Aziridinyl Anions: Generation, Reactivity, and Use in Modern Synthetic Chemistry

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Contents

Saverio Florio received his "Laurea" in Chemistry at the University of Bari (Italy). After being first Assistant Professor and then Associate Professor of Organic Chemistry in 1986, he was appointed Full Professor of Organic Chemistry at the University of Lecce. In 1990, he moved to the University of Bari as the chair of organic chemistry. Currently, he is Director of "Consorzio Interuniversitario sulle Metodologie e Processi Innovativi di Sintesi" (CINMPIS). President of the Division of Organic Chemistry of the Italian Chemical Society from 1997 to 2001, at present he acts as the vice president of the Italian Chemical Society. He is a member of the Scientific Advisory Board of the Ischia IASOC School and member of the "Academy of Science and Arts of Salsburg". Prof. Florio's research interests are concerned with mechanistic studies, stereochemistry, and asymmetric synthesis of small-ring heterocycles. Prof. Florio has published more than 200 papers and for his research work has been awarded with "Ziegler-Natta Lecture" from the German Chemical Society (GDCh) in 2005 and with the "Angelo Mangini Gold Medal" from the Division of Organic Chemistry of the Italian Chemical Society in 2007.

1. Introduction

Aziridines, nitrogen-containing three-membered ring heterocycles, are well established useful and versatile building blocks in organic synthesis and medicinal chemistry.[1] Although less common than the corresponding oxygen-substituted heterocycles, the aziridine functionality is present in many naturally occurring molecules showing significant biological properties, such as azinomycins, mitomycins, ficellomycin, miraziridine, and maduropeptin (Figure 1). In view of this, aziridines have been extensively investigated either from the synthetic or reactional points of view. Concerning the reactivity, the most common transformations of these spring-loaded three-membered ring systems are the ring-opening reactions that can be initiated by both electrophilic and nucleophilic reagents.[2]

Concerning the synthetic methodologies developed for the preparation of aziridines, the main ones are based on cyclization reactions, transfer of nitrogen to olefins,[3] transfer of carbon to imines,[4] addition across the carbon−nitrogen double bond of azirines,[5] reactions of ylides,[6] aza-Darzen approaches,[7] and ring contraction.[8] Another methodology that has gained importance recently is based on the use of metalated aziridines (commonly called aziridinyl anions). The

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Renzo Luisi was born in Luxembourg (EU) in 1971 and started his own career working as an analytical chemist in a wine company from 1990 until 1994. In 1996, he got the M.Sc. degree in Chemistry and Pharmaceutical Technology "summa cum laude" at the University of Bari and after the National service, accomplished as Officer in 1997, started the Ph.D. in Chemical Sciences in 1998 under the supervision of Prof. Saverio Florio. In 1999, he has been visiting scholar at the Roger Adams Laboratories of the School of Chemical Sciences of the University of Illinois (USA) under the supervision of Professor Peter Beak. In 2001, he became Assistant Professor at the University of Bari and in 2005 was appointed Associate Professor of Organic Chemistry at the faculty of Pharmacy of the University of Bari holding the chair of Physical Methods in Organic Chemistry. He is currently an active member of the academic spin-off "Synchimia, Materials and Nanomaterials", is a member of the regulatory and safety commissions of the Department of Medicinal Chemistry of the University of Bari, and serves on the committee of the doctoral school in "Applied Chemical and Enzymatic Synthesis" at the same University. He has been co-author of more than 60 publications in peer-reviewed journals, monographs, book chapters, and proceedings and attended numerous national and international conferences. His research activity mainly pertains to the structure−reactivity relationship, molecular dynamics, multinuclear magnetic resonance of reactive intermediates and the development of new stereoselective synthetic methodologies mediated by organometallic reagents. Recently his research interests shifted to the field of molecular nanotechnology and microfluidic devices. Besides organic chemistry, he enjoys reading, motorcycles, scuba diving, and tasting national and international wines.

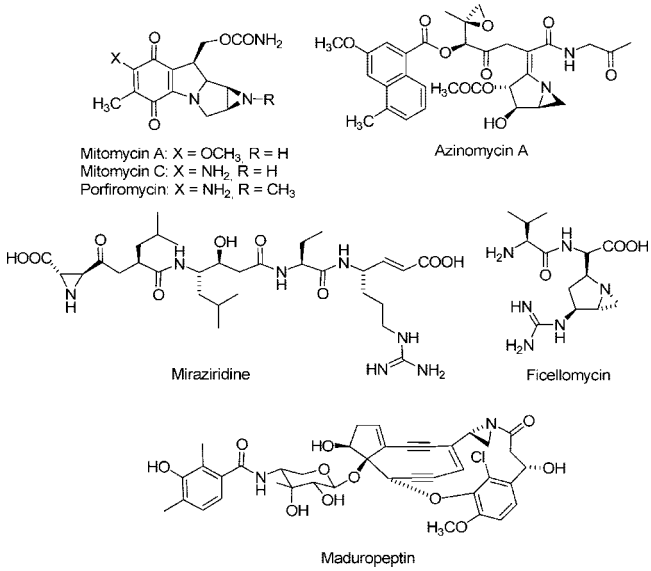


Figure 1.

nomenclature "aziridinyl anion" will be used in a broad sense in this review, identifying a class of metalated intermediates that exhibit mainly nucleophilic reactivity without taking into consideration their real structure in solution, which is in great part still unknown. In 1996, in a review on this topic, Satoh reported: "In contrast to the oxiranyl anions, aziridinyl anions are much more stable. However, very limited reports have appeared so far. For this reason the nature, stability, and reactivity of aziridinyl anions are still somewhat obscure at present. Because aziridines are very useful in synthetic organic chemistry, more studies should be continued for the elucidation of the chemistry of aziridinyl anions".[9] Since then, several research groups worldwide investigated the chemistry of aziridinyl anions disclosing new aspects on their reactivity, structure, and usefulness.[10] This review will try to collect these results and to give an overview on the chemistry of aziridinyl anions and of the structure−reactivity relathionship. The chemistry of aziridinyl anions, which has been substantially developed only over the last 10 years, has been less studied than that of the corresponding oxiranyl anions,[11] showing, however, that there are similarities in the reactivity of these two systems. Indeed, like the oxiranyl anions, the aziridinyl anions can exhibit nucleophilic, electrophilic, and carbenoid reactivity.[12]

2. Classification of Aziridinyl Anions

Traditionally, in order to classify the aziridinyl anions on the basis of their structure, the terms "stabilized" and "not stabilized" have been often used, including in the former notation those with a substituent on the anionic or metal-bearing carbon atom and in the latter notation those without a substituent (except H) on the anionic carbon. This classification can be a little misleading especially now that more types of aziridinyl anions are known and also because it does not take into account the stabilization mechanism (i.e., dipolar or mesomerical stabilization) and the nature of the N-substituent, which could play a role. For this reason a different approach will be followed in this review, classifying the aziridinyl anions on the basis of the nature (electron-withdrawing group, EWG, or electron-donating group, EDG) of the substituent on the nitrogen or carbon atoms of the aziridine ring and on the basis of the methodology used for their generation.

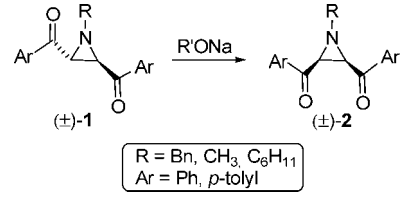
Among the different methodologies now available for the generation of aziridinyl anions, the deprotonation of simpler and easily available parent aziridines, mainly with organolithiums or lithium amides, is one of the most commonly employed because of the ready availability or ease of preparation of the starting materials.

3. Generation of Aziridinyl Anions

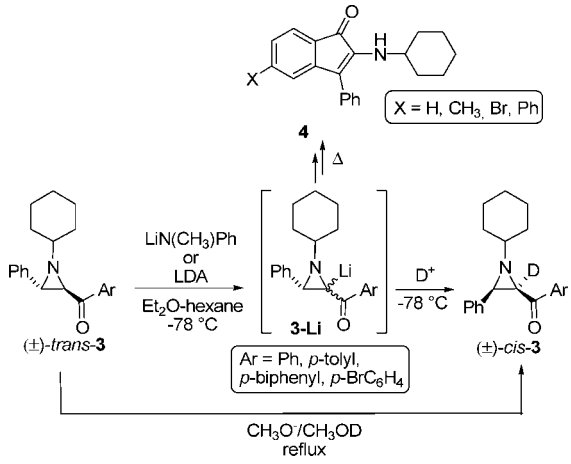
The first hypothesis of the existence of an aziridinyl anion came from Turner's work[13] dealing with the base-induced isomerization of *trans* aziridinyl diketones **1** into the *cis* isomers **2** (Scheme 1).

Successively, in an attempt to elucidate the mechanism of the base-promoted isomerization of aziridinyl ketones *trans*-**3** into indanone derivatives **4**, Cromwell demonstrated

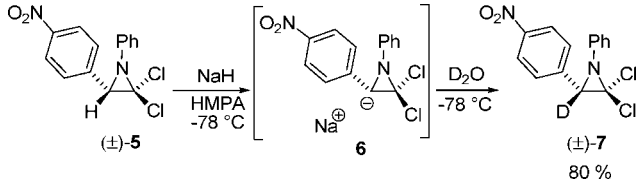
Scheme 1



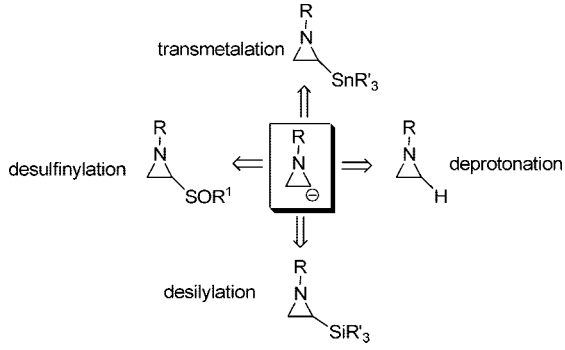
Scheme 2



Scheme 3



Scheme 4



the intermediacy of the lithiated aziridine **3-Li**, which furnished, after quenching with a deuterium source, the isomerized aziridine *cis*-**3** in good yields (Scheme 2). Analogously to the Turner's report, Cromwell demonstrated that this base-induced isomerization−deuteration occurs also under different conditions furnishing preferentially *cis* configured aziridines.[14]

Another early preparation of aziridinyl anion was developed in 1972 by Rubottom and Stevenson who reported that the stable bright purple aziridinyl C-anion **6** could be generated at low temperature upon treatment of aziridine **5** with sodium hydride in HMPA.[15] The proposed aziridinyl C-anion proved to be stable upon warming to −10 °C and could be trapped with D_2O (Scheme 3).

After these seminal works that demonstrated the feasibility of generating an aziridinyl anion and revealed the possibility of trapping it with an electrophile, leaving intact the three-membered ring functionality, research was undertaken in this field, and several methodologies are now available for the generation of such reactive species.

As reported in Scheme 4, aziridinyl anions can be generated by transmetalation from the corresponding organotin derivatives, desulfinylation, desilylation, and deprotonation.

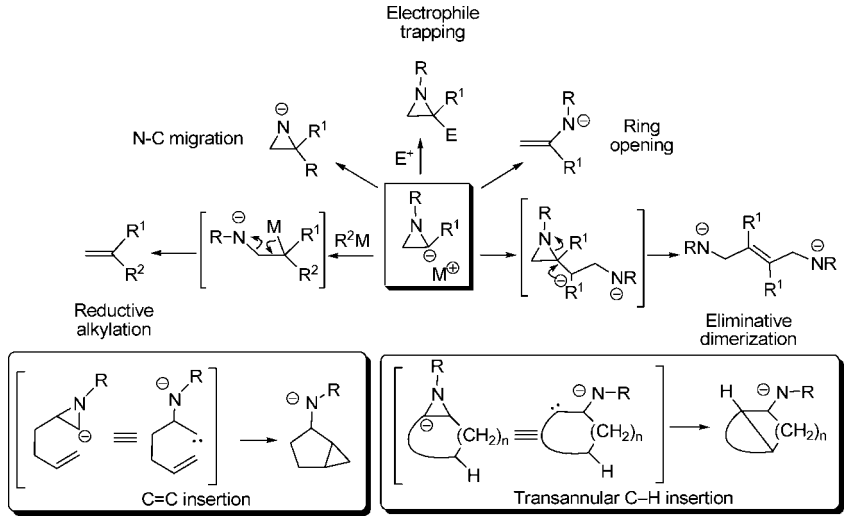
Each methodology has advantages and disadvantages as will be more deeply discussed later. The choice of the right strategy for the employment of aziridinyl anions in a synthetic process will depend on several factors, which include the availability of the starting material, the compatibility of other functionalities with the selected methodology, and the aziridine structure.

4. Reactivity of Aziridinyl Anions

As stated previously, the aziridinyl anions share some aspects of their reactivity with their "cousins" oxiranyl anions even if, at a closer look, some differences can be envisaged (Scheme 5). Indeed, aziridinyl anions exhibit nucleophilic reactivity being trapped with electrophiles, undergo ring-opening reactions leading to the corresponding aza-enolates, and undergo N to C migration giving N-unsubstituted aziridines.

In analogy with oxiranyl anions, carbenoid reactivity has been demonstrated for some aziridinyl anions bearing electron-withdrawing groups (EWG) as the N-substituent. Indeed, typical reactions that can be explained only by admitting a carbenoid reactivity are the reductive alkylation and the eliminative dimerization leading to substituted alkenes, as well as the intramolecular cyclopropanation by

Scheme 5



C=C insertion and the transannular cyclization by C−H insertion. The feasibility of these reactions is strongly dependent on the reaction conditions (i.e., solvent, temperature, ligands) and on structural requirements such as the capability of the aziridine nitrogen to act as a good leaving group. As will be described, the main difference in reactivity between aziridinyl anions and oxiranyl anions resides in the nature of the N-substituent, which can be either an EWG or EDG, which could affect the stereochemistry at the nitrogen as well as the availability of the nitrogen lone pair, which could stabilize or even destabilize the adjacent negative charge on the C-anion; the oxirane oxygen, instead, does not bring about such effects.

5. Generation of Aziridinyl Anions by Deprotonation

Before discussion of the deprotonation reaction of aziridines with organolithiums, a comparison with the α-deprotonation of acyclic amines is due. Among the many types of carbanionic systems, carbanions α to a nitrogen atom are special, because they belong to the group of formally nonstabilized or even destabilized systems. While the nitrogen lone pair can coordinate to an incoming organolithium reagent, it destabilizes the adjacent C−Li bond by antibonding interaction even more than that of lone pairs at oxygen.[16] For this reason, α-lithiated amines are in general not easily accessible by direct deprotonation of amines and usually are obtained by other routes.[17]

Direct deprotonation α to nitrogen is, therefore, difficult unless the nitrogen lone pair is involved in conjugation with an EWG group or delocalized around an aromatic ring. The same conclusion can be drawn for the direct deprotonation of aziridines. To accomplish the aziridine deprotonation with organolithiums (or lithium amides), some structural requirements are needed. In Figure 2 are collected some aziridines that have been successfully deprotonated with organolithiums: they have been distinguished on the basis of the electronic nature of the nitrogen and carbon atom substituents (EWG or EDG).

5.1. Deprotonation of Aziridines with an EWG-Bearing Carbon

The presence of an EWG as the aziridine carbon atom substituent, on the basis of its inductive, conjugative, or complexation effects, promotes deprotonation likely enhancing the kinetic and thermodynamic acidity of the proton to be removed.

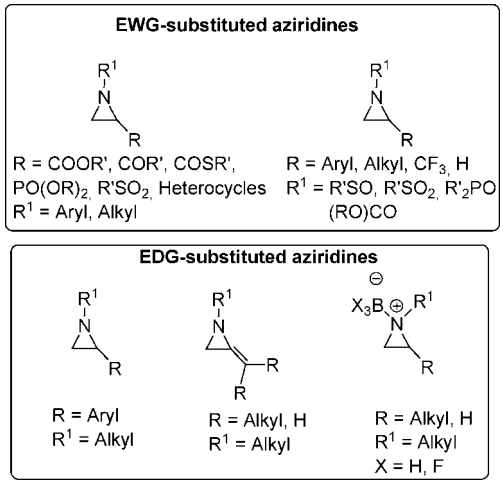


Figure 2.

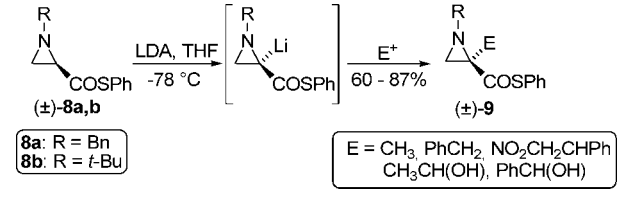
5.2. Deprotonation of *N*-Alkylaziridine Carboxylates and Thiocarboxylates

Deprotonation of aziridine thiocarboxylates had been reported by Seebach[18] who investigated the lithiation of racemic *N*-^{t}Bu and *N*-Bn aziridine thioesters **8a**,**b** with lithium diisopropylamide (LDA). The resulting aziridinyllithiums could be trapped with electrophiles giving 2,2-disubstituted aziridines **9** (Scheme 6).

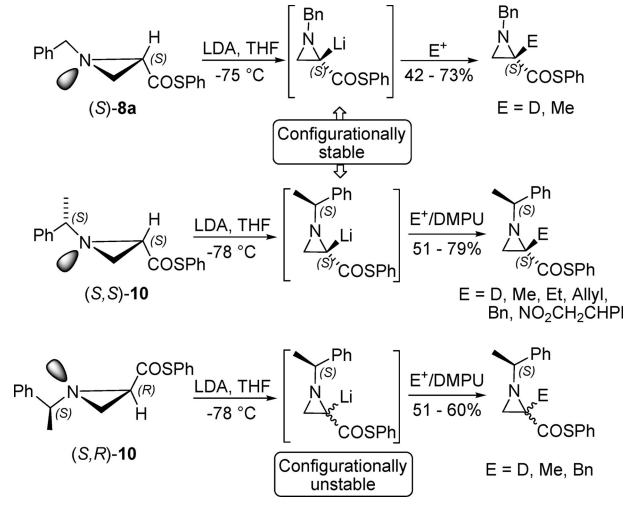
In an effort to expand the utility of this lithiation−trapping sequence, the lithiation of chiral nonracemic aziridines (*S*)-**8a**, (*S*,*S*)-**10**, and (*S*,*R*)-**10** was also investigated. The resulting aziridinyllithiums generated from (*S*)-**8a** and (*S*,*S*)-**10** were found to be configurationally stable, as proven by the analyses of the corresponding deuteration and alkylation products. In contrast, diastereomeric aziridine (*S*,*R*)-**10** underwent epimerization upon lithiation (Scheme 7). The reason for this different behavior was initially attributed to the intermediacy of a planar enolate; however, this hypothesis could not explain the configurational stability observed in the lithiation of chiral aziridine (*S*)-**8a**. It was assumed that a pyramidalized enolate could be compatible with the experimental observations, but this was not demonstrated and the real reason for the different configurational stability was only partially explained some years later by the self-regeneration of stereocenters (SRS) principle.[19]

Nevertheless, Seebach's work is a milestone because it focuses, for the first time, on the possible role of the aziridine nitrogen. It demonstrates that configurationally stable aziridinyllithiums can be easily generated and that the nitrogen configuration should be taken into account to explain the epimerization process. Seebach demonstrated, by NMR experiments, that the nitrogen inversion under the lithiation

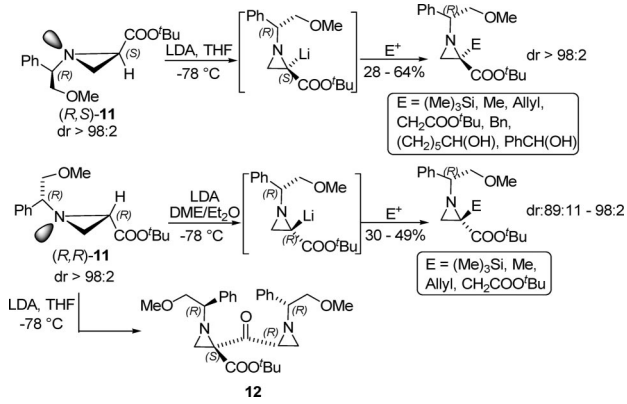
Scheme 6



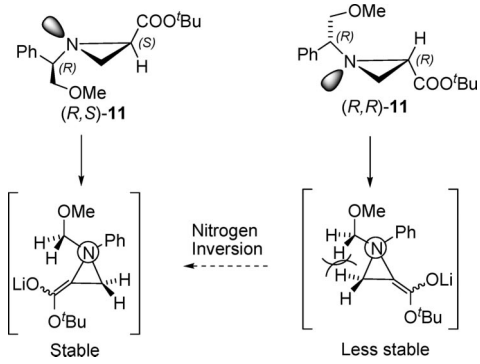
Scheme 7



Scheme 8



Scheme 9

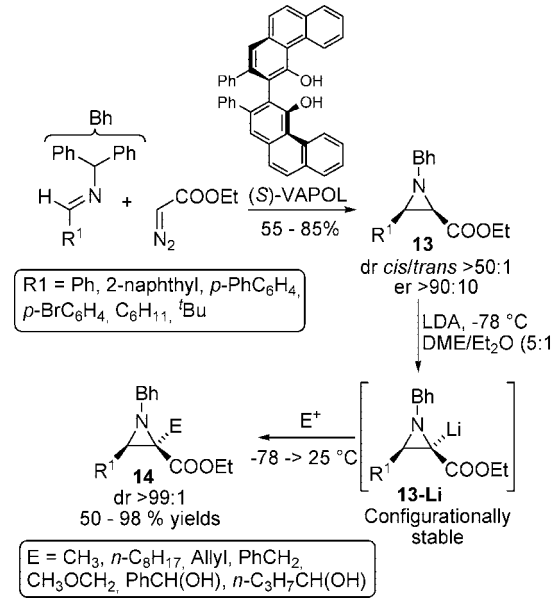


conditions is slow and that probably only one invertomer (indicated in Scheme 7) reacts with LDA.

Later, Husson and co-workers reported on the lithiation of chiral aziridinyl esters (*R*,*R*)-**11** and (*R*,*S*)-**11**, finding again a different reactivity between the two diastereomeric aziridines (Scheme 8).[20] Aziridine (*R*,*S*)-**11** was lithiated with LDA and the corresponding aziridinyllithium reacted with several electrophiles showing complete retention of configuration in the trapping products. In contrast, aziridine (*R*,*R*)-**11** underwent self-condensation leading to compound **12**; however, changing the reaction medium (a mixture of dimethoxyethane (DME)/Et_2O instead of tetrahydrofuran (THF)) allowed for the generation of the corresponding aziridinyllithium and its trapping with electrophiles took place with just a modest epimerization (Scheme 8).

In order to give an explanation to all this, Husson and co-workers studied first the role of the nitrogen lone pair in both the diastereomeric aziridines (*R*,*S*)-**11** and (*R*,*R*)-**11** disclosing, accordingly to Seebach's[18] work, that the nitrogen inversion has a free energy of activation of about 16 kcal mol^{-1} and that the main invertomer is the one that sets the lone pair *trans* to the proton to be removed (see Scheme 8). The authors then investigated the nature of the lithiated intermediates by *in situ* low-temperature IR spectroscopy, finding a complete disappearance of the carbonyl band of the neutral aziridines (*R*,*S*)-**11** and (*R*,*R*)-**11** at 1739 cm^{-1} and the appearance of a new band at 1710 cm^{-1} attributed to the C=C bond of an enolate. With this information in hand, the model reported in Scheme 9 was proposed. This model tries to justify the higher chemical stability of the lithiated intermediate deriving from (*R*,*S*)-**11** on the basis of the lack of steric interactions between the aziridine protons and the methylenic protons of the chiral nitrogen substituent; the different configurational stability has been ascribed to the nitrogen inversion process that favors the more stable enolate.

Scheme 10



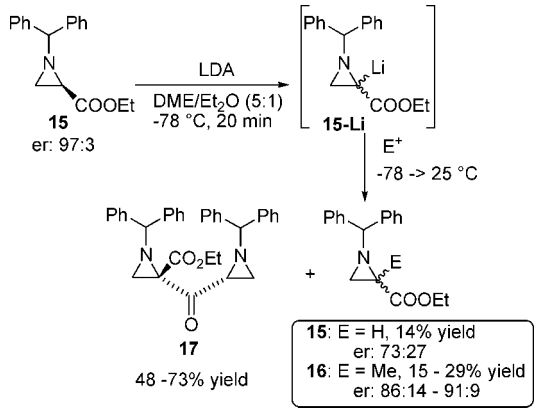
Another example of highly stereoselective alkylation of lithiated aziridine carboxylates has been reported recently by Wulff and co-workers[21] who developed a new process for the catalytic asymmetric synthesis of aziridines. This process is based on the reaction of benzhydryl imines with diazo compounds mediated by chiral boron Lewis acid obtained from VAPOL ligand (Scheme 10).[22] The chiral *cis* configured aziridines **13** were subjected to a further functionalization, by the lithiation/electrophile trapping sequence, obtaining trisubstituted aziridines **14** with high diastereo- and enantioselectivity.

Aziridinyllithiums **13-Li** were found to be chemically and configurationally stable under the reaction conditions and reacted with alkyl halides or carbonyl compounds giving products **14** without loss of optical purity. Moreover, the authors reported that the benzhydryl group has a great influence in the lithiation reaction, compared with a simpler benzyl group, and that the substitution on the aziridine carbon atoms is important to preserve the configuration at the lithiated carbon. In fact, when chiral aziridine **15** (er = 97:3) was deprotonated with LDA and the resulting lithiated intermediate **15-Li** was trapped with a proton source or CH_3I, a loss of the optical purity was observed in the products **15** and **16** together with a variable amount of self-condensation product **17** (Scheme 11).

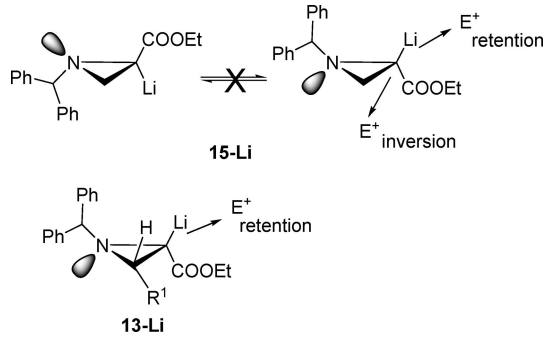
The racemization of **15-Li** was assumed to be dependent on the electrophile, which reacts with pyramidal aziridinyllithium with retention or inversion of configuration. This model could account for the high retentive stereoselectivity observed in the trapping reactions of **13-Li** where the electrophile could approach from the less hindered side (Scheme 12).

At a closer look, the conclusions of Wolff and co-workers on the reasons for the configurational stability or instability of lithiated aziridine carboxylates are different from those of Husson who, however, reports an IR spectroscopic investigation of the lithiated intermediates and ascribes the epimerization to the nitrogen inversion process. Moreover, Sebaach describes retention of configuration in the reaction of lithiated *N*-benzylaziridine thiocarboxylate analogs of Wolff lithiated aziridine **15-Li**, which conversely reacts with

Scheme 11



Scheme 12



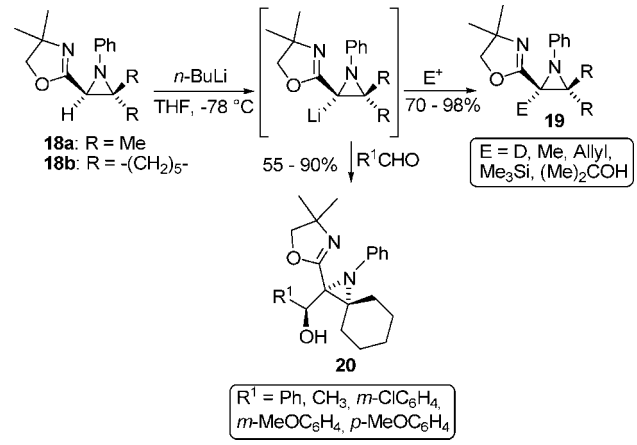
poor stereoselectivity. Even if the systems are slightly different, it is reasonable to argue that, in order to explain these results, more should be known on the real structure, nature, and dynamics in solution of these valuable reactive intermediates.

5.3. Deprotonation of *N*-Alkyl, -Aryl, and Heterocycle-Substituted Aziridines

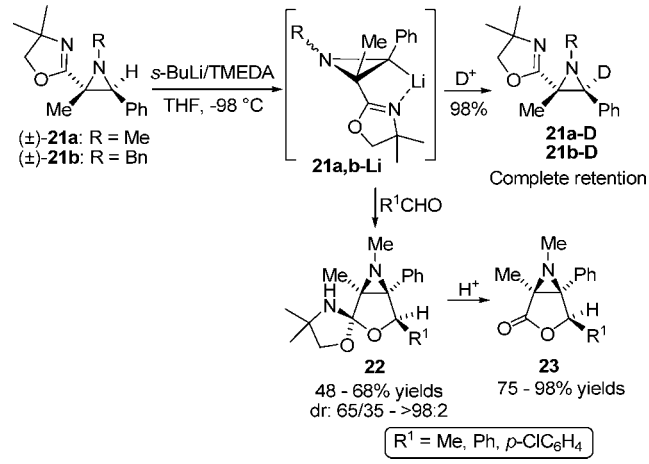
C-Heterosubstitution of aziridines represents an alternative way of enhancing the thermodynamic acidity of the aziridine ring protons thus promoting lithiation. Florio and co-workers reported the deprotonation of *N*-aryl oxazolinylaziridines **18a**,**b** with *n*-BuLi at low temperature generating the corresponding aziridinyllithiums, which reacted with electrophiles giving functionalized aziridines **19**. The reaction with aldehydes took place with very high stereoselectivity furnishing the hydroxyalkylated aziridines **20** (Scheme 13).[23]

Further studies on trisubstituted *N*-alkyl oxazolinylaziridines **21a**,**b** disclosed that the oxazolinyl ring promotes lithiation at the adjacent aziridine ring carbon atom when the α-position is blocked and the oxazoline group sets *cis* to the proton to be removed (Scheme 14).[24] Lithiation of **21a**,**b** using *s*-BuLi/tetramethylethylenediamine (TMEDA) at −98 °C resulted in the formation of aziridinyllithiums **21a**,**b-Li**: deuteration occurred with retention of configuration. It is worth pointing out that the deprotonation would have not occurred without the participation of the oxazolinyl ring.[25] As will be better explained later, simple *N*-alkyl-2-phenylaziridines are exclusively ortho-lithiated under the conditions used for the lithiation of **21a**,**b**. In addition, the synthetic potential of oxazoline-substituted aziridinyllithium **21a-Li** was proven by its trapping with carbonyl compounds,

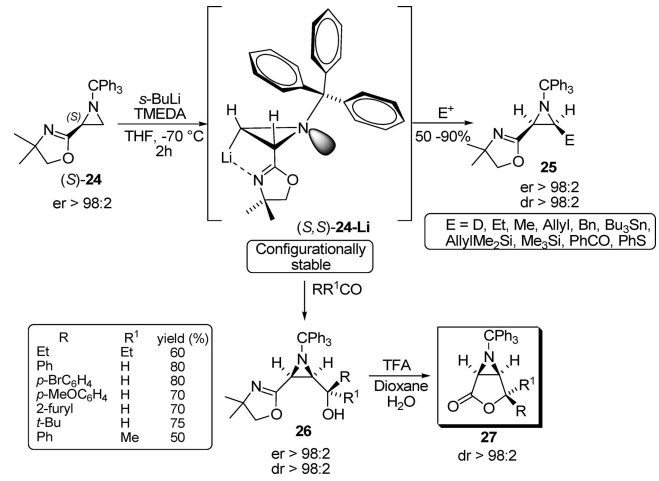
Scheme 13



Scheme 14



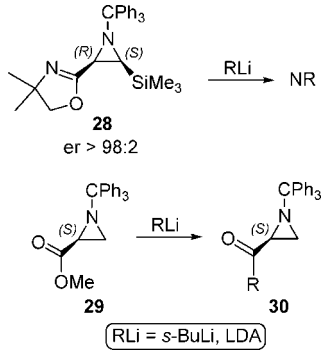
Scheme 15



which furnished spirocyclic compounds **22** and then aziridino-γ-butyrolactones **23** by acidic hydrolysis.

The role of the oxazolinyl ring as lithiation promoter was highlighted also with the chiral terminal *N*-trityl aziridine (*S*)-**24**.[26] Almost surprisingly, when aziridine (*S*)-**24** was subjected to deprotonation with *s*-BuLi/TMEDA at −70 °C, the lithiation occurred at the *β-cis*-position with respect to the oxazolinyl ring (Scheme 15) and not at the more acidic α-position. This was ascribed to the *N*-trityl group, which, as demonstrated by NOESY experiments on (*S*)-**24**, sets in a *trans* relationship with respect to the

Scheme 16



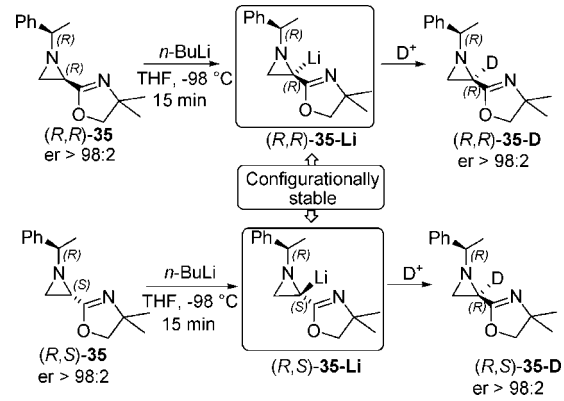
oxazoline ring and prevents lithiation at the α-position likely because of a steric shield that controls the base approach. As result of complexation and stabilization effects brought by the oxazoline ring, the configurationally stable aziridinyllithium (*S*,*S*)-**24-Li** could be generated and used in the preparation of highly enantioenriched *cis* functionalized aziridines **25** and **26** by trapping with several electrophiles (Scheme 15).

Hydroxyalkylated oxazolinylaziridines **26** could be stereoselectively converted into the corresponding aziridino-γ-butyrolactones **27**. The crucial role played by the oxazolinyl ring was further demonstrated by two experiments: (i) no lithiation of aziridine **28** occurs under varied conditions when the *β-cis* position is blocked; (ii) the *N*-trityl aziridine carboxylate **29** undergoes exclusive addition to the ester functionality forming ketone **30** (Scheme 16).

It has been also demonstrated that the steric demand of the N-substituent can affect the regioselectivity of the lithiation reaction. In fact, when *N*-cumyl oxazolinylaziridine **31** was subjected to lithiation with *s*-BuLi, aziridinyllithiums α-**31-Li** and *β*-**31-Li** formed in a 1:2 ratio and trappping with electrophiles gave derivatives α-**33** and *β*-**33**. In contrast, with the less hindered *N*-benzyl oxazolinylaziridine **32**, lithiation occurred at the more acidic α-position producing almost exclusively α-**32-Li** (Scheme 17), which furnished α-functionalized aziridines α-**34** upon electrophilic trapping.

These results, even if they clearly demonstrate that the nitrogen substituent is able to affect the regioselectivity of the lithiation reaction, do not furnish any indication on the configurational stability of this kind of α-lithiated aziridines. For this reason, in our group we have investigated the behavior of the two diastereomeric aziridines (*R*,*R*)-**35** and (*R*,*S*)-**35** both enantioenriched.[27] Both diastereoisomers were regioselectively α-lithiated, using *n*-BuLi in THF, giving the corresponding α-lithiated aziridines (*R*,*R*)-**35-Li** and (*R*,*S*)-**35-Li**, configurationally stable as proven by trapping with a deuterium source (Scheme 18).

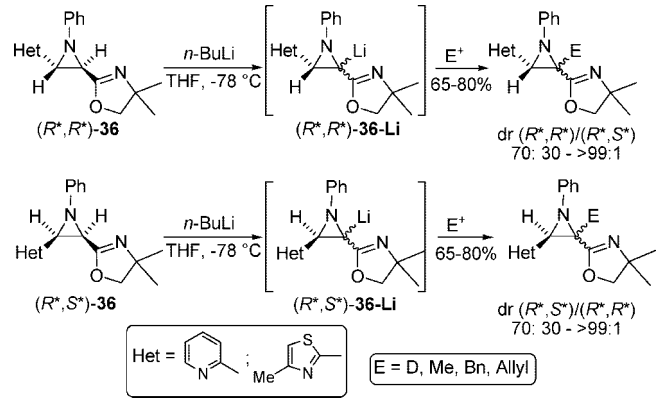
Scheme 18



It is worth pointing out that the corresponding oxazolinyloxiranyllithiums are configurationally unstable.[28]

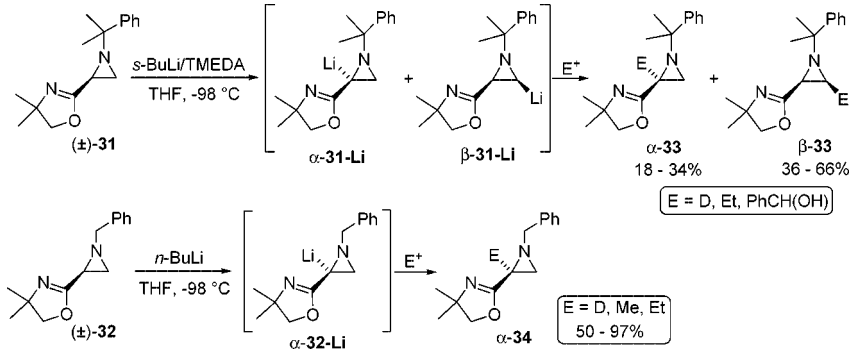
The oxazolinyl group promotes α-lithiation even when the aziridine ring bears other heterocycles.[29] Indeed, diastereomeric aziridines (*R**,*R**)-**36** and (*R**,*S**)-**36** are regioselectively lithiated only at the oxazoline-bearing carbon atom giving aziridinyllithiums (*R**,*R**)-**36-Li** and (*R**,*S**)-**36-Li**, which can be trapped with a variable degree of retention of configuration (Scheme 19).

Scheme 19

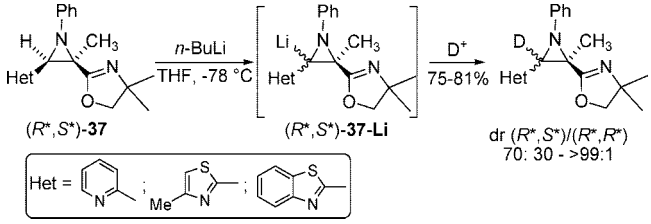


Lithiation occurs at the other heterocycle-substituted carbon atom only in the absence of protons at the oxazoline-bearing carbon atom. In fact, aziridines (*R**,*S**)-**37** were lithiated with *n*-BuLi in THF at −78 °C, producing aziridinyllithiums (*R**,*S**)-**37-Li**, which were trapped with a deuterium source again with a variable degree of stereoselectivity (Scheme 20).

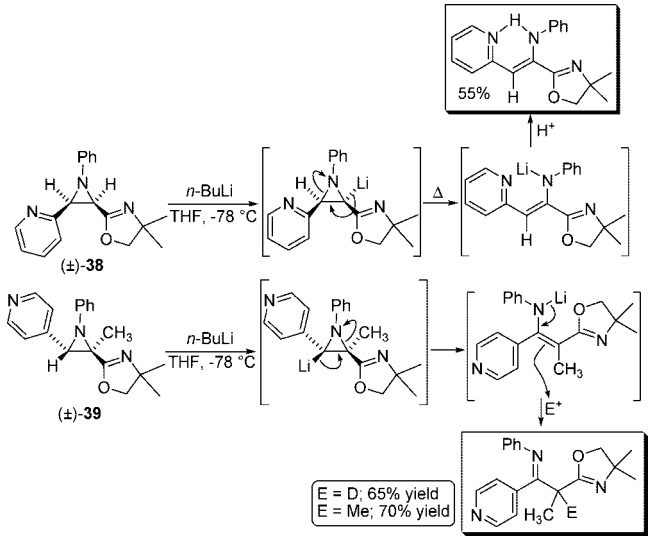
Scheme 17



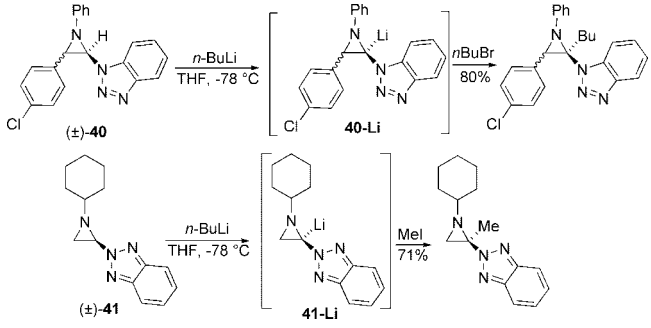
Scheme 20



Scheme 21



Scheme 22

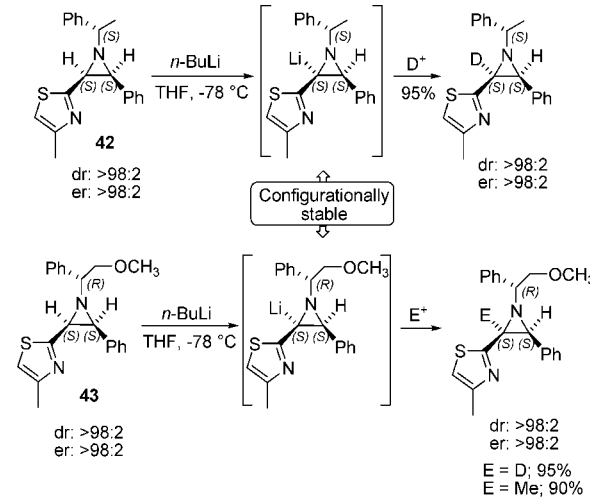


Concerning the thermal stability of lithiated diheterocycle-substituted aziridines, it has been reported that those obtained from aziridines **38** and **39** undergo a ring-opening reaction with formation of the corresponing aza-enolates that could also be trapped with electrophiles (Scheme 21). The exact mechanism of this ring-opening reaction remains unclear.

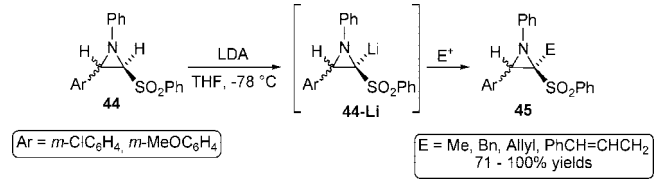
Other examples of heterocycle-promoted lithiation of aziridines have been reported by Katritzky who studied the deprotonation of benzotriazolyl-substituted aziridines **40** and **41** (Scheme 22).[30] Both aziridines were smoothly deprotonated with *n*-BuLi, and the resulting aziridinyllithiums **40-Li** and **41-Li** proved to be stable at −78 °C for 20 min and could be alkylated in good yields. A mixture of *cis* and *trans* aziridines **40** underwent a lithiation reaction producing at the end a mixture of alkylated products.

The configurational stability of lithiated heterocycle-substituted aziridines has been demonstrated with thiazolyl aziridines **42** and **43**. The lithiation/electrophile trapping sequence on enantioenriched aziridines **42** and **43** proceeded with complete retention of configuration and the lithiation occurred regioselectively at the heterocycle-bearing carbon atom (Scheme 23).[31]

Scheme 23



Scheme 24



5.4. Deprotonation of *N*-Aryl Sulfonylaziridines

Few examples have been reported of sulfonylaziridinyl anions.[32] Reutrakul and co-workers[33] reported on the lithiation of aziridines **44** with LDA: deprotonation took place at the α-position, and the resulting aziridinyllithiums **44-Li** could be alkylated to give trisubstituted aziridines **45**. No mention was made of the configurational stability of **44-Li** and of the stereoselectivity of the reaction with electrophiles (Scheme 24).

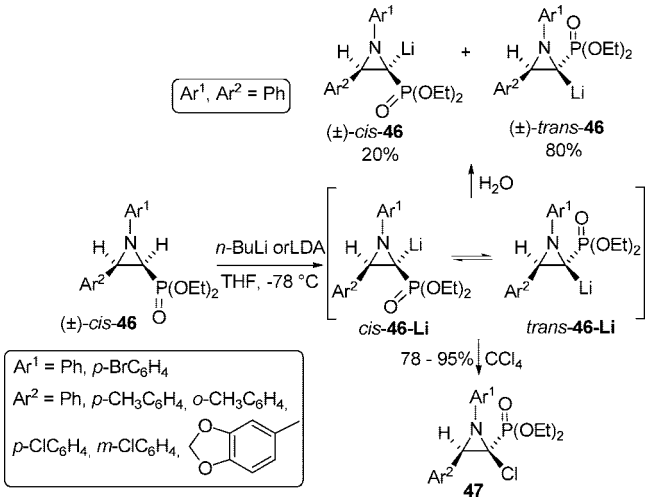
5.5. Deprotonation of *N*-Aryl Aziridinephosphonates

Coutrot reported that aziridinylphosphonate *cis*-**46** could be regioselectively lithiated with *n*-BuLi or LDA at the phosphonyl-substituted carbon atom and that aziridinyllithiums *cis*-**46-Li** quickly equilibrated to *trans*-**46-Li** furnishing, after quenching with H_2O, a mixture of *trans*- and *cis*-**46** in a 80/20 ratio. Attempts to react this equilibrating mixture of aziridinyllithiums with alkylating agents failed.[34] Surprisingly, only carbon tetrachloride could chlorinate **46-Li** to give aziridines **47** in good yields and as single stereoisomers (Scheme 25).

5.6. Deprotonation of Aziridines with an EWG-Bearing Nitrogen

As stated previously, the presence of an EWG on the aziridine carbon atom facilitates the base-promoted deprotonation reaction by inductive, conjugative, or complexation effects. It is expected that the deprotonation of *N*-EWG-substituted aziridines should be equally easy.

Scheme 25



5.7. Deprotonation of *N*-Sulfinyl and *N*-Sulfonylaziridines

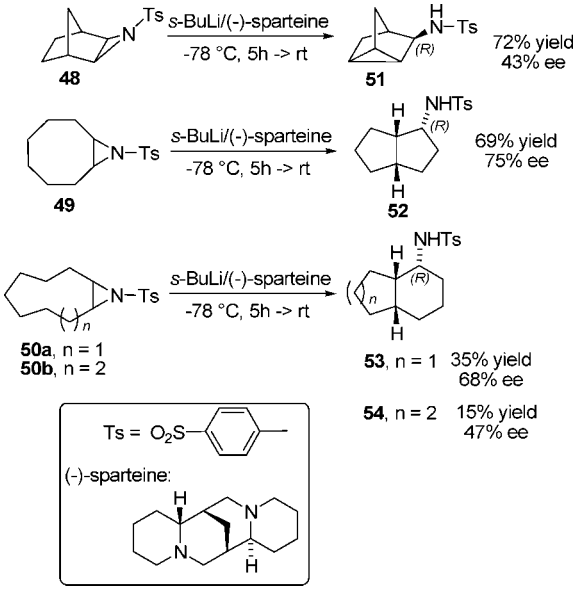
The lithiations of readily available *N*-sulfonyl aziridines[35] have been published in recent years disclosing that in analogy to oxyranyl anions, the resulting aziridinyl anions can behave as carbenoids under particular reaction conditions.

Indeed, Müller and co-workers, while studying the desymmetrization of *N*-sulfonyl aziridines,[36] found that *N*-tosyl aziridines **48**, **49**, and **50a**,**b** react with *s*-BuLi in the presence of (−)-sparteine as chiral ligand, leading to the formation of products **51**, **52**, **53**, and **54** as the result of a transannular C−H insertion process analogous to that observed for oxiranes (Scheme 26).[37]

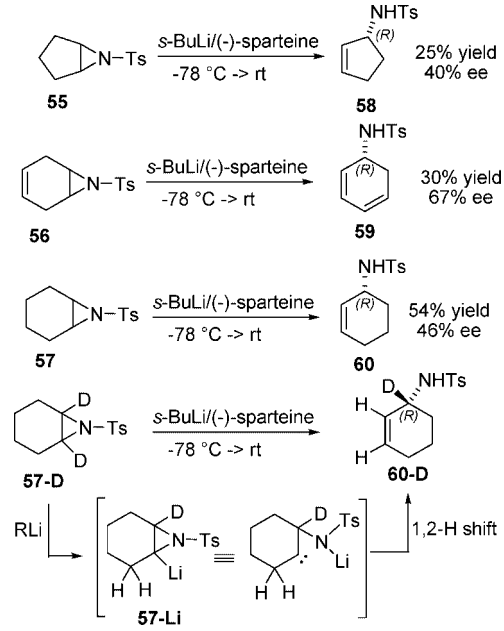
Moreover, Müller reported the reaction of *N*-tosyl aziridines **55**, **56**, and **57** with *s*-BuLi/(−)-sparteine ending up with the formation of allylamines **58**, **59**, and **60**, respectively. To rationalize this outcome a 1,2-H shift was proposed based on the evidence that lithiation−trapping of **57-D** furnished **60-D** via the carbenoidic species **57-Li** (Scheme 27).

Almost at the same time, O'Brien investigated the lithiation reaction of aziridines **55** and **57** with *s*-BuLi/(−)-sparteine disclosing the formation of allylamines **58** and **60**, together with variable amounts of tosylamide ($TsNH_2$) not observed in Müller's work (Scheme 28).[38]

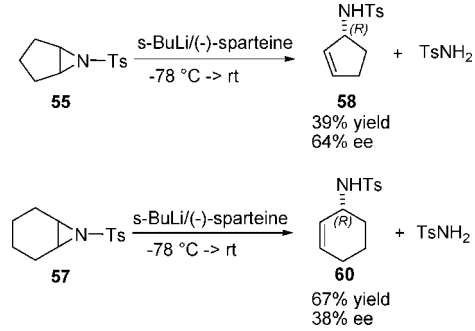
Scheme 26



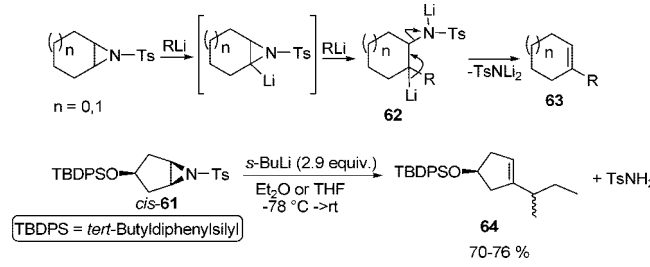
Scheme 27



Scheme 28



Scheme 29

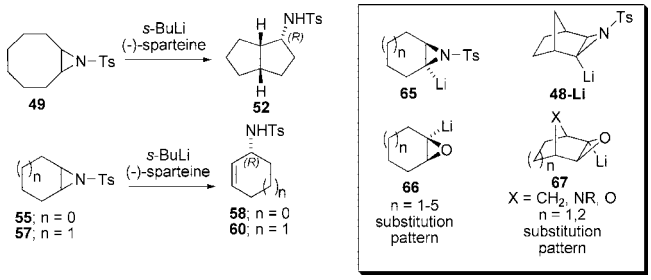


It was just the formation of this side product, deriving from the cleavage of both the C−N bonds of the aziridine ring, that prompted O'Brien to propose a reductive alkylation process as a plausible mechanism for its formation.

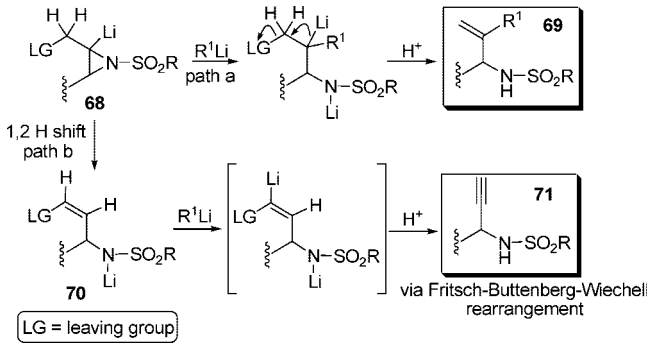
Such a reductive alkylation process is well documented for lithiated oxiranes,[39] which behave as electrophiles under particular reaction conditions. This electrophilic behavior is likely responsible for the $TsNH_2$ formation according to the mechanism reported in Scheme 29. Attack of lithiated aziridine by a second equivalent of organolithium generates a dilithiated adduct **62**, which undergoes $TsNLi_2$ elimination leading to alkene **63**.

Lithiation of *N*-tosyl aziridine *cis*-**61** in Et_2O in the absence of an external ligand afforded alkene **64** (1:1 mixture of

Scheme 30



Scheme 31



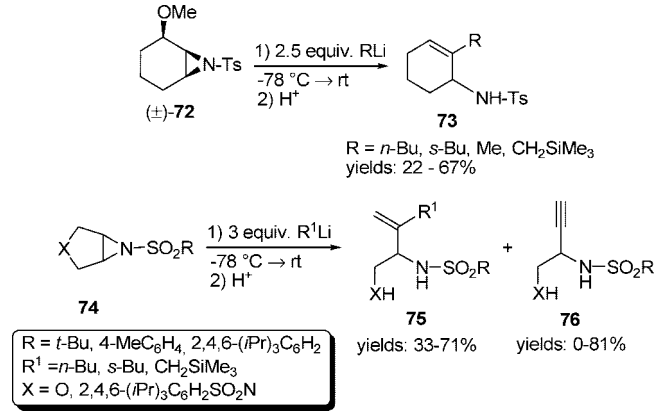
diastereomers) with no evidence for the formation of any allyl sulfonamide. These were the first examples of reductive alkylation of lithiated aziridines leading to substituted alkenes. As will be reported later, such reductive alkylation has been exploited in many useful synthetic transformations.

The sense of asymmetric induction of the *s*-BuLi/(−)-sparteine-induced rearrangement of *N*-tosyl aziridines has been studied by O'Brien who demonstrated that the *N*-tosyl group allows for a complete changeover of the enantioselectivity with respect to the corresponding oxiranes. The rearrangement of aziridines **49**, **55**, and **57** into **52**, **58**, and **60** should involve lithiated intermediate **65** obtained by a preferential lithiation of the *S*-stereocenter as observed also by Müller in the case of **48-Li**. It was proven that lithiated aziridines involved in the rearrangement have opposite stereochemistry with respect to the corresponding lithiated oxiranes **66** and **67** involved in the same kind of rearrangement (Scheme 30).[40]

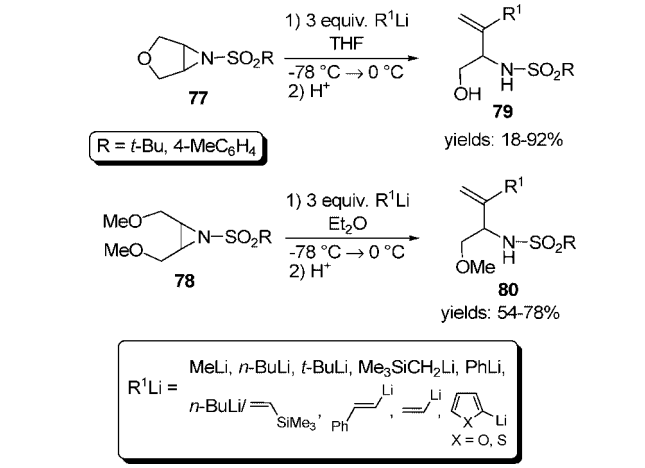
The reductive alkylation has been further investigated by O'Brien and co-workers[41] and exploited for the preparation of allylic sulfonamides and alkynyl amino alcohols and diamines. The general scheme of these transformations is reported in Scheme 31. When the lithiated aziridine bears a suitable leaving group at the carbon adjacent to the lithiated center, as in **68**, two main reaction pathways can be envisaged: (1) a nucleophilic addition of the organolithiums followed by β-elimination with the formation of allylamines **69** (Scheme 31, path a); (2) a 1,2-H shift giving allylamine **70**, which undergoes an organolithium-promoted Fritsch–Buttemberg–Wiechell rearrangement[42] furnishing alkynyl amine **71** (Scheme 31, path b). The carbenoid character of the aziridinyllithium is evident in both pathways.

Applications are reported in Scheme 32, where alkoxides and sulfonamides are used as suitable leaving groups. In the case of **72**, cyclic allylamines **73** were obtained as sole products. By using bicyclic furane and pyrrole derivatives of the kind of **74**, a mixture of allyl and alkynyl amines was obtained in variable ratios depending on the reaction conditions. Alkynyl derivatives **76** could be obtained in high yields

Scheme 32



Scheme 33



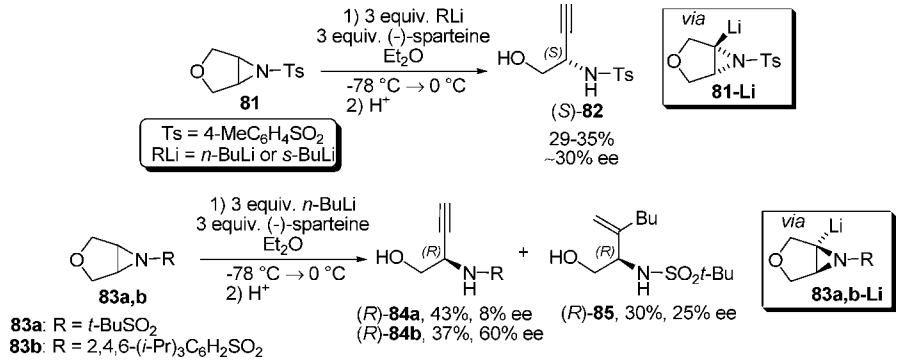
in the presence of a ligand such as pentamethyldiethylenetriamine (PMDTA).

Other examples of useful reductive alkylation reactions of lithiated *N*-sulfonylaziridines have been reported by Hodgson and co-workers who prefer the name of alkylative ring opening for this process.[43] Several allylic amino alcohols **79** and amino ethers **80** have been prepared starting, respectively, from cyclic and acyclic *N*-sulfonyl-protected aziridinyl ethers **77** and **78** (Scheme 33).

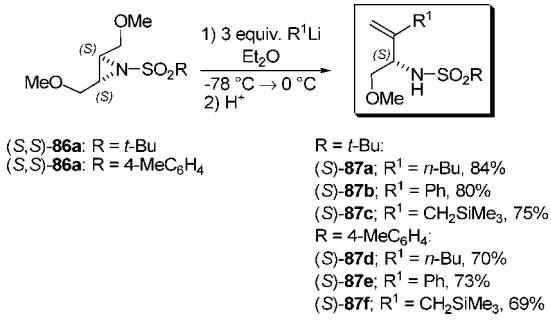
Both tosyl (Ts) and acid-labile *tert*-butylsulfonyl (Bus) nitrogen protection were proven useful in this organolithium-induced transformation. In Bus-protected aziridines, the yields were sensitive to the reaction conditions requiring longer reaction times and higher temperature. In striking contrast with epoxides of acyclic allylic ethers, which do not undergo organolithium-induced alkylative ring opening, *cis*-aziridine (such as **78**) showed a useful reactivity providing several unsatured amino ethers **80**.

Both O'Brien[41] and Hodgson[43] reported attempts to control the enantioselectivity of this transformation by using (−)-sparteine as an external ligand. Both observed that the sense of asymmetric induction depended on the nature of the nitrogen substituent. With aziridine **81**, the reaction with organolithiums in the presence of (−)-sparteine gave alkynyl amino alcohols (*S*)-**82** in moderate yields and enantiomeric excess (Scheme 34), while the use of *N*-Bus- or *N*-2,4,6-triisopropylsulfonyl aziridines **83a**,**b**, under the same reaction conditions, furnished mainly alkynyl amino alcohols (*R*)-**84a**,**b** with a variable degree of stereocontrol. The reaction of **83a** gave also allyl amino alcohol (*R*)-**85**. The reasons

Scheme 34



Scheme 35



for this opposite sense of induction is still an open question but the intermediacy of two differently configured lithiated aziridines (**81-Li** and **83a**,**b-Li**) has been hypothesized.

A more convenient preparation of chiral allylic amino ethers (*S*)-**87a**−**f** has been achieved by alkylative ring-opening reactions of *trans* configured aziridinyl ethers (*S*,*S*)-**86a**,**b** readily available from L-tartaric acid (Scheme 35).

The reductive alkylation (or alkylative ring-opening) reactions of *N*-sulfonyl aziridinyllithiums are a consequence of the carbenoid character of these reactive intermediates. Nevertheless, *N*-sulfonyl aziridinyllithiums can behave as nucleophiles. The first example of lithiated *N*-sulfonyl aziridines acting as nucleophiles was reported by Schaumann[44] in 1991 while investigating the organolithium-mediated ring opening of 1-tosyl-2-phenylaziridines. Unexpectedly, the reaction of *N*-tosyl aziridine **88** with organolithiums gave tricyclic compounds **90a**−**d** after an intramolecular cyclization of **88-Li** to the aromatic ring of the sulfonyl group generating the stabilized anion **89**, which could also be trapped with electrophiles (Scheme 36).

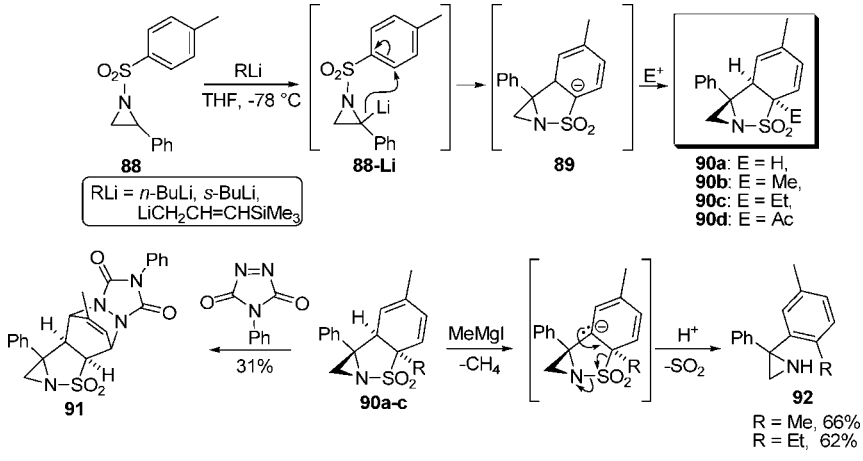
The structure and the stereochemistry of **90b** were ascertained by X-ray analysis, and the utility of compounds **90a**−**c** was tested in a [4 + 2] cycloaddition reaction obtaining compound **91** and in a base-induced rearomatization reaction leading to N-unprotected aziridines **92**.

Only recently, an efficient lithiation/trapping sequence of *N*-Bus-2-phenylaziridine has been reported.[45] The Bus group proved to be more useful than the corresponding arylsulfonyl groups being more easily removed and giving less side reactions. The *N*-Bus-2-phenylaziridine **93** could be regioselectively lithiated at the α-benzylic position using *n*-BuLi at −78 °C in Et_2O, providing aziridinyllithiums **93-Li** and then 2,2-disubstituted aziridines **94a**−**i** upon trapping with electrophiles (Scheme 37).

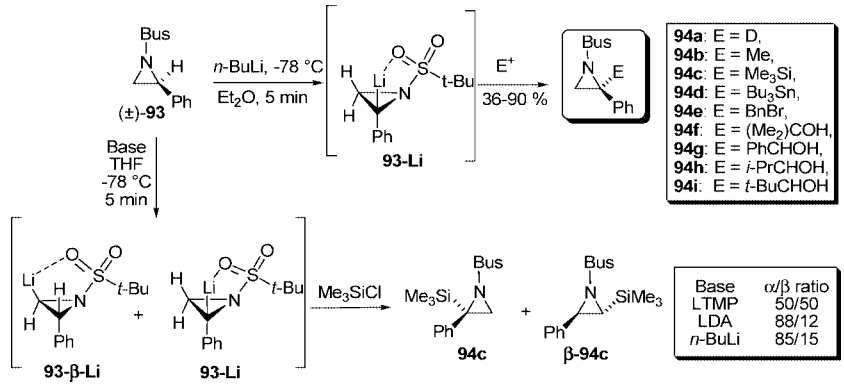
Interestingly, when aziridine **93** was reacted with 3 equiv of LTMP (lithium-2,2,6,6-tetramethylpiperidide) in THF, an equimolar mixture of **93-*β*-Li** and **93-Li** formed as deduced by trapping with TMSCl. The use of LDA or *n*-BuLi, under the same reaction conditions, gave mainly **93-Li**. It remains unclear whether there is a competition in the deprotonation step or an equilibrium between the α- and *β*-lithiated intermediates, which should favor the more stable benzylic position.[46] Moreover, low-temperature NOESY experiments, performed by the authors, disclosed that the Bus group and the phenyl ring in **93** set *trans* to each other suggesting that such a group could play a role in either promoting the deprotonation or stabilizing the lithiated intermediates by chelation. Interestingly, a double functionalization of aziridine **93** to give trisubstituted aziridines **95** via the aziridinyllithium **94b-Li** has been also reported (Scheme 38).

The exclusive formation of aziridines **95** from **93** disclosed that both aziridinyllithiums **93-Li** and **94b-Li** were configu-

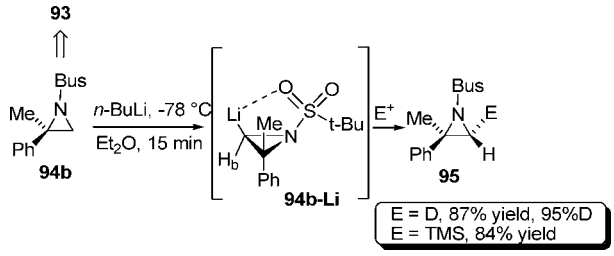
Scheme 36



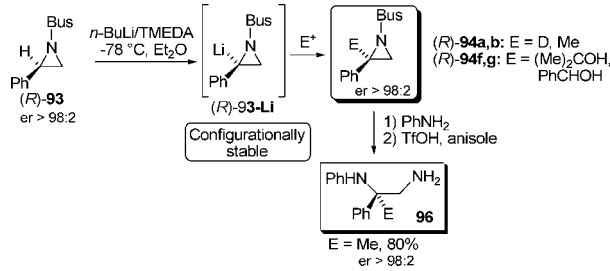
Scheme 37



Scheme 38



Scheme 39



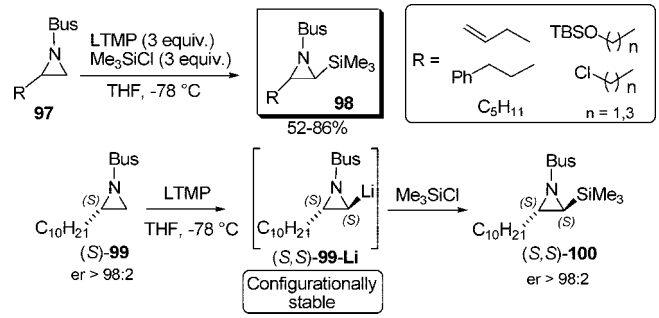
rationally stable. The lithiation/trapping sequence carried out on (*R*)-**93** produced highly enantioenriched 2,2-disubstituted aziridines (*R*)-**94a**,**b** and (*R*)-**94f**,**g**, which are useful intermediates for the preparation of chiral 1,2-diamine **96** by a nucleophilic ring-opening−Bus deprotection sequence (Scheme 39).

Hodgson and co-workers reported that *N*-*tert*-butylsulfonyl 2-alkyl-substituted aziridines **97** underwent a regioselective *β-trans* lithiation.[47] In situ silylation reactions were accomplished with aziridines **97** by using LTMP (3 equiv) at −78 °C. α,*β*-Aziridinylsilanes **98** could be obtained thus demonstrating a wide substitution tolerance in the starting aziridines. In the case of aziridine (*S*)-**99**, the related aziridinyllithium (*S*,*S*)-**99-Li** was found to be configurationally stable and could be converted into chiral silylderivative (*S*,*S*)-**100** (Scheme 40).

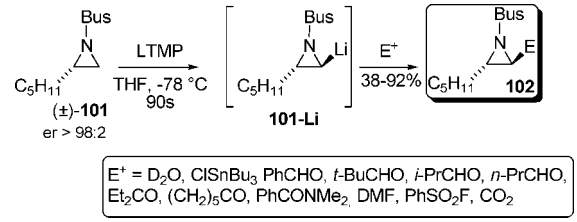
Such aziridinyllithiums were found to be very reactive and, in the case of **101**, the trapping of aziridinyllithium **101-Li** with an external electrophile could be realized within only 90 s after its generation, giving *trans* disubstituted aziridines **102** (Scheme 41).

Hodgson and co-workers reported also the first direct external electrophile trapping of the simple *N*-Bus C-unsubstituted ethylene aziridine **103a**.[48] To accomplish the lithiation of **103a**, *s*-BuLi/TMEDA at very low temperature was used as the base and trapping was realized within 5 min with electrophiles. A number of monosubstituted aziridines

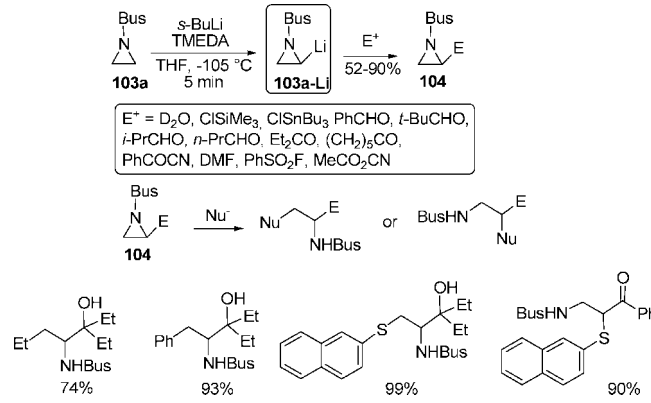
Scheme 40



Scheme 41



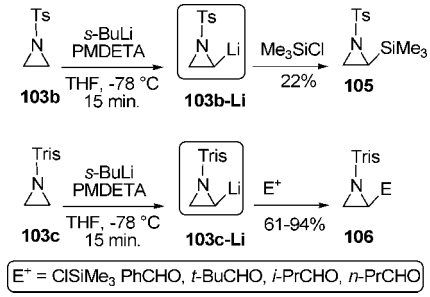
Scheme 42



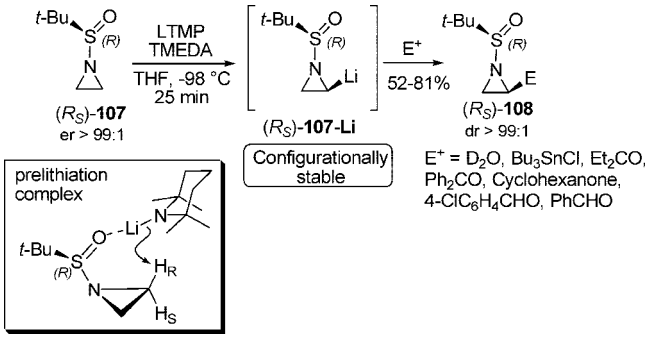
104 were prepared and their synthetic utility was tested in ring-opening reactions promoted by C- and S-nucleophiles (Scheme 42).

In order to overcome the problem of the very low temperatures required for the lithiation of ethylene aziridines, O'Brien reported a comparative study on ethylene aziridines bearing different sulfonyl groups as nitrogen substituent.[49] Aziridines **103b** and **103c**, bearing, respectively, the 4-methylbenzenesulfonyl (Ts) and the 2,4,6-tri-isopropylbenzenesulfonyl (Tris) groups as the N-substituent, were subjected to lithiation with *s*-BuLi (3 equiv) and pentamethyldiethyl-

Scheme 43



Scheme 44



enetriamine (PMDETA) at −78 °C followed by trapping with electrophiles, which gave functionalized aziridines **105** and **106** (Scheme 43). The study disclosed that the Tris group did not suffer from the competing ortho-lithiation observed with the Ts group and that the trapping could be executed within 15 min in order to avoid competitive reactions due to the carbenoid reactivity of the lithiated intermediate.

These results reveal that comparable reactivity can be exhibited in the lithiation/trapping sequence of *N*-tris-substituted aziridine **103c** and *N*-Bus-substituted aziridine **103a**; moreover, the ease of removal of the *tert*-butylsulfonyl group should make this choice more convenient.[50]

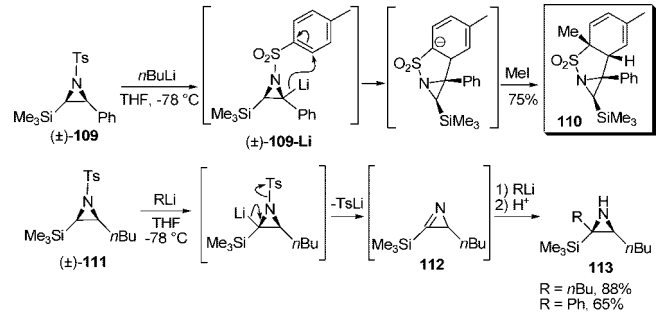
The preparation of chiral aziridines by the lithiation/substitution sequence of simple ethylene aziridines has been achieved elegantly by using the readily available enantioenriched *N*-sulfinyl aziridine (R_S)-**107**.[48] The aziridinyllithium (R_S)-**107-Li** was generated by using LTMP and TMEDA at −98 °C for 25 min, and upon quenching with electrophiles, chiral aziridines (R_S)-**108** were obtained with very high diastereoselectivity (Scheme 44).

The stereochemical analysis of the products demonstrated that (R_S)-**107-Li** was configurationally stable under the reaction conditions, even if the addition to prochiral aldehydes occurred with low stereoselectivity with reference to the newly created stereogenic center. Furthermore, the authors gave a tentative explanation of the observed regioselectivity based on an asymmetric deprotonation involving a complex between the *tert*-butylsulfinyl group and the base, which should favor the preferential H_R proton abstraction (Scheme 44).

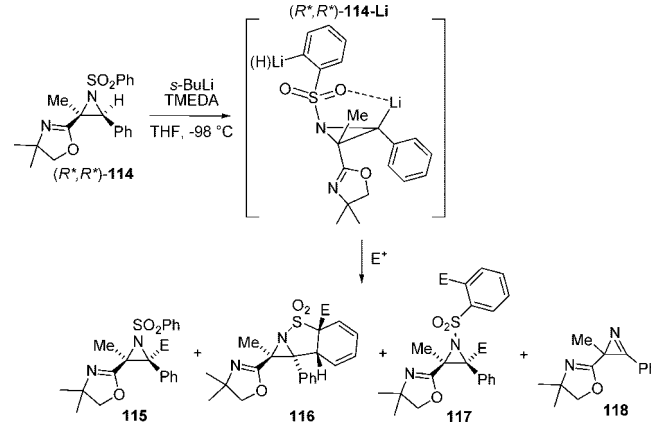
5.8. Other Examples of *N*-Sulfonyl Aziridinyllithiums

In this section, will be reported examples of lithiated *N*-sulfonyl aziridines bearing groups that are themselves capable of promoting lithiation even in absence of *N*-EWG substituents.

Scheme 45



Scheme 46



The lithiation of *cis* configured C-silylated aziridines has been reported by Aggarwal and co-workers.[51] The lithiation of phenyl-substituted *cis*-aziridine **109** followed by quenching with MeI afforded the tricyclic aziridine **110** as a single diastereoisomer (Scheme 45). It is noteworthy that the lithiation takes place at the benzylic position rather than α to the silicon, according to the reactivity of analogous silyloxiranes;[52] and the resulting aziridinyllithium undergoes a dearomatizion reaction involving the arylsulfonyl group just as reported by Schaumann (see Scheme 36).

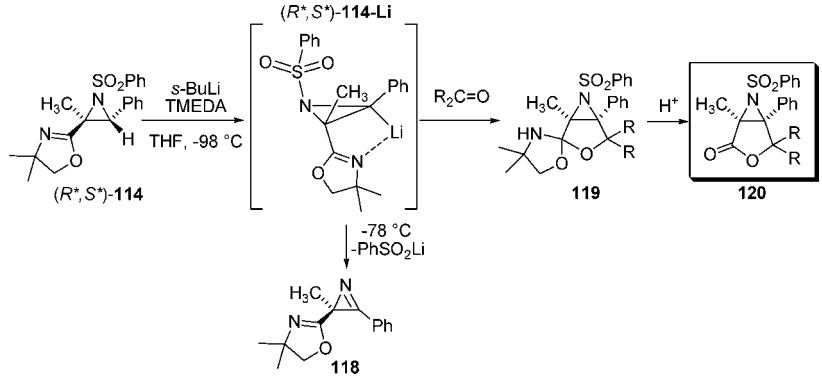
Instead, lithiation of alkyl-substituted *cis*-aziridine **111** occurred at the silicon-bearing carbon, but the resulting aziridinyllithium underwent TsLi elimination forming the azirine **112**, which reacted with the excess organolithium, furnishing trisubstituted aziridines **113** (Scheme 45).

Similarly, lithiation of diastereomeric *N*-sulfonyl oxazolinylaziridines (*R**,*R**)-**114** and (*R**,*S**)-**114**[53] took place at the benzylic position and the resulting aziridinyllithiums (*R**,*R**)-**114-Li** and (*R**,*S**)-**114-Li** were both found to be configurationally stable although differing in their reactivity. Aziridinyllithium (*R**,*R**)-**114-Li** could be trapped with electrophiles, giving aziridines **115**, only with low yield because of side reactions such as the dearomatization, affording tricyclic aziridine **116** and ortho-lithiation furnishing aziridine **117** upon trapping with electrophiles (Scheme 46). Variable amounts of azirine **118** were also observed.

In its turn, diastereomeric aziridinyllithium (*R**,*S**)-**114-Li** did not undergo dearomatization reaction, likely because of the *trans* arrangement between the sulfinyl group and the C−Li bond, and could be trapped with ketones to furnish spirocyclic derivatives **119** and converted into useful aziridine-γ-lactones **120** (Scheme 47).

Moreover, the *trans* arrangement between the sulfonyl group and the C−Li bond in lithiated aziridine (*R**,*S**)-**114-Li** causes

Scheme 47



a fast *trans* β-elimination of lithium phenylsulfinate with formation of azirine **118** almost quantitatively at −78 °C.

The lithiation of chiral *N*-tosyl-2-trifluoromethyl aziridine (*R*)-**121** has been investigated by Uneyama and co-workers.[54] The aziridinyllithium (*R*)-**121-Li**, generated at very low temperature with *n*-BuLi, reacted with electrophiles with retention of configuration furnishing disubstituted aziridines **122** (Scheme 48). α-Trifluoromethyl-α- and β-amino acids such as **123** could be subsequently prepared.

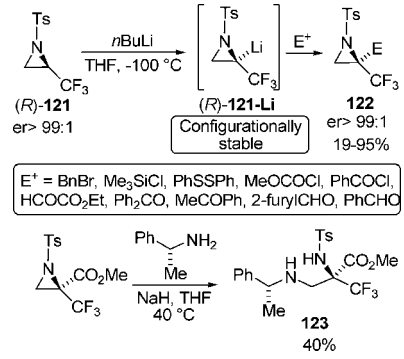
6. Deprotonation of N-Phosphinyl, N-Boc, and N-Phosphonate Aziridines: N → C Group Migration

The *N*-phosphinyl group proved to be useful as promoter of deprotonation in diastereomeric oxazolinylaziridines (*R**,*R**)-**124** and (*R**,*S**)-**124**.[24] Diastereoisomer (*R**,*S**)-**124** could be smoothly lithiated providing configurationally stable (*R**,*S**)-**124-Li**, which, upon trapping with acetone, gave first spirocyclic derivative **125** and aziridine-γ-lactone **126** after acidic hydrolysis (Scheme 49). The lithiation−deuteration of diastereomeric aziridine (*R**,*R**)-**124** showed a different reactivity depending on the base used for the deprotonation: the use of *s*-BuLi gave a certain degree of epimerization furnishing, upon quenching with D_2O, a mixture of epimers (*R**,*R**)-**124-D** and (*R**,*S**)-**124-D**; the use of LDA gave a more pronounced epimerization and favored the N to C migration of the phosphinyl group leading to aziridine **127** (Scheme 49).

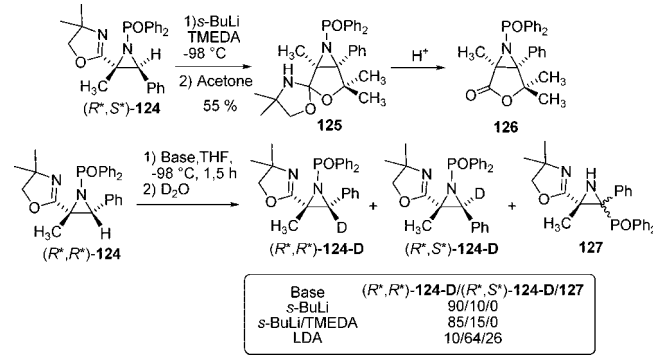
The deprotonation of *N*-*tert*-butoxycarbonyl (Boc)-substituted aziridines was reported by Beak and co-workers for the first time and relies on an in situ lithiation/silylation sequence.[55] *N*-Boc aziridine from propene **128** was lithiated with *s*-BuLi in the presence of TMEDA and an excess of Me_3SiCl at −78 °C to give a mixture of *trans*/*cis* aziridinylsilanes **129** likely derived from the trapping of the corresponding aziridinyllithium (Scheme 50). Unfortunately, an attempt to trap it with an external electrophile failed. Some 10 years later Florio, Luisi, and co-workers reported that *N*-Boc-2-phenylaziridine **130** underwent a very fast and highly stereoselective N to C [1,2] lithiation-induced shift, furnishing 2,2-disubstituted aziridine **131** (Scheme 50).[56]

Such an N → C migration was also observed and nicely exploited by Hodgson and co-workers in the lithiation/trapping sequence of *N*-Boc and *N*-phosphonate aziridines.[57] As in Beak's work, it was found that the lithiation−trapping of aziridine **132** could be accomplished only with the *in situ* quenching technique using TMSCl as the electrophile (Scheme 51). The reaction was highly regio- and stereoselective furnishing *trans*-configured silylaziridines **133**. Attempts to use D_2O as an external electrophile failed because of the fast N to C [1,2] lithiation-induced shift, and *trans* aziridine carboxylate **134** was the only product isolated (Scheme 51). Furthermore, the authors demonstrated, by a crossover experiment on a 1:1 mixture of aziridines **135a,b** that the N → C migration is an intramolecular process leading exclusively to aziridine carboxylates **136** and **137** (Scheme 51).

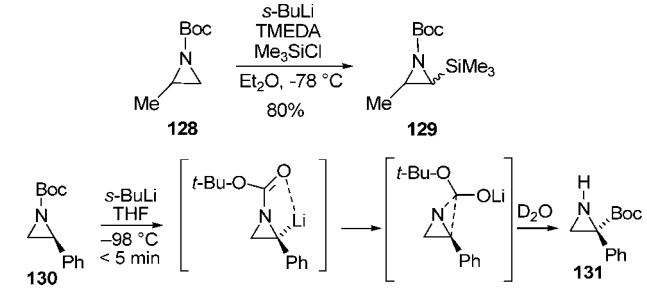
Scheme 48



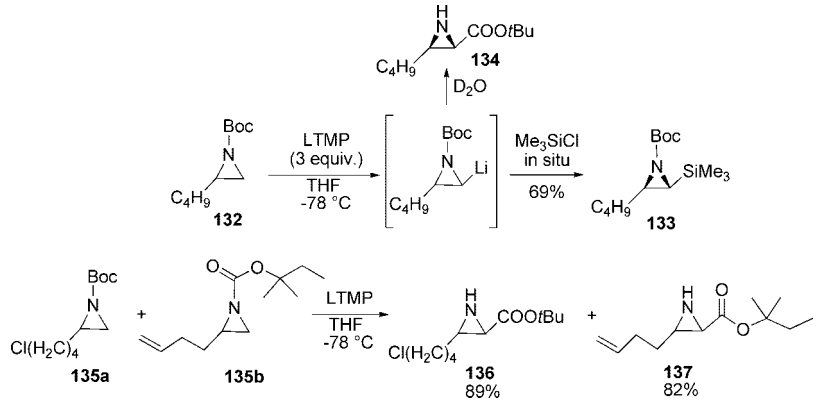
Scheme 49



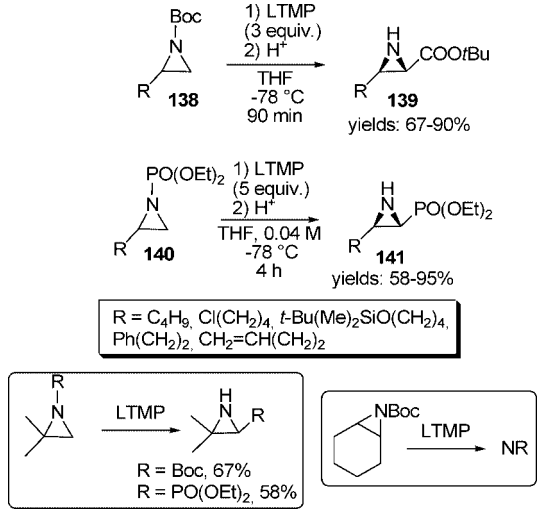
Scheme 50



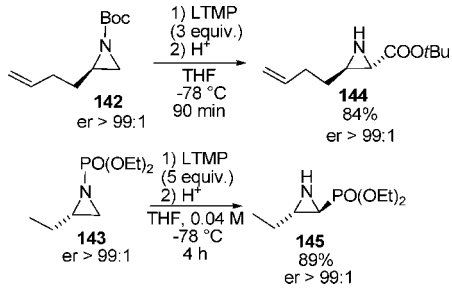
Scheme 51



Scheme 52



Scheme 53



The Boc N → C migration was exploited for the preparation of several *trans*-configured aziridine carboxylates **139** from *N*-Boc aziridines **138**. This methodology, although under slightly different experimental conditions, was extended to *N*-phosphonate aziridine **140**, which furnished the useful aziridine phosphonate **141** (Scheme 51). The scope of the methodology was verified also on 2,2-disubstituted aziridines, which gave the expected aziridine carboxylate or phosphonate, while 2,3-disubstituted aziridine did not undergo any transformation upon reaction with LTMP (Scheme 52).

The stereoselectivity of the N to C [1,2] lithiation-induced shift was also investigated on chiral aziridines **142** and **143**, which gave, respectively, highly enantioenriched aziridine carboxylate **144** and phosphonate **145** (Scheme 53).

However, the N → C migration of *N*-Boc aziridinyllithiums can be avoided under peculiar reaction conditions. Indeed, as reported in the synthetic application section of this review, Aggarwal and co-workers succeeded in the lithiation/borylation sequence of some *N*-Boc aziridines and developed a new stereoselective synthesis of 1,2-amino alcohols (see Scheme 95).

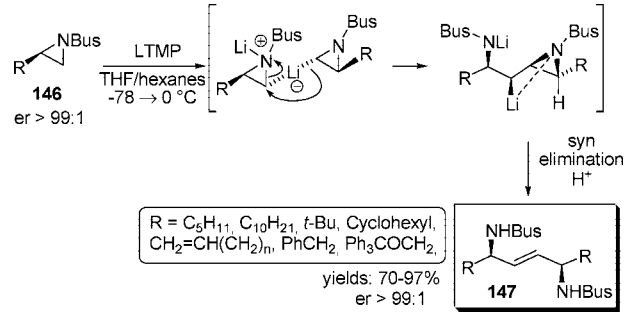
7. Carbenoid Reactivity of N-Sulfonyl Aziridinyllithiums: Eliminative Dimerization and Intramolecular Cyclopropanation

As previously mentioned, the carbenoid reactivity of lithiated aziridines has been recognized only recently thanks to Müller and O'Brien's study on the C−H insertion and reductive alkylation.[36,38] The carbenoid-type reactivity has been demonstrated to occur only with lithiated aziridines bearing an EWG as the nitrogen substituent and under certain reaction conditions.

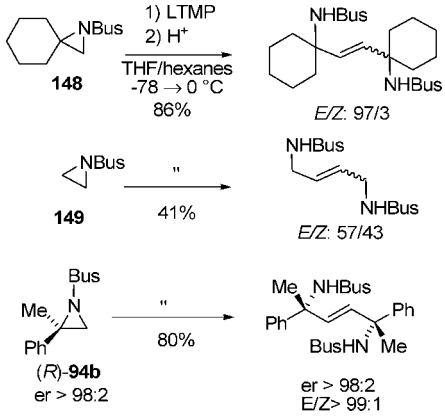
The eliminative dimerization of the kind described for lithiated oxiranes[58] has been reported for the first time by Hodgson and co-workers for aziridinyllithiums derived from terminal *N*-Bus-protected aziridines **146**.[59] The reaction proceeded smoothly with complete *E* selectivity furnishing protected 2-ene-1,4-diamines **147** through a regioselective *trans*-β-lithiation followed by dimerization of two aziridinyllithiums, according to the mechanistic pathway reported in Scheme 54. It is worth nothing that the same reaction on the analogous lithiated oxiranes was found to be less stereoselective giving a mixture of *E* and *Z* 2-ene-1,4-diols. The dimerization of chiral monosubstituted aziridines produced chiral alkenes without loss of their optical purity.

The dimerization showed a lower stereoselectivity, giving a mixture of alkenes, with symmetrical 2,2-disubstituted aziridines **148** and with ethylene aziridines **149**, while the use of chiral unsymmetrical 2,2-disubstituted aziridine (*R*)-**94b**[45] gave the corresponding 2-ene-1,4-diamine again with high *E* selectivity (Scheme 55).

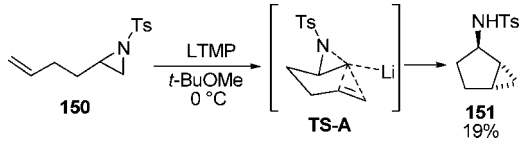
Scheme 54



Scheme 55



Scheme 56



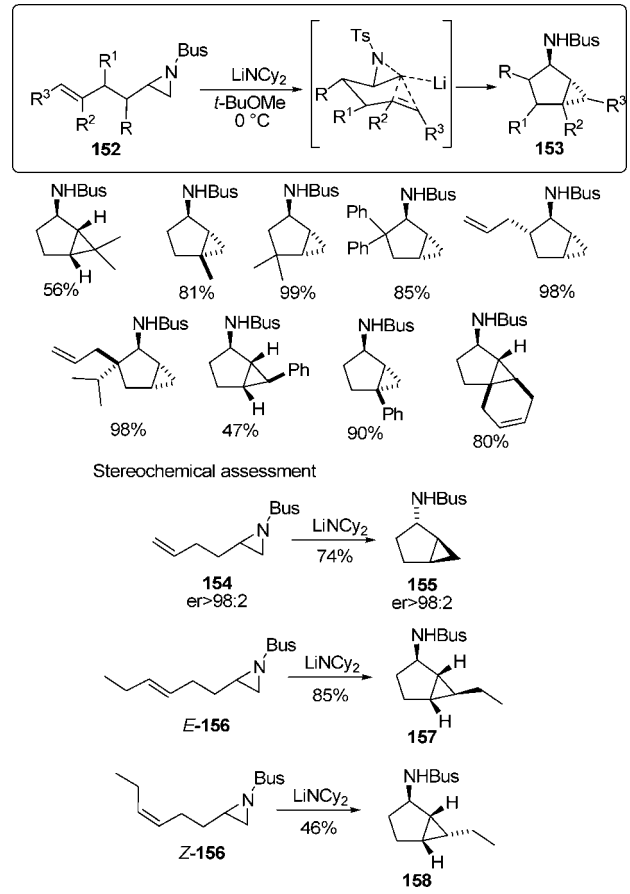
Hodgson and co-workers demonstrated that lithiated aziridines underwent also an alternative carbenoidic reaction, namely, intramolecular cyclopropanation, to access 2-aminobicyclo[3.1.0]-hexanes.[60] This kind of lithiation-induced cyclopropanation, which occurs also with lithiated oxiranes,[61] was initially investigated with *N*-tosyl aziridine **150** by using LTMP as the base, which furnished poor yield of bicyclic product **151**. The stereochemistry of **151** could be the result of the stereoselective intramolecular addition of the lithium carbenoid to the double bond through the transition state TS-A (Scheme 56).

Reaction optimization identified the Bus group as the best N-substituent and the lithium dicyclohexylamide ($LiNCy_2$) as the best lithiating agent. Furthermore, the operative conditions were found to be crucial, the slow addition of the aziridine to the base being necessary to avoid side reactions, such as the previously described dimerization, and secure higher yields.

The scope of the reaction was examined on various functionalized aziridines **152**, which furnished bicyclo[3.1.0]-hexanes **153** in good yields (Scheme 57). The high stereospecificity of the process was demonstrated by using enantioenriched aziridine **154**, which gave the product **155** without erosion of enantiomeric purity, and evaluating the double bond geometry effect with aziridines *E*-**156** and *Z*-**156**, which furnished bicyclic derivatives **157** and **158**, respectively, as single diastereoisomers (Scheme 57).

In conclusion, the analysis of EWG-bearing aziridines showed that it is relatively easy to generate aziridinyllithiums by deprotonation if the "activating" group is on either the aziridine carbon or the nitrogen atom. Differences in chemical and configurational stability could emerge even if most of the *N*-EWG-substituted lithiated aziridines seem to be configurationally stable. Another important point is the carbenoid reactivity of *N*-EWG-substituted aziridinyllithiums neglected in the past that now has been widely demonstrated and extensively applied in synthesis. The next section will describe the reactivity of aziridinyllithiums generated by deprotonation of *N*-EDG-substituted aziridines.

Scheme 57



8. Deprotonation of Aziridines with an EDG-Bearing Nitrogen

8.1. The Case of *N*-Alkyl Arylaziridines

The importance of the electronic effect of the aziridine nitrogen substituent is noticeable from the comparison between the *N*-Bus-2-phenylaziridine **93**, which could be regioselectively deprotonated at the α-benzylic position,[45] and the *N*-methyl-2-phenylaziridine **159**, which, in striking contrast, underwent a regioselective ortho-lithiation at the aromatic ring (Figure 3).[56]

Indeed, Florio, Luisi, and co-workers reported that the reaction of *N*-alkyl-2-phenylaziridines **160** with *s*-BuLi, unexpectedly, generated ortho-lithiated aziridines **160-Li** thus disclosing the ability of the aziridine ring to act as a directing metalation group (Scheme 58).[56] The synthetic versatility of **160-Li** was proven by its trapping with a range of electrophiles that furnished functionalized aziridines **161**, while the use of carbonyl compounds resulted in the formation of isobenzofurans **162**. The use of alkylborates as electrophiles, followed by reaction with KHF_2, gave cyclic aziridinedifluoroborates **163**, which behave as Suzuki−Miyaura reagents in palladium-catalyzed cross-coupling reactions.[62] The aziridine ring is able to direct the lithiation also in *ortho*-tolyl

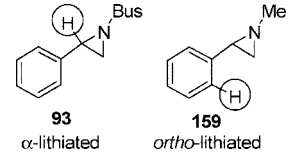
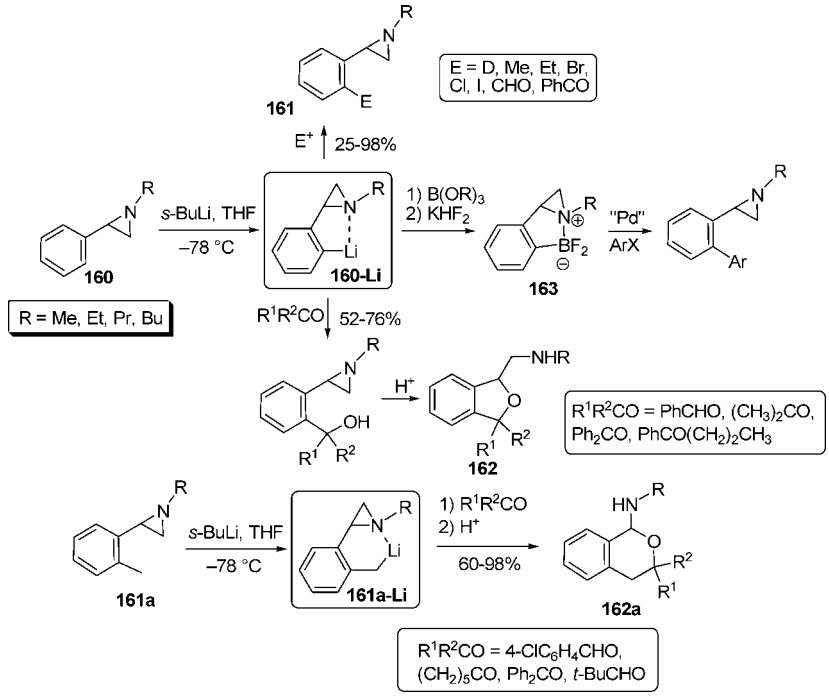
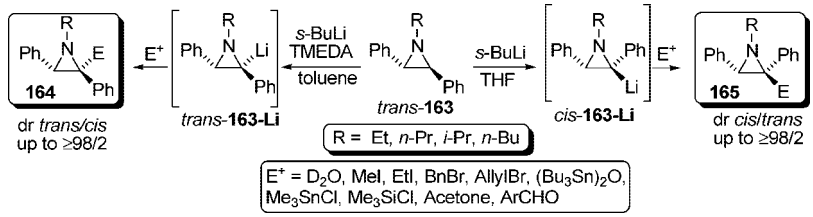


Figure 3.

Scheme 58



Scheme 59



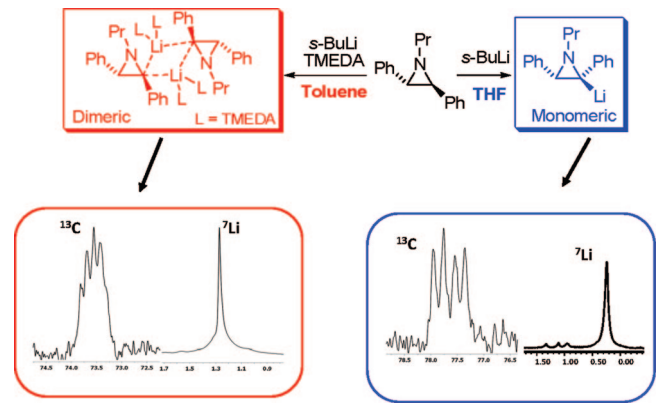
aziridine **161a**; in this case the exclusive lateral lithiation was observed as a consequence of preferential benzylic proton removal and complexation phenomenon. Even in the case of lithiated intermediate **161a-Li**, the synthetic usefulness was demonstrated with the preparation of benzopyrans **162a** (Scheme 58).[63]

The same authors observed a different regioselectivity in the lithiation/trapping sequence of *cis* and *trans* configured *N*-alkyl-2,3-diphenyl aziridines. When *trans* aziridine **163** was treated with *s*-BuLi in THF, a regioselective α-benzylic deprotonation took place with the formation of lithiated intermediate *cis*-**163-Li**, while when the same sequence was performed in toluene (or hexane), in the presence of TMEDA, lithiated intermediate *trans*-**163-Li** formed (Scheme 59).[64] Trapping with electrophiles of *trans*- and *cis*-**163-Li** allowed for the stereoselective synthesis of trisubstituted aziridines **164** and **165**.

The configuration of the lithiated intermediates *cis*- and *trans*-**163-Li** (R = *n*-Pr) was established by a multinuclear magnetic resonance investigation, the first to be reported for lithiated aziridines.[65] On the basis of the $^{13}C-^{7}Li$ coupling constants and multiplicity jointly to NOESY and heteronuclear correlation experiments, a *cis*-configured monomeric aziridinyllithium in THF and a *trans*-configured homochiral dimeric aziridinyllithium, tightly bonded to the TMEDA in toluene (or hexane) have been proposed (Scheme 60).

Further investigation demonstrated that a polar solvent such as the THF or the presence of a crown ether able to chelate the lithium ion could promote the *trans* to *cis*

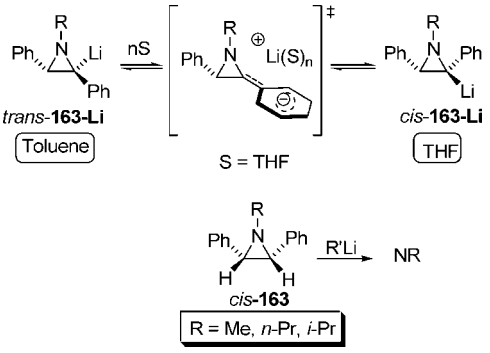
Scheme 60



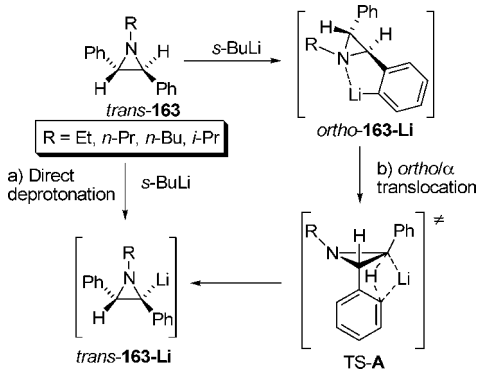
isomerization in toluene. The proposed model that accounts for the *trans* to *cis* isomerization (in THF) could be the one depicted in Scheme 61. THF should solvate the lithium ion of *trans*-**163-Li** as soon as it is formed thus promoting a quick isomerization to the thermodynamically more stable *cis*-**163-Li**, which should exist as a contact ion pair as suggested by the $^{13}C-^{7}Li$ coupling constant value.

It was also reported that aziridine *cis*-**163** did not undergo any deprotonation under varied reaction conditions (Scheme 61). Thus, while *N*-alkyl-2-phenylaziridines could be smoothly ortho-lithiated, and *trans*-*N*-alkyl-2,3-diphenylaziridines could be regioselectively α-lithiated, with a stereochemistry controlled by the reaction medium (i.e., inversion in THF and

Scheme 61



Scheme 62



retention in toluene), unexpectedly, *cis* configured 1-alkyl-2,3-diphenylaziridines could not be lithiated at all.

This intriguing reactivity showed by *N*-alkyl arylaziridines, depending on the nature of the substituents at the aziridine carbon atoms as well as on their stereochemistry, has been rationalized on the basis of experimental evidence and taking into account the role of the aziridine nitrogen and its dynamics.[66]

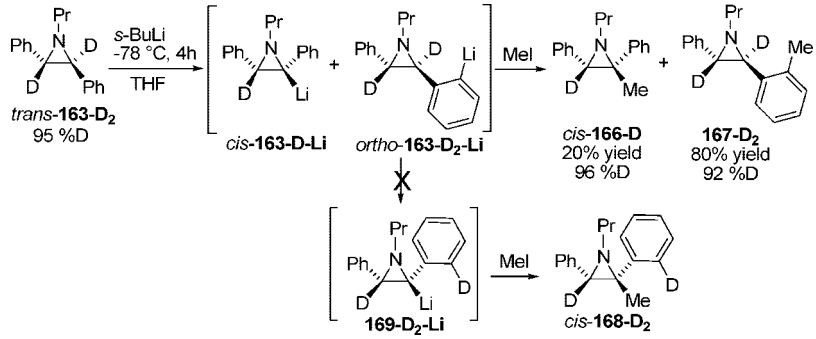
With reference to the α- vs ortho competition observed in the lithiation of monophenyl- and *trans*-diphenylaziridines (such as **160** and **163**), in principle, two alternatives were envisaged to explain the α-lithiation of aziridines *trans*-**163** (Scheme 62): (a) direct α-deprotonation giving *trans*-**163-Li**, which could undergo the *trans* to *cis* isomerization depending on the reaction conditions; (b) ortho-lithiation, giving *ortho*-**163-Li**, followed by an ortho to α translocation giving *trans*-**163-Li** (the result of a kinetically favored ortho deprotonation followed by the removal of thermodynamically more acidic benzylic proton). The four centers transition state **TS-A** (assumable exclusively for *ortho*-**163-Li**) at first glance would explain the different regioselectivity observed in the lithiation of the *N*-alkyl-2-phenylaziridines **160**, where, due to the presence of only one benzylic hydrogen, the exclusive ortho-lithiation takes place.

The ortho/α translocation has been excluded by an elegant experiment on doubly deuterium-labeled aziridine *trans*-**163-D_2**, which, when subjected to lithiation with *s*-BuLi in THF, furnished a mixture of α- and ortho-lithiated aziridines *cis*-**163-D-Li** and *ortho*-**163-D_2-Li** in a 20/80 ratio. Such a value was based on the ratio of the methylated product *cis*-**166-D** and **167-D_2** obtained after trapping with iodomethane (Scheme 63). This outcome clearly demonstrates that no translocation occurs because the expected α-methylated aziridine *cis*-**168-D_2**, which would result from the trapping of **169-D_2-Li**, was not found.

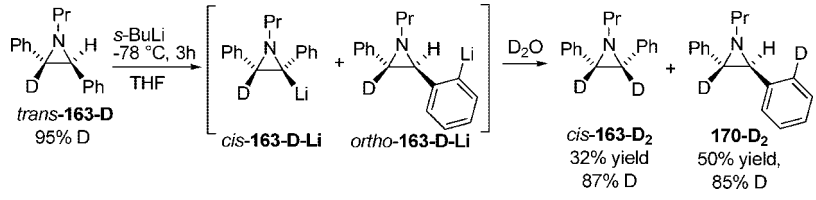
A similar result was also observed in the lithiation of the monodeuterated aziridine *trans*-**163-D**, which gave a mixture of ortho and α-lithiated aziridines *ortho*-**163-D-Li** and *cis*-**163-D-Li** in a 45:55 ratio as established by NMR analysis. Trapping with deuterium furnished aziridines *cis*-**163-D_2** and **170-D_2**, which showed, to some extent, erosion of deuterium content (Scheme 64).

Moreover, the presence of *ortho*-**163-D_2-Li** and *ortho*-**163-D-Li** has been explained with the complex induced proximity effect (CIPE)[67] mechanism and taking into account the nitrogen dynamics. Indeed, the NMR analysis of aziridines *trans*-**163-D** and *trans*-**163-D_2** revealed the presence of two slowly equilibrating nitrogen invertomers in a 50:50 ratio. Therefore, with reference to aziridine *trans*-**163-D**, assuming a precomplexation to the base as a prerequisite for the deprotonation and an operative kinetic isotope effect, the deprotonation should take place at the more easily removable protons for proximity reasons, namely, the ortho position for complex **B** and the α position for complex **A** (Scheme 65). Accordingly, α-lithiation of **A**, occurring after the

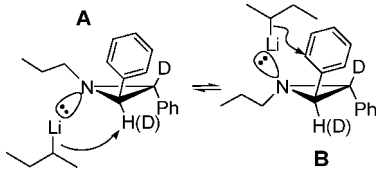
Scheme 63



Scheme 64



Scheme 65

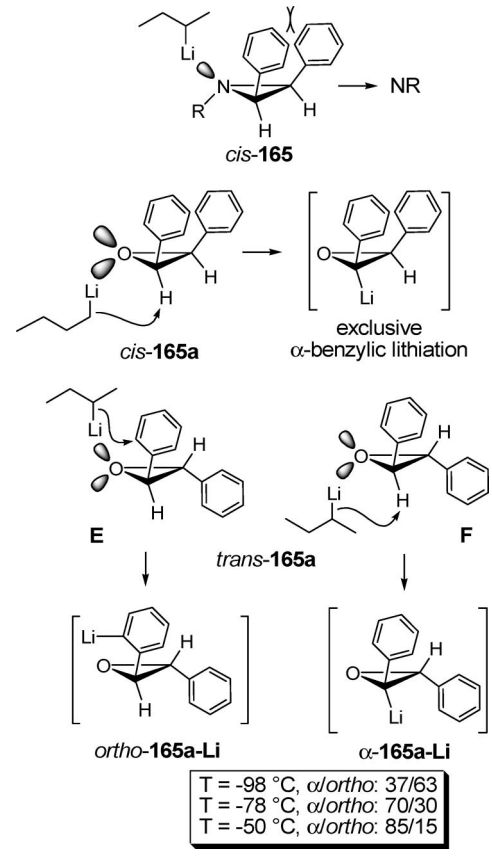


complex formation between *s*-BuLi and aziridine, followed by *trans* to *cis* isomerization (in THF), would generate *cis*-**163-D-Li**. On the other hand, invertomer **B** would undergo either ortho-deprotonation or α-dedeuteration, the ortho-deprotonation being preferred likely because of a kinetic isotope effect.[68] This latter possibility is particularly evident in the lithiation of *trans*-**163-D$_2$** where almost the 80% of ortho-lithiated intermediate has been generated.

Having excluded the ortho/α translocation process, the different regioselectivity between *N*-alkyl-monophenylaziridines and *trans*-*N*-alkyl-2,3-diphenylaziridines was addressed assuming that the ortho-lithiation was a kinetically favored process and that the α-lithiation was the thermodynamic one, because of the higher acidity of the benzylic protons. A model has been proposed that takes into consideration the nitrogen dynamics, complexation effect, and relative rates of the deprotonation reactions (k_3, k_4) with respect to the rates of nitrogen inversion (k_1, k_2) (Scheme 66).

The model, which could be profitably applied to *N*-alkyl aziridines with a nonequimolar distribution of the nitrogen invertomers, assumes that for proximity effect, complex **D** should give ortho-lithiation and complex **C** α-lithiation.[69] Thus, in lithiations carried out at low temperature, where the rate of nitrogen inversion is expected to be low and likely k_1 and k_2 are much lower than k_4 and k_3, if the major invertomer is the one that puts the lone pair on the same side of the phenyl ring, complex **D** would form and then undergo ortho-lithiation. By contrast, at higher temperatures a complete inversion of regioselectivity is expected, according to the Curtin−Hammett principle, by assuming k_1 and $k_2 \gg k_3 > k_4$. In the case of *N*-alkyl-2-phenylaziridines (such as **160**), existing as the sole invertomer (dr >99:1) that puts the lone pair on the same side of the phenyl ring, exclusively ortho-lithiation is observed. This model is able to address also the lack of reactivity found with *cis* configured diphenyl aziridines *cis*-**163**. In this case, it has been demonstrated that the only detectable invertomer, at −78 °C, is the one that puts the lone pair on the same side of the phenyl rings and, therefore, the interaction with the lithiating agent would give a complex of the kind of **D** and then ortho-lithiation. It is likely that the *cis* relationship between the phenyl rings could cause steric hindrance preventing the correct alignment of the C−H to be removed reducing the reactivity (Scheme 67). Conversely, it has been reported that the corresponding stilbene oxide *cis*-**165a** underwent regioselective α-lithiation likely as a consequence of the presence of the additional

Scheme 67

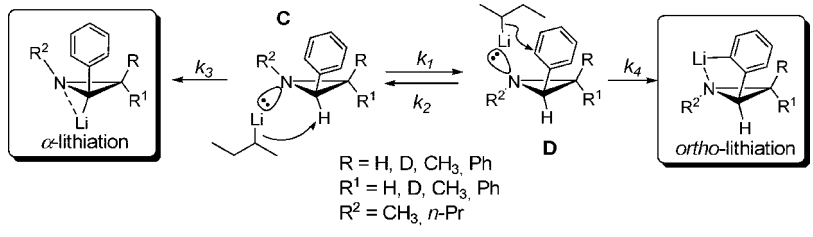


lone pair on the oxygen atom, allowing the complexation with the lithiating agent and favoring the deprotonation at the more acidic benzylic position. Confirmation of this hypothesis comes from the reactivity observed for the isomeric stilbene oxide *trans*-**165a**, which underwent competitive α- and ortho-lithiation giving the corresponding lithiated intermediates α-**165a-Li** and *ortho*-**165a-Li** in a ratio that depended on the reaction temperature (Scheme 67). It is likely that complexes **E** and **F** could give rise, respectively, to *ortho*-**165a-Li** and α-**165a-Li**. Accordingly, at higher temperature lithiation occurred mainly at the thermodynamically favored benzylic position, while at lower temperature the kinetically favored ortho-position was lithiated.[70]

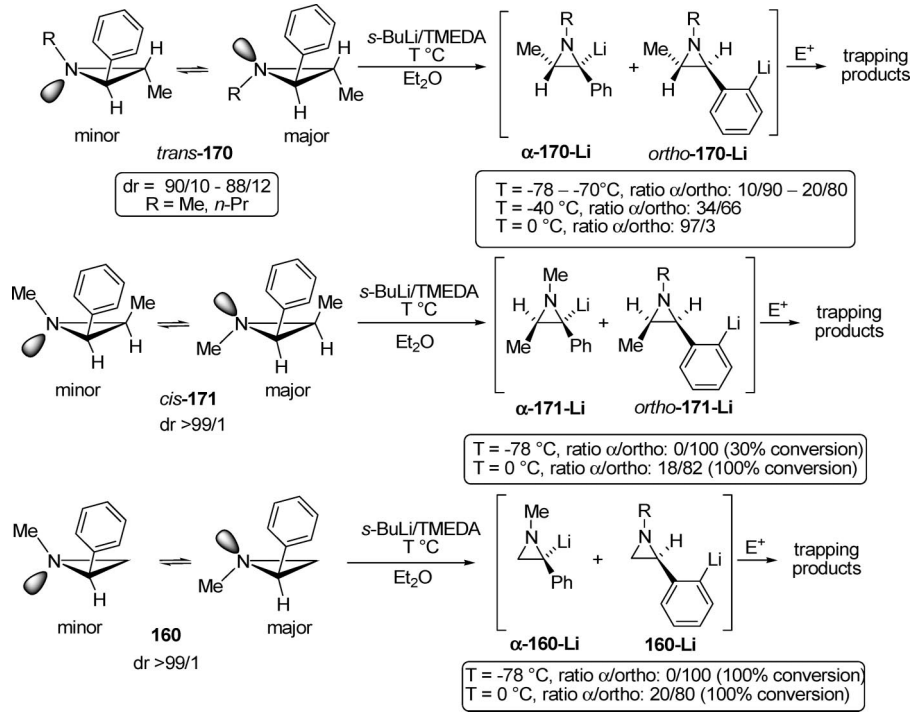
The model has been further supported experimentally by performing the lithiation/trapping sequence at different temperatures on aziridines *trans*-**170**, *cis*-**170**, and **160** (Scheme 68).

By NMR and NOESY experiments, it was demonstrated that aziridines *trans*-**170** had two slowly equilibrating invertomers (dr 90/10−88/12) and the major ones set the nitrogen lone pair *cis* to the phenyl ring. Thus, at low temperature (−78 °C) lithiation of *trans*-**170** occurred

Scheme 66



Scheme 68



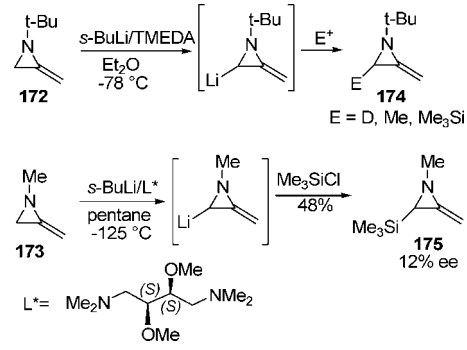
preferentially at the ortho position giving *ortho*-**170-Li** while α-**170-Li** was present as minor product (ratio α/ortho 10/90−20/80). By contrast, when the lithiation was performed at higher temperature (0 °C), lithiation took place preferentially at the thermodynamically favored α-benzylic position (here again likely k_1 and $k_2 \gg k_4$ and k_3), giving mainly α-**170-Li** (ratio α/ortho 97/3). As predictable, at an intermediate temperature between −78 and 0 °C (i.e., −40 °C), a mixture of *ortho*-**170-Li** and α-**170-Li** was obtained (ratio α/ortho 34/66). Trapping of the lithiated intermediates at −78 or at 0 °C allowed for a regioselective synthesis of ortho or α-functionalized aziridines (Scheme 68). With aziridines *cis*-**171** and **160**, where a single nitrogen invertomer (dr > 99/1) that set the nitrogen lone pair and the phenyl ring in a *cis* arrangement could be detected, lithiation occurred exclusively at the ortho position (α/ortho ratio: 0/100) at low temperature (−78 °C) accordingly again with the model in Scheme 66. In the case of aziridine *cis*-**171**, only a low conversion was observed, likely as a consequence of a reduced reactivity still ascribable to steric hindrance. A competitive α-benzylic lithiation was observed when the lithiation of *cis*-**171** and **160** was performed at higher temperature (α/ortho ratio ∼20/80).

The reported results on the lithiation of *N*-alkyl arylaziridines disclosed that several factors could affect the reactivity (aziridine substitution, stereochemistry, solvent, temperature) and that the aziridine nitrogen and its dynamics play an important role in determining the regioselectivity.

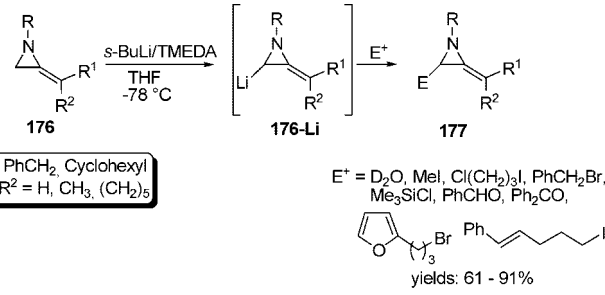
8.2. Deprotonation of *N*-Alkyl Methyleneaziridines

The deprotonation of *N*-alkyl aziridines devoid of substituents at the anionic carbon are rather rare. Pioneering work on unsubstituted aziridinyl anions have been reported by Quast and Vélez who demonstrated that 1-*tert*-butyl-2-methyleneaziridine **172** could be deprotonated with *s*-BuLi/TMEDA at −78 °C and reacted with a limited range of electrophiles (MeOD, MeI, or Me_3SiCl) to furnish functionalized aziridines **174**.[71] An attempt to induce asymmetry in the lithiation/silylation of 1-methyl-2-methyleneaziridine **173**, by using (*S*,*S*)-1,4-bis(dimethylamino)-2,3-dimetoxybutane as an external chiral ligand, gave silylaziridine **175** only with poor enantioselectivity (Scheme 69).

Scheme 69



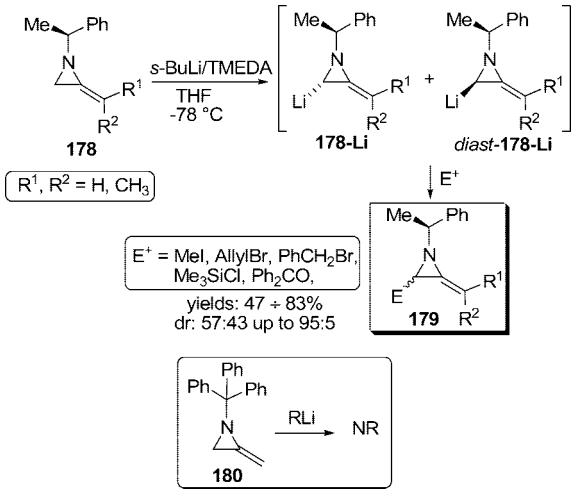
Scheme 70



Some years later, Shipman and co-workers reported an extension of the reactivity of *N*-alkylmethylene aziridines of the kind of **176** providing a highly practical approach to several C-3 substituted methyleneaziridines **177** (Scheme 70).[72]

With the aim to develop a stereocontrolled lithiation/alkylation sequence, the same authors investigated the

Scheme 71



reactivity of chiral aziridines **178** where the chirality was introduced on the alkyl nitrogen substituent (Scheme 71). A variable degree of stereocontrol was observed in the lithiation/electrophile trapping sequence depending on the nature of the alkylidene substituents R^1 and R^2. Nevertheless, it was suggested that the selectivity most likely arises from diastereocontrol in the deprotonation reaction, which should give lithiated intermediates **178-Li** and *diast*-**178-Li** supposed to be configurationally stable. The possible role of the nitrogen inversion in the selectivity of the lithiation process was also considered but not yet demonstrated. Not unexpectedly, sterically hindered *N*-trityl methylene aziridine **180** did not undergo any lithiation under varied conditions.

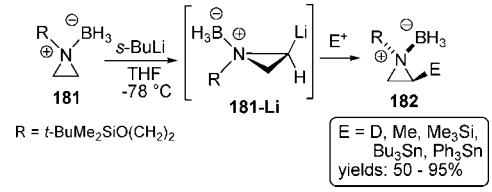
The stereoselective lithiation/electrophilic trapping sequence of methyleneaziridines deserves further investigation in order to highlight the role of the aziridine nitrogen and the neighboring exocyclic double bond. This is desirable because functionalized methyleneaziridines have been proven to be very useful building blocks in organic synthesis for the preparation of a wide range of molecular architectures.[73]

8.3. Lewis Acid-Promoted Deprotonation of *N*-Alkyl Aziridines

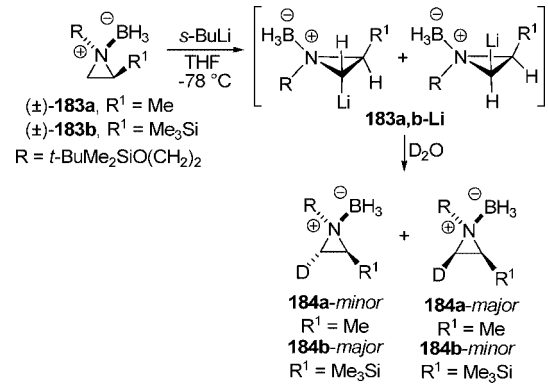
While the direct metalation of *N*-alkyl ethylene aziridines is quite difficult and has not been reported yet, the deprotonation of the corresponding borane complexes is feasible and has been reported for the first time by Vedejs and Kendall.[74] Aziridine−borane complex **181**, promptly available by reacting the parent aziridines with borane, could be deprotonated with *s*-BuLi giving the corresponding aziridinyllithium **181-Li**, which was trapped with electrophiles furnishing products **182** as exclusive isomers (dr > 95:5). Interestingly, a stereochemical analysis of the trapping products revealed a *cis* relationship between the electrophile (E) and the BH_3 group, suggesting that a lithiation *syn* to the boron atom had occurred (Scheme 72).

Further experiments were consistent with a dominant aziridine lithiation *syn* to the BH_3 group. The *syn*-directing effect of the borane has been regarded as a noncovalent version of the complex-induced proximity effect (CIPE). The authors suggested that electrostatic interactions, resulting from the attraction between partially negative hydridoborate bonds and the partially positive lithium atom, were responsible for the *syn*-direction of the lithiation. However, it was also demonstrated that this *syn*-directed lithiation could be

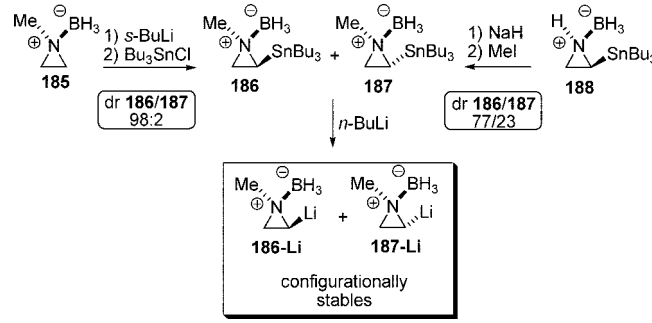
Scheme 72



Scheme 73



Scheme 74

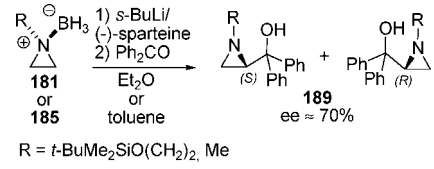


overcome by steric effects. In fact, in the lithiation of substituted aziridine **183a** a *syn*-direction was still observed after trapping of **183a-Li** with a deuterium source furnishing aziridines **184a**-*major* as the main product. Conversely, when the same lithiation/deuteration sequence was executed on aziridine **183b**, the main product was **184b**-*major* resulting from an *anti*-lithiation likely ascribable to the bulky Me_3Si group (Scheme 73). Nevertheless, these results on substituted aziridine−borane complexes disclose that a double functionalization is possible and that the regioselectivity can be tuned by changing the steric demand of the aziridine substituent.

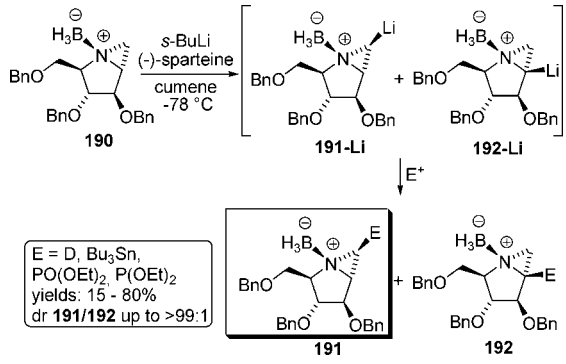
The configurational stability of aziridinyllithiums generated from aziridine−borane complexes has been demonstrated by tin−lithium exchange experiments on stannylated aziridines **186** and **187** (Scheme 74). The lithiation/trapping sequence of aziridine **185** produced aziridines **186** and **187** in a 98:2 ratio, according to a regioselective *syn*-directed lithiation, while the methylation of aziridine **188** furnished **186** and **187** in a 77:23 ratio. When this mixture was subjected to the tin−lithium exchange reaction, a mixture of aziridinyllithiums **186-Li** and **187-Li** formed, which proved to be configurationally stable by electrophilic trapping.

The configurational stability of this kind of aziridinyllithiums was exploited for an enantioselective synthesis of aziridines. Vedejs and co-workers reported the lithiation/trapping sequence of aziridine **181** or **185** performed in the presence of (−)-sparteine as chiral ligand. BH_3-free func-

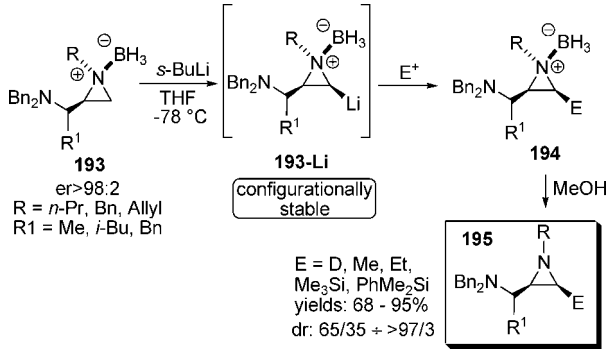
Scheme 75



Scheme 76



Scheme 77



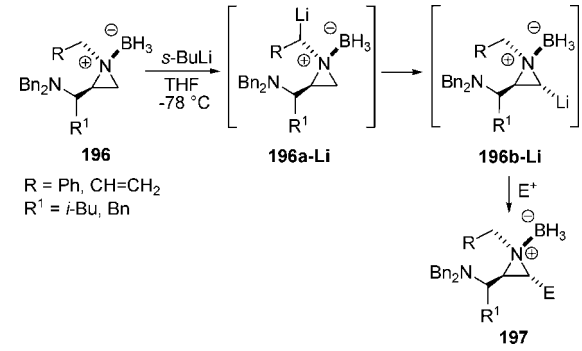
tionalized aziridine **189** was obtained with reasonable enantioselectivity (Scheme 75).[75]

Another example of a (−)-sparteine-mediated stereoselective functionalization of sugar-derived aziridine−borane complex has been reported by Bisseret and co-workers (Scheme 76).[76] Aziridine−borane complex **190** underwent a *syn*-directed lithiation to furnish aziridinyllithiums **191-Li** and **192-Li** in a ratio that depended on the reaction conditions and on the electrophile. Bulky electrophiles (≠ D), although with modest yields, gave a high level of stereoselectivity furnishing almost exclusively products **191** resulting from a retentive trapping of **191-Li**.

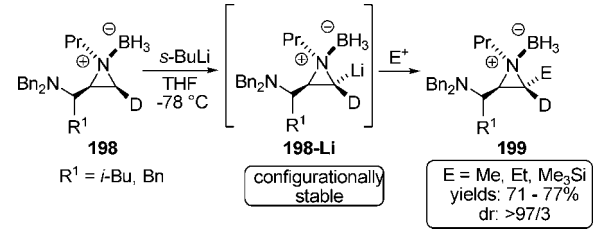
A different approach for the enantioselective synthesis of aziridines has been followed by Concellón and co-workers who reported a stereoselective functionalization of a chiral aziridine−borane complex by the lithiation/trapping sequence (Scheme 77).[77] According to the results reported by Vedejs and co-workers, again a *syn*-directed lithiation was observed with aziridines **193**, and the corresponding aziridinyllithiums **193-Li** were found to be configurationally stables. Trapping of **193-Li** with electrophiles allowed for the preparation of *cis* configured aziridine−borane complexes **194**, which upon BH_3 removal furnished chiral aziridines **195**.

A low level of stereoselectivity was observed in the lithiation/trapping sequence of *N*-benzyl- and *N*-allyl-substituted aziridine−borane complexes; such aziridinyllithiums being configurationally stables, the low stereoselectivity was ascribed to a competing deprotonation of the N-substituent (Scheme 78). In the case of aziridine−borane complexes **196**, it is supposed, but not demonstrated, that **196a-Li** could form first and then undergo to an intramolecular H−Li exchange to furnish **196b-Li**, which upon electrophile trapping produces **197**, thus lowering the level of the stereoselectivity.

Scheme 78



Scheme 79



A nice double functionalization experiment was also reported on deuterated aziridines **198** (Scheme 79). It was demonstrated that a kinetic-isotope effect was operative and that the lithiation took place anti to the BH_3 group giving **198-Li**, which was stereoselectively trapped with electrophiles furnishing aziridines **199**. These experiments proved that the aziridinyllithiums **198-Li** were configurationally stable, under the time scale of the experiment, and that the *syn*-direcetd lithiation could be prevented even by an isotopic effect.

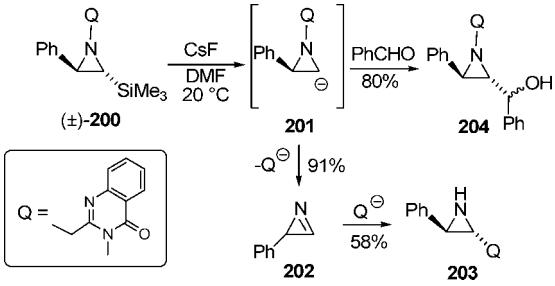
9. Alternative Routes for the Generation of Aziridinyl Anions

Altough the deprotonation reaction has been demonstrated to be a straightforward methodology for the generation of aziridinyl anions, different routes have also been reported. In particular, three main methodologies have been investigated and will be described in the next paragraphs.

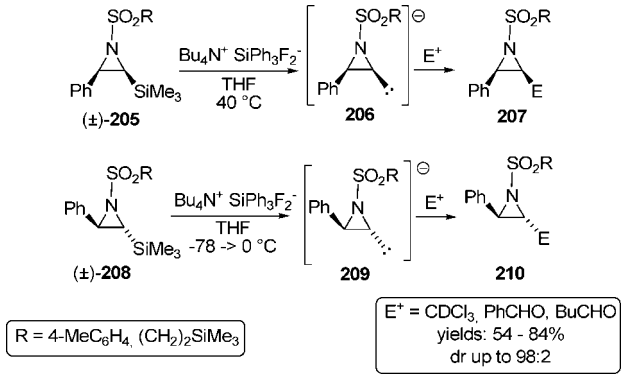
9.1. Aziridinyl Anions by Desilylation

According to the chemistry of silyloxiranes,[78] silylaziridines also undergo fluorodesilylation reactions providing the corresponding aziridinyl anions. Atkinson and co-workers reported the first example of aziridinyl anion generated by fluorodesilylation.[79] The *trans* configured aziridine silane **200**, when reacted with cesium fluoride, generated the corresponding aziridinyl anion **201**, which in the absence of an external electrophile underwent an intramolecular elimination of the quinazolone N-substituent to give the azirine **202**, which upon addition to the C=N bond generated aziridine **203**. The putative aziridinyl anion **201**, in the presence of benzaldehyde, furnished only *trans*-aziridines **204** (Scheme 80).

Scheme 80



Scheme 81

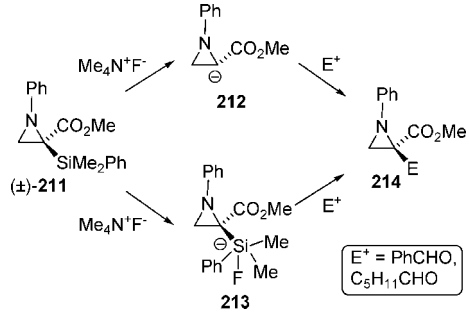


Aggarwal and co-workers reported a stereoselective functionalization of silylaziridines by a fluorodesilylation/electrophile trapping sequence.[80,51] Several *cis* aziridines **205** were desilylated using tetrabutylammonium triphenyldifluorosilicate (TBAT) and the resulting aziridinyl anions **206** were efficiently trapped with aldehydes or a deuterium source providing aziridines **207** (Scheme 81). The silyl group was substituted with retention of configuration, and high selectivity was observed in the newly created stereogenic center in the reactions with aldehydes. Equally highly stereoselective was the fluorodesilylation/electrophile trapping sequence of *trans* aziridine **208**, which furnished *trans* aziridine **210** likely derived from **209** (Scheme 81).

The stereospecific substitution of the silyl group in **205** and **208** was supposed to pass through configurationally stable aziridinyl anions even if the real nature and aggregation state of this kind of reactive intermediates has not yet been proven. Bassindale, Taylor, and co-workers reported the fluorodesilylation reaction of *N*-phenyl silylaziridines by using dry tetramethylammonium fluoride.[81] Trapping with aldehydes was reported to occur only with silylaziridine **211**, which furnished **214**. Two different intermediates were proposed to accomplish this transformation, the aziridinyl anion **212** or the pentacoordinate silicon intermediate **213** (Scheme 82). For both silylaziridines and silyloxiranes the involvement of a free carbanion or a pentacoordinate silicon is still debated, and both intermediates have been also proposed in the fluorodesilylation of allyltrialkylsilanes[82] or silylcyclopropanes.[83]

Nevertheless, the fluorodesilylation/electrophile trapping protocol has been proven to be successful only with a limited number of aldehydes.

Scheme 82



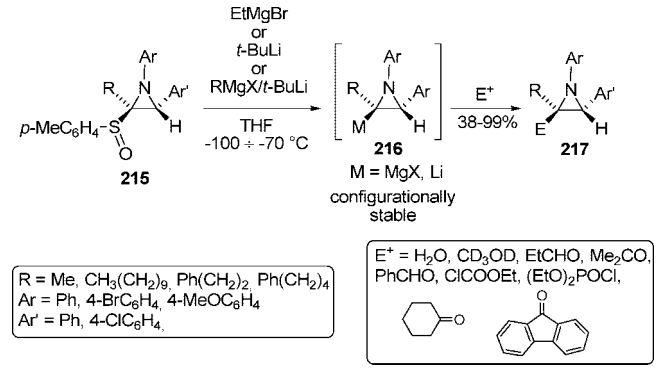
9.2. Aziridinyl Anions Generated by Desulfinylation

In accordance with the reported alkylmetal-mediated displacement of sulfinyl group from epoxysulfoxides,[84] which generated the corresponding oxiranyl anions, sulfinylaziridines undergo desulfinylation reactions. Satoh and co-workers reported that aziridinyl anions could be generated by reacting sulfinylaziridines with organolithiums or Grignard reagents.[85] The use of EtMgBr promoted a magnesium-sulfoxide exchange giving an aziridinylmagnesium while the use of *t*-BuLi gives the corresponding aziridinyllithium. This reaction has been reported to occur with several *N*-aryl substituted sulfinylaziridines of the kind of **215** to furnish the aziridinyl anions **216**, which have been proven to be configurationally stable, under the reaction conditions and stereoselectively trapped with electrophiles furnishing aziridines **217** (Scheme 83). The reaction occurred with aldehydes, even if a poor stereoselectivity was observed at the newly created stereogenic center, and with ketones, while the use of alkyl halides was unsuccessful under the conditions reported in Scheme 83.

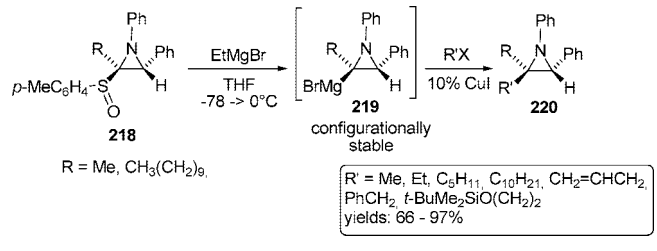
The alkylation reaction has been found to occur only with aziridinylmagnesium in the presence of CuI.[86] Thus, aziridines **218** underwent magnesium/sulfoxide exchange reactions generating a configurationally stable aziridinyl Grignard **219** that was coupled with alkyl- and benzylhalides to furnish aziridine **220** in good yields and with high stereoselectivity (Scheme 84).

The configurational stability of aziridinylmagnesium, generated by desulfinylation, has been exploited for the enantioselective functionalization of chiral sulfinylaziridines.

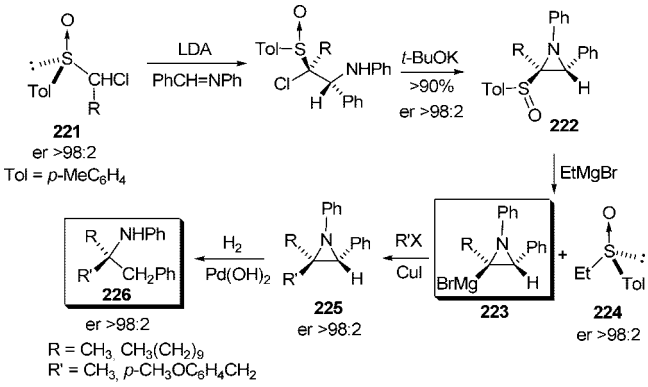
Scheme 83



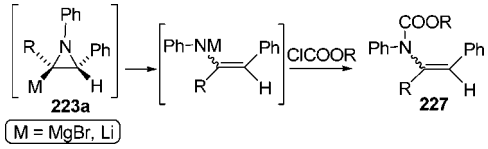
Scheme 84



Scheme 85



Scheme 86



The sequence desulfinylation/electrophile trapping/reduction allowed for an enantioselective synthesis of chiral amines with a quaternary chiral center. An aza-Darzens reaction carried out on chiral chloroalkyl sulfoxides **221** afforded chiral sulfinylaziridines **222** with high yields and optical purity (Scheme 85). Magnesium-sulfoxide echange of **222** generated aziridinylmagnesium **223** and chiral sulfoxide **224**. Alkylation of **223** gave chiral aziridines **225**, which upon reduction furnished chiral amines **226** in high optical purity. It is noteworthy that the stereochemical analysis of sulfoxide **224** revealed that the exchange reaction was highly stereospecific and occurred with inversion of configuration at the sulfur chiral center.

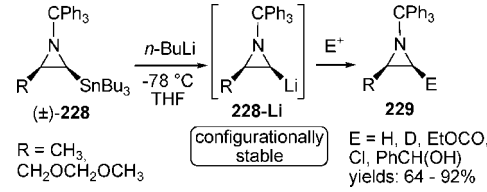
Concerning the thermal stability of this kind of aziridinyl anions generated by desulfinylation reaction, it was observed that low temperatures, in the range −100 up to −70 °C, were needed for aziridinyllithiums in order to avoid decomposition whereas aziridinylmagnesium could be kept without decomposition or epimerization several hours at room temperature. The main side reaction, observed for aziridinyl anions of the kind of **223a**, was a ring opening forming an enamine, which in some cases was trapped with a hard electrophile such as ethyl chloroformate to furnish the corresponding amide **227** (Scheme 86).

9.3. Aziridinyl Anions Generated by Tin−Lithium Exchange Reaction

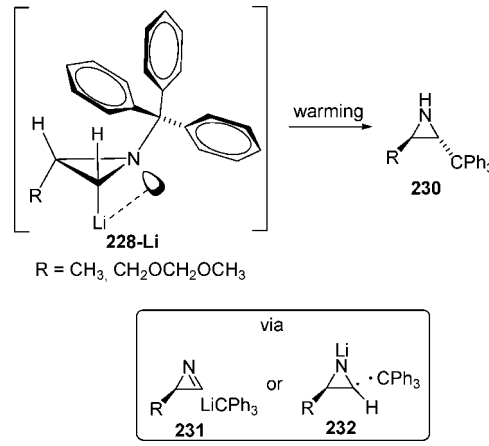
Another methodology for the generation of aziridinyl anions is based on the tin/lithium exchange reaction that has been reported for the first time by Vedejs and Moss.[87] *N*-Trityl aziridines **228** underwent tin−lithium exchange reaction in the presence of *n*-BuLi at low temperature, generating aziridinyllithiums **228-Li**, which proved to be configurationally stable and gave access to *cis*-2,3-disubstituted aziridines **229** upon reaction with electrophiles (Scheme 87).

It was also observed that aziridinyllithiums **228-Li** were stable at low temperature likely because of the enforced *syn* arrangement of the C−Li and the nitrogen lone pair, disclosing also a decomposition pattern different from that observed with the corresponding oxiranyllithiums (i.e.,

Scheme 87



Scheme 88



α-elimination, dimerization, ring opening). When **228-Li** was warmed to room temperature an N to C migration of the trityl group occurred giving aziridine **230** (Scheme 88). Two possible mechanisms were hypothesized, one polar involving the azirine **231** and one radical involving intermediates of the kind of **232** (Scheme 88).

Other examples of tin−lithium exchange reaction for the generation of aziridinyllithiums have been already described in Scheme 74.

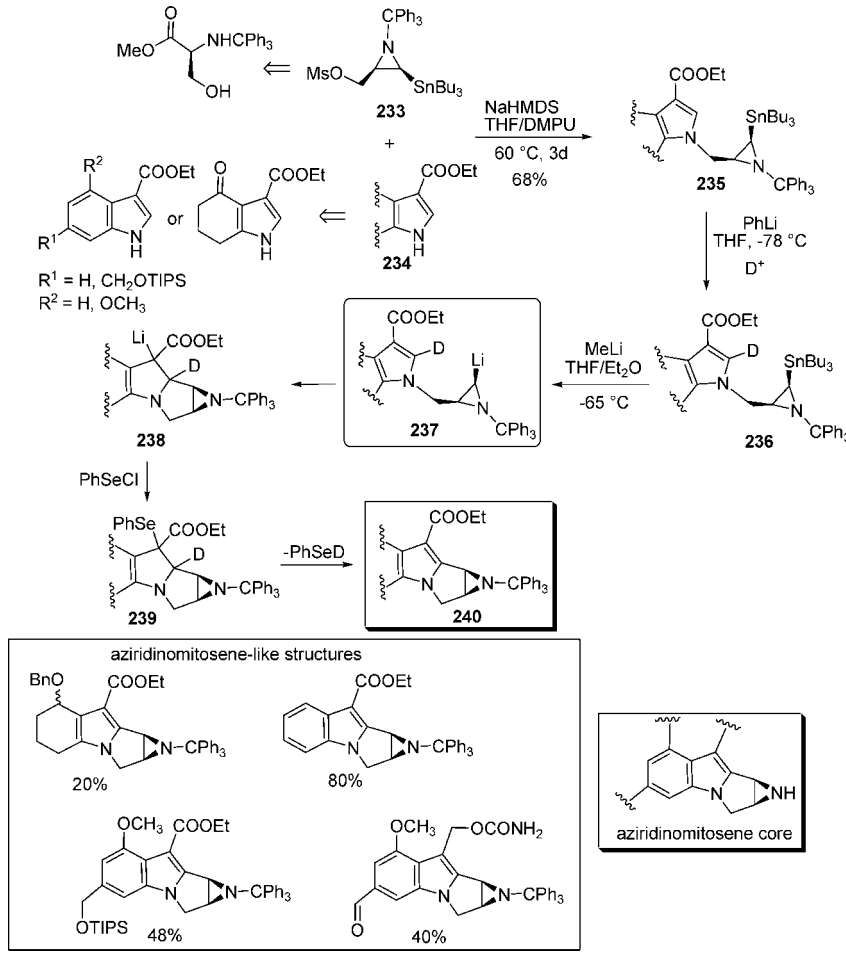
10. Synthetic Applications of the Aziridinyl Anion Methodology (AAM)

In this part of the review, some examples on the synthetic utility of the aziridinyl anion methodology have been collected. Several authors exploited the reactivity of aziridinyl anions in multistep synthesis, in the preparation of useful target molecules, or in the development of new synthetic methodologies.

The AAM has been exploited for the preparation of aziridinomitosene-like scaffolds **240**, with potential antitumor activity (Scheme 89).[88] The synthetic approach is based on an intramolecular Michael addition of lithiated aziridine **237**, generated by tin/lithium exchange reaction of **236**. The starting aziridine **235** was prepared by nucleophilic coupling of pyrrole or indole derivatives **234** on mesilated aziridine **233** obtained from *N*-trityl serine methylester. It was found that **235** did not undergo tin/lithium exchange reaction because of the competing lithiation at the pyrrole C2 position. Deuterium C2-protected derivative **236** was found to undergo smooth tin/lithium exchange reaction giving **237**, which furnished **238**, which once trapped with PhSeCl gave **239**. Elimination of PhSeD gave access to *N*-trityl derivatives **240**, which possess the aziridinomitosene skeleton. The role of the deuterium, which affects the regioselectivity of the lithiation and behaves as removable protecting group, is remarkable.

Functionalized methyleneaziridines, accessible by the lithiation/electrophilic trapping sequence, have been recog-

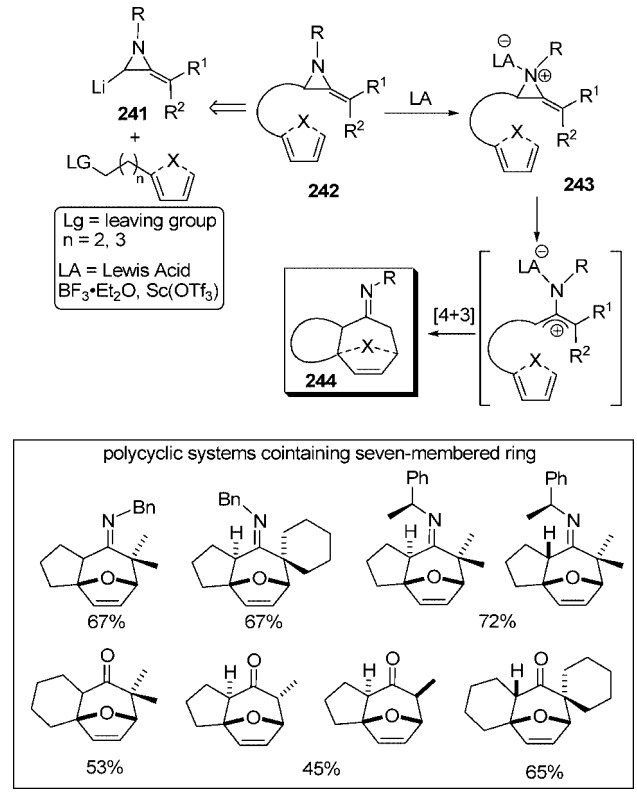
Scheme 89



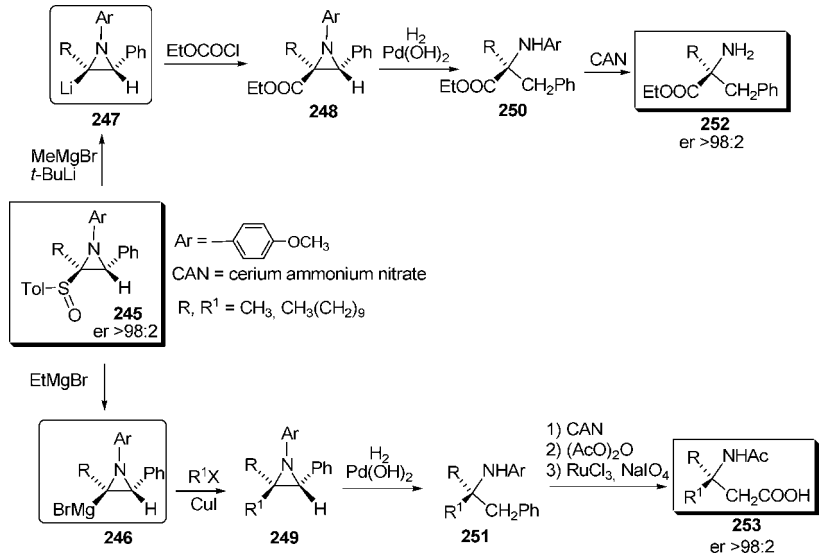
nized to be useful vehicles in organic synthesis.[73] As an example, the trapping reaction of lithiated alkylideneaziridines **241** with alkylhalides carrying a 1,3-diene unit allowed the preparation of alkylated products **242**, which have been successfully used for a Lewis acid-catalyzed intramolecular [4 + 3] cycloaddition reaction (Scheme 90).[89] Reaction of derivatives **242** with a Lewis acid gave aziridinium ions **243**, which underwent a ring-opening reaction generating aminoallyl cations, which reacted with the 1,3-diene moiety furnishing polycyclic systems **244**. Polycyclic derivatives with imine or carbonyl functionality were obtained depending on the reaction conditions.

Aziridinyl anions obtained by the desulfinylation methodology have been used for the enantioselective synthesis of α- or *β*-amino acids **252** and **253** (Scheme 91).[90] Starting from optically active sulfinylaziridine **245**, the reaction with MeMgBr/*t*-BuLi generated the configurationally stable aziridinyllithium **247**, which could be trapped with ethyl chloroformate to furnish aziridinecarboxylate **248**. Reduction of **248** gave α-functionalized phenylalanine ester **250**, which upon oxidative removal of the N-protecting group produced amino ester **252** in high optical purity. Treatment of aziridine **245** with EtMgBr generated the corresponding aziridinylmagnesium **246**, yet configurationally stable, which was alkylated to furnish **249**. Palladium-catalyzed reduction with hydrogen gave amine **251** with a quaternary stereogenic center, which upon oxidative N-deprotection, nitrogen acylation, and aryl oxidation furnished highly enantioenriched *β*-amino acids **253**.

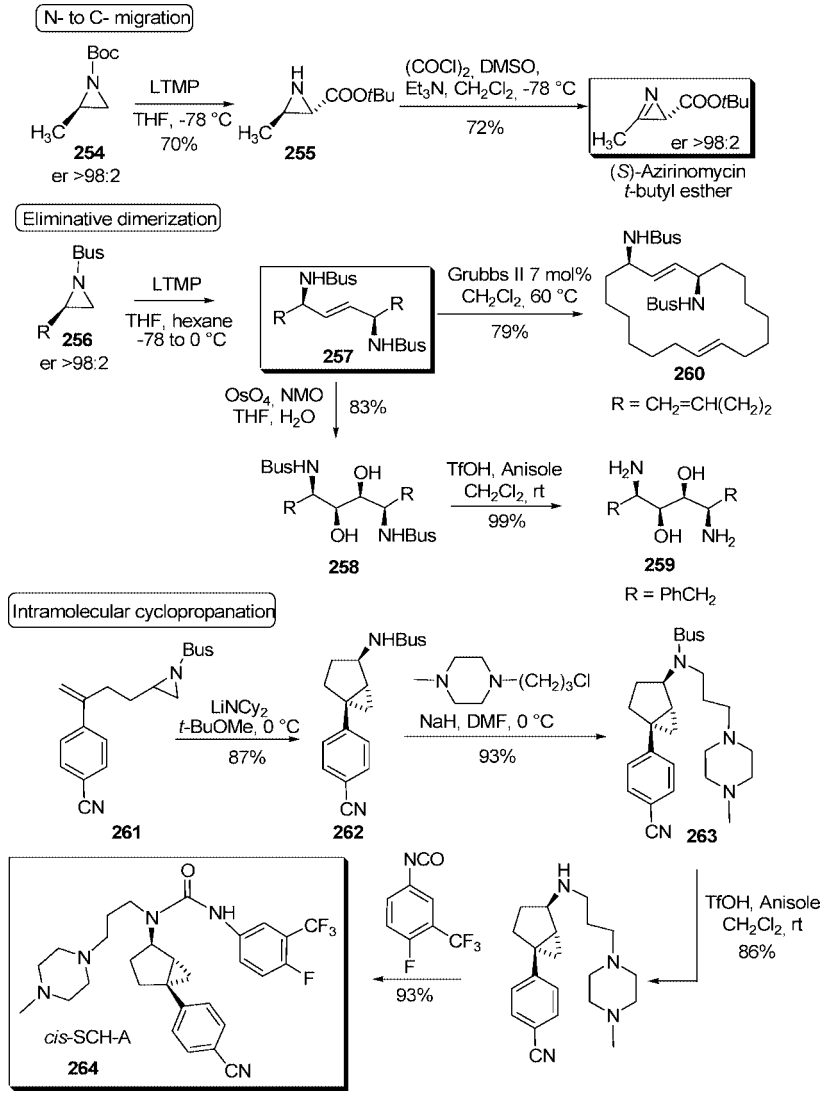
Scheme 90



Scheme 91

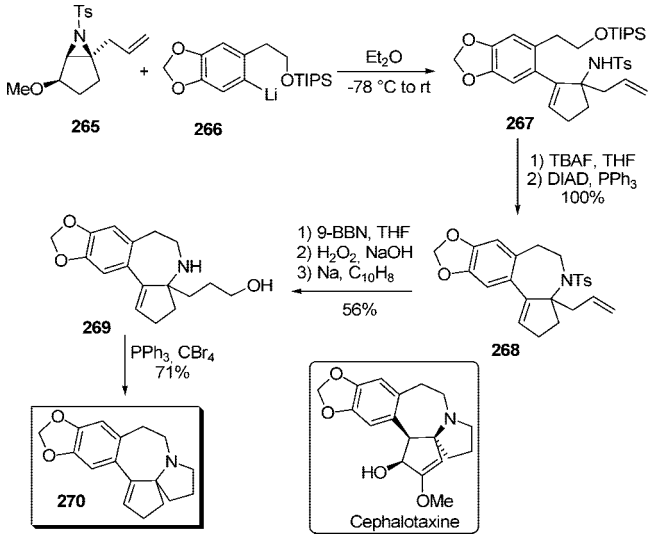


Scheme 92

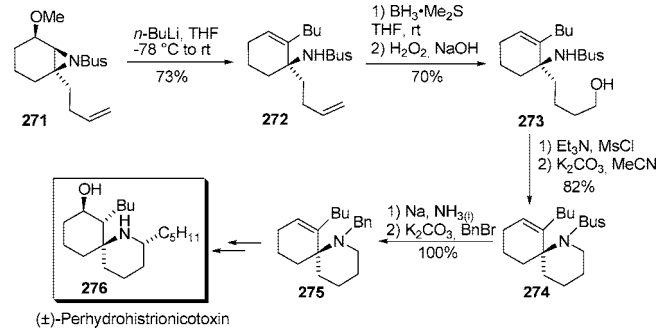


The already described highly stereoselective N to C [1,2] lithiation-induced shift has been exploited for an enantioselective preparation of the *tert*-butyl ester of the natural product azirinomycin (Scheme 92).[91] Simply starting from optically active *N*-Boc aziridine **254**, readily available from the corresponding chiral propylene oxide, lithiation with LTMP induced the 1,2 shift of the *tert*-butoxycarbonyl group with formation of **255**. Swern oxida-

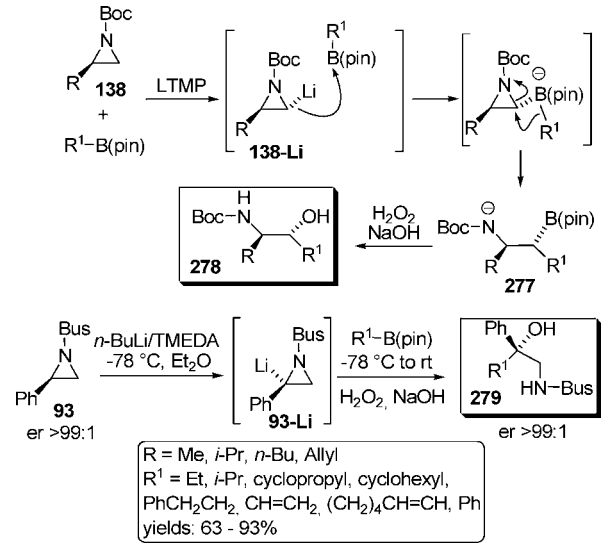
Scheme 93



Scheme 94



Scheme 95



tion furnished the enantioenriched (*S*)-azirinomycin derivative in good yield.

The carbenoidic behavior of aziridinyllithiums was proven to be useful for the preparation of target molecules. In particular, the eliminative dimerization of chiral *N*-Bus aziridines **256** furnished ene−diamines **257** in high optical purity, which served as building blocks for the preparation of chiral macrocycle **260** by an olefin metathesis reaction and for the preparation of biologically relevant chiral diaminodiol **259** via oxidation and *tert*-butylsulfonyl deprotection. The intramolecular cyclopropanation reaction occurring with suitable lithiated aziridines has been successfully applied in the synthesis of the epimer of the antagonist of melanin-concentrating hormone receptor (MCH-R1) *cis*-SCH-A. The synthetic protocol started with aziridine **261**, which underwent a stereoselective lithiation-induced cyclopropanation furnishing **262**. Nitrogen functionalization gave **263**, which after *tert*-butylsulfonyl deprotection and reaction with isocyanate gave the target molecule **264** in very good yield.

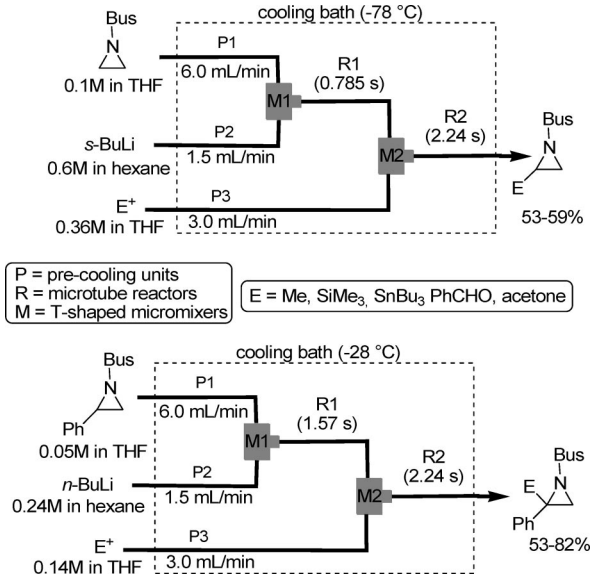
The reductive alkylation process that produces allyl amines, which can serve as useful building blocks in the preparation of more complex structures, represents another example of non-nucleophilic behavior of lithiated aziridines. For example, the reaction of aryllithium **266** with aziridine **265** produced cyclopentyl amine **267**, which upon desilylation followed by cyclization furnished the polycyclic derivative **268** (Scheme 93).[92] Hydroboration/oxidation of the vinyl unit furnished alcohol **269**; a Mitsunobu cyclization reaction provided the azaspirocycle **270** possessing the pentacyclic ring system of the naturally occurring alkaloid cephalotaxine.

A similar protocol, based on the reductive alkylation of lithiated aziridines, has been followed for the preparation of an intermediate for the synthesis of perhydrohistrionicotoxin (Scheme 94).[93] *N*-Bus-protected cyclohexylaziridine **271** was reacted with 3 equiv of *n*-BuLi furnishing cyclohexene derivative **272** in good yield; hydroboration/oxidation gave alcohol **273**, which was cyclized to spiro derivative **274**. Deprotection of the *tert*-butylsulfonyl group of **274** followed by benzylation furnished azaspirocycle **275**, which could be converted into perhydrohistrionicotoxin using a combination of reported procedures.[94]

Aziridinyl anions have been employed as useful reagents in the development of new stereoselective processes. An example is given by the stereospecific [1,2] alkyl shift of "ate" complexes obtained by a lithiation/borylation sequence (Scheme 95).[95] When lithiation of aziridines **138** was performed in the presence of an alkyl boronate, the formed ate complex underwent a stereoselective B to C migration of the alkyl group ending up with the formation of β-amino boronate **277**, which under oxaditive conditions furnished 1,2 amino alcohols **278**. This process, which has been proven to be highly stereospecific, when executed on chiral *N*-Boc aziridines led to enantioenriched 1,2 amino alcohols. A different regioselectivity was observed with chiral 2-phenyl-substituted *N*-Bus aziridine **93**, which were lithiated at the benzylic position and, upon borylation/oxidation, gave chiral amino alcohols **279** bearing a quaternary stereogenic center.

The lithiation/electrophilic trapping protocol has been also developed by using the microreactor technology. Microreactors are emerging as a useful tool to conduct very fast and sensitive reactions in highly controlled and reproducible conditions.[96] Those aspects are very important especially when the reactivity is strictly related to a rigorous control of the reaction parameters as in the case of metalated aziridines that could undergo side reactions. It has been reported that *N*-Bus ethylene aziridine, which is lithiated in a macrobatch reactor in the presence of TMEDA at −105 °C, could also be efficiently lithiated and trapped in a microflow system at higher temperature (−78 °C) and without using TMEDA (Scheme 96).[97] Analogously, *N*-Bus 2-phenyl-aziridine underwent the lithiation/trapping sequence at −28 °C and without TMEDA, while macrobatch conditions required −78 °C and the use of TMEDA. The use of higher temperature, the absence of TMEDA, and the sensibly

Scheme 96



reduced reaction times realized in the microreactors make the use of the AAM very much appealing for synthetic purposes in both academia and industry.

11. Concluding Remarks

The high synthetic usefulness of aziridines has been often confined to their electrophilic nature, undergoing nucleophilic ring-opening reactions, as usually taught in organic chemistry courses. The aim of this review is to highlight other aspects of aziridine reactivity, now well out of their infancy. Indeed, aziridines can be easily metalated, generating the corresponding aziridinyl anions, which could act as nucleophiles leaving the three-membered ring functionality intact or, under certain circumstances, as carbenoids thus disclosing an interesting reactional scenery. Even if the reactivity of aziridinyl anions closely mirrors that of the corresponding oxiranyl anions, the investigations of the last 10 years demonstrated that additional factors should be taken into consideration when the generation of metalated aziridines is concern.

When the aziridinyl anions are generated by deprotonation, the nature of the ring substituents (at either the nitrogen or carbon atoms) must be taken into account for the same deprotonation reaction to be successful. In addition, the regio- and stereoselectivity of the deprotonation reaction could be greatly affected by dynamic phenomena related to the aziridine nitrogen inversion process. In view of this, models based on a dynamically controlled metalation need to be considered.

There are no doubts, nowadays, that metalated aziridines can be easily employed in many target oriented and asymmetric syntheses. Nevertheless, their nature, structure, and dynamics in solution are rather obscure at present, and deep mechanistic and spectroscopic investigations could help to shed light on these aspects.

12. Acknowledgments

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