*R*,*S*)-**9**-inv of about 7.3 kcal mol^{-1}, respectively (Figure 4). The difference in energy between (*R*,*S*)-**9** and (*R*,*R*)-**9** was only $\Delta G^{\neq}_{(298)} = 0.26$ kcal mol^{-1}.

On the basis of the computed structures obtained for the neutral aziridines (*R*,*R*)-**9** and (*R*,*S*)-**9** and the estimated value of the inversion barrier, it seems reasonable to assume that the deprotonation reaction could involve invertomer **A** (Scheme 4).

Computational analysis on lithiated oxazolinylaziridines (*R*,*R*)-9 and (*R*,*S*)-9: With the aim of explaining the configurational stability observed with this type of lithiated oxazolinylaziridines, which is in striking contrast with the bias to epimerization of lithiated oxazolinyloxiranes, a computational analysis with the hybrid GGA M06-2X functional with the 6-31+G(d) basis set[28] was undertaken.

Gas-phase calculations on diastereoisomeric lithiated aziridines (*R*,*S*)-**9**-Li and (*R*,*R*)-**9**-Li were performed taking into consideration also the corresponding nitrogen invertomers (Table 4). The computational analysis of (*R*,*S*)-**9**-Li gave (*R*,*S*)-**9**-η_3-*N*-Li as equilibrium geometry (relative energy = 0 kcal mol^{-1}), in which the Li atom is coordinated to the C=N double bond of the oxazoline ring and could likely benefit from extra stabilization by the phenyl ring of the *N*-substituent (Figure 5). This type of η_3-coordination has been already observed by FTIR and NMR spectroscopic analysis on α-lithiated oxazolinyloxiranes in THF solution.[29] The extra stability from the interaction with the phenyl group is not possible in the invertomer (*R*,*S*)-**9**-*N*-Li-inv.

The *O*-chelated structure (*R*,*S*)-**9**-*O*-Li was also found as a local minimum, but was 5.9 kcal mol^{-1} less stable than (*R*,*S*)-**9**-η_3-*N*-Li.[30] Optimization on the nitrogen invertomer revealed that the equilibrium geometry (*R*,*S*)-**9**-*N*-Li-inv was almost 10.3 kcal mol^{-1} less stable than (*R*,*S*)-**9**-η_3-*N*-Li and that the Li ion could be chelated by the lone pair of electrons on the aziridine nitrogen atom (Li30–N4 = 1.89 Å). Similar conclusions were obtained from the analysis with the MP2 method (Table 4).

The computed structures obtained in the analysis of (*R*,*R*)-**9**-Li showed again that an η_3-coordinated intermediate (*R*,*R*)-**9**-η_3-*N*-Li (0 kcal mol^{-1} rel. energy) was more stable than (*R*,*R*)-**9**-*O*-Li and (*R*,*R*)-**9**-*N*-Li-inv by about 8.5 and 11.9 kcal mol^{-1}, respectively (Figure 6). A comparison between neutral and lithiated aziridines (*R*,*S*)-**9** and (*R*,*S*)-**9**-η_3-*N*-Li reveals that the C2–C5 and C5–N6 bond lengths are 1.48 and 1.28 Å, respectively, in the neutral aziridine versus 1.43 and 1.31 Å, respectively, in the lithiated intermediate. Similar bond lengths have also been computed for (*R*,*R*)-**9** and (*R*,*R*)-**9**-η_3-*N*-Li (1.48 and 1.28 Å in the neutral aziridine versus 1.43 and 1.30 Å in the lithiated intermediate). These values suggest that the aziridine carbon atoms likely do not change their hybridization upon lithiation and that the negative charge could not be delocalized into the oxazolinyl ring, which is in contrast with lithiated aziridine-carboxylate compounds in which an enolate-like structure has been taken into consideration.[8,9]

By considering the optimized structures (*R*,*S*)-**9**-η_3-*N*-Li and (*R*,*R*)-**9**-η_3-*N*-Li, their energy difference was 5.4 kcal mol^{-1}, the former being more stable than the latter. This result contrasts with the experimental evidence in THF in which lithiated aziridine (*R*,*R*)-**9**-Li proved to be more thermally stable than (*R*,*S*)-**9**-Li. Such a different stability could be justified because these computed structures do not take into account aggregation phenomena.[31]

Nevertheless, to validate the computational results in the gas-phase experimentally, the lithiation of aziridines (*R*,*S*)-**9** and (*R*,*R*)-**9** was performed in a less polar and non-coordi-

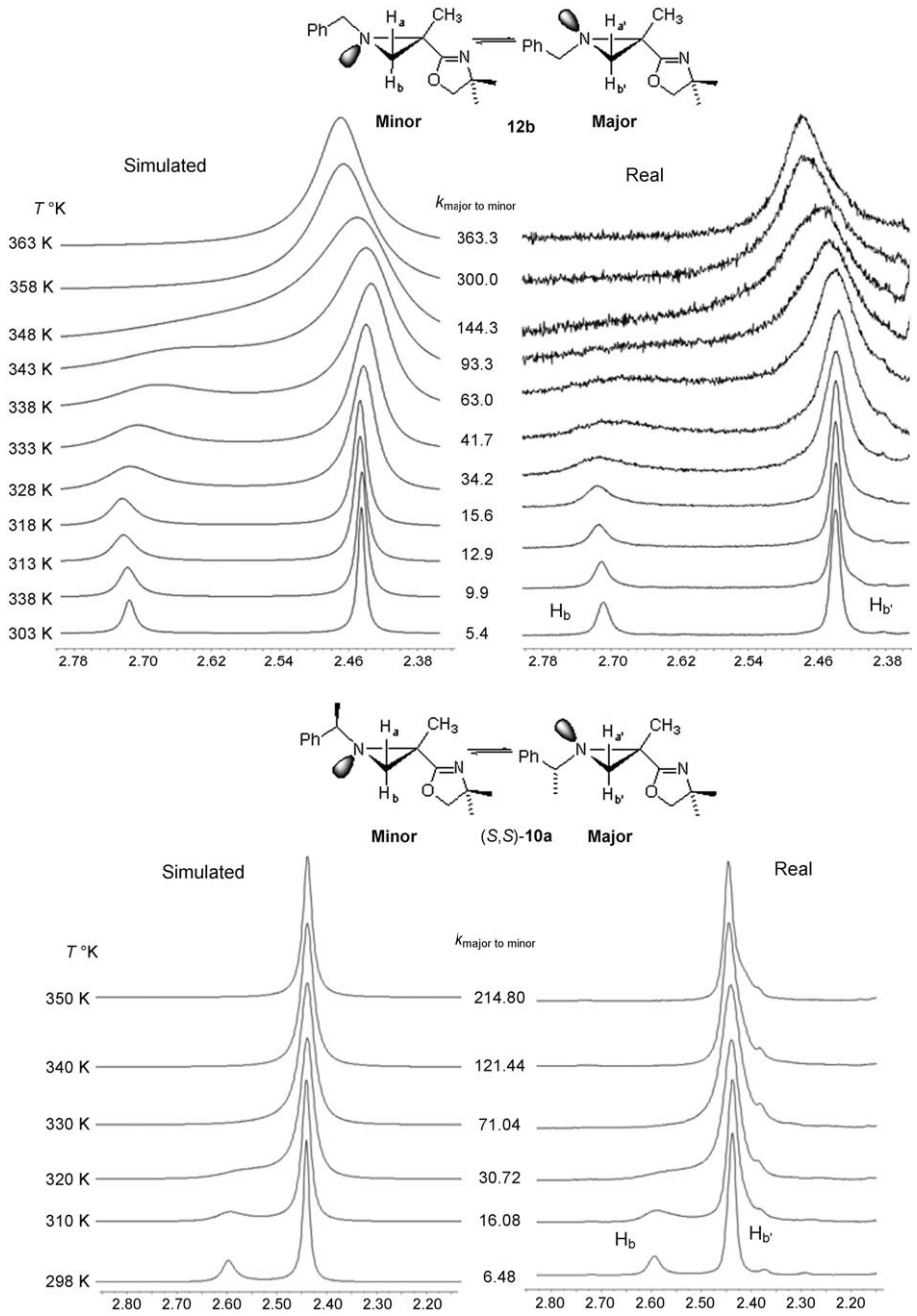


Figure 3. Line-shape analysis on oxazolinylaziridines **12b** and (*S*,*S*)-**10a**.

nating solvent such as toluene. Surprisingly, lithiation of aziridines (*R*,*S*)-**9** and (*R*,*R*)-**9** with *n*BuLi (1.5 equiv) in toluene at −78 °C for 4 hours followed by trapping with a deuterium source gave (*R*,*S*)-**9**-D and (*R*,*R*)-**9**-D in 80 % isolated yield and with 95 % deuterium content and in both cases without epimerization (d.r. > 98:2). This result showed that lithiated aziridines (*R*,*S*)-**9**-Li and (*R*,*R*)-**9**-Li were both chemically and configurationally stable in toluene. According to the computational result in the gas phase, (*R*,*S*)-**9**-Li was chemically stable in toluene but decomposes under the same reaction conditions in THF (Table 1, entry 10).

The high configurational stability observed in toluene can be explained by taking into account the epimerization process depicted in Scheme 5 and the equilibrium geometries found computationally. If we consider the epimerization of (*R*,*S*)-**9**-Li, which would give (*R*,*R*)-**9**-Li, and vice versa, it would occur through two inversions: one involving the lithiated carbon atom (C−Li inversion in Scheme 5) and one involving the aziridine nitrogen atom (N−R inversion in Scheme 5). Regardless of the inversion that occurs first, two intermediates result that set the oxazolinyl ring and substituent on the aziridine nitrogen atom in a *cis* relationship. From calculations such intermediates might correspond to (*R*,*S*)-**9**-η_3-*N*-Li-inv and (*R*,*R*)-**9**-η_3-*N*-Li-inv, which are higher in energy (Table 4) with respect to the corresponding equilibrium geometries of (*R*,*S*)-**9**-η_3-*N*-Li and (*R*,*R*)-**9**-η_3-*N*-Li.

Therefore, it could be reasonable to ascribe the high configurational stability observed in toluene to a high-energy barrier associated with the inversion processes involved in the epimerization mechanism.

For the sake of comparison, the DFT computational analysis of lithiated oxazolinylaziridines (*R*,*R*)- and (*R*,*S*)-**9**-Li was also performed on the corresponding THF solvates (Table 5). The structure of disolvated derivatives were analyzed by considering that just two THF ligands could fill the coordination sphere of the lithium atom also coordinated to two other atoms.

The disolvated (*R*,*S*)-**9**-*N*-Li·2 THF, which again shows η_3-coordination for the lithium ion in addition to the two THF ligands (Figure 7), was found as equilibrium geometry. However, comparison with the unsolvated (*R*,*S*)-**9**-*N*-Li showed a slight lengthening of the C2−Li, C5−Li, and N6−Li bonds as a consequence of the presence of the two THF molecules. A comparison between (*R*,*S*)-**9**-*N*-Li-inv·2 THF and (*R*,*S*)-**9**-*N*-Li-inv discloses that the two THF molecules prevent the coordination of the lithium ion by the aziridine ring nitrogen

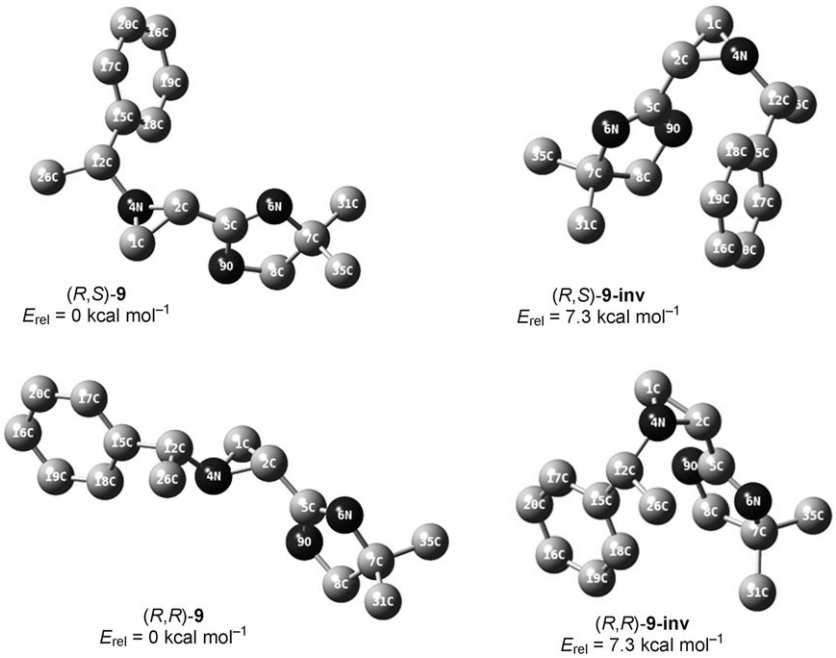


Figure 4. Optimized structure for (*R*,*R*)-**9** and (*R*,*S*)-**9** by using the M06-2X functional.

Regardless of the solvent and aggregation effects, which are difficult to demonstrate without spectroscopic support,[33] the results of the DFT analysis reveal that, in accord with a similar study on oxazolinyloxiranes,[28] the most stable intermediates are η_3-coordinated species, which, in this case, set the oxazoline group and the *N*-substituent in a *trans* relationship. This computational evidence combined with the structural analyses of the neutral aziridines (*R*,*S*)-**9** and (*R*,*R*)-**9** and the reactivity observed in toluene, allows us to propose path b in Scheme 4 as a likely mechanism for the α-lithiation reaction, which could be an example of dynamically controlled lithiation.[34] In addition, the high barrier for nitrogen inversion (ca. 16 kcal mol^{-1}) and the higher computed stability of (*R*,*S*)-**9**-η_3-*N*-Li and (*R*,*R*)-**9**-η_3-*N*-Li, with respect to (*R*,*S*)-**9**-*N*-Li-inv and (*R*,*R*)-**9**-*N*-Li-inv, could justify the configurational stability of this type of aziridinyllithium compounds.[35]

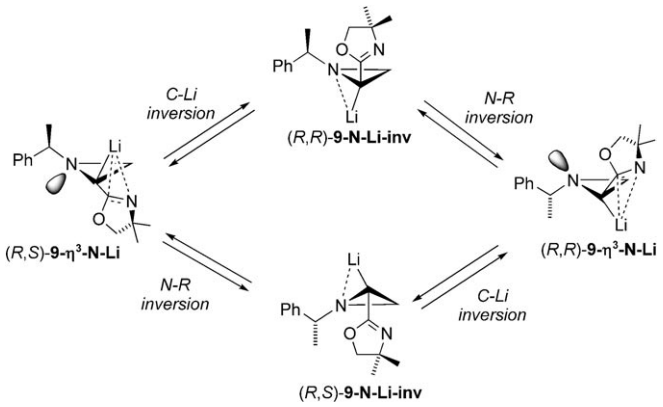
atom, thus lowering the energy of this invertomer. The THF solvation also prevents the additional coordination brought by the phenyl ring (see the structure of (*R*,*S*)-**9**-*N*-Li for comparison).

The disolvated (*R*,*R*)-**9**-*N*-Li·2THF (Figure 8) was found as equilibrium geometry for the *R*,*R* diastereoisomer, and the nitrogen invertomer that corresponds to (*R*,*R*)-**9**-*N*-Li-inv·2THF was not found (Table 5). However, the analysis of the disolvated species showed that for both diastereomeric lithiated aziridines (*R*,*R*)- and (*R*,*S*)-**9**-Li·2THF, η_3-coordinated intermediates bearing the oxazolinyl ring and the *N*-substituent in a *trans* relationship were predicted to be more stable.[32] In addition, it was possible to assess the extra coordination brought by the phenyl ring in (*R*,*S*)-**9**-Li in the gas phase.

Table 5. Relative energies [kcal mol^{-1}] for disolvated lithiated oxazolinylaziridines (*R*,*R*)- and (*R*,*S*)-**9**-Li in THF.

Molecule	G MP2[a,b]	G M062X[a]
(*R*,*S*)-**9**-Li-inv·2THF	3.45	3.30
(*R*,*S*)-**9**-*N*-Li·2THF	0	0
(*R*,*S*)-**9**-*O*-Li·2THF	8.65	8.12
(*R*,*R*)-**9**-Li-inv·2THF	–[c]	–[c]
(*R*,*R*)-**9**-*N*-Li·2THF	0.21	0
(*R*,*R*)-**9**-*O*-Li·2THF	0	2.25

[a] Relative energies in kcal mol^{-1}. [b] G MP2//M062X. [c] Not found as equilibrium geometry.



Scheme 5. Epimerization mechanism of lithiated oxazolinylaziridines.

Additional reactivity: From the reaction performed in toluene, useful insights were obtained that support the model proposed in Scheme 4. Indeed, compounds (*R*,*S*)-**13** and (*R*,*R*)-**13**, likely formed by nucleophilic attack of *n*BuLi on the oxazoline C=N bonds of (*R*,*S*)-**9** and (*R*,*R*)-**9**, respectively, were isolated in yields of 15% and as a mixture of two diastereomers (d.r. = 1:1 for (*R*,*S*)-**13** and 70:30 for (*R*,*R*)-**13**).[36] Because the addition of an organolithium species to the oxazoline C=N double bond is not an easy event unless favored by peculiar stereoelectronic requirements,[37] the formation of (*R*,*S*)-**13** and (*R*,*R*)-**13** has to be explained. As reported in Scheme 6 and in accord with the model depicted in Scheme 4, the lone pair of electrons on the nitrogen atom of the major invertomer **A** could form a complex with

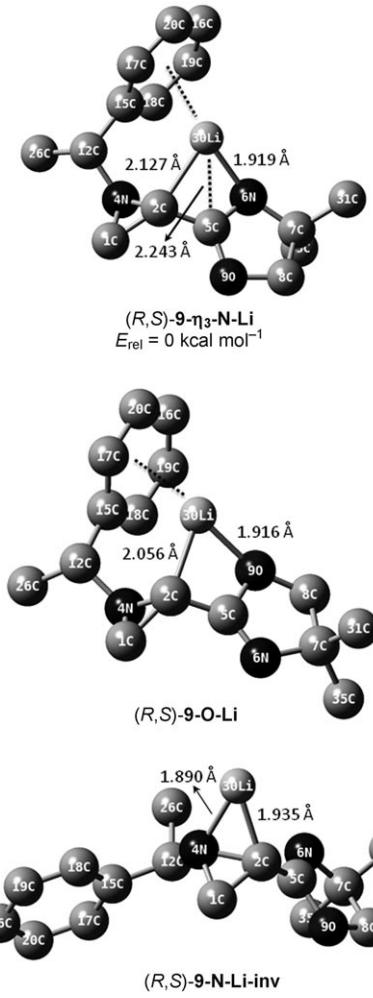


Figure 5. Computed equilibrium geometries (M06-2X) from the analysis of (*R*,*S*)-**9**-Li.

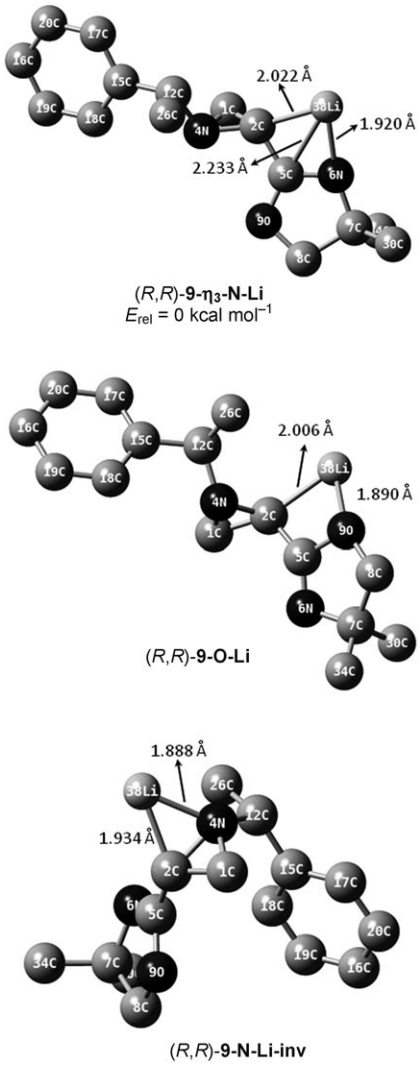


Figure 6. Computed equilibrium geometries (M06-2X) from the analysis of (*R*,*R*)-**9**-Li.

*n*BuLi, which as it is close to the oxazolinyl ring, could attack the C=N bond.[38]

To unequivocally characterize (*R*,*S*)-**13** and (*R*,*R*)-**13**, they were subjected to acidic hydrolysis of the oxazolidinyl ring, thus obtaining chiral ketoaziridines (*R*,*S*)-**14** and (*R*,*R*)-**14** (95% yield) and disclosing a new potentially useful transformation of chiral oxazolinylaziridines.

To further prove that the nitrogen dynamics and complexation phenomena could likely be responsible of the unusual C=N double-bond addition, the reactivity of α-functionalized aziridines (*S*,*S*)-**10a** and (*S*,*R*)-**11a** was investigated (Scheme 7). When these aziridines were treated with *n*BuLi at −78°C for 4 h, before quenching with a proton source, only the starting materials were recovered. A different result was obtained in the reaction with *n*BuLi at 0°C. In this case, the C=N addition occurred, thus obtaining ketoaziridines (*S*,*S*)-**15** and (*S*,*R*)-**15** in 75% yield with high enantioenrichment (e.r. > 98:2) after acidic hydrolysis of the crude reaction mixture.

These results could be reasonably explained by taking into consideration the effect of the temperature on the nitrogen dynamics and ultimately on the reactivity of oxazolinylaziridines toward *n*BuLi.

If one consider the distribution of the invertomers for (*S*,*S*)-**10a** and (*S*,*R*)-**11a** in toluene (Table 3), two equilibrating nitrogen invertomers in major/minor ratios of 83:17 and 77:23, respectively, can be found. Assuming that only the minor invertomers possess the stereochemical requirements (that is the *cis* relationship between the lone pairs of electrons on the nitrogen atom and the oxazoline ring) for the C=N addition, the reactivity of the corresponding complex with *n*BuLi will be enhanced at a higher temperature. In fact, the lack of reactivity observed at low temperature (−78°C) is likely to be a consequence of the low rate of nitrogen inversion and a slow rate of the reaction between the minor invertomers and *n*BuLi.[39] In contrast, at a higher temperature (0°C) there is a faster nitrogen inversion and faster reaction with *n*BuLi, which ends up with the C=N addition.

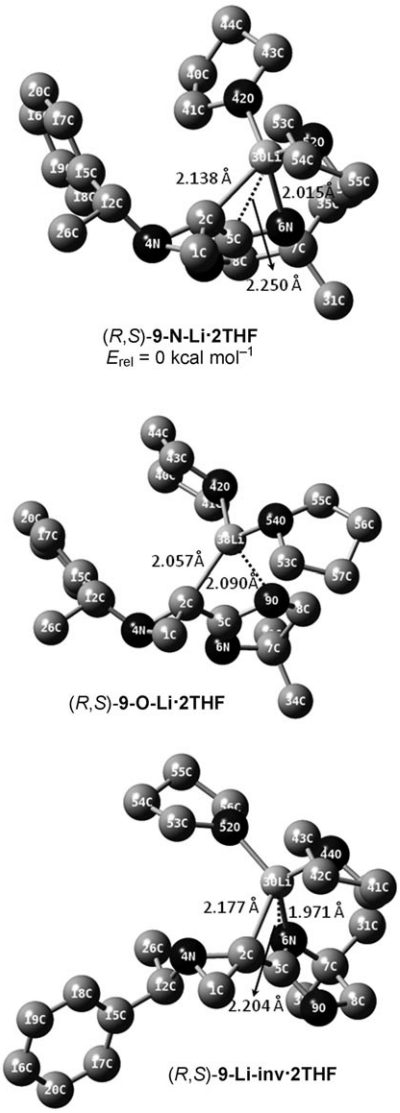


Figure 7. Computed equilibrium geometries (M06-2X) for THF-disolvated (*R*,*S*)-**9**-Li.

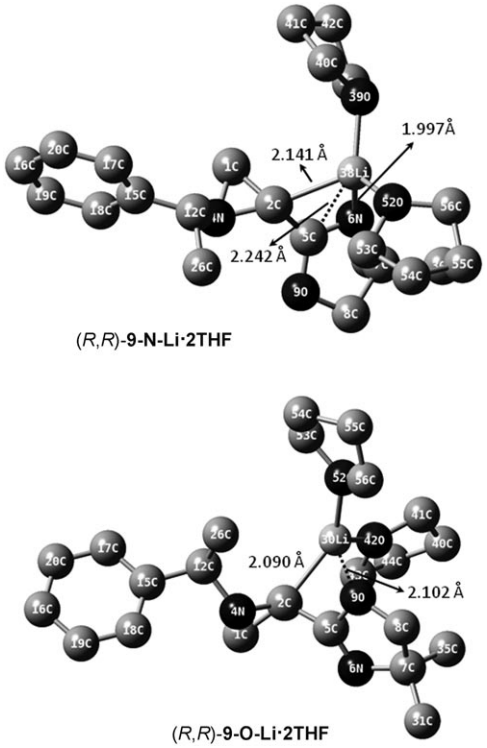
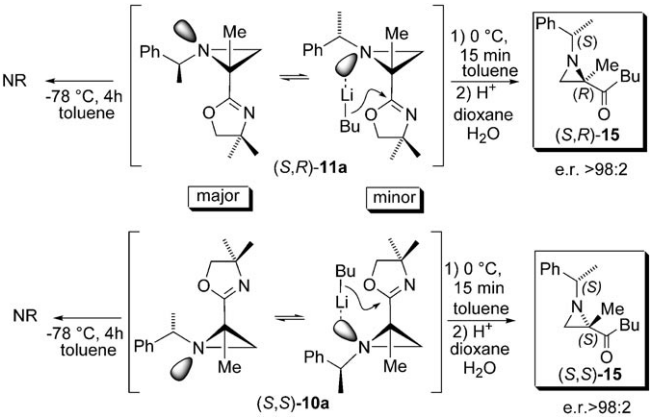
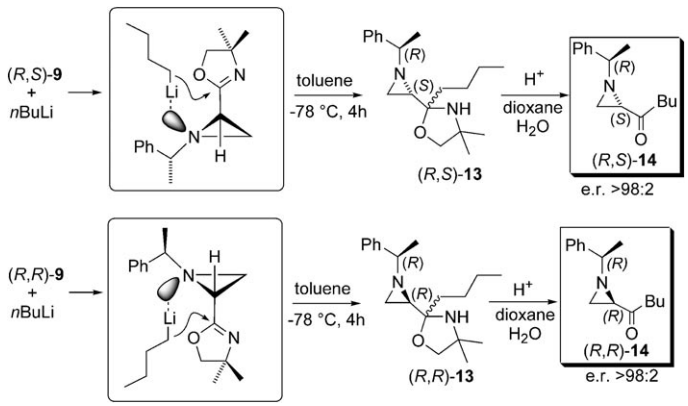


Figure 8. Computed equilibrium geometries (M06-2X) for THF-disolvated (*R*,*R*)-**9**-Li.



Scheme 7. Dynamically controlled reactivity of α-functionalized oxazolinylaziridines.



Scheme 6. Competitive addition reaction that leads to enantioenriched ketoaziridines **14**.

Therefore, it could be argued that by controlling the nitrogen dynamics it could be possible to address the reactivity of oxazolinylaziridines and prepare useful chiral 2,2-disubstituted ketoaziridines.

Conclusion

It has been demonstrated that enantiomerically enriched 1-phenylethyloxazolinylaziridines undergo exclusive α-lithiation and that the resulting lithiated species are generally

configurationally stable under the given experimental conditions. This finding is in striking contrast with α-lithiated oxazolinyloxiranes, which are quite prone to undergo fast racemization (or epimerization) when generated from optically pure precursors. The reason for this different behavior has been rationalized by considering the role of the aziridine nitrogen atom and its dynamics, which has been evaluated by NMR spectroscopic experiments and DFT calculations, which furnished η_3-coordinated species for both diastereomeric lithiated aziridines in the gas phase and disolvated species in THF.

The role of the oxazolinyl group in promoting α-lithiation without self-condensation, as instead observed with lithiated aziridinecarboxylates (Figure 1) is remarkable because it allows an efficient lithiation/trapping sequence. Moreover, our work has further demonstrated that in either α-lithiated oxazolinyloxiranes or aziridines there is likely no delocalization of the negative charge into the oxazolinyl group.

It has also been demonstrated that oxazolinylaziridines could undergo a C=N addition when treated with an organolithium species, thus giving oxazolidine derivatives that are precursors of useful chiral ketoaziridines. A model based on the nitrogen dynamics and complexation phenomena has been proposed to explain this unexpected reaction pathway. This model is based on dynamically controlled reactivity. Further investigations will focus on the extension and exploitation of this concept in synthesis.[40]

Acknowledgements

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[31] a) A.-M. Sapse, D. C. Jain, K. Raghavachari *in Lithium Chemistry: A Theoretical and Experimental Overview* (Eds.: A.-M. Sapse, P. von R. Schleyer), Wiley, Weinheim, **1995**, pp. 45–65; b) V. H. Gessner, C. Daschlein, C. Strohmann, *Chem. Eur. J.* **2009**, *15*, 3320–3334.

[32] The roles of aggregation phenomena and solvation are being evaluated computationally and experimentally on more simple *N*-alkyloxazolinylaziridines, and the results will be reported in due course.

[33] It has been reported that the solvent could affect the aggregation state of lithiated aziridines, see: V. Capriati, S. Florio, R. Luisi, A. Mazzanti, B. Musio, *J. Org. Chem.* **2008**, *73*, 3197–3204; attempts to run multinuclear magnetic resonance experiments in [D_8]THF and [D_8]toluene on lithiated aziridines (*R*,*R*)-**9**-Li and (*R*,*S*)-**9**-Li failed to provide structural insight.

[34] The proposed model assumes that oxazolinylaziridines can break down *n*BuLi aggregates; the importance of the aggregation/reactivity relationship has been highlighted recently, see: a) A. C. Jones, A. W. Sanders, M. J. Bevan, H. J. Reich, *J. Am. Chem. Soc.* **2007**, *129*, 3492–3493; b) C. Strohmann, V. H. Gessner, *Angew. Chem.* **2007**, *119*, 8429–8432; *Angew. Chem. Int. Ed.* **2007**, *46*, 8281–8283.

[35] A double inversion has been also suggested for the epimerization of lithiated pyrrolidines that occurs at high temperature, see: N. J. Ashweek, P. Brandt, I. Coldham, S. Dufour, R. E. Gawley, F. R. Haeffner Klein, G. Sanchez-Jimenez, *J. Am. Chem. Soc.* **2005**, *127*, 449–457.

[36] It is likely that two diastereomers are obtained from the same complex as a consequence of the attack of the BuLi on both faces of the oxazoline C=N bond; the ^{13}C NMR spectrum shows the signals of two quaternary carbons at $\delta = 96$–97 ppm, which belong to the C2 of the oxazolidine ring, and the absence of the oxazoline C=N signal usually found at around $\delta = 160$ ppm; examples of related structures have been reported, see: V. Capriati, L. Degennaro, S. Florio, R. Luisi, *Eur. J. Org. Chem.* **2002**, 2961–2969.

[37] Nucleophilic addition to the oxazoline C=N bond is reported to occur with O nucleophiles, see: a) R. Luisi, V. Capriati, S. Florio, T. Vista, *J. Org. Chem.* **2003**, *68*, 9861–9864; b) R. Luisi, V. Capriati, L. Degennaro, S. Florio, *Org. Lett.* **2003**, *5*, 2723–2726; c) V. Capriati, L. Degennaro, R. Favia, S. Florio, R. Luisi, *Org. Lett.* **2002**, *4*, 1551–1554; for an example of a Grignard addition, see: S. Florio, E. Epifani, G. Ingrosso, R. Sgarra, *Tetrahedron* **1984**, *40*, 5089–5095.

[38] The addition of alkyllithium compounds to the oxazoline C=N bond is quite a difficult process, see: A. I. Meyers, *J. Org. Chem.* **2005**, *70*, 6137–6151; however, when the peculiar proximity effect is realized for stereochemical reasons this type of addition could be feasible, see: a) V. Capriati, S. Florio; R. Luisi, F. M. Perna, *J. Org. Chem.* **2007**, *72*, 6316–6319; b) M. Iguchi, K-i. Yamada, K. Tomioka in *Topics in Organometallic Chemistry, Vol. 5* (Ed.: D. M. Hodgson), Springer, Berlin, **2003**, pp. 45–59.

[39] With reference to the C=N addition reaction, it is worth noting that the major invertomer would produce unreactive complexes with *n*BuLi because of the *anti* relationship between the oxazoline ring and the lone pair of electrons on the aziridine nitrogen atom.

[40] The synthetic procedures and spectral characterization data for the prepared compounds are given in the Supporting information for this article, which is available on the WWW under http://www.chemeurj.org/or from the author.

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