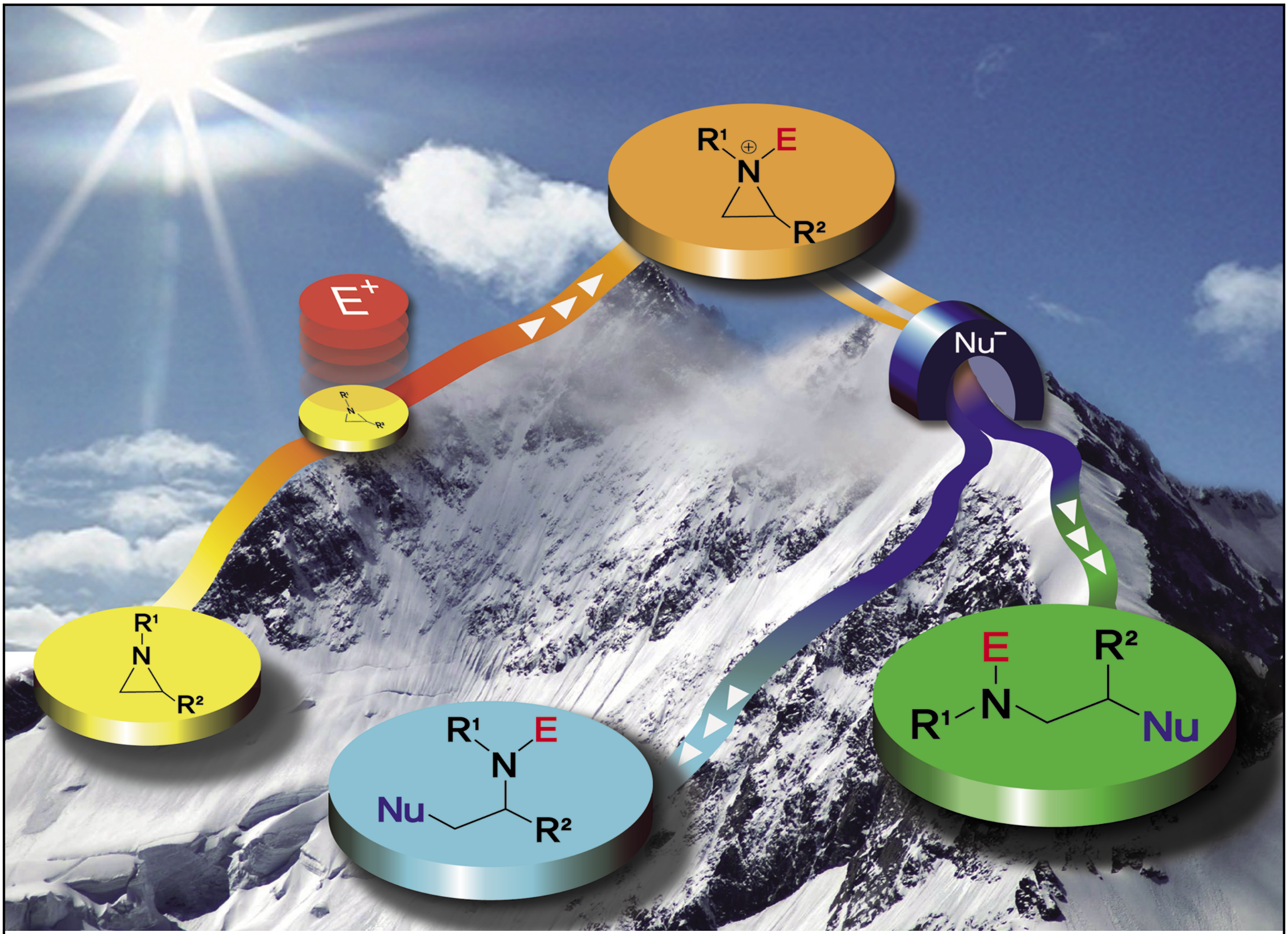

Featuring research from the group of Professor Hyun-Joon Ha at Department of Chemistry, Hankuk University of Foreign Studies, Yongin, Korea.

Regioselectivity in the ring opening of non-activated aziridines

The ring opening of non-activated 2-substituted aziridine is initiated by the reaction with the electrophile followed by the nucleophilic attack to either C1 or C2. Its regiochemical pathway depends on the nature of the C2 substituent, the electrophile and the nucleophile in a predictable manner.

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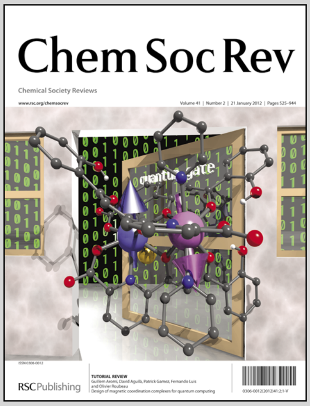

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CRITICAL REVIEW

Regioselectivity in the ring opening of non-activated aziridines

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In this *critical review*, the ring opening of non-activated 2-substituted aziridines *via* intermediate aziridinium salts will be dealt with. Emphasis will be put on the relationship between the observed regioselectivity and inherent structural features such as the nature of the C2 aziridine substituent and the nature of the electrophile and the nucleophile. This overview should allow chemists to gain insight into the factors governing the regioselectivity in aziridinium ring openings (81 references).

1. Introduction

The aziridine moiety represents one of the most valuable three-membered ring systems in organic chemistry,[1] and the regiocontrolled ring opening of C-substituted aziridines constitutes a powerful approach toward the preparation of a large variety of functionalized nitrogen-containing target compounds.[2] The ring opening of activated aziridines, *i.e.* aziridines bearing an electron-withdrawing group at nitrogen, has been studied intensively in that respect, showing the regiochemical pathway to be independent of the structural features of these aziridines as well as the nature of the participating nucleophiles.[1d] In that respect, the regioselectivity in the ring-opening reactions of 2-substituted activated aziridines has been shown to be quite straightforward, mostly involving the nucleophilic attack at the less hindered aziridine carbon atom,[3] with some exceptional cases comprising the nucleophilic attack at the allylic and the benzylic position of the aziridine moiety.[4]

In recent years, non-activated aziridines, which have to be activated prior to ring opening due to the presence of an electron-donating substituent at nitrogen, have also shown

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Sonja Stanković was awarded the Diploma of higher education with the title of Graduate Research and Development Chemist in 2007 (Kragujevac, Serbia). Subsequently, she performed PhD studies at the University of Kragujevac, Serbia for two years which resulted in 15 articles in international peer-reviewed journals. In 2009, she enrolled in a PhD program at Ghent University, Belgium, with Prof. N. De Kimpe and Prof. M. D'hooghe as promoters. Her main research study includes the synthesis of different classes of non-activated aziridines and their usage as flexible synthons in heterocyclic chemistry. She is the author of 18 publications in international peer-reviewed journals.

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Matthias D'hooghe obtained a Master degree in Bioscience Engineering-Chemistry in 2001 and a PhD degree in 2006, both from Ghent University (Belgium). In 2007, he became Assistant Professor in the group of Prof. N. De Kimpe. In 2009, he performed a short postdoctoral stay at Eindhoven University of Technology (The Netherlands) with Prof. D. Vogt. In 2010, he was promoted to Associate Professor at the Department of Sustainable Organic Chemistry and Technology, Faculty of Bioscience Engineering, Ghent University. His main research interests include the chemistry of small-ring azaheterocycles such as aziridines, azetidines and β-lactams. He is the author of 70 publications in international peer-reviewed journals.

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considerable attention as valuable intermediates for further synthetic elaboration. Moreover, the reactivity and applications of non-activated aziridines often appear to be different as compared to activated aziridines and epoxides, providing interesting opportunities for the selective synthesis of a variety of functionalized amines through intermediate aziridinium ions.

It should be noted that aziridinium ions can be obtained *via* two main pathways, *i.e.* through intramolecular nucleophilic substitution of amines bearing a leaving group at the β-position, or through *N*-functionalization of neutral aziridines. The study of ring-opening reactions of aziridinium ions obtained through cyclization of β-amino alcohols, the most prominent representatives of the first approach toward aziridinium intermediates, has been covered recently in a comprehensive way.[5]

Commonly applied methodologies for the second approach toward aziridinium salts, *i.e.* *N*-functionalization of non-activated aziridines, involve the formation of highly electrophilic intermediates through *N*-alkylation, *N*-acylation, *N*-protonation or *N*-complexation with Lewis acids, which then can easily be opened by different types of nucleophiles. Moreover, if non-activated, 2-substituted aziridines **1** are used, the issue of regioselectivity in the ring opening of the corresponding intermediate aziridinium salts **2** becomes important, since two regioisomeric ring-opened amines can be obtained. As depicted in Scheme 1, ring opening of aziridinium salts **2**

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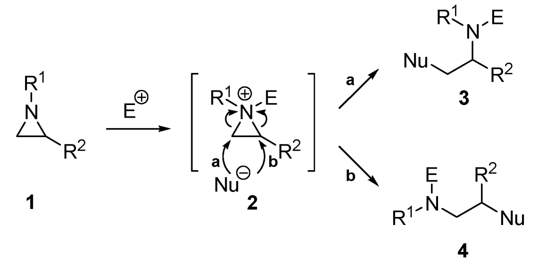
Norbert De Kimpe

Norbert De Kimpe obtained the PhD degree (1975) from Ghent University. He performed postdoctoral research work at the University of Massachusetts (Boston) (1979) and at the CNRS (Paris, France) (1983). He is full professor at Ghent University and was a guest professor at the Universities of Perpignan, Helsinki, Leuven, Siena, Barcelona, Sofia, Buenos Aires, and Pretoria. He was awarded the degree of Doctor honoris causa from the Russian Academy of Sciences in Novosibirsk (1998) and from the University of Szeged (Hungary) (2007). He is Member of the Royal Flemish Academy of Belgium and the European Academy of Sciences and Arts, and is Fellow of the Royal Society of Chemistry. He is the author of 560 articles in international SCI-journals. His research interests include the synthesis of bioactive heterocycles and natural products, and flavour chemistry.

Hyun-Joon Ha

Hyun-Joon Ha obtained his BS degree of chemistry in 1982 from Seoul National University with honor and his PhD in 1987 from Brown University. After a postdoctoral fellowship at Stanford University, he returned to Korea in 1988, and accepted the position of senior research scientist at KIST. In 1991, he joined the faculty of the chemistry department at Hankuk University of Foreign Studies, and is now a full professor of this department. His research interests include the exploitation of aziridine, asymmetric synthesis of biologically active molecules, and lipase-mediated chiral resolutions. He has published over 110 peer-reviewed papers and holds several patents.

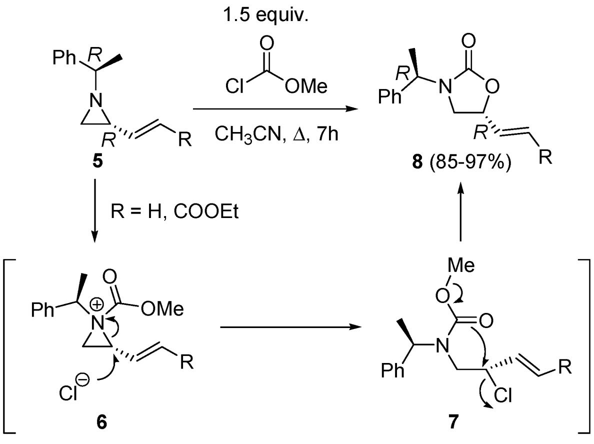


Scheme 1

can occur at the unsubstituted (path a) or at the substituted (path b) aziridine carbon atom, leading either to α-branched amines **3** (path a) or to β-branched amines **4** (path b).

In this review, the ring opening of non-activated 2-substituted aziridines **1** (R^1 = electron-donating group) *via* intermediate aziridinium salts **2** will be dealt with. Emphasis will be put on the relationship between the observed regioselectivity and inherent structural features such as the nature of the C2 aziridine substituent and the nature of the electrophile and the nucleophile. In the end, all relevant information will be combined into a general scheme allowing chemists to gain insight into the factors governing the regioselectivity in aziridinium ring openings, which might eventually be used in a predictive way.

In the following paragraphs, literature reports on the ring opening of non-activated 2-substituted aziridines will be organized first according to the nature of the substrate, *i.e.* distinction will be made between the reactivities of 2-(1-alkenyl)-, 2-aryl-, 2-acyl- and 2-alkylaziridines. Within these sections, the information will be subdivided based on the type of electrophile used for the activation of the aziridine moiety, *i.e.* the use of Lewis acids (*N*-complexation), carbonyl electrophiles (*N*-acylation, *N*-alkoxycarbonylation or related approaches), acids (*N*-protonation), alkyl halides or alkyl triflates (*N*-alkylation), and silylation reagents (*N*-silylation).



Scheme 2

2. Activation and ring opening of 2-(1-alkenyl)aziridines

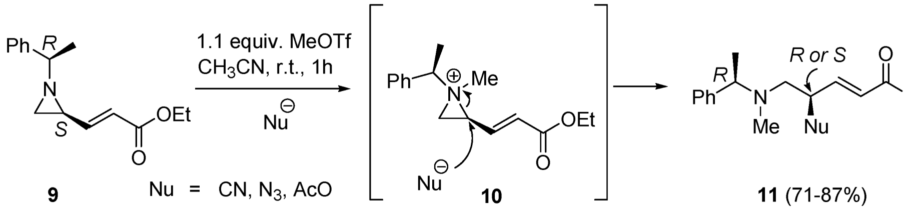
When the R^2 substituent in aziridines **1** (Scheme 1) is a 1-alkenyl group, the nucleophilic attack generally occurs at the more substituted carbon atom of the aziridine moiety. Although very few reports on the ring opening of this type of aziridines are available in the literature, all the examples give a straightforward picture regarding their regioselective ring opening, which seems to be independent of the type of nucleophile and electrophile used in these reactions. The observed regioselectivity can be rationalized considering the allylic activation in these compounds (resonance stabilization of the developing carbenium ion at C2), which has also been described in the ring-opening reactions of vinyloxirane and activated vinylaziridine derivatives.[6]

Aziridinium ion formation through *N*-alkoxycarbonylation

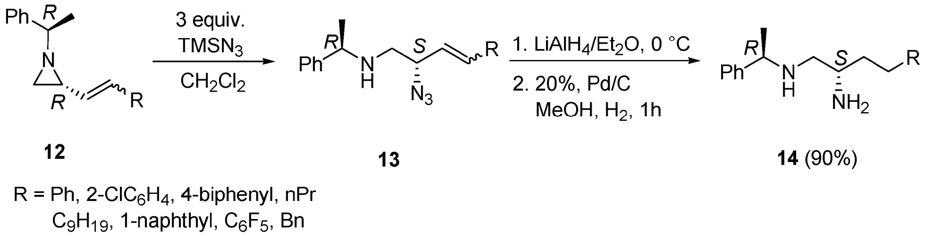
A single report considering the ring opening of 2-(1-alkenyl)-aziridines through *N*-alkoxycarbonylation has been provided by Ha *et al.*,[7] in which the transformation of 2-vinylaziridines **5**, prepared from the corresponding aldehydes *via* a Horner–Wadsworth–Emmons reaction or a Wittig reaction, toward oxazolidin-2-ones **8** has been investigated. The reaction of aziridines **5** with methyl chloroformate was shown to proceed *via* cyclization of chlorocarbamates **7** (Scheme 2). The identification of intermediates **7** suggested that the reaction comprised a double S_N2 inversion process. Thus, *N*-methoxycarbonylation provided the activated aziridinium species **6**, which underwent a regioselective C2–N bond cleavage by the chloride ion *via* an S_N2 process. Subsequently, intramolecular cyclization of the carbamate **7** (implying a second S_N2 process) furnished oxazolidin-2-ones **8** in good yields with a net retention of configuration at C2 as defined in aziridines **5** (Scheme 2).

Aziridinium ion formation through *N*-alkylation

The ring opening of aziridinium species **10**, obtained by *N*-methylation of the chiral 2-alkenylaziridine **9** using methyl trifluoromethanesulfonate (MeOTf), follows the same route as the *N*-alkoxycarbonylation approach (Scheme 2), giving rise to β-branched ring-opening products **11** *via* ring opening at C2. The reaction showed complete regio- and stereoselectivity toward the synthesis of a variety of optically pure amines **11** (Scheme 3).[8]



Scheme 3



Scheme 4

Activation and ring opening of 2-(1-alkenyl)aziridines *via* silylation

Even though the nature of trimethylsilyl reagents is different as compared to other electrophiles used for the activation of the aziridine moiety, ring opening of non-activated 2-alkenylaziridines has been shown to be successful in the presence of TMSN$_3$ (trimethylsilyl azide), resulting in the formation of the corresponding C2 ring-opening products.

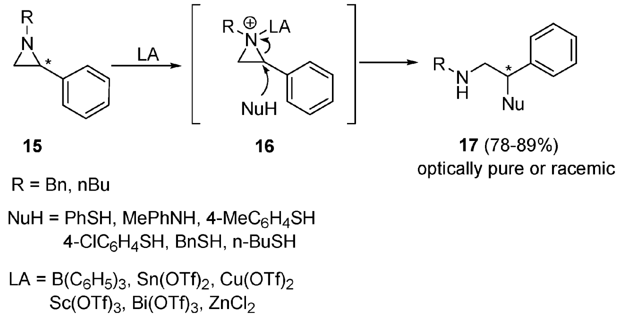
For example, the reaction of 2-(1-alkenyl)aziridines **12** with TMSN$_3$ furnished 1-amino-2-azido-3-alkenes **13** after regioselective cleavage of the C2–N bond (Scheme 4).[9] The latter azides **13** were subsequently used for the synthesis of 1,2-diaminoalkanes **14** *via* azide reduction and alkene hydrogenation.

3. Activation and ring opening of 2-arylaziridines

Analysis of a large number of reported examples revealed the more hindered aziridine carbon atom in 2-arylaziridinium salts to be the more favorable place for nucleophilic attack, furnishing the C2 ring-opening products as the single or the major regioisomers. In general, activation of 2-phenylaziridines through complexation of the aziridine moiety with Lewis acids is followed by nucleophilic attack at the more substituted carbon atom (benzylic position). In a single example, the Lewis acid-catalyzed ring opening of 2-(2-pyridyl)aziridines gave either one or two regioisomers depending on the reaction conditions used, while acylation and protonation of 2-arylaziridines furnished only the C2 ring-opening products.

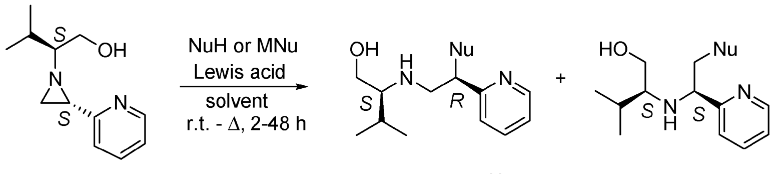
Aziridinium ion formation through *N*-complexation with Lewis acids

The reaction of 2-phenylaziridines **15** (optically pure or racemic) with different nucleophiles and Lewis acids gave amines **17** regio- and stereospecifically as a result of the nucleophilic attack at the benzylic position of the corresponding aziridinium complexes **16** (Scheme 5). For example, the ZnCl$_2$-catalyzed and B(C$_6$F$_5$)$_3$-catalyzed reaction of 1-benzyl-2-phenylaziridine (**15**, R = Bn) with aliphatic and aromatic thiols afforded 2-benzylamino-1-phenylethyl sulfides (**17**, Nu = SR) in good yields (78–89%).[10,11] In that paper, previously reported results were revised,[12] in which the synthesis of the amines derived from attack at the C3 carbon atom was reported. In addition to the ZnCl$_2$-catalyzed reaction, the same C2-regioselectivity has also been observed in Bi(OTf)$_3$- and Sc(OTf)$_3$-catalyzed reactions of the same aziridine **15** (R = Bn) with aliphatic as well as aromatic thiols, providing high yields of only one regioisomer **17**.[13] The reaction of 2-phenylaziridines **15** with aromatic amines in the presence of Sn(OTf)$_2$ or Cu(OTf)$_2$ as catalysts again gave the products derived from nucleophilic attack at the benzylic position of the aziridinium intermediates **16**.[14]



Scheme 5

As compared to the reactivity of 2-phenyl-substituted aziridines **15**, the regioselectivity in the reactions of 2-(2-pyridyl)-substituted aziridine **18** with a variety of different N-, S-, and O-nucleophiles was not always straightforward.[15] It was shown that the ring opening of aziridine **18** gave the products **19**, resulting from nucleophilic attack at the more substituted aziridine carbon, either exclusively or together with the alternative regioisomeric products **20** depending on the type of nucleophile, Lewis acid and solvent used (Scheme 6). The ring opening of 2-(2-pyridyl)aziridine **18** with heteronucleophiles applying optimized experimental conditions, *i.e.*, in an acetonitrile–water mixture as the solvent and in the presence of a catalytic amount of cerium(III) chloride heptahydrate, proved to be a useful route toward a variety of difunctionalized pyridines. For example, using these conditions, the ring opening of aziridine **18** with NaN$_3$ was straightforward, giving regioisomer **19** as a single product. Reactions with other nucleophiles such as water, amines and thiols also gave the C2 ring-opening products **19** as the major regioisomers. On the other hand, higher amounts of regioisomers **20** were reported when LiClO$_4$ or Zn(OTf)$_2$ were used to catalyze the ring opening of aziridine **18**. In this way, it was possible to modify the regioselectivity of the ring-opening process by the proper choice of reagent, Lewis acid and solvent.[15] Nevertheless, it should be noted that complexation of the Lewis acid with both nitrogen atoms might have a profound influence on the reaction outcome of the above described ring-opening reactions, making a general conclusion on the regioselectivity regarding the ring opening of 2-(2-pyridyl)aziridine **18** premature.



18 **19** (40-100%) **20** (0-60%)

NuH or MNu = H_2O, NaN_3, $BnNH_2$, $4\text{-}MeOC_6H_4NH_2$
Bn_2NH, 2-naphthylSH, PhSH
BnSH, nBuSH, tBuSH

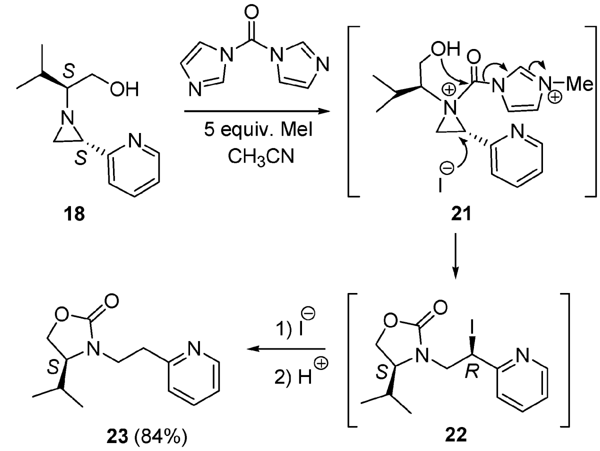
Lewis acid = $CeCl_3{\cdot}7H_2O$, $Ce(NH_4)_2(NO_3)_6$
$AlCl_3$, $Zn(OTf)_2$, $LiClO_4$

solvent = $CH_3CN\text{-}H_2O$ (9:1), $EtOH\text{-}H_2O$ (1:1)
CH_3CN, CH_2Cl_2, THF

Scheme 6

Aziridinium ion formation through *N*-carbamoylation or *N*-acylation

The reactions of the above mentioned chiral 2-(2-pyridyl)-substituted aziridines **18** with an excess of both carbonyldiimidazole (CDI) and reactive alkyl halides, performed with the intention to prepare halogenated products resulting from the ring opening of the aziridine by the halide ion, have been evaluated by the same group.[16] In this study, it has been observed that when methyl iodide was used, optically pure non-halogenated oxazolidin-2-one **23** was formed. In order to explain the presence of this compound, the iodide **22**, derived from nucleophilic attack at the more substituted carbon atom of aziridinium species **21**, was proposed as an intermediate (Scheme 7). At the same time, intramolecular nucleophilic addition of the remote hydroxyl group across the carbonyl moiety in intermediate **21** furnished the oxazolidinone ring. Subsequently, the intermediate heterobenzylic iodide **22** has been proposed to be reduced by the excess of iodide affording oxazolidin-2-one **23**. The reducing properties of the iodide ion and of hydrogen iodide in this type of transformations had already been reported in the literature.[17]



18 **21** **22** **23** (84%)

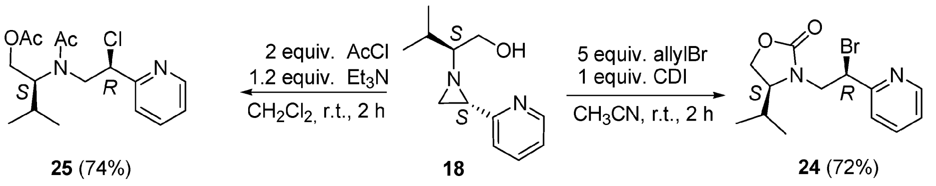
Scheme 7

In order to account for the proposed mechanism, the aziridine **18** has been treated separately with either CDI and an excess of allyl bromide in acetonitrile at room temperature, or two equiv. of acetyl chloride, furnishing compounds **24** and **25**, respectively (Scheme 8). Both products resulted from the fission of the benzylic C2–N bond by bromide or chloride in the intermediate aziridinium salt.[16]

Aziridinium ion formation through *N*-protonation

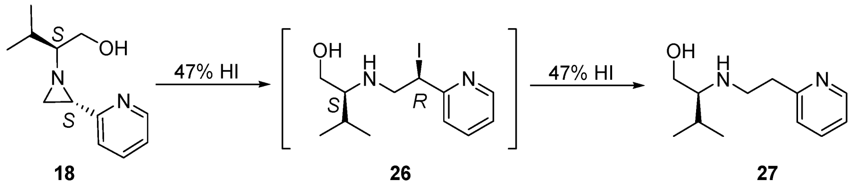
In accordance with the previously described results, the acid-mediated ring opening of 2-arylaziridines has been shown to result in the formation of the corresponding C2 ring-opening products, either as single isomers or, in exceptional cases, together with small amounts of the C3 ring-opening products. Thus, when 2-(2-pyridyl)aziridine **18** was protonated with an excess of hydrogen iodide, the amine **27** was obtained (Scheme 9).[16] The presence of this amine has been explained to be mediated by the formation of the intermediate β-iodoamine **26**, resulting from iodide attack at the more substituted carbon atom of aziridine **18**, and further reduction by the excess of hydrogen iodide through a halophilic reaction and subsequent protonation to form the amine **27**.

Moreover, after heating a mixture of the same aziridine **18** and *p*-toluenesulfonic acid (20 mol%) in a 9 : 1 acetonitrile–water system at reflux temperature for 6 h, a mixture of the regioisomeric ring-opening products **19** and **20** (82 : 18) was obtained, which were separated by column chromatography (Scheme 6).[15]

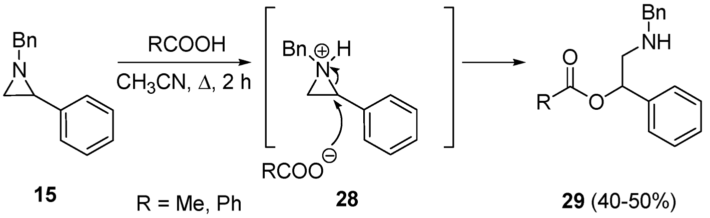


25 (74%) **18** **24** (72%)

Scheme 8



Scheme 9



Scheme 10

Similarly, the reaction of 1-benzyl-2-phenylaziridine **15** with aliphatic and aromatic acids in acetonitrile gave the amino esters **29** as the major isomers furnished by nucleophilic attack of the corresponding carboxylates at the benzylic position of aziridinium species **28** (Scheme 10).[18]

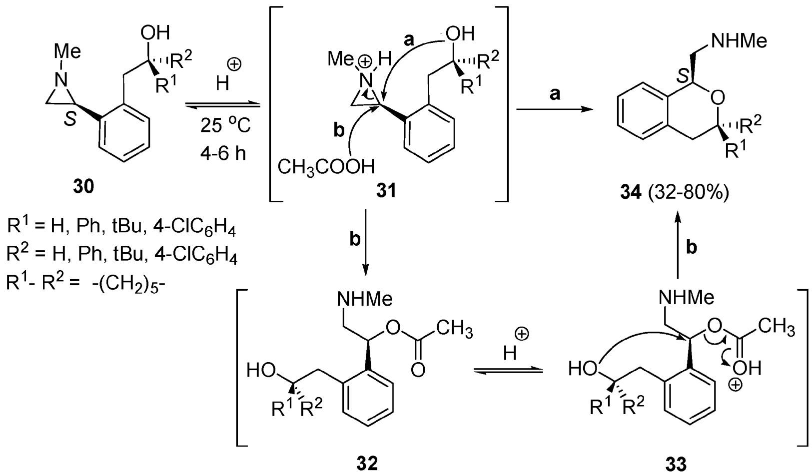
In addition, a mixture of 2-arylaziridine, *p*-toluidine and silica gel (activated at 120 °C under vacuum for 6 h) has been reported to afford the corresponding vicinal diamine as a result of the exclusive attack at the more hindered carbon atom of the aziridine ring,[19] and hydrogen fluoride has also been described to combine regiospecifically with 2-phenylaziridines to give 2-fluoroamines in good yields.[20]

In accordance with these results, the synthesis of isochromans **34**, resulting from the cyclization of a number of 1-methylaziridines **30** using several proton sources (TFA, $(COOH)_2$, HCOOH, H_2SO_4) and different solvents (THF, CH_3CN, Et_2O, dioxane/H_2O), has been elucidated.[21] Acetic acid, either as a proton source or as a solvent, at room temperature proved to be superior for the preparation of isochromans **34**. Two plausible reaction mechanisms are depicted in Scheme 11. The first approach involves nitrogen protonation and ring opening at the benzylic carbon atom by the remote hydroxyl group (path a), whereas the second pathway involves the intermediacy of an acetate **32** (path b) followed by nucleophilic displacement of acetic acid by the hydroxyl group. In both cases, the nucleophilic attack occurs at the benzylic position of the aziridine ring. Determination of the stereochemistry of the obtained products **34** showed pathway a to be the predominant one.[21]

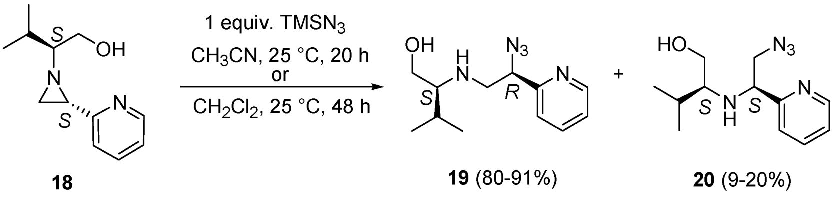
Finally, the *in situ* activation of the aziridine moiety in the transformation of 2-aryl-3-(hydroxymethyl)aziridines into 2-amino-3-aryl-3-methoxypropane-1-ols was assigned to hydrogen bridge formation between the aziridine nitrogen and methanol. It has been shown that also in this case the reaction proceeds through regio- and stereoselective ring opening at the benzylic position of the corresponding aziridine moiety.[22]

Activation and ring opening of 2-arylaziridines *via* silylation

The same regioselectivity has been observed in the case of ring opening of 2-(2-pyridyl)aziridine **18** by $TMSN_3$, providing the C2 ring-opening product **19** as the major isomer (Scheme 12).[15]



Scheme 11



Scheme 12

4. Activation and ring opening of 2-acylaziridines

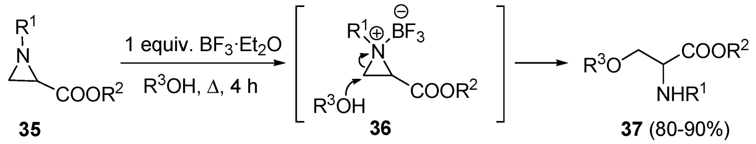
The regioselectivity of the ring opening of 2-acylaziridines appears to be both nucleophile- and electrophile-dependent. However, in most cases the products obtained result from the attack at the more hindered aziridinium carbon atom (*i.e.* the α-carbon atom with respect to the carbonyl moiety), especially when the nucleophile is an azide, halide or cyanide ion. On the other hand, the reactions of 2-acylaziridines with alcohols gave rise to ring opening at the less hindered aziridine carbon atom.

Aziridinium ion formation through *N*-complexation with Lewis acids

The ring-opening reactions of 2-(alkoxycarbonyl)aziridines **35** using various alcohols turned out to be regioselective, giving rise to α-amino esters **37**. This reaction proceeded through nucleophilic attack at the less hindered side of the aziridinium moiety in intermediates **36** (Scheme 13).[23] In addition, the ring-opening reactions of aziridine-2-carboxamide, aziridine-2-carboxylate and 2-acetylaziridines by water and different alcohols, promoted by the presence of $BF_3{\cdot}Et_2O$, have been shown to follow the same regioselectivity.[24]

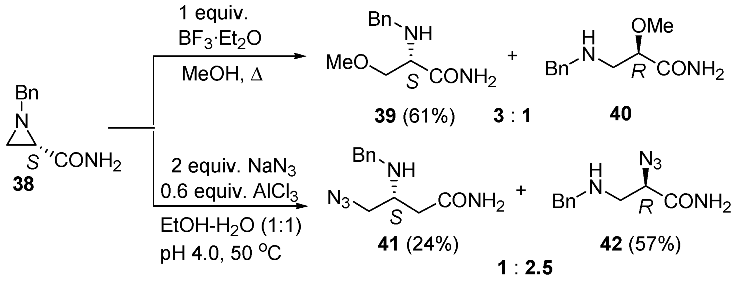
A nucleophile-dependent regioselectivity has been observed in ring-opening reactions of 2-carbamoylaziridine **38**, described by Gotor and coworkers.[25] Aziridine **38** was heated under reflux in methanol in the presence of a diethyl ether–boron(III) fluoride complex (Scheme 14), leading to a 3 : 1 mixture of the C3 and C2 ring-opening products, respectively, from which the former, *i.e.* enantiopure α-amino amide (*S*)-**39**, was isolated in 61% yield. On the other hand, when aziridine **38** was reacted with sodium azide and aluminium(III) chloride in aqueous ethanol, the formation of a 1 : 2.5 mixture of azides **41** and **42** was observed (Scheme 14).[25]

The ring opening of *tert*-butyl *N*-benzylaziridine-2-carboxylate **43** with a higher order butylcuprate or *n*-BuMgCl in the presence of $BF_3{\cdot}Et_2O$ has been studied by Baldwin *et al.*[26] However, a mixture of products **44** and **45** in low yields was observed resulting from attack of the organometallic reagent at both C2 and C3 of the corresponding aziridinium intermediate (Scheme 15).

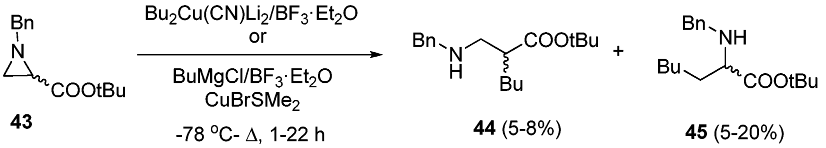


R^1 = iPr, Bn, c-C_6H_{11}
R^2 = Me, iPr
R^3 = Me, $(CH_3)_2CHCH_2$, HC≡CCH_2, iPr, tBu

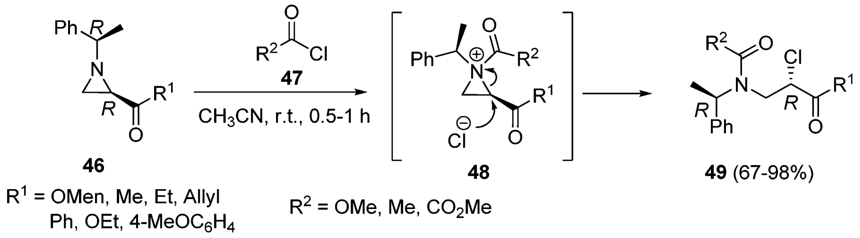
Scheme 13



Scheme 14



Scheme 15

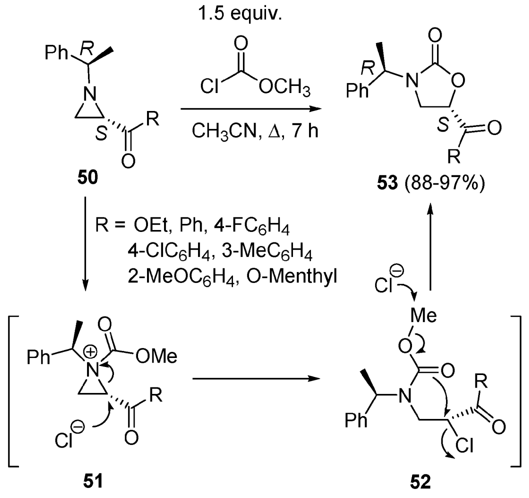


Scheme 16

Aziridinium ion formation through *N*-acylation or *N*-alkoxycarbonylation

Various 2-acylaziridines **46** have been subjected to reactions with different acyl chlorides **47** to furnish β-amino-α-chloro-carbonyl compounds **49** in a regioselective and stereospecific way (Scheme 16).[27] The acyl chlorides were able to both activate the aziridine ring and provide the nucleophile leading to the ring-opening reactions. The ring nitrogen reacts readily with acyl chlorides toward intermediate aziridinium ions **48**, which are highly activated and smoothly react with the incoming chloride nucleophile. All ring-opening reactions were shown to be highly selective in terms of regio- and stereochemistry, implying that the bond between C2 and the ring nitrogen was labile and that the reaction proceeded with complete inversion of the configuration at C2.

As previously described for 2-vinylaziridines **5** (Scheme 2), the synthesis of oxazolidin-2-ones can also derive from *N*-methoxycarbonylation of 2-acyl- or 2-(alkoxycarbonyl)-aziridines **50**. Methoxycarbonylation of the nucleophilic nitrogen of aziridines **50** gave aziridinium ions **51**, which were regioselectively attacked by the resulting chloride anion to give chlorides **52**. Chlorosubstituted intermediates **52** were then converted into oxazolidin-2-ones **53** through an intramolecular S_N2 reaction (Scheme 17). The formation of the aziridinium intermediates **51** was also evidenced by the isolation of an intermediate **52** (R = OEt) when the reaction was performed in toluene instead of acetonitrile. Furthermore, when carbamate **52** (R = OEt) was heated under reflux in acetonitrile, oxazolidinone **53** was formed in an excellent yield.[7]



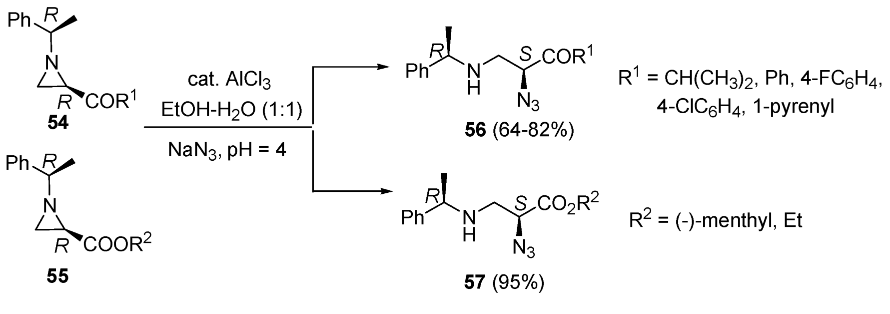
Scheme 17

Aziridinium ion formation through *N*-protonation

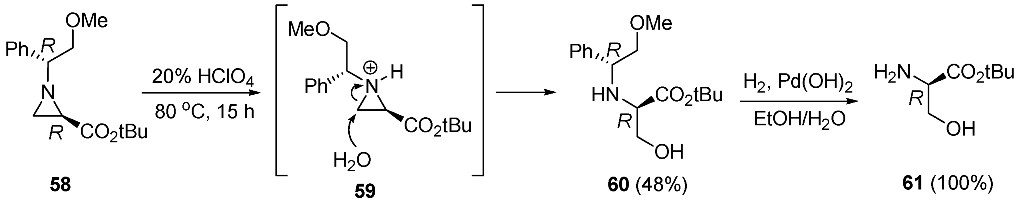
The ring-opening reactions of enantiomerically pure 2-acyl- and 2-(alkoxycarbonyl)aziridines **54** and **55** with azide in an aqueous acidic medium (pH = 4, adjusted by the addition of sulfuric acid) have been described to proceed efficiently and stereoselectively to give 3-amino-2-azidoketones **56** or 3-amino-2-azidopropionates **57**, respectively, in the presence of 10 mol% of $AlCl_3{\cdot}6H_2O$ (Scheme 18).[28] Bearing in mind the low activity of $AlCl_3{\cdot}6H_2O$ as a Lewis acid, the presence of sulfuric acid is considered to be responsible for the activation of the aziridine moiety through *N*-protonation.

To assign the absolute configuration of aziridine **58**, this compound has been treated with 20% $HClO_4$ to obtain the ring-opened product **60**, which was subsequently transformed to the *tert*-butyl ester of D-serine **61** in quantitative yield (Scheme 19).[29] In this approach, water attacked the non-substituted carbon atom of the intermediate aziridinium ion **59** to furnish β-aminoalcohol **60**. However, the C3 regioselectivity in this case could be also attributed to the Lewis acid character of $HClO_4$ rather than only protonation of nitrogen in aziridine **58**.

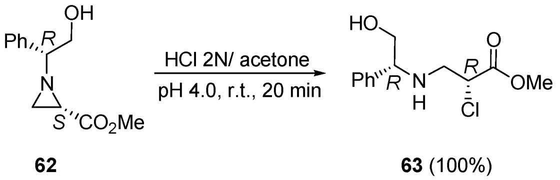
On the other hand, the selective ring opening of aziridine **62** (or its epimeric version) can be explained by an S_N2



Scheme 18



Scheme 19



Scheme 20

mechanism in which the chloride ion attacks at C2 with inversion of stereochemistry (Scheme 20).[30] The regiospecific ring opening by the chloride ion can be further rationalized considering an enhanced electrophilicity at C2 due to intramolecular hydrogen bonding between the carbonyl and the hydroxyl group.

In analogy with the previous example, nucleophilic attack by bromide (from hydrobromic acid) at the more hindered side of the aziridine ring has been shown to occur in the regiospecific ring opening of 2-acylaziridines providing the corresponding bromoesters through *N*-protonation.[31]

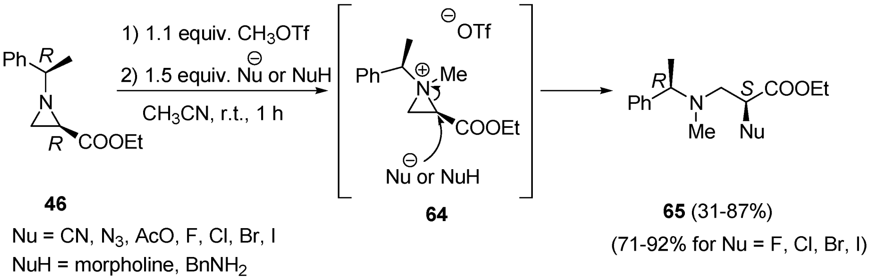
Aziridinium ion formation through *N*-alkylation

The presence of an ethoxycarbonyl substituent in aziridines **46** contributes to the activation of the bond between C2 and the ring nitrogen toward approaching nucleophiles. First, the ring is further activated by *N*-methylation using methyl triflate, followed by ring opening of aziridinium salt **64** by different nucleophiles to yield the ring-opened products **65**. The attack was shown to occur regioselectively at the more hindered carbon atom of the aziridine ring (Scheme 21).[8] In recent work,[32] different tetrabutylammonium halides ($Bu_4N^+X^-$) have been used as halide sources for the ring opening of aziridinium triflates **64** in acetonitrile. In the same manner, the 2-(ethoxycarbonyl)aziridinium salt **64** gave only the corresponding secondary halides **65** by ring opening at the activated α-carbonyl atom, and no primary halides were retrieved (Scheme 21, Nu = F, Cl, Br, I).

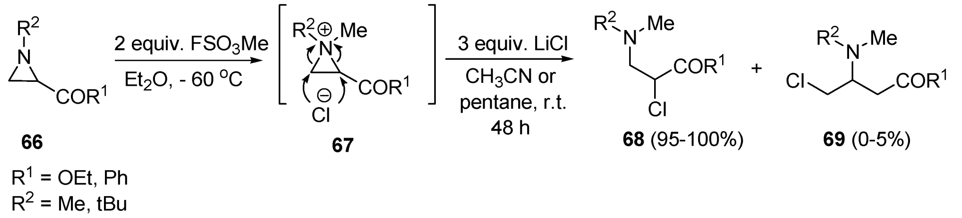
In addition, aziridines **66** have been treated with methyl fluorosulfonate to afford the corresponding aziridinium salts **67** in high yields,[33] which were characterized by ring-opening reactions using lithium chloride. In accordance with the above-mentioned reactions, the attack occurred at the more hindered side furnishing isomers **68**, while only in one case (R^1 = OEt, R^2 = Me) the isomer **69** was present as well in 5% (Scheme 22).

5. Activation and ring opening of 2-alkylaziridines

The regioselectivity of the ring opening of 2-alkylaziridines has been the topic of a considerable number of literature reports, giving a better insight into the reactivity of this type of aziridines which is mostly influenced by the nature of the nucleophile and the type of electrophile used for the activation of the aziridine moiety. It has been observed that protonic acid- and Lewis acid-catalyzed reactions result mainly in the ring opening of the aziridine moiety at the less hindered



Scheme 21



Scheme 22

aziridinium carbon atom. The ring opening with acyl halides, which act at the same time as the activator of the aziridine moiety and the source of the nucleophile, gave mixtures of both regioisomers, with the C2 ring-opening product as the major component. When phosgene, carbon dioxide or acetic acid was used to activate the ring, the less substituted carbon atom appeared to be the more favored place for nucleophilic attack. On the other hand, it was shown that ring opening of 2-alkylaziridines is nucleophile-dependent when the aziridine ring is activated *via* alkylation. Thus, if bromide, iodide and chloride are used as nucleophiles in benzyl bromide- or methyltriflate-activated reactions, the aziridine moiety is regioselectively opened at the C2 position through thermodynamic control. However, with the fluoride ion as the nucleophile, both regioisomers were formed, with a major amount of the C3 ring-opened product. The reactions with other nucleophiles such as amines, azides or alcohols proceeded mainly through nucleophilic attack at the non-substituted aziridine carbon atom.

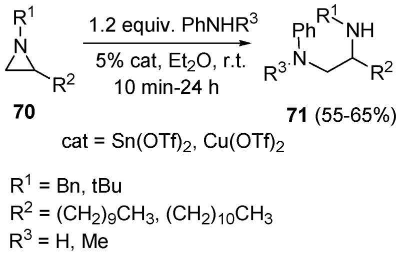
Aziridinium ion formation through *N*-complexation with Lewis acids

The reaction of 2-alkylaziridines **70** with aromatic amines provided 1,2-diamines **71** after nucleophilic attack of the amine at the less substituted aziridine carbon atom (Scheme 23).[14] A peculiar feature of this reaction is the fact that only aromatic amines successfully opened the aziridines. Aliphatic amines, such as diethylamine, *n*-butylamine, benzylamine and pyrrolidine, failed to react with aziridines **70** at room temperature for one day in the presence of a catalytic amount of copper(II) or tin(II) triflate. It was assumed that a "loose" complex of an aromatic amine and the catalyst coordinated with the aziridine nitrogen and initiated the ring-opening reaction. Aliphatic amines—by virtue of their higher basicity—made stronger complexes to the copper(II) and tin(II) triflate which failed to activate the aziridine.[14]

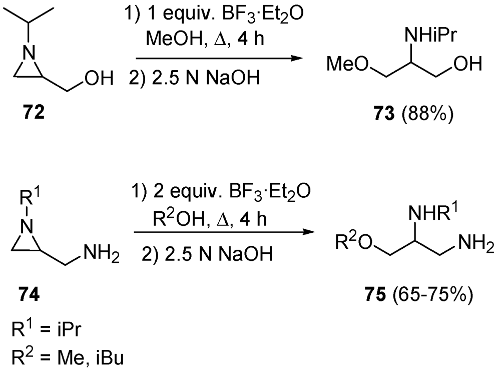
The same regioselectivity was observed in the $BF_3{\cdot}Et_2O$-mediated ring opening of 2-(hydroxymethyl)aziridines **72** and 2-(aminomethyl)aziridines **74** (Scheme 24) by different alcohols, providing an entry toward α-branched amines **73** and **75** through ring opening by methanol or *i*-BuOH at C3.[23,34]

The ring opening of 2-butylaziridine **76** with thiol in the presence of a catalytic amount of $ZnCl_2$ has been shown to follow the same route as in previous examples furnishing thioether **77** in 95% yield (Scheme 25).[12]

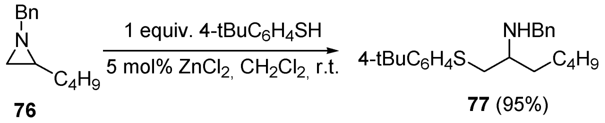
Besides, the aziridine ring of 1-(2-methoxy-1-phenylethyl)-2-methylaziridine has been opened at the C3 position with lithium dimethylcuprate in the presence of $BF_3{\cdot}Et_2O$.[35]



Scheme 23



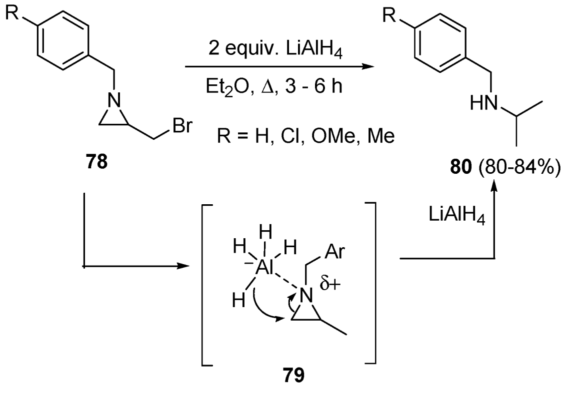
Scheme 24



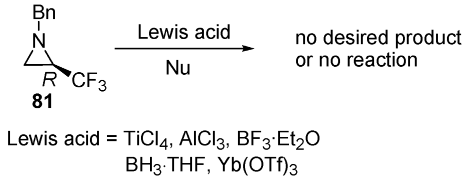
Scheme 25

Recently, the same conclusion on the regioselectivity has been deduced in the ring opening of 2-(bromomethyl)-aziridines **78** using $LiAlH_4$.[36] The suggested mechanistic pathway for this transformation consists of an initial reductive debromination of the starting aziridines **78** toward 2-methylaziridines **79**, which subsequently suffered from reductive ring opening by a hydride ion to yield isopropylamines **80** (Scheme 26). Apparently, the reducing agent acts both as the activator of the aziridine ring (through coordination of aluminium with nitrogen), and as the provider of the nucleophile (hydride) which opens up the ring at the less hindered position. In addition, 2-(acetoxymethyl)-, 2-(methoxymethyl)- and 2-(phenoxymethyl)aziridines were treated with $LiAlH_4$ under microwave irradiation, giving rise to either β-amino alcohols, isopropylamines or 1-methoxypropan-2-amines depending on the reaction conditions.[36]

However, Uneyama and coworkers[37] have reported the unsuccessful transformation of chiral 2-(trifluoromethyl)-aziridines **81** toward ring-opened products by using Lewis acids as catalysts and aliphatic amines as nucleophiles (Scheme 27). In this case, the reduced basicity of the aziridine nitrogen atom due to the strong electron-withdrawing effect of



Scheme 26



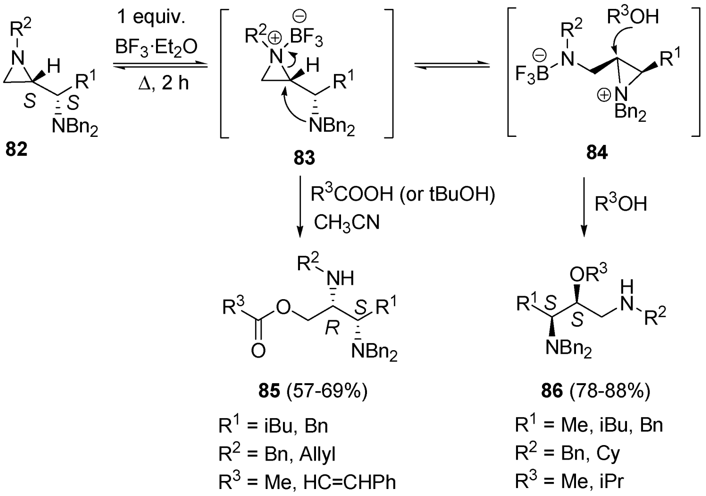
Scheme 27

the CF_3 group clearly hampered the formation of aziridinium-like intermediates.

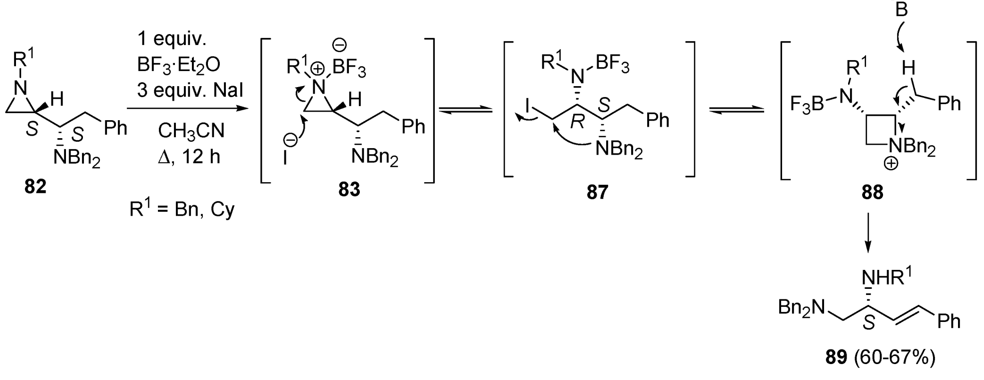
In the next part, the regioselectivity in the ring opening of 2-(1-aminoalkyl)aziridines **82** was described to be dependent on the type of nucleophile used to open the aziridinium moiety. In a detailed study, Concellón *et al.*[38] have reported the ring opening of aziridines **82** by alcohols and carboxylic acids in the presence of $BF_3{\cdot}Et_2O$, providing C3 (**85**) and C2 (**86**) ring-opening products, respectively (Scheme 28). It was suggested that, after coordination of the aziridine nitrogen to the Lewis acid, an intramolecular ring opening at C2 by nucleophilic attack of the dibenzylamino group afforded the aziridinium salts **84** with inversion of configuration. Alcohols (R^3OH) induced ring opening of aziridinium salts **84** to afford 2-alkoxy-1,3-diamines **86**, with a second inversion of configuration at the C2. In the case of *tert*-butylalcohol the reaction takes place through **83** due to steric hindrance. In the presence of a carboxylic acid, the prevalence of intermediates **84** may be diminished due to protonation of the dibenzylamino group, reducing its ability to open the aziridine to form **84**, which resulted in the nucleophilic attack of carboxylic acid at the less hindered carbon atom of intermediate **83**.

Furthermore, the use of iodide as a nucleophile in the ring-opening reaction of aziridines **82** in the presence of $BF_3{\cdot}Et_2O$ gave 4-phenylbut-3-en-1,2-diamines **89** (Scheme 29). It was assumed that the iodide attacks the aziridine ring at C3 affording iodo diamines **87**. These intermediates are prone to undergo ring closure to produce azetidinium salts **88**, which undergo a spontaneous α-elimination yielding chiral diamines **89**.[38] However, the possible complexation of both nitrogen atoms in aziridine **82** with the Lewis acid might influence the regiochemical pathway in this reaction.

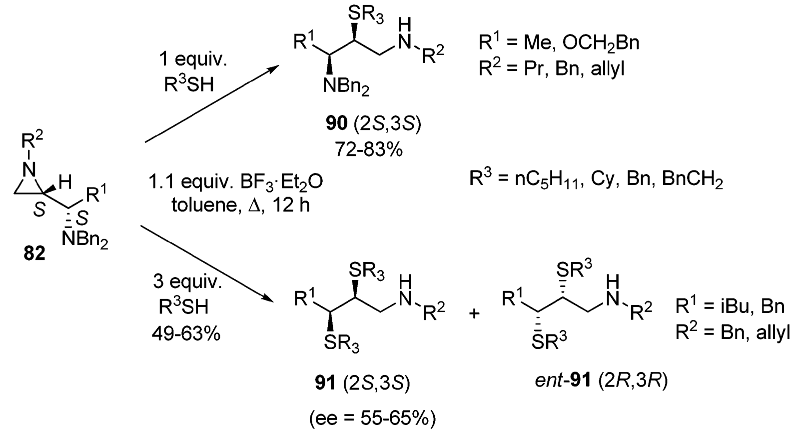
The ring opening of 2-(1-aminoalkyl)aziridines **82** by other nucleophiles has also been studied by the same group. For example, the $BF_3{\cdot}Et_2O$-mediated ring-opening reactions of aziridines **82** with water have been shown to be completely regio- and stereoselective, involving ring opening at C2 and retention of configuration at this center.[39]



Scheme 28



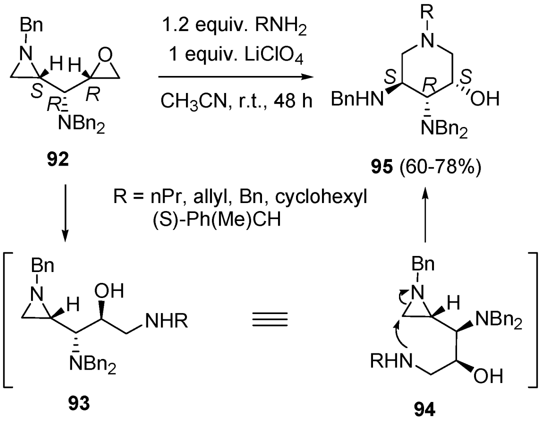
Scheme 29



Scheme 30

Furthermore, the reaction of 2-(1-aminoalkyl)aziridines **82** (R^1 = Me, $BnOCH_2$) with one equiv. of a thiol also proceeded regio- and stereoselectively, and it was shown that one alkylthio group was incorporated in the final product **90**.[40] When slightly modified reaction conditions (*i.e.* 3 equiv. of thiols, $BF_3{\cdot}Et_2O$ and reflux) were applied to aziridines **82** (R^1 = Bn, iBu), (2*S*,3*S*)-2,3-bis(alkylthio)alkan-1-amines **91** were isolated instead (Scheme 30). ^{1}H and ^{13}C NMR analyses of compounds **91** showed the incorporation of two alkylthio groups and the disappearance of signals corresponding to the dibenzylamino group. No other regio- or diastereoisomers were observed in the crude reaction mixtures. It has been demonstrated that the regioselectivity of this reaction is also dependent on the nature of the substituent R^1.

Although this particular example falls outside the scope of this review, the participation of the C2 aziridine substituent in ring openings has also been shown in the reaction of epoxyaziridine **92** with primary amines in the presence of lithium perchlorate. The reaction has been carried out with total chemo- and regioselectivity, affording chiral polyfunctionalized piperidines **95** as the sole products in good yields.[41] The formation of compounds **95** can be explained by amine-induced ring opening of the oxirane ring at the less hindered position to afford diamino alcohols **93** (Scheme 31). Theoretically, this intermediate could further react through aziridine ring opening by the hydroxyl group or through the amine function, yielding tetrahydrofurans, pyrrolidines, or piperidines. However, trisubstituted piperidines **95** were detected as the sole reaction products. Apparently, the terminal amino group in intermediate **94** participates in an intramolecular nucleophilic attack across the aziridine ring—probably activated by the Lewis acid, although previous reports suggested otherwise[38,39]—at the less hindered position, affording the piperidine ring system.

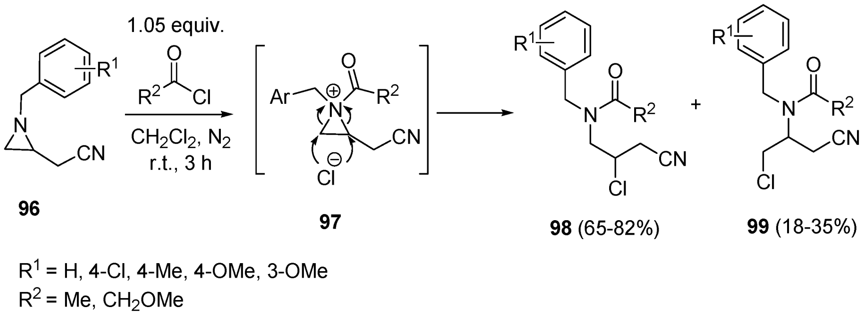


Scheme 31

Aziridinium ion formation through *N*-acylation or *N*-carboxylation

In comparison with acid- and Lewis acid-catalyzed reactions, the ring opening of 2-alkylaziridines with acyl halides showed to be less straightforward, providing either single C2 ring-opening products or regioisomeric mixtures depending on the type of electrophile for the activation of the aziridine moiety. Treatment of 2-(cyanomethyl)aziridines **96** with an acid chloride in dichloromethane resulted in a mixture of β-chloroamine derivatives **98** as the major constituents and regioisomers **99** as the minor products (Scheme 32).[42] The acid chloride readily reacts with the basic nitrogen lone pair of aziridines **96**, affording highly electrophilic aziridinium intermediates **97** which are prone to undergo ring opening by the *in situ* liberated chloride anion. A distinct preferential attack of chloride at the more hindered aziridine carbon was observed, affording mainly *N*-(2-chloro-3-cyanopropyl)amides **98** in good yields. The formation of the minor regioisomers **99** is the result of the ring opening of aziridinium salts **97** at the less hindered position.

Applying the same reasoning, Higashiyama *et al.*[43] have explained a new method for the preparation of chiral β-amino alcohols **104** through a regio- and stereocontrolled ring opening of chiral aziridines **100**. The high regio- and stereocontrol of this transformation is probably due to the intermediacy of *N*-acylaziridinium salts **101** resulting from the reaction with acetyl chloride (Scheme 33). Subsequently, these *N*-acylaziridinium salts **101** undergo a ring-opening reaction *via* an anti-attack of chloride at the C2 position. Next, the resulting *N*-acyl-β-chloroamines **102** are readily converted into the transient oxazolinium derivatives **103** through internal



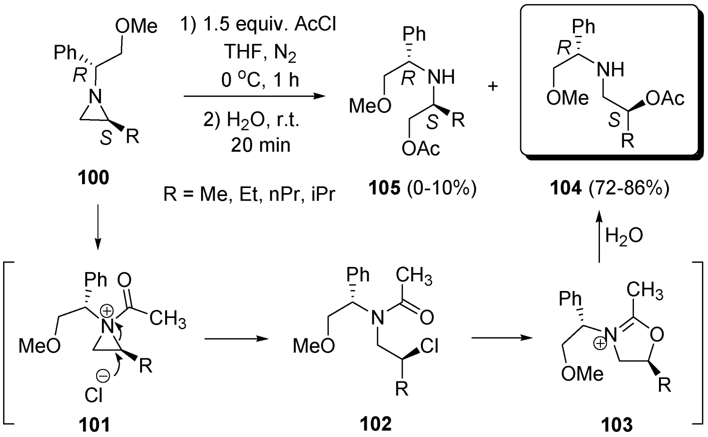
Scheme 32

chloride displacement by the oxygen nucleophile. Finally the oxazolinium derivative **103** is hydrolyzed to yield β-amino alcohols **104** as the major products.

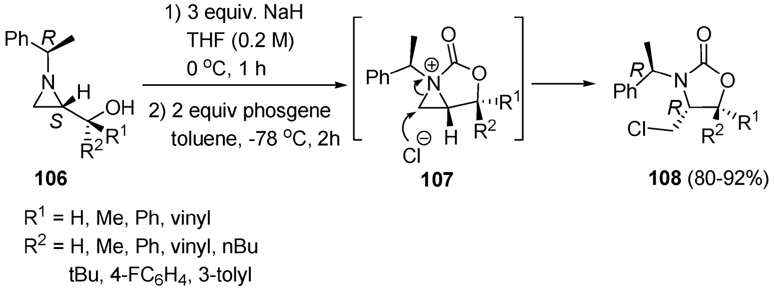
However, when phosgene, carbon dioxide or carbonyldiimidazole (CDI) was used to activate the ring, the less substituted carbon atom appeared to be the more favored place for nucleophilic attack. Thus, a highly regioselective nucleophilic ring opening of 2-(1-hydroxyalkyl)aziridines **106** in the presence of phosgene has been observed to afford oxazolidinones **108** (Scheme 34).[44] Phosgene acts as a cyclizing agent of the amino alcohol moiety to form reactive cyclic carbamates **107**, which suffer from ring opening by the chloride ion at the less hindered side of the aziridine moiety to form oxazolidinones **108**. In the same manner, 2-(aminomethyl)aziridines have been converted to valuable 4,5-disubstituted imidazolin-2-ones by treatment with triphosgene and NaH in THF.[45]

In a similar way, the same oxazolidinone derivatives have been prepared starting from 2-(hydroxymethyl)aziridines and iodotrimethylsilane in the presence of carbonyldiimidazole (CDI).[46]

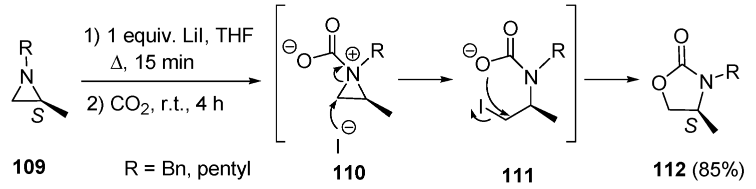
Finally, in order to explain the conversion of enantiomerically pure 2-methylaziridines **109** into oxazolidinones **112** using CO_2, Pinhas and Hancock suggested two possible mechanisms, one of which is shown in Scheme 35.[47] This approach concerns the reaction of CO_2 with the aziridine nitrogen atom (*N*-carboxylation) to give aziridinium ion **110**, which then undergoes ring opening by iodide to generate intermediate **111**. Spontaneous cyclization of the latter intermediate produces 4-methyloxazolidinone **112** as the major regioisomer. In addition, to a minor extent, the aziridinium salt **110** is attacked at the more hindered carbon atom and gives the isomeric 5-methyloxazolidinone as the final product.



Scheme 33



Scheme 34



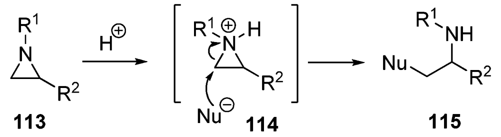
Scheme 35

In light of the known reactivity of non-activated aziridines, however, the addition of aziridine **109** across CO_2 is highly unlikely. Thus, the other proposed pathway, consisting of the initial ring opening of aziridine **109** by iodide to form the corresponding β-iodoamine, followed by addition of this lithium amide across CO_2 and subsequent ring closure, seems to be much more plausible. In addition to the proposed routes, the alternative way for the formation of the corresponding products *via* [2 + 3] cycloaddition should not be completely excluded.

Aziridinium ion formation through *N*-protonation

In general, the ring-opening reactions of 2-alkylaziridines **113** in the presence of different acids take place with high regioselectivity, revealing the C3 position of the aziridine ring as the most favorable place for nucleophilic attack (Scheme 36).

For example, the ring opening of 2-alkylaziridines **116** by acetic acid in dichloromethane has been shown to be a very efficient method for the regioselective formation of β-amino alcohol derivatives **118**, indicating that acetate attacks the less sterically hindered C3 position of the intermediate aziridinium salts **117** (Scheme 37).[48–57]

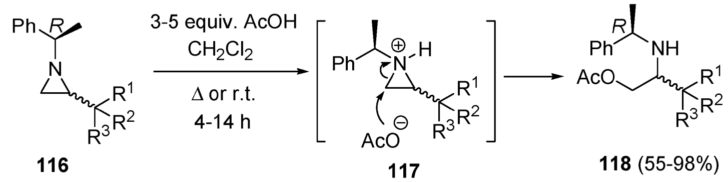


Scheme 36

In addition, Higashiyama *et al.*[43] have performed a number of reactions on the chiral 2-alkyl-substituted aziridines **100** using acetic acid to yield the ring-opening products **119** after C3–N bond cleavage of the aziridine ring. In most cases, these reactions showed excellent regioselectivity, except in the case of a sterically small substituent (R = Me, ratio **119**/**120** = 8/1) (Scheme 38).

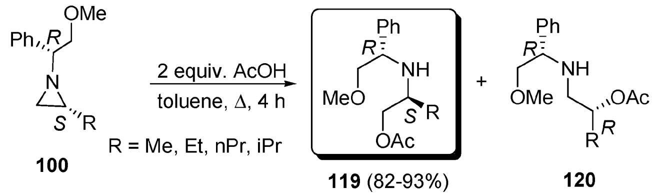
Also, 1-benzyl-2-(trifluoromethyl)aziridine **81** was shown to be a good substrate for acid-promoted ring-opening reactions with different nucleophiles, furnishing β-cleaved products **122** (β-amino halides, alcohols, ethers, sulfides and selenides) in good yields (40–98%) (Scheme 39).[37] Therein, it has been observed that sulfuric acid-catalyzed ring opening of aziridine **81** by EtOH and ring-opening reactions of the same aziridine **81** by PhSH, promoted by sulfuric or trifluoromethanesulfonic acid, resulted in higher yields of the corresponding β-aminoethers **122** (Nu = OEt) or β-aminosulfides **122** (Nu = SPh), respectively.[37]

Recently, ring opening of 1-arylmethyl-2-(cyanomethyl)-aziridines **96** with HBr has been reported to afford 3-(arylmethyl)-amino-4-bromobutyronitriles **124** *via* regiospecific ring opening



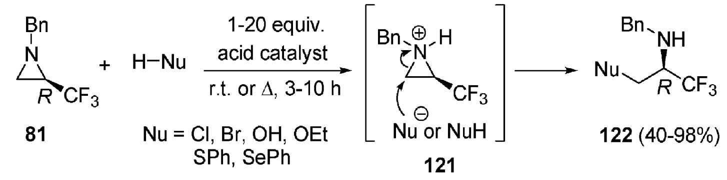
R^1 = H, iBu, OH
R^2 = Et, iBu, $C_{15}H_{31}$, OH, OTBS
R^3 = H, OMe, 3-(C_8H_{17})C_6H_4, 4-(C_8H_{17})C_6H_4, CH(OH)$C_{14}H_{29}$
Bn, $CH_2COOtBu$, Ph, Me, tBu, 1-naphthyl, 2-MeC_6H_4
2-MeOC_6H_4, 2-naphthyl, 4-ClC_6H_4, 4-FC_6H_4, O-(2-iodo)C_6H_4
O-(2-bromo-4-fluoro)C_6H_4, O-(2-bromo)naphthyl, 2-iodobenzyl
CH_2-(2-bromo)naphthyl, HC≡C$C_{13}H_{27}$

Scheme 37

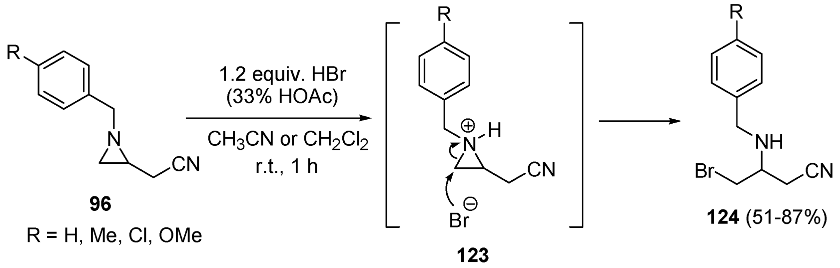


	119/120
R = Me	89/11
R = Et	97/3
R = nPr	95/5
R = iPr	99/1

Scheme 38



Scheme 39

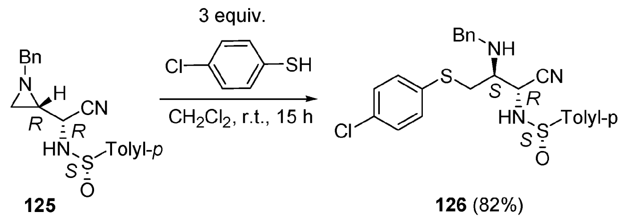


Scheme 40

at the unsubstituted aziridine carbon atom of the intermediate aziridinum salts **123** (Scheme 40).[58]

Furthermore, the ring-opening reaction of chiral α,β-diaminonitrile **125** with 4-chlorothiophenol afforded the corresponding α-(*N*-sulfinylamino)-β-benzylaminonitrile **126** in 82% yield (Scheme 41).[59]

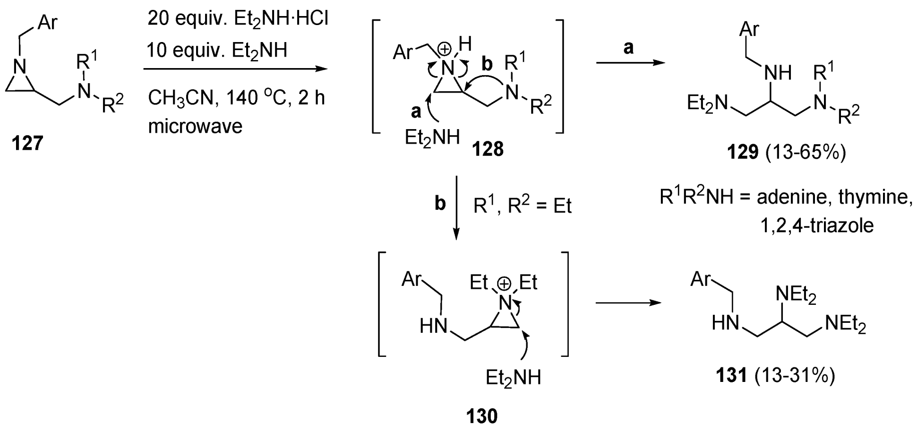
In the same manner, the treatment of 2-(hydroxymethyl)-aziridines with thiophenol has been described to lead to the exclusive formation of the ring-opened β-amino alcohols after attack of the thiolate anion at the less sterically hindered C3 position.[60,61] The nitrogen atom of an aziridine is a sufficiently strong base to pick up the proton from the thiol, resulting in an aziridinium intermediate which is further attacked by a thiophenolate ion. A kinetic study of this ring-opening reaction showed that the reaction rate increases with the acidity of thiols.[58] Following the same regiospecific route, the reaction of enantiomerically pure 2-(hydroxymethyl)aziridines with acetic acid or thiophenols has been used as an efficient protocol for preparing optically active oxazolidinones.[44]



Scheme 41

A highly C3 regioselective ring opening has also been observed in the reactions of 2-(aminomethyl)aziridines with alcohols in the presence of one equiv. of *p*-toluenesulfonic acid in CH_3CN/ROH (7/1).[38] The same aziridines were also reacted with water in the presence of *p*-toluenesulfonic acid to afford 2,3-diaminoalkan-1-ols in high yields. Depending on the conditions applied, small amounts of the C2 ring-opening products were isolated in some cases.[39]

In a recent report,[62] 2-(aminomethyl)aziridines **127**, prepared *via* nucleophilic substitution of 2-(bromomethyl)aziridines[63] with different amines, were subjected to the diethylamine/diethylamine hydrochloride system in acetonitrile using microwave irradiation. In this way, biologically relevant 1,2,3-triaminopropanes **129** were formed after ring opening of intermediate activated species **128** at the less hindered carbon atom of the aziridinium ion (path a, Scheme 42).

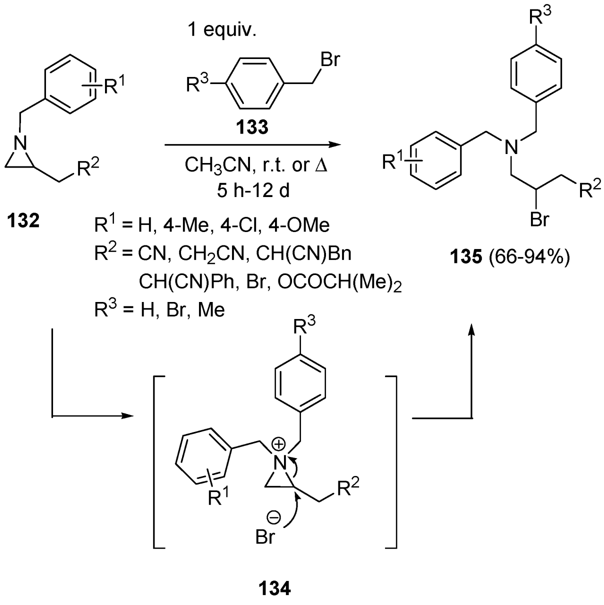


Scheme 42

However, in the case of 2-(*N*,*N*-diethylaminomethyl)aziridines **127** ($R^1 = R^2 = Et$), a mixture of regioisomers (**129**/**131** = 3/2) was obtained. This was explained by an additional rearrangement of aziridinium salts **128** to the corresponding 1,1-diethylaziridinium intermediates **130**, which were subsequently attacked by diethylamine at C3 to furnish 1-(arylmethyl)amino-2,3-bis(*N*,*N*-diethylamino)propanes **131** (path b, Scheme 42).

Aziridinium ion formation through *N*-alkylation

2-(Bromomethyl)-, 2-(aryloxymethyl)-, 2-(alkanoyloxymethyl)-, 2-(cyanomethyl)-, and 2-(2-cyanoethyl)aziridines **132** show the same reactivity toward arylmethyl bromides **133** in acetonitrile, giving a regiospecific ring opening of the intermediate aziridinium salts **134** by bromide attack at the more hindered aziridine carbon atom, affording ring-opened products **135** in high purity (Scheme 43). For example, treatment of 1-arylmethyl-2-(cyanomethyl)aziridines **132** ($R^2 = CN$) with benzyl bromide **133** ($R^3 = H$) in acetonitrile afforded 4-amino-3-bromobutanenitriles **135**,[58,64] and 2-(2-cyanoethyl)aziridines **132** ($R^2 = CH_2CN$) afforded novel 5-amino-4-bromopentanenitriles **135** in excellent yields after reflux for 5 h.[65,66] 4-Amino-3-bromobutanenitriles **135** ($R^2 = CN$) could be further transformed into 3,4-diaminobutanenitriles *via* nucleophilic attack of pyrrolidine at the more hindered carbon atom of the same aziridinium intermediate **134**.[64] Analogously, treatment of 2-(aryloxymethyl)aziridines **132** ($R^2 = OAr$) with benzyl bromide in acetonitrile also afforded *N*-(2-bromo-3-aryloxypropyl)amines **135** as the sole reaction products.[32,67]

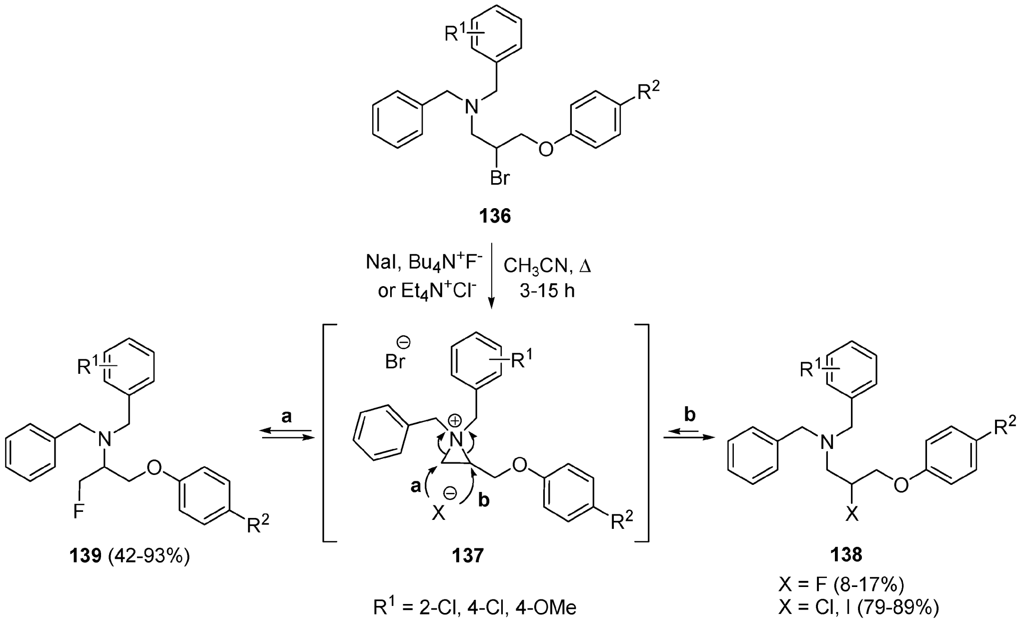


R^1 = H, 4-Me, 4-Cl, 4-OMe
R^2 = CN, CH_2CN, CH(CN)Bn, CH(CN)Ph, Br, $OCOCH(Me)_2$
R^3 = H, Br, Me

Scheme 43

In another study, β-bromoamines **136** were used to provide the corresponding chlorides, iodides and fluorides by treatment with different halide sources ($Et_4N^+Cl^-$, NaI and $Bu_4N^+F^-$).[32] In the case of chlorides and iodides, the intermediate aziridinium species **137** were regioselectively opened at the C2 position affording secondary halides **138**, while in the case of fluorides a mixture of regioisomers **138** and **139** was obtained, in which the primary fluorides **139** were predominant (ratio **139**/**138** = 5.6/1) (Scheme 44). It has been demonstrated that bromide-, iodide- and chloride-promoted ring opening of aziridinium ions **137** is under thermodynamic control while ring opening with fluorides is kinetically controlled, which can be attributed to the poor leaving-group capacity of fluoride as compared to the other halides, which prevents thermodynamic equilibration.

Aziridine ring opening at the more substituted carbon atom of the aziridine moiety has also been observed in a study on enantiomerically pure 2-(aryloxymethyl)aziridines.[68] The same observations were deduced in the case of 2-(bromomethyl)-[69] and



X = F (8-17%)
X = Cl, I (79-89%)

R^1 = 2-Cl, 4-Cl, 4-OMe
R^2 = H, Cl

Scheme 44

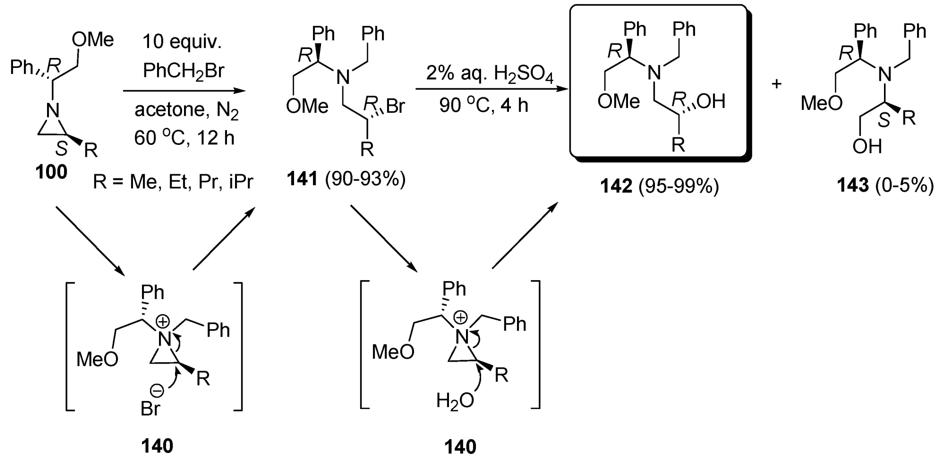
2-(alkanoyloxymethyl)aziridines,[70] affording 1-[di(arylmethyl)-amino]-2,3-dibromopropanes and *N*-(2-bromo-3-alkanoyl-oxypropyl)amines, respectively, upon treatment with benzyl bromide in acetonitrile.

In accordance with these results, chiral aziridines **100** have been shown to afford β-bromoamines **141** upon treatment with benzyl bromide by C2–N bond cleavage of the aziridinium salts **140**. Next, treatment of β-bromoamines **141** with 2% aqueous sulfuric acid at 90 °C for 4 h gave, through formation of the same intermediates **140**, the β-amino alcohols **142** in good yields *via* ring opening at C2 (Scheme 45).[43]

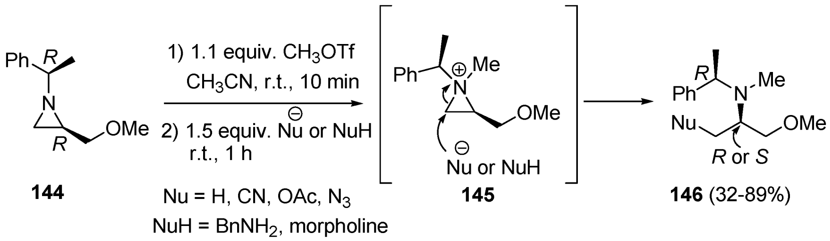
When (2*R*)-[(1*R*)-phenylethyl]-2-(methoxymethyl)aziridine **144** was treated with methyl trifluoromethanesulfonate (CH_3OTf), followed by reaction with different nucleophiles such as N_3^-, AcO^-, CN^-, morpholine, $BnNH_2$ and H^-, single regioisomers **146** were obtained through ring opening at the less hindered side (C3) (Scheme 46).[8]

The opposite regioselectivity in the ring opening of intermediates **145** as compared to the reactions with benzyl bromide (C2 selectivity) probably derives from the nature of the nucleophile used in these ring-opening reactions. This can further be sustained considering the synthesis of β-haloamines in the reactions of the same substrates **144**, activated with CH_3OTf, with different halide sources ($Bu_4N^+X^-$) to yield mixtures of regioisomers **147** and **148** depending on the halide used.[32] Therein, as in the case of benzyl bromide, a complete C2 regioselectivity was observed in the synthesis of secondary bromides, iodides and chlorides **148** (X = Br, I, Cl), whereas in the case of fluorides a regioisomeric mixture of primary and secondary fluorides **147** and **148** (3 : 1, X = F) was obtained (Scheme 47). It was shown that the ring-opening reactions of 1,1,2-trialkyl-aziridinium ions **145** with chlorides, bromides and iodides take place under thermodynamic control, while fluoride-induced ring opening proceeded under kinetic control (*vide supra*).[32]

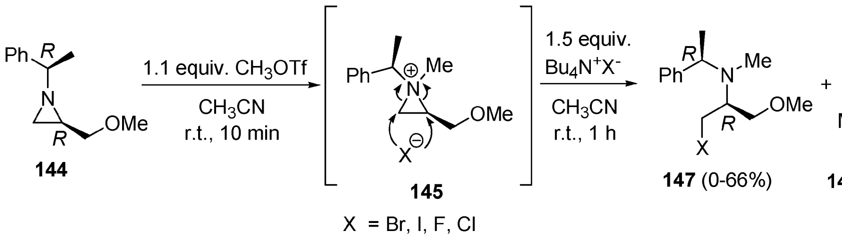
A C3 regioselectivity has been observed in the methylation of the nitrogen atom of 2-(trifluoromethyl)aziridine **81** by either $MeI{\cdot}AgBF_4$ or $Me_3O^+{\cdot}BF_4^-$ to form the intermediate aziridinium salt **149**, which is then ring opened by various nucleophiles at the less hindered carbon atom to afford chiral amines **150** (Scheme 48).[37]



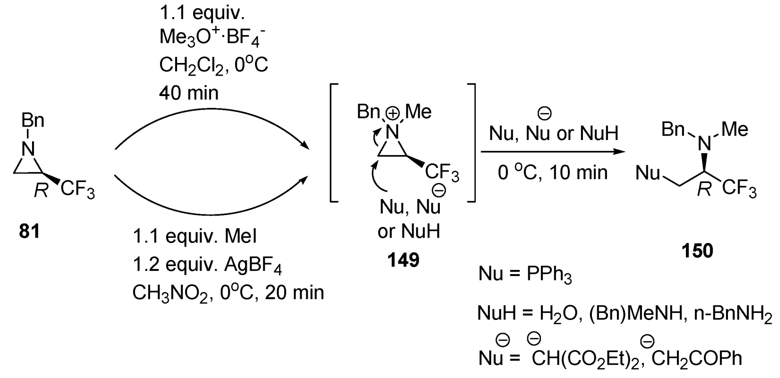
Scheme 45



Scheme 46



Scheme 47



Scheme 48

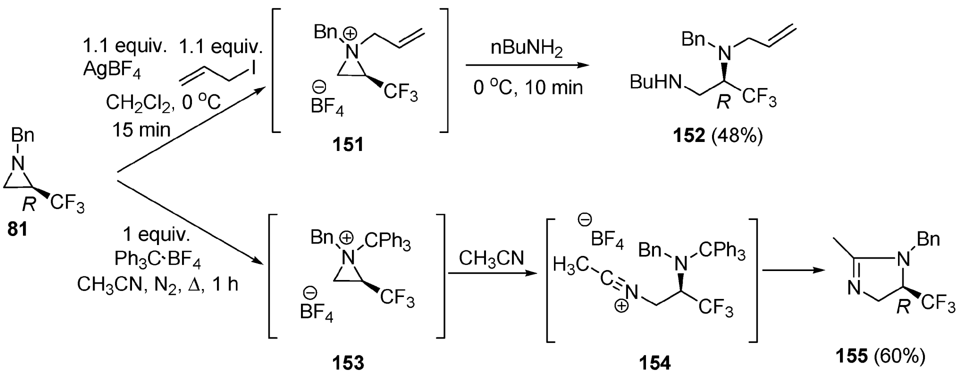
Although *N*-methylation is useful to induce ring opening, it is less suitable if further synthetic elaboration is required because of the associated difficulty in the deprotection. Therefore, *N*-allylation and *N*-tritylation of aziridine **81** have been investigated in the same work.[37] To prepare practically useful *N*-protected compounds, allyl iodide was allowed to react with aziridine **81** in the presence of $AgBF_4$. The generated aziridinium salt **151** was then quenched with *n*-$BuNH_2$, resulting in the production of diamine **152** in 48% yield (Scheme 49). Alternatively, the trityl group was introduced using $Ph_3C{\cdot}BF_4$ in acetonitrile. The aziridinium salt **153** underwent a Ritter type reaction with acetonitrile, and subsequent cyclization produced imidazoline **155** in 60% yield.

In a recent report, intramolecular alkylation of aziridines **156** (or their diastereomeric counterparts), prepared *via* alkylation of 2-(2-cyano-2-phenylethyl)aziridines[65] with 1-bromo-2-chloroethane, was shown to be useful for the preparation of stereodefined piperidines **158** after regiospecific nucleophilic attack by chloride at the less hindered carbon atom of the aziridine moiety in bicyclic aziridinium intermediates **157** (Scheme 50).[71] Bicyclic aziridinium intermediates have frequently been reported in the literature, although usually they are formed through nucleophilic displacement within larger azaheterocyclic ring systems such as 2-(halomethyl)azetidines,[72] -pyrrolidines[73] and -piperidines.[74] These examples fall outside the scope of this review and will thus not be dealt with here.

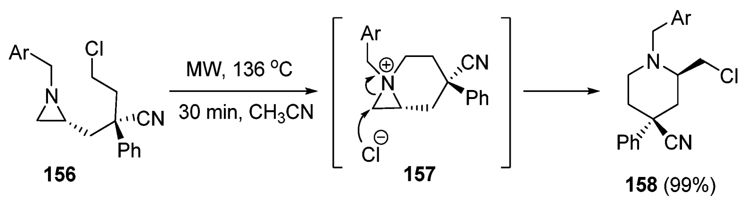
Bearing in mind the above-described reports, it can be concluded that regioselectivity in the ring opening of 2-alkylaziridines, activated through alkylation, is dependent on the substrate, nucleophile and alkylating reagent used in these reactions.

Activation and ring opening of 2-alkylaziridines *via* silylation

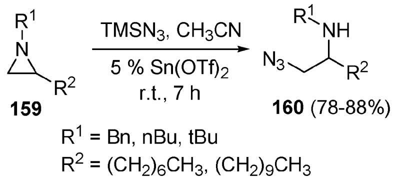
It has been reported that 2-alkylaziridines undergo ring opening at the less substituted aziridine carbon atom upon treatment with $TMSN_3$, which has been used for the activation of the aziridine ring and to provide azide as a nitrogen source to attack one of the aziridine carbon atoms. For example, the



Scheme 49



Scheme 50

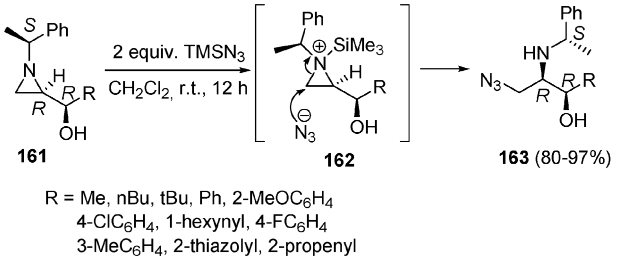


Scheme 51

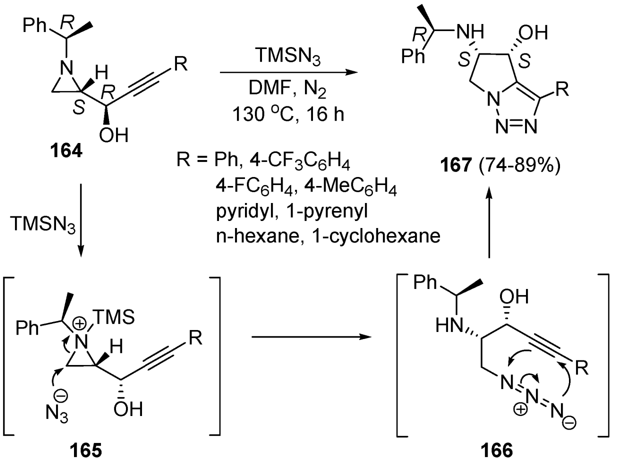
ring opening of 2-alkylaziridines **159** with TMSN$_3$ in acetonitrile using 5 mol% of Sn(OTf)$_2$ has been shown to be very effective and provided high yields of the corresponding azides **160**, resulting from azide attack at the less hindered side of the aziridine ring (Scheme 51).[75]

Similarly, the ring opening of chiral 2-(1-hydroxyalkyl)-aziridines **161** has been shown to give β-azidoamines **163** through C3–N bond cleavage by the azide nucleophile (Scheme 52).[76] Furthermore, aziridines **161** can be regioselectively opened with iodide from iodotrimethylsilane (TMSI) to yield β-iodoamines through C3 ring opening.[76]

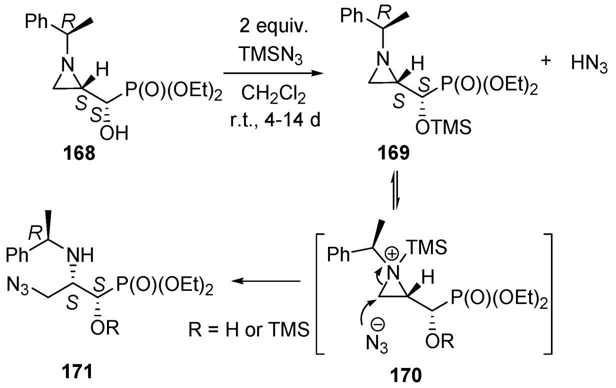
The same behavior of 2-alkylaziridines has also been described in the synthesis of bicyclic triazoles **167**, which were obtained when chiral 1-(aziridin-2-yl)propargylic alcohols **164** were reacted with azidotrimethylsilane (Scheme 53).[77] It has been suggested that the silylation of the aziridine nitrogen atom provided the activated aziridinium species **165**, which were then regioselectively opened through fission of the C3–N bond by nucleophilic attack of the *in situ* liberated azide toward azido alcohols **166**. Consequently, an intramolecular 1,3-dipolar cycloaddition efficiently converted azido alkynes **166** to the corresponding bicyclic triazoles **167**.



Scheme 52



Scheme 53



Scheme 54

Finally, in a report by Wróblewski and Drozd,[78] the regioselective ring opening of chiral 2-substituted aziridinephosphonates **168** has been investigated. After optimizing the reaction conditions, 3-azido-1-hydroxyphosphonates **171** (or their O-TMS derivatives) were obtained in high yields. Whereas initially *N*-silylated aziridinium species **170** could be invoked as intermediates, the authors suggested an alternative pathway involving silylation of the hydroxyl group in phosphonates **168** or hydrolysis of trimethylsilyl azide with adventitious water to produce hydrogen azide, which transforms the aziridine ring into intermediate aziridinium ions through *N*-protonation. Under these conditions, regiospecific ring opening by azide at the C3 position takes place (Scheme 54).[78]

6. Theoretical aspects and insights obtained *via* computational chemistry

In recent years, high-level computational analyses have been deployed successfully to shed more light on the reactivity profile of aziridinium intermediates and to provide a rationale for experimentally observed regio- and stereochemical preferences in their ring opening reactions.[32,58,64,68,79,80] In this section, a short overview of recent achievements in that respect is presented.

The nucleophile-dependent regioselectivity in the ring opening of the chiral 1-benzyl-1-(α(*R*)-methylbenzyl)-2(*S*)-(phenoxymethyl)aziridinium ion (i, Fig. 1) has been subjected to several

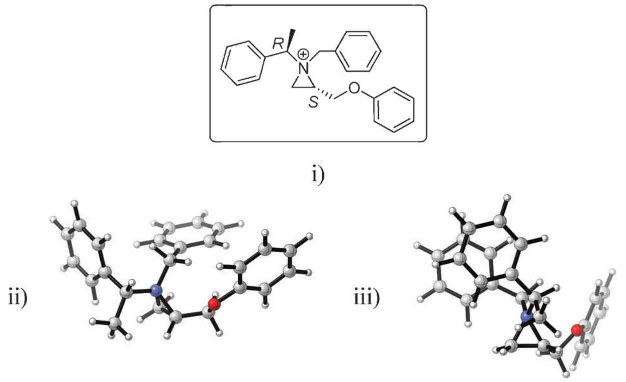
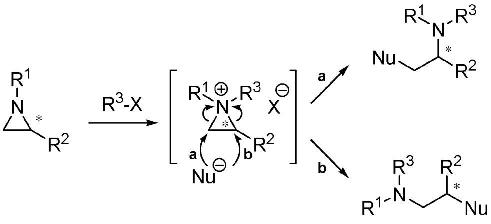


Fig. 1 (i) Intramolecular π–π stacking in 1-benzyl-1-(α(*R*)-methylbenzyl)-2(*S*)-(phenoxymethyl)aziridinium ion. (ii) T-stacking. (iii) Parallel-displaced.

computational studies to rationalize the observed experimental outcomes. Intramolecular π–π stacking interactions among aromatic substituents were identified and suggested to add stability to these intermediate species. T-stacking interactions were shown to be more favourable than parallel-displaced conformations (ii and iii, Fig. 1).[80] Another critical aspect in simulations was the effective inclusion of the solvent environment, since nucleophilic substitution reactions are known to be highly influenced by the nature of the solvent. The qualitative pictures of the energy landscapes were shown to be significantly dependent on the inclusion of the solvent and in the absence of these critical stabilizing effects, experimentally observed regioselectivities could not be reproduced.



Scheme 55

The role of the nucleophile was investigated by considering hydride donors (borohydride and aluminium hydride) as well as halides and their propensities for attacking the unsubstituted (pathway a) *versus* substituted (pathway b) aziridine carbons (Scheme 55).

In the case of hydride donors (BH_4^- and AlH_4^-), the attack at the less hindered ring carbon of the 1-benzyl-1-(α(*R*)-methylbenzyl)-2(*S*)-(phenoxymethyl)aziridinium ion (Fig. 1) was shown to be the kinetic route and incidentally led to the thermodynamically favourable product (Fig. 2),[79,80] as observed experimentally.

However, a systematic study for the ring opening in the halide series revealed that the rationale behind the observed regioselectivities for the halides was less straightforward.[32] The overall picture for halide-induced ring opening showed that the less hindered route (pathway a) is always kinetically preferred, yet the hindered route leads to the thermodynamic product (Fig. 3). However, the eventual outcome depends on the hardness/softness and leaving group ability of the nucleophile (halide). If the nucleophile is a good leaving group (soft

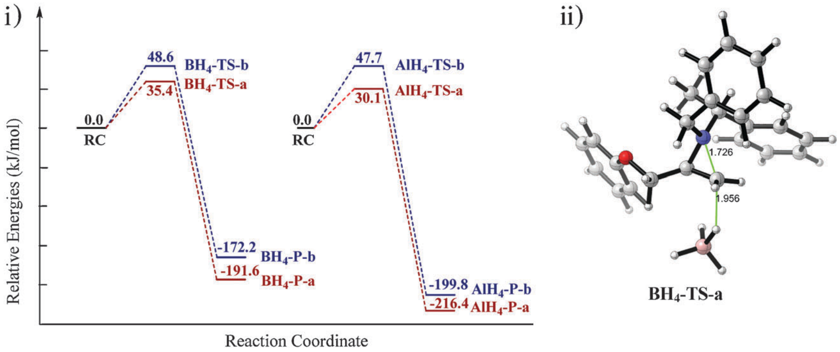


Fig. 2 (i) Free energy profile for the hydride-induced ring opening of the 1-benzyl-1-(α(*R*)-methylbenzyl)-2(*S*)-(phenoxymethyl)aziridinium ion (Fig. 1) at the less hindered (pathway a) and hindered (pathway b) ring carbons. (ii) Transition state geometry for bromohydride attack at unhindered aziridine carbon (SCS-MP2/6-31++G(d,p))//B3LYP/6-31++G(d,p) at 298 K and 1 atm).

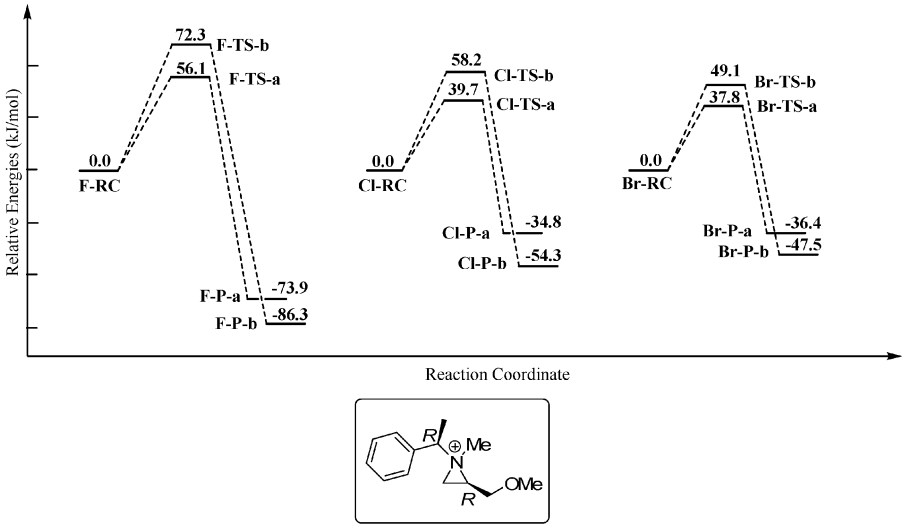


Fig. 3 Free energy profile for the halide-induced ring opening of the 1-methyl-1-(α(*R*)-methylbenzyl)-2(*R*)-(methoxymethyl)aziridinium ion at the less hindered (pathway a) and hindered (pathway b) ring carbons (MPW1B95/6-31++G(d,p)//B3LYP/6-31++G(d,p) at 298 K and 1 atm).

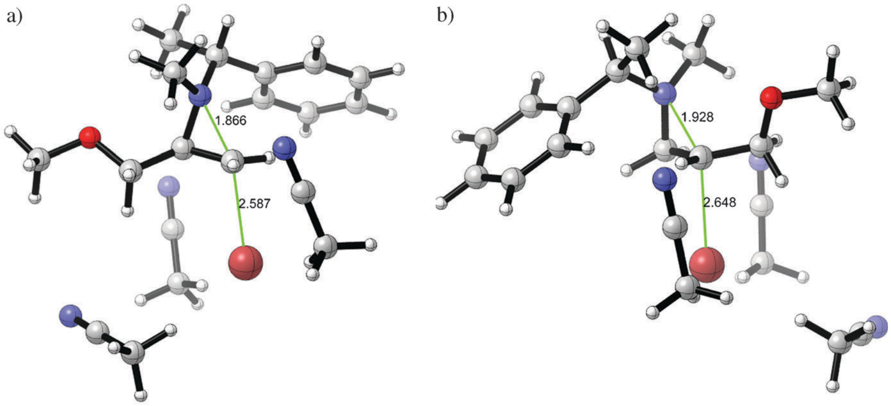


Fig. 4 Transition state geometries for bromide attack on the (a) less hindered and (b) hindered carbon atom of the 1-methyl-1-(α(*R*)-methylbenzyl)-2(*R*)-(methoxymethyl)aziridinium ion (Fig. 3) (MPW1B95/6-31++G(d,p)//B3LYP/6-31++G(d,p)).

nucleophile, bromide), back reaction barriers are sufficiently low to allow equilibration and the thermodynamic product will prevail. If the nucleophile is a poor leaving group (hard nucleophile, fluoride), the back reaction is unlikely and the kinetic route will dictate the reaction outcome.

For the chloride case, equilibration is slow, and therefore the kinetic product is initially observed during the reaction. However, the final product is dictated by thermodynamic stability. In the case of bromides, equilibration is so rapid that the initial formation of the kinetic product is not observed and the thermodynamic product forms immediately. Theoretical results were in perfect agreement with experimental findings, also pointing to the well-known trend in nucleophile strength and leaving group ability throughout the halide series. Explicit solvation (Fig. 4, acetonitrile molecules) was used to stabilize ionic species, as this was proven to significantly influence the energy landscape of S_N2 reactions.[32,58,64,68,80,81]

7. General overview and conclusions

The ring-opening reactions of non-activated 2-substituted aziridines **1** have been described in a large number of reports, providing an insight into the regioselectivity depending on the nature of the nucleophile, the type of activation of the aziridine moiety and the nature of the substituents on the aziridine ring. These reactions proceed *via* formation of intermediate aziridinium ions **2**, which are then opened at the more (path a) or/and the less substituted carbon atom (path b) toward amines **3** and **4**, respectively (Scheme 1). Based on these data, a general overview is provided in Table 1 as a practical guide. Bearing this in mind, it might be possible to predict a regioselective preference for other so far unexamined ring-opening reactions of non-activated 2-substituted aziridines as well.

Table 1 Regioselectivity in the ring opening of non-activated 2-substituted aziridines depending on the substrate and the electrophile

	E^+				
R^1	LA	RCO^+	H^+	R^+	TMS^+
$–CH{=}CH_2$, $–CH{=}CH–COOEt$	*C2*[b]	C2	*C2*[b]	C2	C2
Aryl	C2	C2	C2	*C2*[b]	*C2*[b]
COR, COOR, $CONH_2$	C3	C2	C2	C2	*C2*
Alkyl	C3	C2 and/or C3	C3	C3[a]	C3

[a] Only halides attack the C2 position. [b] Proposed regioselectivity (no experimental data available).

Acknowledgements

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