To my family

Mami, Tati i Bakiju

“Our virtues and our failings are inseparable, like force and matter.
When they separate, man is no more.”

Nikola Tesla

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UNIVERSITEIT GENT

Sonja Stanković

Study of non-activated 2-(bromomethyl)aziridines and 2-bromomethyl-2-methylaziridines as versatile synthons in heterocyclic chemistry

Thesis submitted in fulfillment of the requirements
for the degree of Doctor (PhD) in Applied Biological Sciences: Chemistry

Dutch translation of the title

Studie van niet-geactiveerde 2-(broommethyl)aziridinen en 2-broommethyl-2-methylaziridinen als veelzijdige bouwstenen in de heterocyclische chemie

Cover illustration:

The triangles stand for aziridine building blocks
The squares stand for azetidine building blocks
The rings stand for spirocyclic building blocks

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The author, *The promoters,*

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Kao što možete da vidite ispred, lista ljudi kojima sam se zahvalila je jako duga ali nikada ne može da se uporedi sa podrškom i ljubavi koju sam dobila od mojih dragih osoba iz Srbije.

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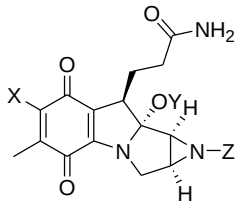
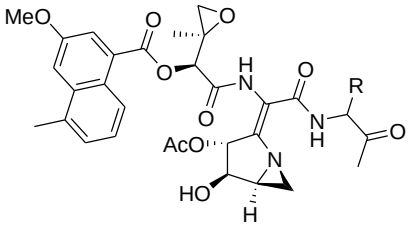
1 Introduction and Goals

Many of biologically important molecules such as drugs and natural products accommodate a heterocyclic moiety in their framework. Within the class of small, nitrogen-containing heterocycles, aziridines and azetidines comprise a remarkable group of strained compounds with diverse synthetic and biological applications.

As powerful alkylating agents, aziridines have an inherent *in vivo* potency, often based primarily on toxicity rather than specific activity.[1] There are, however, several classes of aziridine-containing natural products, for example pertaining to the Mitosane **1** and Azinomycin family **2** (Figure 1), with anti-tumor and antibiotic activity.[2]



1
Mitomycins A-C
X = OMe, NH_2; Y = H, Me;
Z = H, Me

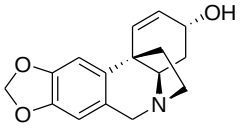


2
Azinomycins A-B
R = H, CHO

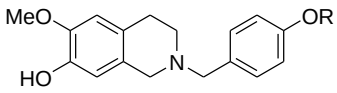
Figure 1

However, aziridines showed to be much more valuable as versatile synthons to access a window of different synthetically and biologically important molecules.[3] In terms of synthetic transformation, their utility relates to selective ring-opening reactions.[4] The transformations of these strain-loaded three-membered rings (113 kJ/mol)[5] allow for regio- and stereoselective installation of a wide range of functional groups in a 1,2-relationship with respect to the nitrogen atom.

Aziridines are also useful intermediates in the synthesis of a whole variety of natural products, such as the Amaryllidaceae alkaloid crinine **3**[6] and 2-benzylisoquinoline alkaloids sendaverine and corgoine **4a** and **4b**[7] (Figure 2).



3
Crinine



4a Sendaverine (R = Me)
4b Corgoine (R = H)

Figure 2

Aziridines can be classified as "activated" and "non-activated" depending on the type of the substituent on the ring nitrogen atom. Activated aziridines, bearing an electron-withdrawing group at the nitrogen, can easily be opened without prior activation. On the other hand, non-activated aziridines, containing

an electron-donating group at the nitrogen atom, have to be activated through quaternization prior to nucleophilic ring opening. The chemistry of non-activated aziridines is far less explored as compared to the chemistry of activated aziridines,[4,5a, 8] and therefore the main goal of this PhD thesis is to further investigate and expand the synthetic potential of this interesting class of compounds.

Next to aziridines, their higher homologues, i.e. azetidines, also exhibit a wide range of biological activities,[9] in addition to their peculiar chemical properties associated with the ring strain.[10] L-Azetidine-2-carboxylic acid **5** (Figure 3), the first azetidine natural product that has been discovered, was isolated from *Convallaria majalis* (lily of the valley) in 1955.[11] The research into the role of this molecule has shown it to be important for the inhibition of the proliferation of *Escherichia coli*, alteration of the structure of collagen, keratin and hemoglobin in human proteins, and teratogenic effects and various malformations in animals.[10d] Examples of other natural products containing an azetidine ring include mugineic acid **6**, 2'-deoxymugineic acid **7** and nicotianamine **8**, which are produced in plants to aid in the uptake of iron for chlorophyll biosynthesis.[12] Penaresidin A and B (**9** and **10**) have also been the targets of several syntheses, as they have been found to exhibit biological activity in the activation of ATPase in actomycin.[13] The most recently reported natural product containing the azetidine moiety, calydaphninone **11**, was isolated from the leaves and twigs of *Daphniphyllum calycillum* in 2007.[14] This molecule, containing a 4-azatricyclo[5.2.2.0]undecane core, represents one of the most complex azetidine-containing natural products known to date.

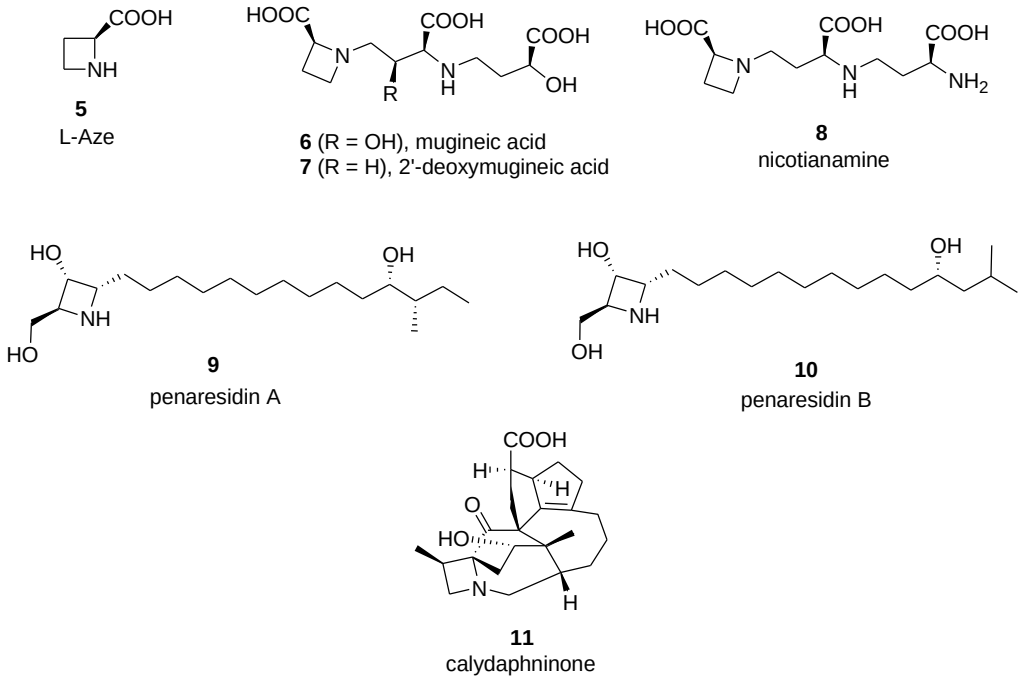


Figure 3

Among synthetically obtained azetidines, 3-substituted azetidines have been shown to possess a wide range of biological activities. For example, 1-cyclohexyl-3-guanidinoazetidine **12** exhibits antihypertensive activity,[15] and various 3-carbamoyl-oxy-substituted azetidines **13** have been used in a primary pharmacological screening showing tranquillising activity on the central nervous system of

the tested animals.[16] Furthermore, azetidine **14** and derivatives have been shown to behave as CNS stimulants devoid of peripheral anticholinergic activity,[17] and 1,3,3-trinitroazetidine (TNAZ) **15** is a member of an important class of explosives and propellants[18] (Figure 4).

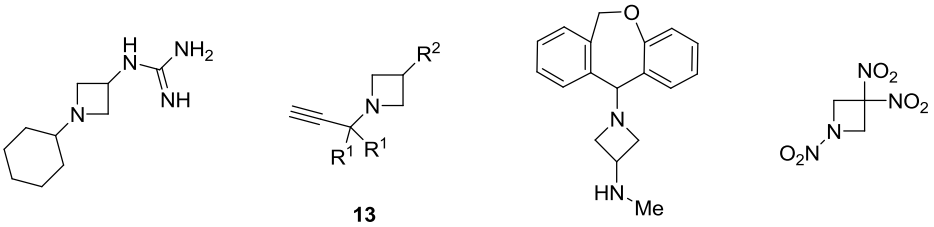
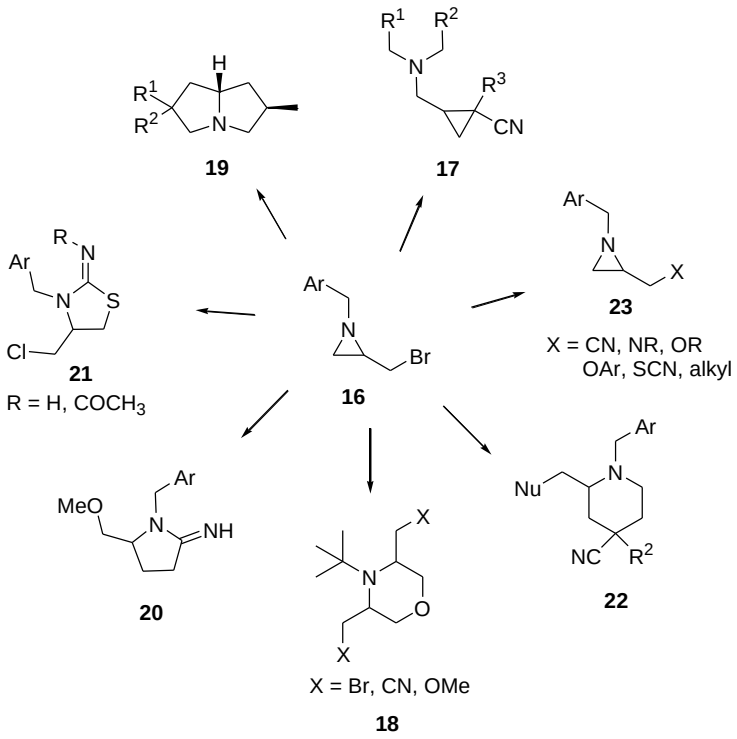


Figure 4

In light of the diverse synthetic and biological applications of azetidine-containing compounds, many efforts will be devoted to the synthesis of novel classes of functionalized azetidines and their further transformations in this doctoral study.

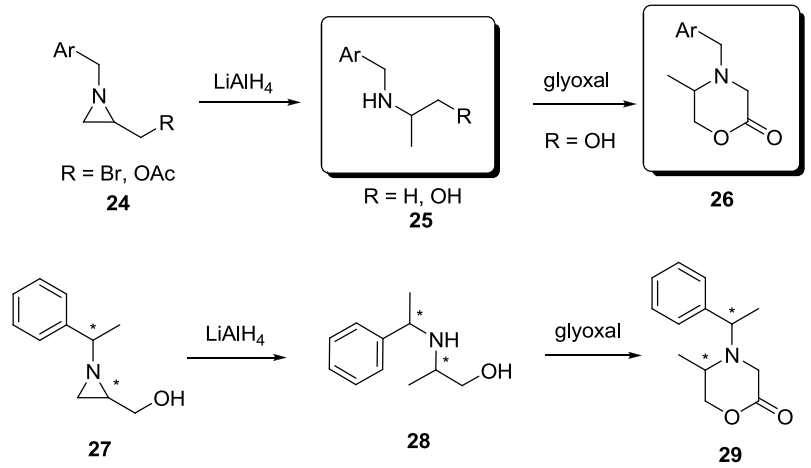
In the first part of this PhD thesis, the reactivity and synthetic potential of 2-(bromomethyl)aziridines **16** toward ring transformation and ring opening will be investigated. Aziridines **16** have proven to be valuable synthons for the preparation of wide variety of azaheterocyclic compounds and ring-opened amines such as cyclopropanes **17**,[19] morpholines **18**,[20] pyrrolizidines **19**,[21] 2-iminopyrrolidines **20**,[21] 2-imino-1,3-thiazoli(di)nes **21**[22] and piperidine derivatives **22**[23] (Scheme 1). In addition, the nucleophilic substitution of bromide in 2-(bromomethyl)aziridines with various heteroatom nucleophiles[20,22,24] and carbon nucleophiles[19,25] has provided a convenient access toward a variety of 2-substituted aziridines **23**.



Scheme 1

In comparison to the huge number of reports on the ring opening of aziridines by other nucleophiles, their ring opening by hydrides has received very limited interest in the literature despite the synthetic potential of this approach. It should be mentioned that $LiAlH_4$ has been mainly used to reduce functional groups in compounds incorporating an aziridine unit without affecting the three-membered ring itself.[26]

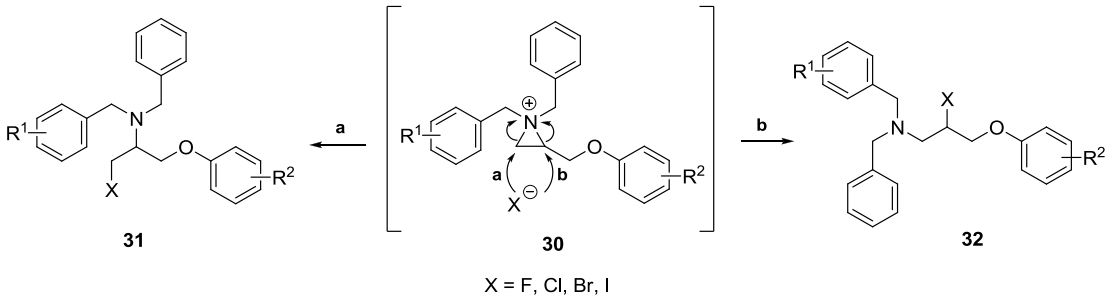
Bearing in mind the lack of studies concerning the behavior of non-activated aziridines with respect to $LiAlH_4$, the reactivity of 2-(bromomethyl)aziridines **24** (R = Br) and 2-(acetoxymethyl)aziridines **24** (R = OAc) toward $LiAlH_4$ will be studied in the first part of this PhD thesis. In this way, the reductive cleavage of these substrates **24** could provide an access toward biologically and synthetically relevant species such as isopropylamines **25** (R = H) and useful β-amino alcohols **25** (R = OH) through an unprecedented hydride-induced ring opening of non-activated aziridines (Scheme 2). β-Amino alcohols are applied extensively in organic chemistry as a building blocks in designing natural and biologically active substances,[27] and their chiral versions are also used in catalytic asymmetric synthesis.[28] Compounds **25** (R = OH) could then be further used as suitable substrates for the preparation of six-membered oxazaheterocycles **26**, known to be formed in the reaction with glyoxal.[29] In light of the importance of chirality in medicinal chemistry, the synthesis of enantiopure amino alcohols **28** and morpholin-2-ones **29** will be explored starting from the commercially available 2-(hydroxymethyl)aziridines **27** using the same synthetic approach (Scheme 2).



Scheme 2

The ring opening of aziridinium salts by halides constitutes a convenient approach towards β-halo amines, which are generally recognized as useful building blocks in organic chemistry and valuable targets in medicinal chemistry (nitrogen mustards – chemotherapy agents).[30] The issue of regioselectivity in the ring opening of 2-substituted non-activated aziridines by halides has been addressed in a few literature reports,[31] however, up to now no systematic study has been performed in which aziridinium substrates derived from non-activated aziridines are subjected to ring opening by fluoride, chloride, bromide and iodide.

Therefore, in the second part of this work, a systematic study on the ring opening of *in situ* generated aziridinium salts **30** by halides will be investigated. The ring opening of aziridinium salts **30** can occur at the unsubstituted (path a) or the substituted aziridine carbon atom (path b), leading either to primary halides **31** (path a) or secondary halides **32** (path b). As the selective synthesis of secondary bromides has been reported before upon treatment of aziridinium salts **30** with benzyl bromide,[31c] the scope and underlying factors will be studied thoroughly in this part.

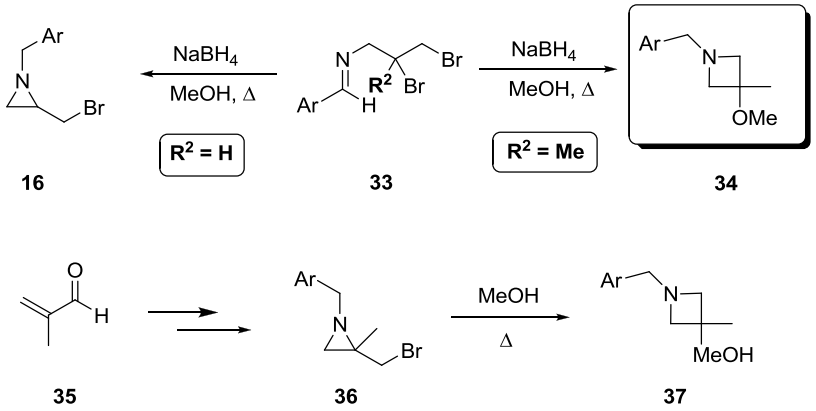


Scheme 3

As mentioned before, the reactivity of 2-(bromomethyl)aziridines **16**, prepared by $NaBH_4$-reduction of *N*-alkylidene-(2,3-dibromopropyl)amines **32** (R^2 = H) in methanol under reflux has been the subject of many literature reports from the Department of Sustainable Organic Chemistry and Technology. In a preliminary study,[32] it has been shown that structurally similar *N*-alkylidene-(2,3-dibromo-2-methylpropyl)amines **33** (R^2 = Me) afforded 3-methoxyazetidines **34** under the same reaction

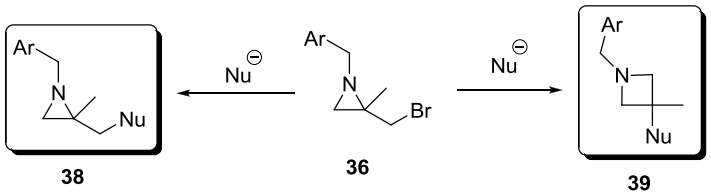
conditions (Scheme 4). In addition, a single example of the synthesis of aziridines **36** starting from 2-methylacrolein **35**, using bromination, imination and subsequent $NaBH_4$-mediated ring closure of the corresponding imines at room temperature has been provided (Scheme 4).[33]

Therefore, in order to elucidate this unexpected reactivity of imines **33** (R^2 = Me), and to assess the influence of an additional methyl substituent in substrates **33** (R^2 = Me) on the reaction outcome, the kinetically controlled synthesis of 2-bromomethyl-2-methylaziridines **36** will be investigated in the third part of this PhD thesis. Subsequently, the ring expansion of aziridines **36** to azetidines **37** could be then investigated by heating these species **36** in methanol under reflux. In addition, high-level molecular modeling calculations at the Center for Molecular Modeling (UGent) will be employed for the theoretical elucidation of the reaction mechanism.



Scheme 4

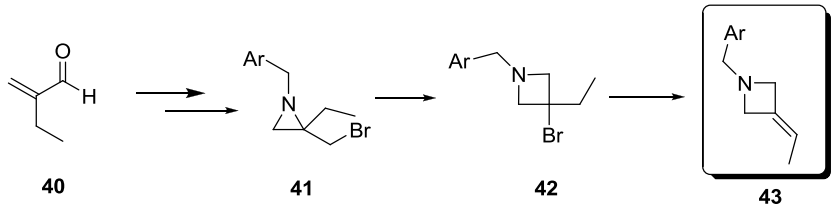
In addition, the reactivity of 2-bromomethyl-2-methylaziridines **36** toward oxygen, sulfur, and carbon nucleophiles in different solvent systems will be investigated. In this way, aziridines **36** could provide an access to novel functionalized aziridines **38** via direct nucleophilic substitution or to azetidines **39** via ring expansion (Scheme 5). Given the peculiar nature of aziridine to azetidine ring expansions, particular attention will be devoted to unravel this unknown chemistry from both, an experimental and theoretical point of view.



Scheme 5

The last part of this PhD thesis will be devoted to the synthesis and functionalization of 3-ethylideneazetidines **43**, obtained from the corresponding 3-bromo-3-ethylazetidines **42** through dehydrobromination, which could be prepared by the ring expansion of 2-bromomethyl-2-methylaziridines **41** (Scheme 6). Although the combination of two functionalities, i.e., an azetidine

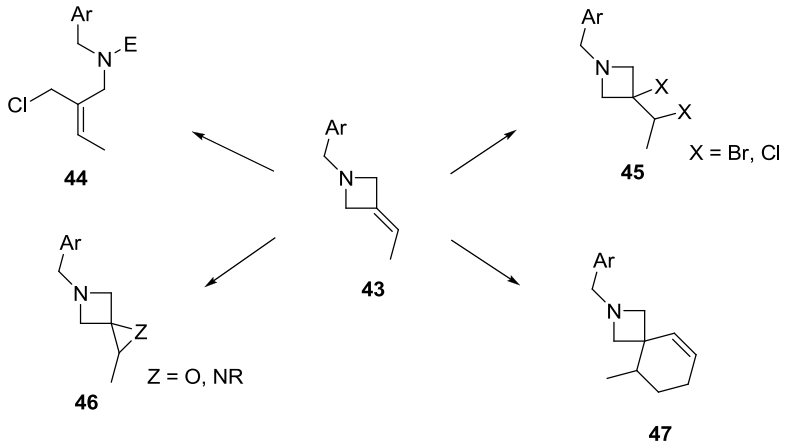
moiety and an exocyclic double bond, might result in unstable structures, azetidines **43** might still be considered as valuable substrates for further elaboration.



40 **41** **42** **43**

Scheme 6

In that respect, two aspects of the reactivity of 3-ethylideneazetidines **43** could then be studied separately, i.e., the activation and subsequent ring opening of the azetidine moiety on the one hand, and functionalization of the exocyclic double bond on the other. In this way, azetidines **43** could provide an entry toward novel allylic amines **44**, 3-halo-3-(1-haloethyl)azetidines **45** and different spirocyclic building blocks **46** and **47** (Scheme 7).



44 **45** **43** **46** **47**

Scheme 7

2 Literature review

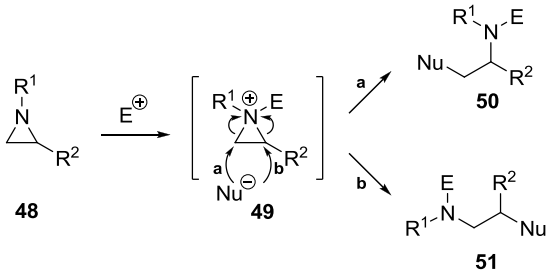
In this chapter, a literature review on the ring opening of non-activated 2-substituted aziridines via intermediate aziridinium salts will be dealt with. Emphasis will be put on the relationship between the observed regioselectivity and inherent structural features such as the nature of the C2 aziridine substituent and the nature of the electrophile and the nucleophile.

Regioselectivity in the ring opening of non-activated aziridines[34]

2.1 Introduction

The aziridine moiety represents one of the most valuable three-membered ring systems in organic chemistry,[3a,4,5a,8,35] 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.[36] 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 from the structural features of these aziridines as well as from the nature of the participating nucleophiles.[4a] 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,[37] with some exceptional cases comprising the nucleophilic attack at the allylic and benzylic position of the aziridine moiety.[38]

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 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 mentioned that the ring opening of aziridinium ions obtained through cyclization of β-amino alcohols has been covered recently in a comprehensive way.[39]
If non-activated, 2-substituted aziridines **48** are used, the issue of regioselectivity in the ring opening of the corresponding intermediate aziridinium salts **49** becomes important, since two regioisomeric ring-opened amines can be obtained. As depicted in Scheme 8, ring opening of aziridinium salts **49** can occur at the unsubstituted (path a) or at the substituted (path b) aziridine carbon atom, leading either to α-branched amines **50** (path a) or to β-branched amines **51** (path b).



Scheme 8

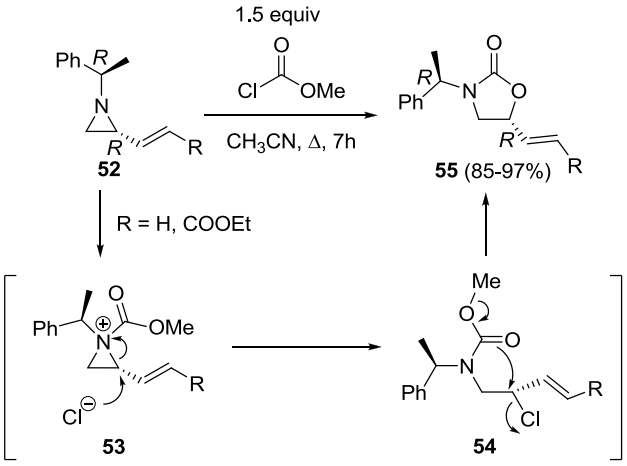
In the following paragraphs, literature reports on the ring opening of non-activated 2-substituted aziridines will be organized at first according to the nature of the substrate, i.e., distinction will be made between the reactivity of 2-(1-alkenyl)-, 2-aryl-, 2-acyl- and 2-alkylaziridines. Within these 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).

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

When the R^2 substituent in aziridines **48** (Scheme 8) 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.[40]

2.2.1 Aziridinium ion formation through N-alkoxycarbonylation

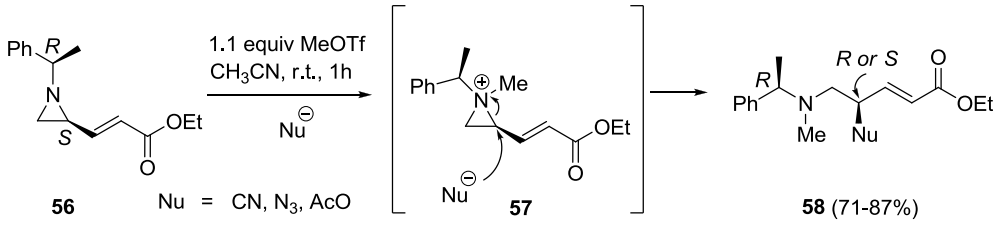
A single report considering the ring opening of 2-(1-alkenyl)aziridines through *N*-alkoxycarbonylation has been provided by Ha *et al.*,[41] in which the transformation of 2-vinylaziridines **52**, prepared from the corresponding aldehydes via a Horner–Wadsworth–Emmons reaction or a Wittig reaction, toward oxazolidin-2-ones **55** has been investigated. The reaction of aziridines **52** with methyl chloroformate was shown to proceed via cyclization of chlorocarbamates **54** (Scheme 9). The identification of intermediates **54** suggested that the reaction comprised a double S_N2 inversion process. Thus, *N*-methoxycarbonylation provided the activated aziridinium species **53**, which underwent a regioselective C2-N bond cleavage by the chloride ion via an S_N2 process. Subsequently, intramolecular cyclization of the carbamate **54** (implying a second S_N2 process) furnished oxazolidin-2-ones **55** in good yields with a net retention of configuration at C2 as defined in aziridines **52** (Scheme 9).



Scheme 9

2.2.2 Aziridinium ion formation through N-alkylation

The ring opening of aziridinium species **57**, obtained by *N*-methylation of the chiral 2-alkenylaziridine **56** using methyl trifluoromethanesulfonate (MeOTf), follows the same route as the *N*-alkoxycarbonylation approach (Scheme 9), giving rise to β-branched ring-opening products **58** via ring opening at C2. The reaction showed complete regio- and stereoselectivity toward the synthesis of a variety of optically pure amines **58** (Scheme 10).[42]

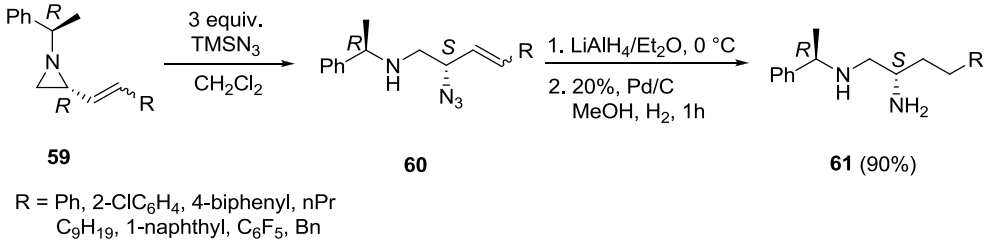


Scheme 10

2.2.3 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 **59** with $TMSN_3$ furnished 1-amino-2-azido-3-alkenes **60** after regioselective cleavage of the C2-N bond (Scheme 11).[43] The latter azides **60** were subsequently used for the synthesis of 1,2-diaminoalkanes **61** via azide reduction and alkene hydrogenation.



59 **60** **61** (90%)

R = Ph, 2-ClC$_6$H$_4$, 4-biphenyl, nPr
C$_9$H$_{19}$, 1-naphthyl, C$_6$F$_5$, Bn

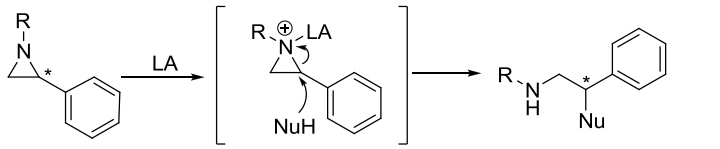
Scheme 11

2.3 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.

2.3.1 Aziridinium ion formation through N-complexation with Lewis acids

The reaction of 2-phenylaziridines **62** (optically pure or racemic) with different nucleophiles and Lewis acids gave amines **64** regio- and stereospecifically as a result of the nucleophilic attack at the benzylic position of the corresponding aziridinium complexes **63** (Scheme 12). For example, the $ZnCl_2$-catalyzed and $B(C_6F_5)_3$-catalyzed reaction of 1-benzyl-2-phenylaziridine (**62**, R = Bn) with aliphatic and aromatic thiols afforded 2-benzylamino-1-phenylethyl sulfides (**64**, Nu = SR) in good yields (78-89%).[44,45] In that paper, previously reported results were revised,[46] 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 **62** (R = Bn) with aliphatic as well as aromatic thiols, providing high yields of only one regioisomer **64**.[47] The reaction of 2-phenylaziridines **62** 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 **63**.[48]



62 **63** **64** (78-89%)
optically pure or racemic

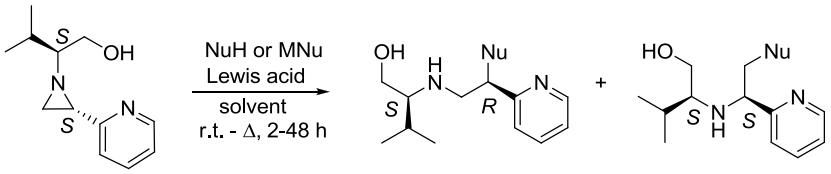
R = Bn, nBu

NuH = PhSH, MePhNH, 4-MeC_6H_4SH
4-ClC_6H_4SH, BnSH, n-BuSH

LA = $B(C_6H_5)_3$, $Sn(OTf)_2$, $Cu(OTf)_2$
$Sc(OTf)_3$, $Bi(OTf)_3$, $ZnCl_2$

Scheme 12

As compared to the reactivity of 2-phenyl-substituted aziridines **62**, the regioselectivity in the reactions of 2-(2-pyridyl)-substituted aziridine **65** with a variety of different N-, S-, and O-nucleophiles was not always straightforward.[49] It was shown that the ring opening of aziridine **65** gave the products **66**, resulting from nucleophilic attack at the more substituted aziridine carbon, either exclusively or together with the alternative regioisomeric products **67** depending on the type of nucleophile, Lewis acid and solvent used (Scheme 13). The ring opening of 2-(2-pyridyl)aziridine **65** 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 **65** with NaN_3 was straightforward, giving regioisomer **66** as a single product. Reactions with other nucleophiles such as water, amines and thiols also gave the C2 ring-opening products **66** as the major regioisomers. On the other hand, higher amounts of regioisomers **67** were reported when $LiClO_4$ or $Zn(OTf)_2$ were used to catalyze the ring opening of aziridine **65**. In this way, it was possible to modify the regioselectivity of the ring-opening process by the proper choice of the reagent, Lewis acid and solvent.[49] 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 **65** premature.



65 **66** (40-100%) **67** (0-60%)

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

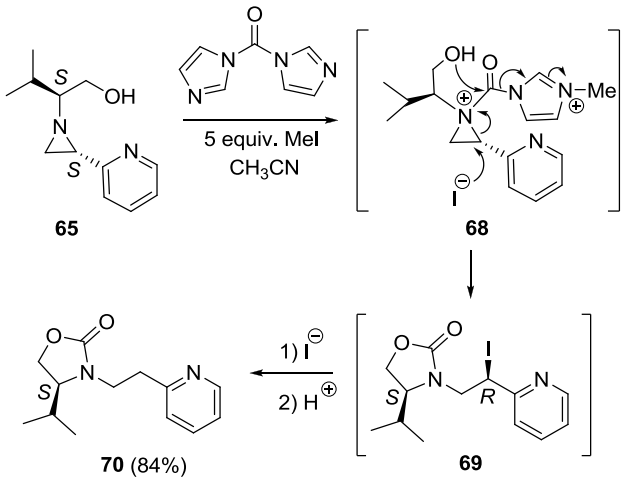
Lewis acid = $CeCl_3 \cdot 7H_2O$, $Ce(NH_4)_2(NO_3)_6$
$AlCl_3$, $Zn(OTf)_2$, $LiClO_4$

solvent = CH_3CN-H_2O (9:1), EtOH-H_2O (1:1)
CH_3CN, CH_2Cl_2, THF

Scheme 13

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

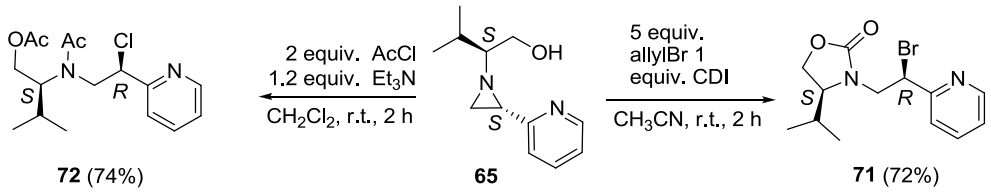
The reactions of above mentioned chiral 2-(2-pyridyl)-substituted aziridines **65** with an excess of both carbonyldiimidazole (CDI) and reactive alkyl halides, performed with the intention to prepare halogenated products resulting from the ring opening of the aziridine by the halide ion, have been evaluated by the same group.[50] In this study, it has been observed that when methyl iodide was used, optically pure non-halogenated oxazolidin-2-one **70** was formed. In order to explain the presence of this compound, the iodide **69**, derived from nucleophilic attack at the more substituted carbon atom of acylated aziridinium species **68**, was proposed as an intermediate (Scheme 14). At the same time, intramolecular nucleophilic addition of the remote hydroxyl group across the carbonyl moiety in intermediate **68** furnished the oxazolidinone ring. Subsequently, the intermediate (hetero)benzylic iodide **69** has been proposed to be reduced by the excess of iodide affording oxazolidin-2-one **70**. The reducing properties of the iodide ion and of hydrogen iodide in this type of transformations had already been reported in the literature.[51]



65 **68** **69** **70** (84%)

Scheme 14

In order to account for the proposed mechanism, the aziridine **65** has been treated separately with either CDI and an excess of allyl bromide in acetonitrile at room temperature, or with two equiv of acetyl chloride, furnishing compounds **71** and **72**, respectively (Scheme 15). Both products resulted from the fission of the benzylic C2-N bond by bromide or chloride in the intermediate aziridinium salt.[50]

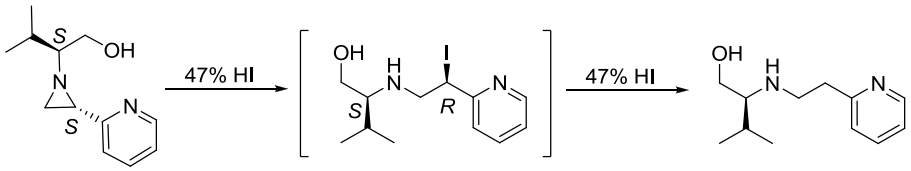


72 (74%) **65** **71** (72%)

Scheme 15

2.3.3 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 **65** was protonated with an excess of hydrogen iodide, the amine **74** was obtained (Scheme 16).[50] The presence of this amine has been explained to be mediated by the formation of the intermediate β-iodoamine **73**, resulting from iodide attack at the more substituted carbon atom of aziridine **65**, and further reduction by the excess of hydrogen iodide through a halophilic reaction and subsequent protonation to form the amine **74**.

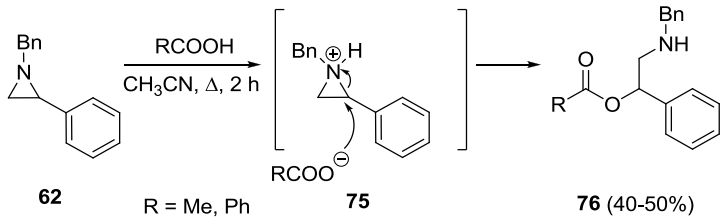


65 **73** **74**

Scheme 16

Moreover, after heating a mixture of the same aziridine **65** 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 **66** and **67** (82:18) was obtained, which were separated by column chromatography (Scheme 13).[49]

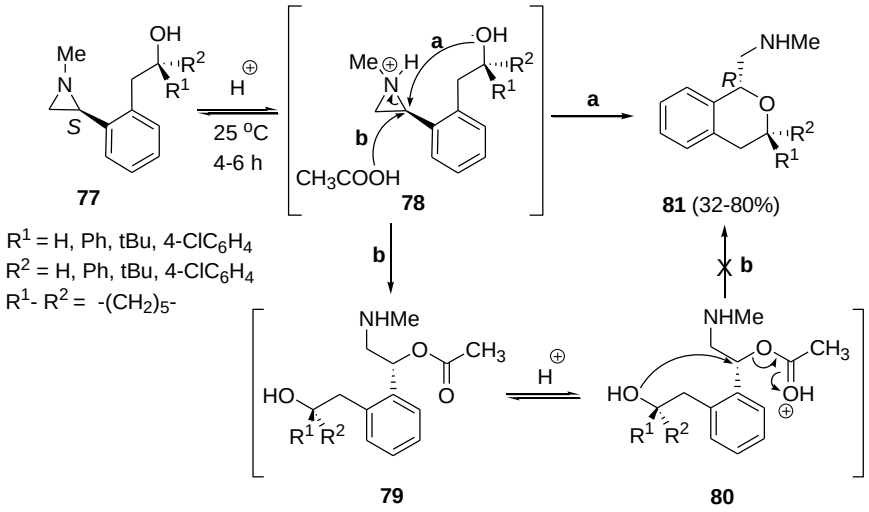
Similarly, the reaction of 1-benzyl-2-phenylaziridine **62** with aliphatic and aromatic acids in acetonitrile gave the amino esters **76** as the major isomers furnished by nucleophilic attack of the corresponding carboxylates at the benzylic position of aziridinium species **75** (Scheme 17).[52]



Scheme 17

In addition, a mixture of a 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,[53] and hydrogen fluoride has also been described to combine regiospecifically with 2-phenylaziridines to give secondary fluorides in good yields.[54]

In accordance with these results, the synthesis of isochromans **81**, resulting from the cyclization of a number of 1-methylaziridines **77** 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.[55] Acetic acid, either as a proton source or as a solvent, at room temperature proved to be superior for the preparation of isochromans **81**. Two plausible reaction mechanisms are depicted in Scheme 18. 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 **79** (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 **81** showed pathway **a** to be the predominant one.[55]



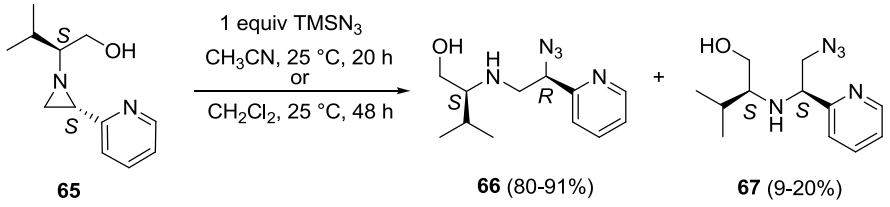
Scheme 18

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.[56]

2.3.4 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 **65** by $TMSN_3$, providing the C2 ring-opening product **66** as the major isomer (Scheme 19).[49]



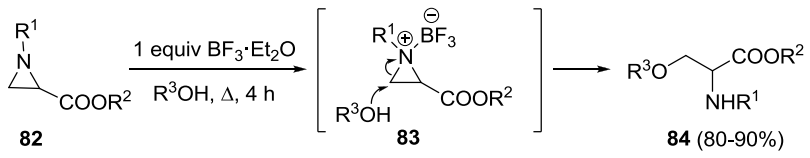
Scheme 19

2.4 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.

2.4.1 Aziridinium ion formation through N-complexation with Lewis acids

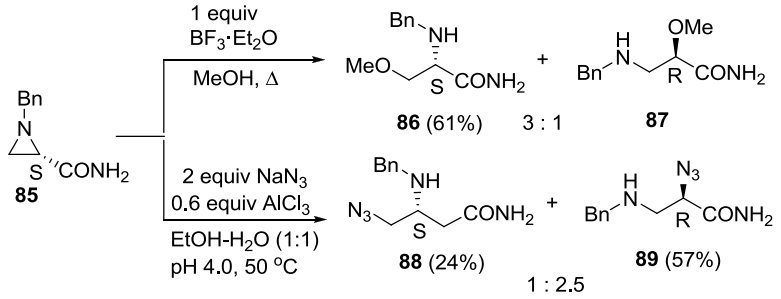
The ring-opening reactions of 2-(alkoxycarbonyl)aziridines **82** using various alcohols turned out to be regioselective, giving rise to α-amino esters **84**. This reaction proceeded through nucleophilic attack at the less hindered side of the aziridinium moiety in intermediates **83** (Scheme 20).[57] 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.[58]



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

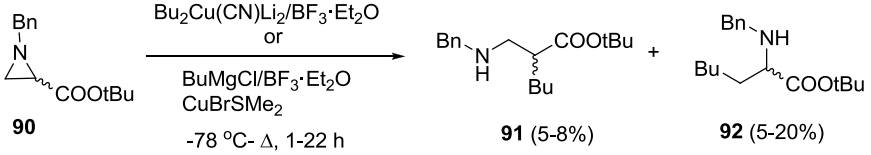
Scheme 20

A nucleophile-dependent regioselectivity has been observed in ring-opening reactions of 2-carbamoylaziridine **85**, described by Gotor *et al.*[59] Aziridine **85** was heated under reflux in methanol in the presence of a diethyl ether-boron(III) fluoride complex (Scheme 21), leading to a 3:1 mixture of the C2 and C3 ring-opening products, respectively, from which the former, i.e., enantiopure α-amino amide (*S*)-**86**, was isolated in 61% yield. On the other hand, when aziridine **85** was reacted with sodium azide and aluminium(III) chloride in aqueous ethanol, the formation of a 1:2.5 mixture of azides **88** and **89** was observed (Scheme 21).[59]



Scheme 21

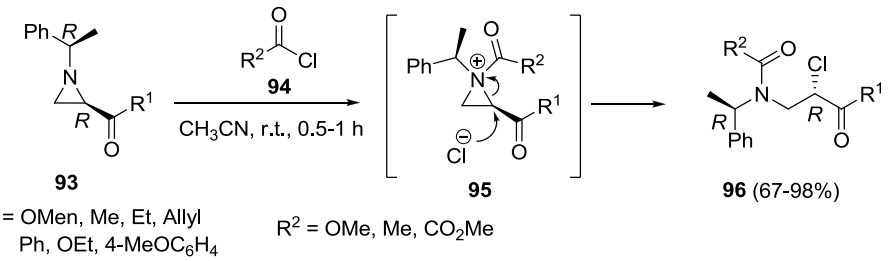
The ring opening of *t*-butyl *N*-benzylaziridine-2-carboxylate **90** with a higher order butylcuprate or nBuMgCl in the presence of $BF_3{\cdot}Et_2O$ has been studied by Baldwin *et al*.[60] However, a mixture of products **91** and **92** in low yields was observed resulting from attack of the organometallic reagent at both C2 and C3 of the corresponding aziridinium intermediate (Scheme 22).



Scheme 22

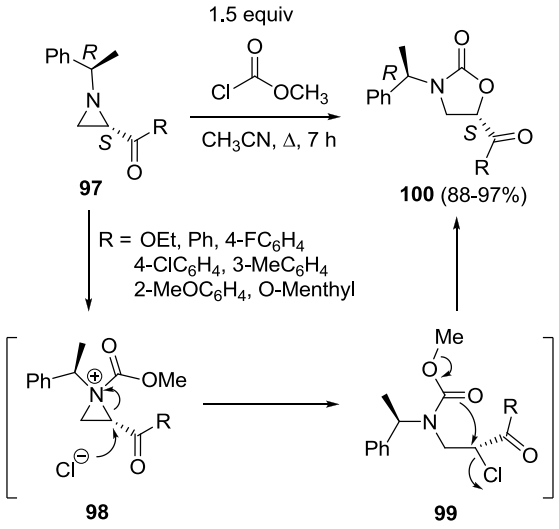
2.4.2 Aziridinium ion formation through N-acylation or N-alkoxycarbonylation

Various 2-acylaziridines **93** have been subjected to reactions with different acyl chlorides **94** to furnish β-amino-α-chlorocarbonyl compounds **96** in a regioselective and stereospecific way (Scheme 23).[61] The acyl chlorides were able to both activate the aziridine ring and to provide the nucleophile leading to the ring-opening reactions. The ring nitrogen reacts readily with acyl chlorides toward intermediate aziridinium ions **95**, 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.



Scheme 23

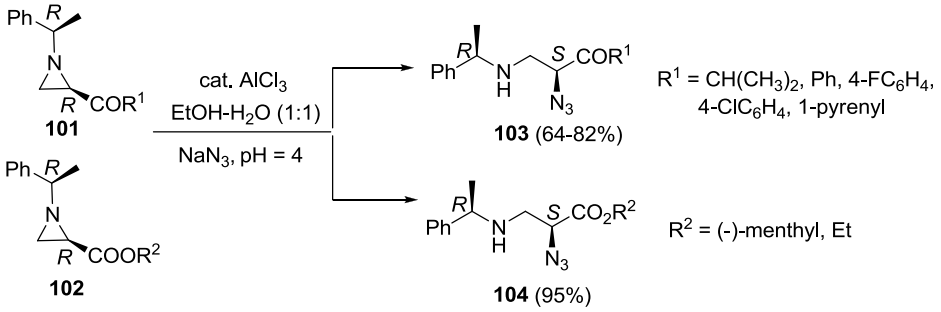
As previously described for 2-vinylaziridines **52** (Scheme 9), the synthesis of oxazolidin-2-ones can also derive from *N*-methoxycarbonylation of 2-acyl- or 2-(alkoxycarbonyl)aziridines **97**. Methoxycarbonylation of the nucleophilic nitrogen of aziridines **97** gave aziridinium ions **98**, which were regioselectively attacked by the resulting chloride anion to give the chlorides **99**. Chlorosubstituted intermediates **99** were then converted into oxazolidin-2-ones **100** through an intramolecular S_N2 reaction (Scheme 24). The formation of the aziridinium intermediates **98** was also evidenced by the isolation of an intermediate **99** (R = OEt) when the reaction was performed in toluene instead of acetonitrile. Furthermore, when carbamate **99** (R = OEt) was heated under reflux in acetonitrile, oxazolidinone **100** was formed in an excellent yield.[41]



Scheme 24

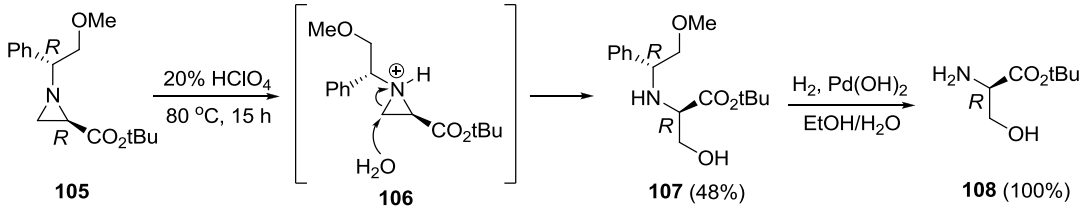
2.4.3 Aziridinium ion formation through N-protonation

The ring-opening reactions of enantiomerically pure 2-acyl- and 2-(alkoxycarbonyl)aziridines **101** and **102** 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 **103** or 3-amino-2-azidopropionates **104**, respectively, in the presence of 10 mol% of $AlCl_3 \cdot 6H_2O$ (Scheme 25).[62] Bearing in mind the low activity of $AlCl_3 \cdot 6H_2O$ as a Lewis acid, the presence of sulfuric acid (which was used to adjust pH) is considered to be responsible for the activation of the aziridine moiety through *N*-protonation.



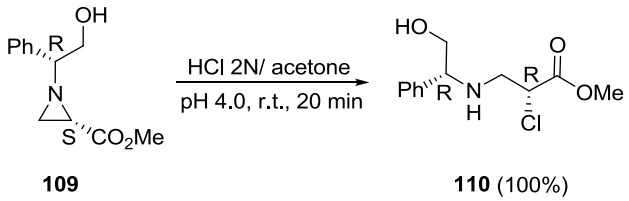
Scheme 25

To assign the absolute configuration of aziridine **105**, this compound has been treated with 20% $HClO_4$ to obtain the ring-opened product **107**, which was subsequently transformed to the tert-butyl ester of D-serine **108** in quantitative yield (Scheme 26).[63] In this approach, water attacked the nonsubstituted carbon atom of the intermediate aziridinium ion **106** to furnish β-aminoalcohol **107**. 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 **105**.



Scheme 26

On the other hand, the selective ring opening of aziridine **109** (or its epimeric version) can be explained by an S_N2 mechanism in which the chloride ion attacks at C2 with inversion of stereochemistry (Scheme 27).[64] 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.

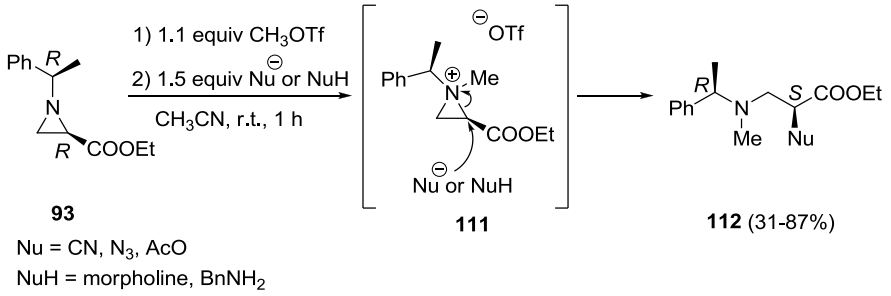


Scheme 27

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.[65]

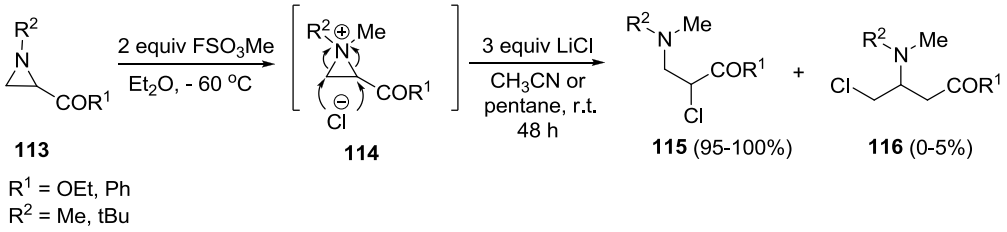
2.4.4 Aziridinium ion formation through N-alkylation

The presence of an ethoxycarbonyl substituent in aziridines **93** 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 **111** by different nucleophiles to yield the ring-opened products **112**. The attack was shown to occur regioselectively at the more hindered carbon atom of the aziridine ring (Scheme 28).[42]



Scheme 28

In addition, aziridines **113** have been treated with methyl fluorosulfonate to afford the corresponding aziridinium salts **114** in high yields,[66] 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 **115**, while only in one case (R^1 = OEt, R^2 = Me) the isomer **116** was present as well in 5% (Scheme 29).



Scheme 29

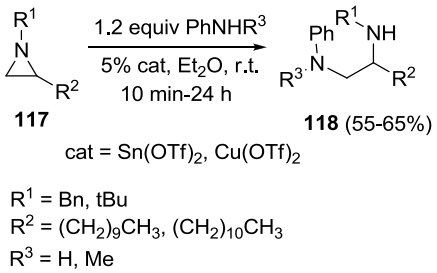
2.5 Activation and ring opening of 2-alkylaziridines

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 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 were 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 was 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, azide or alcohols proceeded mainly through nucleophilic attack at the non-substituted aziridine carbon atom.

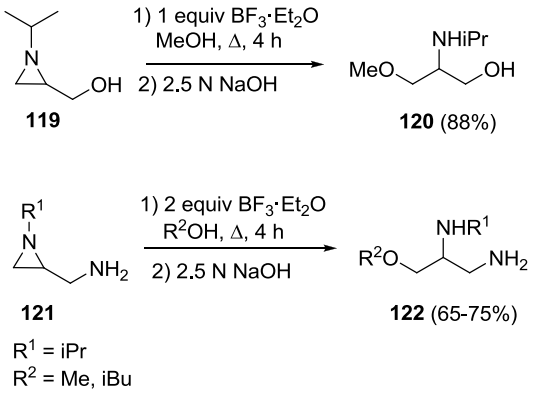
2.5.1 Aziridinium ion formation through N-complexation with Lewis acids

The reaction of 2-alkylaziridines **117** with aromatic amines provided 1,2-diamines **118** after nucleophilic attack of the amine at the less substituted aziridine carbon atom (Scheme 30).[48] 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 **117** 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.[48]



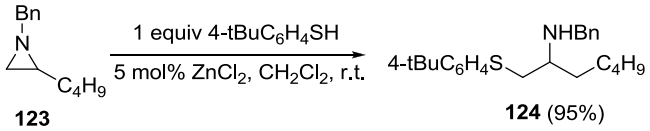
Scheme 30

The same regioselectivity was observed in the $BF_3{\cdot}Et_2O$-mediated ring opening of 2-(hydroxymethyl)aziridines **119** and 2-(aminomethyl)aziridines **121** (Scheme 31) by different alcohols, providing an entry toward α-branched amines **120** and **122** through ring opening by methanol or *i*-BuOH at C3.[57,59]



Scheme 31

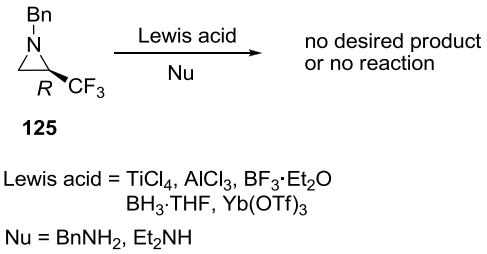
The ring opening of 2-butylaziridine **123** with thiol in the presence of a catalytic amount of $ZnCl_2$ has been shown to follow the same route as in previous examples furnishing thioether **124** in 95% yield (Scheme 32).[46]



Scheme 32

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 $BF_3{\cdot}Et_2O$.[67]

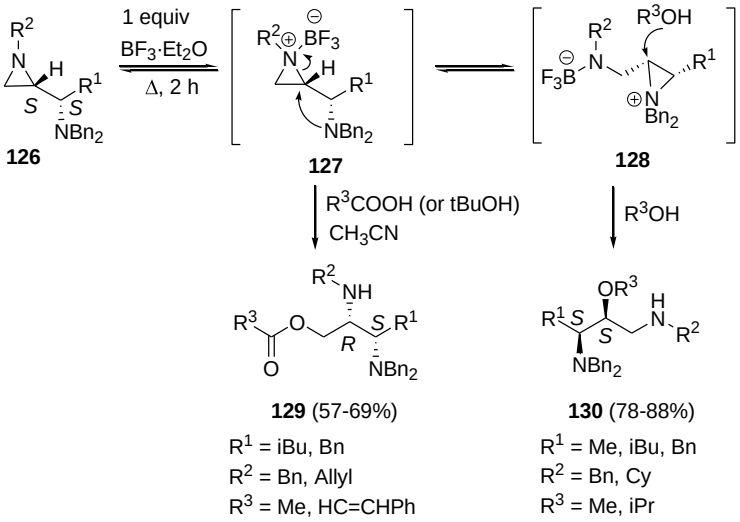
However, Uneyama *et al.*[68] have reported the unsuccessful transformation of chiral 2-(trifluoromethyl)aziridines **125** toward ring-opened products by using Lewis acids as catalyst and aliphatic amines as nucleophiles (Scheme 33). In this case, the reduced basicity of the aziridine nitrogen atom due to the strong electron-withdrawing effect of the CF_3 group clearly hampered the formation of aziridinium-like intermediates.



Scheme 33

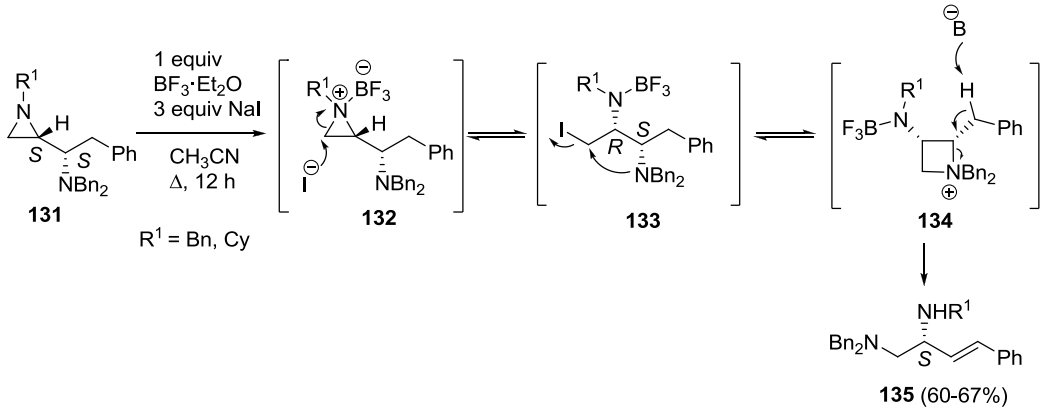
In the next part, the regioselectivity in the ring opening of 2-(1-aminoalkyl)aziridines **126** was described to be dependent on the type of nucleophile used to open the aziridinium moiety. In a

detailed study, Cancellon *et al*.[69] have reported on the ring opening of aziridines **126** by alcohols and carboxylic acids in the presence of $BF_3{\cdot}Et_2O$, providing C2 (**129**) and C3 (**130**) ring-opening products, respectively (Scheme 34). 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 **128** with inversion of configuration. Alcohols (R^3OH) induced ring opening of aziridinium salts **128** to afford 2-alkoxy-1,3-diamines **130**, with a second inversion of configuration at the C2. In the case of *t*-butylalcohol (R^3 = tBu) the reaction takes place through **127** due to steric hindrance. In the presence of a carboxylic acid, the prevalence of intermediates **128** may be diminished due to protonation of the dibenzylamino group, reducing its ability to open the aziridine to form **128**, which resulted in the nucleophilic attack of carboxylic acid at the less hindered carbon atom of intermediate **127**.



Scheme 34

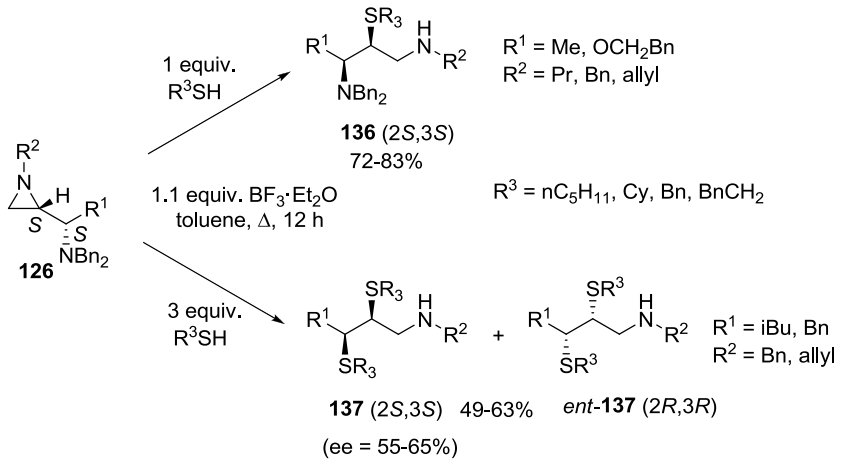
Furthermore, the use of iodide as a nucleophile in the ring-opening reaction of aziridines **131** in the presence of $BF_3{\cdot}Et_2O$ gave 4-phenylbut-3-en-1,2-diamines **135** (Scheme 35). It was assumed that the iodide attacks the aziridine ring at C3 affording iodo diamines **133**. These intermediates are prone to undergo ring closure to produce azetidinium salts **134**, which undergo a spontaneous *α*-elimination yielding chiral diamines **135**.[69] However, the possible complexation of both nitrogen atoms in aziridine **131** with the Lewis acid might influence the regiochemical pathway in this reaction.



Scheme 35

The ring opening of 2-(1-aminoalkyl)aziridines **131** 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 **131** with water has been shown to be completely regio- and stereoselective, involving ring opening at C2 and retention of configuration at this center.[70]

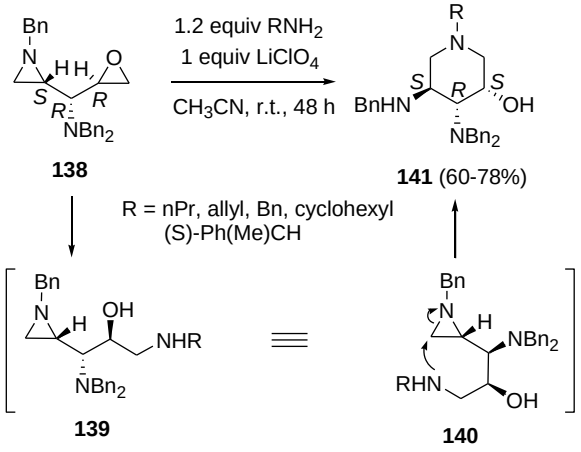
Furthermore, the reaction of 2-(1-aminoalkyl)aziridines **126** (R^1 = Me, $BnOCH_2$) with one equiv of a thiol also proceeded regio- and stereoselectively, and it was shown that one alkylthio group was incorporated in the final product **136**.[71] When slightly modified reaction conditions (i.e., 3 equiv of thiols, $BF_3{\cdot}Et_2O$ and reflux) were applied to aziridines **126** (R^1 = Bn, iBu), (2*S*,3*S*)-2,3-bis(alkylthio)alkan-1-amines **137** were isolated instead (Scheme 36). ^1H and ^{13}C NMR analyses of compounds **137** 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.



Scheme 36

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 **138** with primary amines in the presence of lithium perchlorate. The reaction has been carried out with total

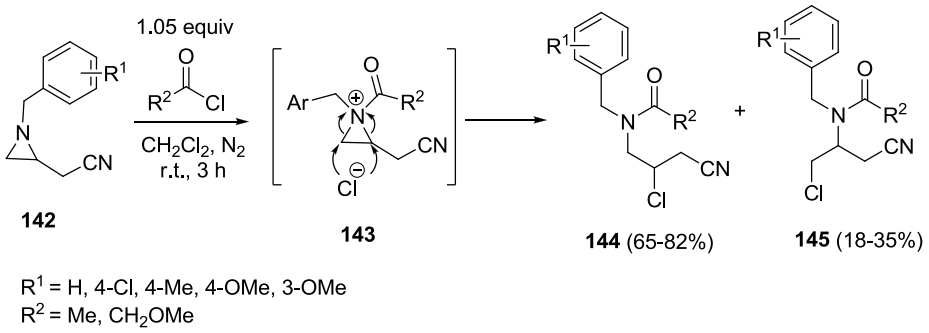
chemo- and regioselectivity, affording chiral polyfunctionalized piperidines **141** as the sole products in good yields.[72] The formation of compounds **141** can be explained by amine-induced ring opening of the oxirane ring at the less hindered position to afford diamino alcohols **139** (Scheme 37). 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 **141** were detected as the sole reaction products. Apparently, the terminal amino group in intermediate **140** participates in an intramolecular nucleophilic attack across the aziridine ring - probably activated by the Lewis acid, although previous reports suggested otherwise[69,70] - at the less hindered position, affording the piperidine ring system.



Scheme 37

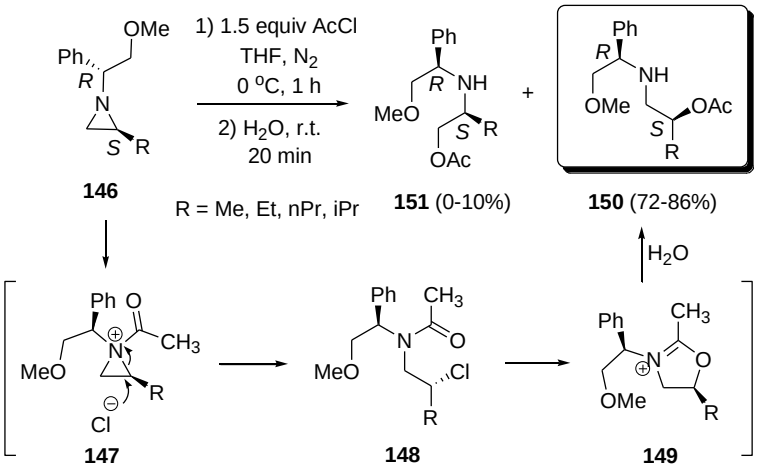
2.5.2 Aziridinium ion formation through N-acylation or N-carboxylation

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 **142** with an acid chloride in dichloromethane resulted in a mixture of β-chloroamine derivates **144** as the major constituents and regioisomers **145** as the minor products (Scheme 38).[73] The acid chloride readily reacts with the basic nitrogen lone pair of aziridines **142**, affording highly electrophilic aziridinium intermediates **143** 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 **144** in good yields. The formation of the minor regioisomers **145** is the result of the ring opening of aziridinium salts **143** at the less hindered position.



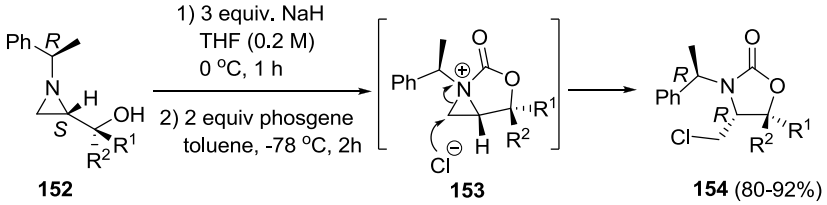
Scheme 38

Applying the same reasoning, Higashiyama *et al.*[74] have explained a new method for the preparation of chiral β-amino alcohols **150** through a regio- and stereocontrolled ring opening of chiral aziridines **146**. The high regio- and stereocontrol of this transformation is probably due to the intermediacy of *N*-acylaziridinium salts **147** resulting from the reaction with acetyl chloride (Scheme 39). Subsequently, these *N*-acylaziridinium salts **147** undergo a ring-opening reaction via an anti-attack of chloride at the C2 position. Next, the resulting *N*-acyl-β-chloroamines **148** are readily converted into the transient oxazolinium derivatives **149** through internal chloride displacement by the oxygen nucleophile. Finally the oxazolinium derivative **149** is hydrolized to yield β-amino alcohols **150** as the major products.



Scheme 39

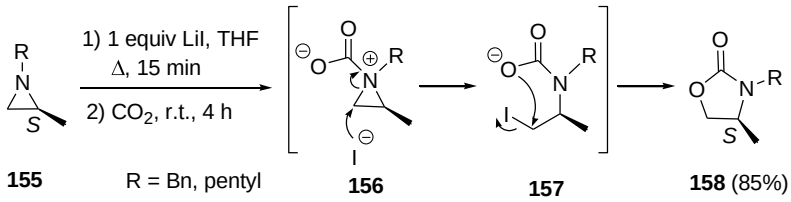
However, when phosgene, carbon dioxide or carbonyldiimidazole (CDI) were used to activate the ring, the less substituted carbon atom appeared to be the more favored place for nucleophilic attack. Thus, a highly regioselective nucleophilic ring opening of 2-(1-hydroxyalkyl)aziridines **152** in the presence of phosgene has been observed to afford oxazolidinones **154** (Scheme 40).[75] Phosgene acts as a cyclizing agent of the amino alcohol moiety to form reactive cyclic carbamates **153**, which suffer from ring opening by the chloride ion at the less hindered side of the aziridine moiety to form oxazolidinones **154**. 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.[76]



Scheme 40

In a similar way, the same oxazolidinone derivatives have been prepared starting from 2-(hydroxymethyl)aziridines and iodotrimethylsilane in the presence of carbonyldiimidazole (CDI).[77]

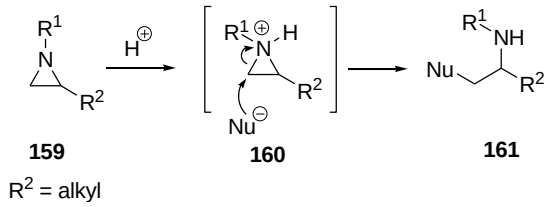
Finally, in order to explain the conversion of enantiomerically pure 2-methylaziridines **155** into oxazolidinones **158** using CO_2, Pinhas and Hancock suggested two possible mechanisms, one of which is shown in Scheme 41.[78] This approach concerns the reaction of CO_2 with the aziridine nitrogen atom (*N*-carboxylation) to give aziridinium ion **156**, which then undergoes ring opening by iodide to generate intermediate **157**. Spontaneous cyclization of the latter intermediate produces 4-methyloxazolidinone **158** as the major regioisomer. In addition, to a minor extent, the aziridinium salt **156** is attacked at the more hindered carbon atom and gives the isomeric 5-methyloxazolidinone as the final product. In light of the known reactivity of non-activated aziridines, however, the addition of aziridine **155** across CO_2 is highly unlikely. Thus, the other proposed pathway, consisting of the initial ring opening of aziridine **155** 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.



Scheme 41

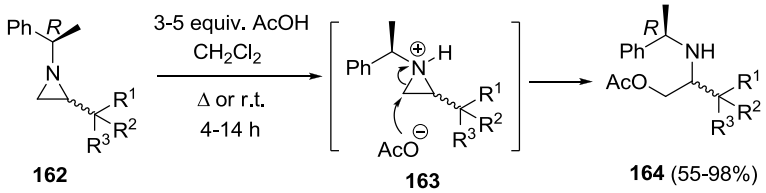
2.5.3 Aziridinium ion formation through N-protonation

In general, the ring-opening reactions of 2-alkylaziridines **159** 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 42).



Scheme 42

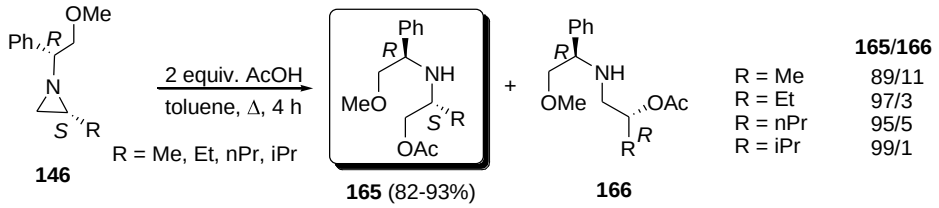
For example, the ring opening of 2-alkylaziridines **162** by acetic acid in dichloromethane has been shown to be a very efficient method for the regioselective formation of β-amino alcohol derivatives **164**, indicating that acetate attacks the less sterically hindered C3 position of the intermediate aziridinium salts **163** (Scheme 43).[28a,79,80,81,82,83,84,85,86,87]



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, $HC{\equiv}CC_{13}H_{27}$

Scheme 43

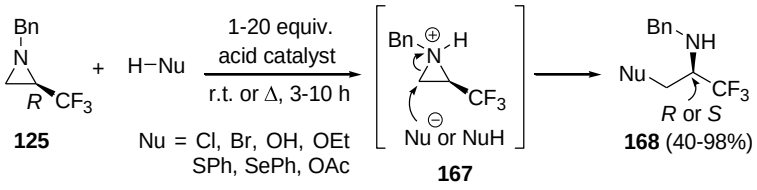
In addition, Higashiyama *et al.*[74] have performed a number of reactions on the chiral 2-alkyl-substituted aziridines **146** using acetic acid to yield the ring-opening products **165** after C3-N bond cleavage of the aziridine ring. In most cases, these reactions showed excellent regioselectivity, except in the case of a sterically small substituent (R = Me, ratio **165**/**166** = 89/11) (Scheme 44).



Scheme 44

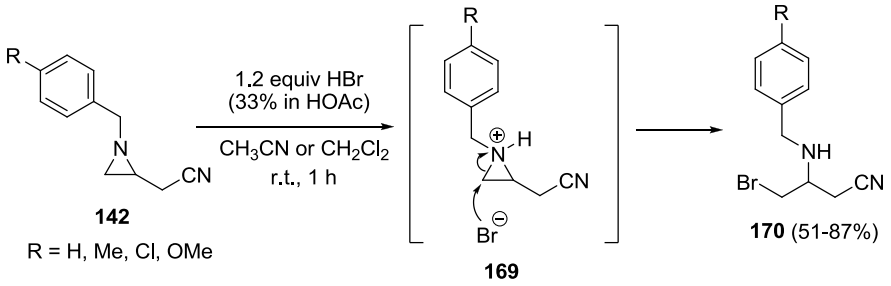
Also, 1-benzyl-2-(trifluoromethyl)aziridine **125** was shown to be a good substrate for acid-promoted ring-opening reactions with different nucleophiles, furnishing β-cleaved products **168** (β-amino halides, alcohols, ethers, sulfide and selenides) in good yields (40-98%) (Scheme 45).[68] Therein, it has been observed that sulfuric acid-catalyzed ring opening of aziridine **125** by EtOH and ring-opening reactions of the same aziridine **125** by PhSH, promoted by sulfuric or trifluoromethanesulfonic acid, resulted in higher yields of the corresponding β-aminoethers **168** (Nu = OEt) or β-aminosulfides **168** (Nu = SPh), respectively.[68] In addition, the ring opening of racemic analogues of aziridine **125** with acetic acid

resulted in a slower formation (up to 7 days) of amines **168** (Nu = OAc), probably due to the weaker acidity of acetic acid.[88]



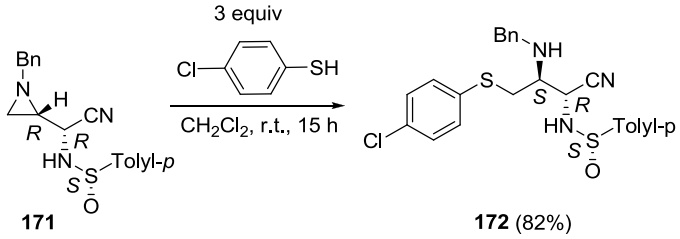
Scheme 45

Recently, ring opening of 1-arylmethyl-2-(cyanomethyl)aziridines **142** with HBr has been reported to afford 3-(arylmethyl)amino-4-bromobutyronitriles **170** via regiospecific ring opening at the unsubstituted aziridine carbon atom of the intermediate aziridinum salts **169** (Scheme 46).[31a]



Scheme 46

Furthermore, the ring-opening reaction of chiral α,β-diaminonitrile **171** with 4-chlorothiophenol afforded the corresponding α-(*N*-sulfinylamino)-β-benzylaminonitrile **172** in 82% yield (Scheme 47).[89]

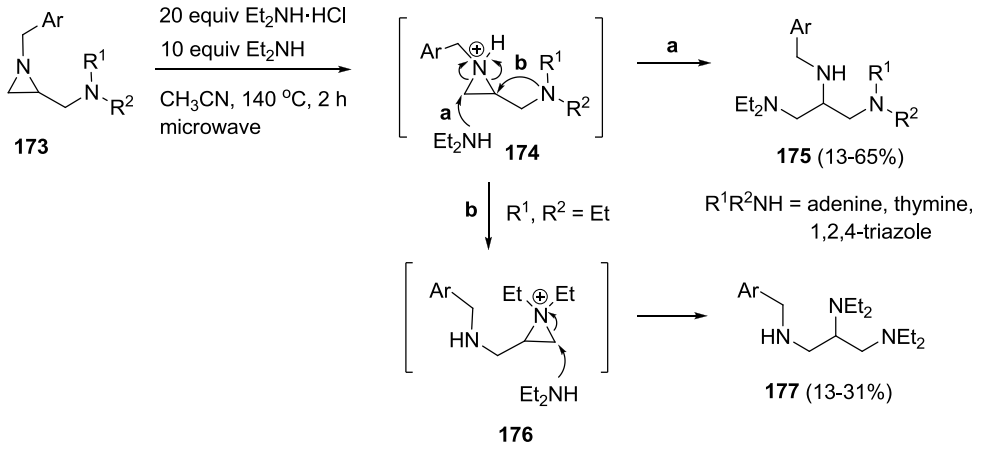


Scheme 47

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.[90,91] The nitrogen atom of an aziridine is a sufficiently stong base to pick up the proton from the thiol, resulting in an aziridinium intermediate which is further attacked by thiophenolate ion. A kinetic study of this ring-opening reaction showed that the reaction rate increases with the acidity of thiols.[31a] 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.[75]

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).[69] 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.[70]

In a recent report,[24b] 2-(aminomethyl)aziridines **173**, prepared via nucleophilic substitution of 2-(bromomethyl)aziridines[22,25b] 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 **175** were formed after ring opening of intermediate activated species **174** at the unhindered carbon atom of the aziridinium ion (path **a**, Scheme 48). However, in the case of 2-(*N*,*N*-diethylaminomethyl)aziridines **173** ($R^1 = R^2 = Et$), a mixture of regioisomers (**175**/**177 =** 3/2) was obtained. This was explained by an additional rearrangement of aziridinium salts **174** to the corresponding 1,1-diethylaziridinium intermediates **176**, which were subsequently attacked by diethylamine at C3 to furnish 1-(arylmethyl)amino-2,3-bis(*N*,*N*-diethylamino)propanes **177** (path **b**, Scheme 48).

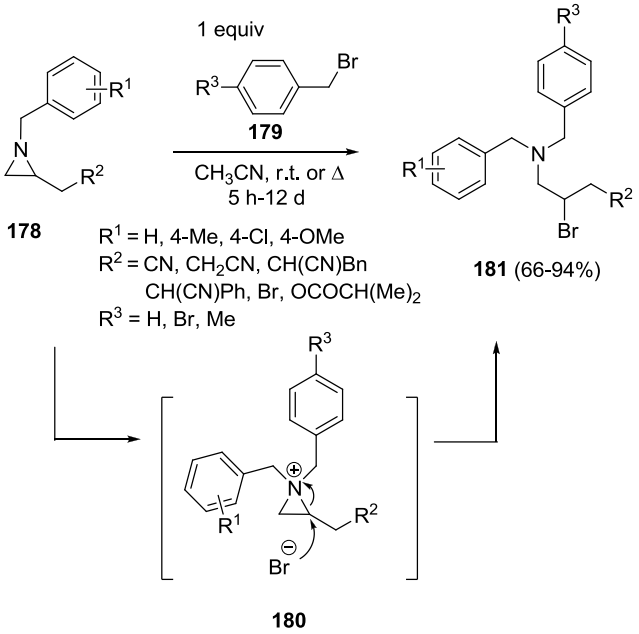


Scheme 48

2.5.4 Aziridinium ion formation through N-alkylation

2-(Bromomethyl)-, 2-(aryloxymethyl)-, 2-(alkanoyloxymethyl)-, 2-(cyanomethyl)-, and 2-(2-cyanoethyl)aziridines **178** show the same reactivity toward arylmethyl bromides **179** in acetonitrile, giving a regiospecific ring opening of the intermediate aziridinium salts **180** by bromide attack at the more hindered aziridine carbon atom, affording ring-opened products **181** in high purity (Scheme 49). For example, treatment of 1-arylmethyl-2-(cyanomethyl)aziridines **178** (R^2 = CN) with benzyl bromide **179** (R^3 = H) in acetonitrile afforded 4-amino-3-bromobutanenitriles **181**,[31a,b] and 2-(2-cyanoethyl)aziridines **178** ($R^2 = CH_2CN$) afforded novel 5-amino-4-bromopentanenenitriles **181** in excellent yields after reflux for 5 h.[19] 4-Amino-3-bromobutanenitriles **181** (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 **180**.[31b] Analogously, treatment of 2-

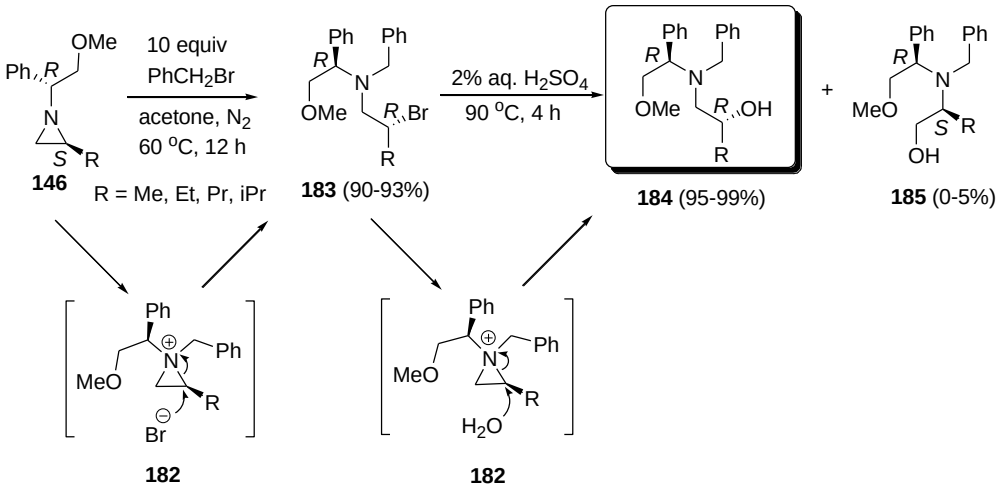
(aryloxymethyl)aziridines **178** (R^2 = OAr) with benzyl bromide in acetonitrile also afforded *N*-(2-bromo-3-aryloxypropyl)amines **181** as the sole reaction products.[92]



Scheme 49

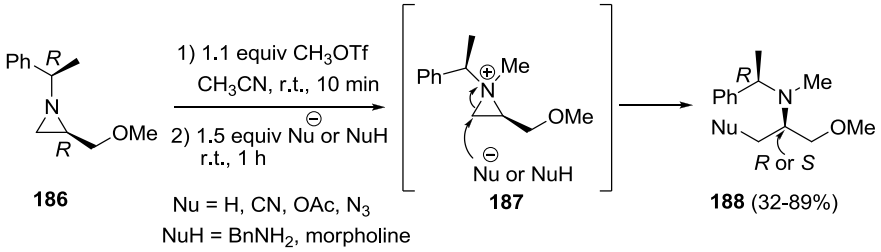
Aziridine ring opening at the more substituted carbon atom of the aziridine moiety has also been observed in a study on enantiomerically pure 2-(aryloxymethyl)aziridines.[31c] The same observations were deduced in the case of 2-(bromomethyl)-[93] and 2-(alkanoyloxymethyl)aziridines,[94] affording 1-[di(arylmethyl)amino]-2,3-dibromopropanes and *N*-(2-bromo-3-alkanoyloxypropyl)amines, respectively, upon treatment with benzyl bromide in acetonitrile.

In accordance with these results, chiral aziridines **146** have been shown to afford β-bromoamines **183** upon treatment with benzyl bromide by C2-N bond cleavage of the aziridinium salts **182**. Next, treatment of β-bromoamines **183** with 2% aqueous sulfuric acid at 90 °C for 4 h gave, through formation of the same intermediates **182**, the β-amino alcohols **184** in good yields via ring opening at C2 (Scheme 50).[74] However, the formation of **184** via a direct bromide displacement in substrates **183** should not be excluded.



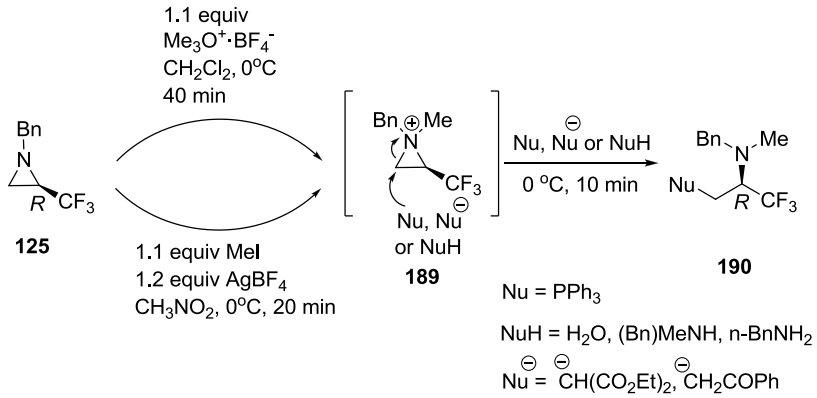
Scheme 50

When (2*R*)-[(1*R*)-phenylethyl]-2-(methoxymethyl)aziridine **186** 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 **188** were obtained through ring opening at the less hindered side (C3) (Scheme 51).[42]



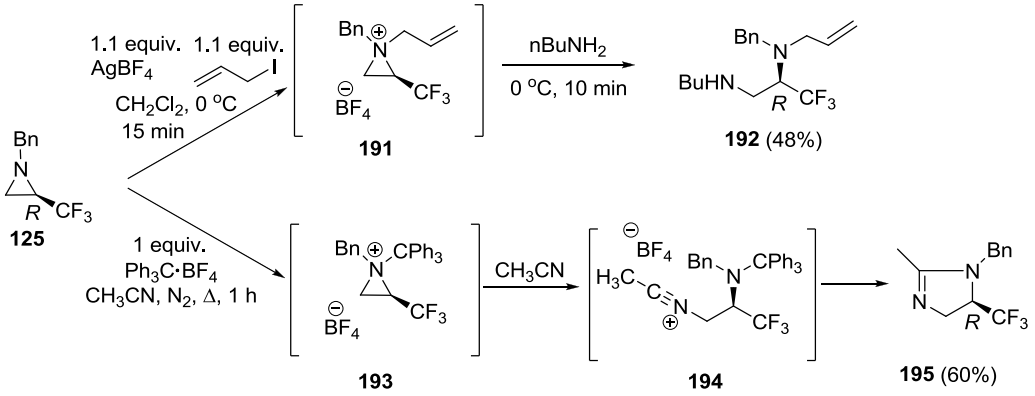
Scheme 51

The C3 regioselectivity has been observed in the methylation of the nitrogen atom of 2-(trifluoromethyl)aziridine **125** by either MeI·$AgBF_4$ or $Me_3O^+ \cdot BF_4^-$ to form the intermediate aziridinium salt **189**, which is then ring opened by various nucleophiles at the less hindered carbon atom to afford chiral amines **190** (Scheme 52).[68]



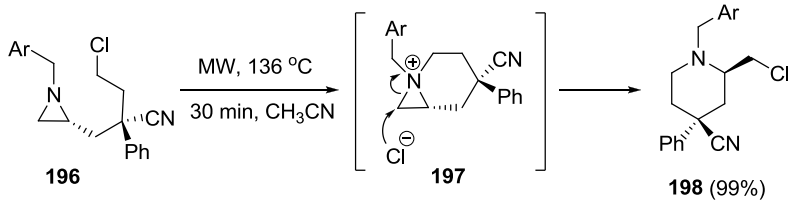
Scheme 52

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 **125** have been investigated in the same work.[69] To prepare practically useful *N*-protected compounds, allyl iodide was allowed to react with aziridine **125** in the presence of $AgBF_4$. The generated aziridinium salt **191** was then quenched with $nBuNH_2$, resulting in the production of diamine **192** in 48% yield (Scheme 53). Alternatively, the trityl group was introduced using $Ph_3C{\cdot}BF_4$ in CH_3CN. The aziridinium salt **193** underwent a Ritter type reaction with CH_3CN, and subsequent cyclization produced imidazoline **195** in 60% yield. In addition, the successful C3-regioselective ring opening of racemic variants of aziridine **125** via *N*-benzylation and subsequent ring opening by iodide has also been reported recently.[88]



Scheme 53

In a recent report, intramolecular alkylation of aziridines **196** (or their diastereomeric counterparts), prepared via alkylation of 2-(2-cyano-2-phenylethyl)aziridines[19a] with 1-bromo-2-chloroethane, was shown to be useful for the preparation of stereodefined piperidines **198** after regiospecific nucleophilic attack by chloride at the less hindered carbon atom of the aziridine moiety in bicyclic aziridinium intermediates **197** (Scheme 54).[23] Bicyclic aziridinium intermediates have frequently been reported in the literature, although usually they are formed through nucleophilic displacement within other azaheterocyclic ring systems such as 2-(halomethyl)aziridines,[95] -pyrrolidines[96] and -piperidines.[97] These examples fall outside the scope of this review and will thus not be dealt with here.

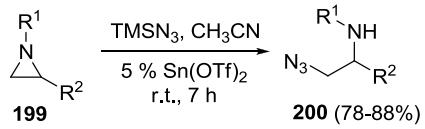


Scheme 54

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.

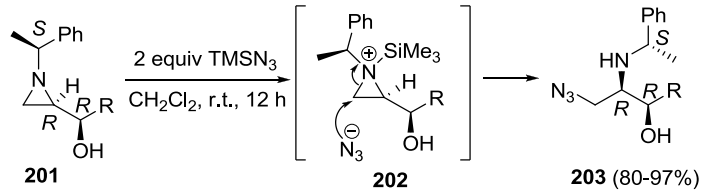
2.5.5 Activation and ring opening of 2-alkylaziridines via silylation

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 ring opening of 2-alkylaziridines **199** with $TMSN_3$ in MeCN using 5 mol% of $Sn(OTf)_2$ has been shown to be very effective and provided high yields of the corresponding azides **200**, resulting from azide attack at the less hindered side of the aziridine ring (Scheme 55).[98]



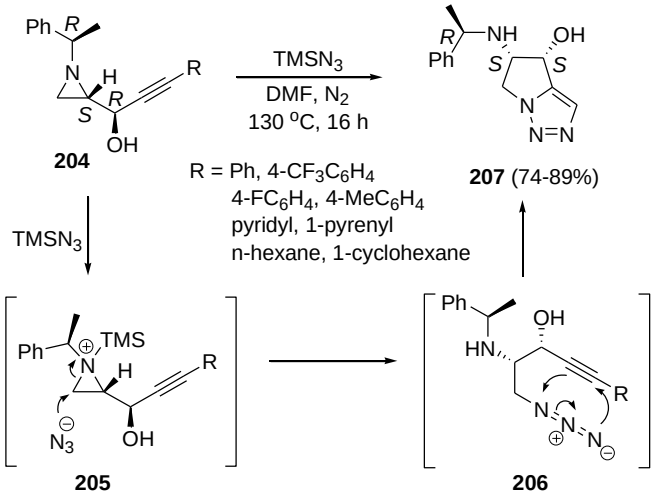
Scheme 55

Similarly, the ring opening of chiral 2-(1-hydroxyalkyl)aziridines **201** has been shown to give β-azidoamines **203** through C3-N bond cleavage by the azide nucleophile (Scheme 56).[99] Furthermore, aziridines **201** can be regioselectively opened with iodide from iodotrimethylsilane (TMSI) to yield β-iodoamines through C3 ring opening.[99]



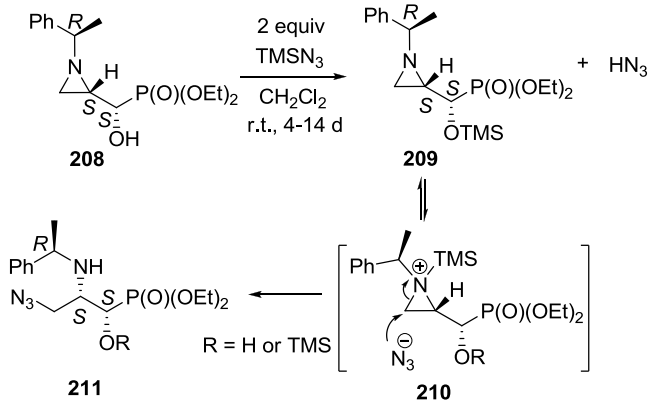
Scheme 56

The same behavior of 2-alkylaziridines has also been described in the synthesis of bicyclic triazoles **207**, which were obtained when chiral 1-(aziridin-2-yl)propargylic alcohols **204** were reacted with azidotrimethylsilane (Scheme 57).[100] It has been suggested that the silylation of the aziridine nitrogen atom provided the activated aziridinium species **205**, which were then regioselectively opened through fission of the C3-N bond by nucleophilic attack of the *in situ* liberated azide toward azido alcohols **206**. Consequently, an intramolecular 1,3-dipolar cycloaddition efficiently converted azido alkynes **206** to the corresponding bicyclic triazoles **207**.



Scheme 57

Finally, in a report by Wróblewski *et al*.,[101] the regioselective ring opening of chiral 2-substituted aziridinephosphonates **208** has been investigated. After optimizing the reaction conditions, 3-azido-1-hydroxyphosphonates **211** (or their O-TMS derivatives) were obtained in high yields. Whereas initially *N*-silylated aziridinium species **210** could be invoked as intermediates, the authors suggested an alternative pathway involving silylation of the hydroxyl group in phosphonates **208** 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 58).[101]



Scheme 58

2.6 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.[31,102] In this section, a short overview of recent achievements in that respect are presented.

The nucleophile-dependent regioselectivity in the ring opening of the chiral 1-benzyl-1-(α(*R*)-methylbenzyl)-2(*S*)-(phenoxymethyl)aziridinium ion (i, Figure 5) has been subjected to several 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, Figure 5).[96] 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 picture of the energy landscapes were shown to be significantly dependent on the inclusion of solvent and in the absence of these critical stabilizing effects, experimentally observed regioselectivities could not be reproduced.

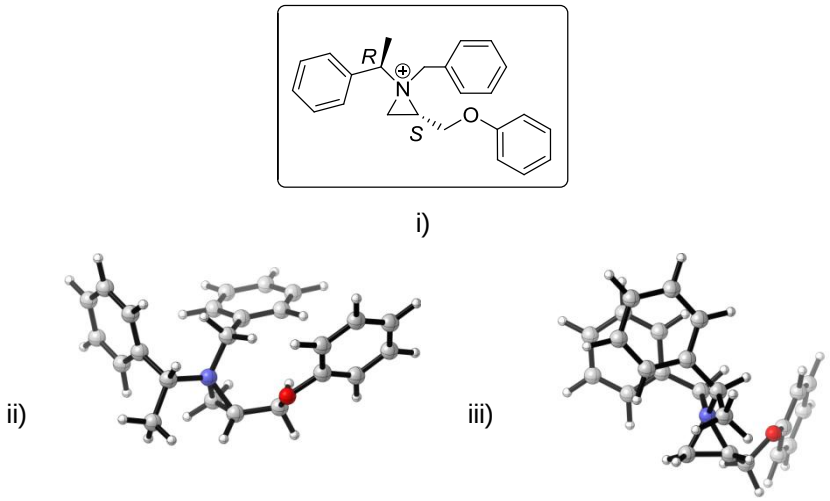
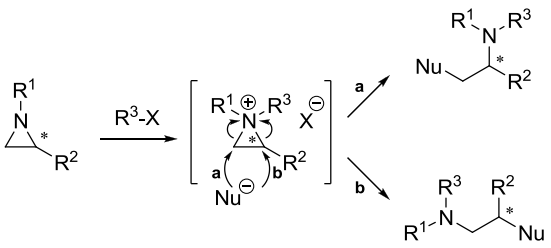


Figure 5. Intramolecular π-π stacking in 1-benzyl-1-(α(*R*)-methylbenzyl)-2(*S*)-(phenoxymethyl)aziridinium ion. ii) T-stacking iii) Parallel-displaced

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 59).

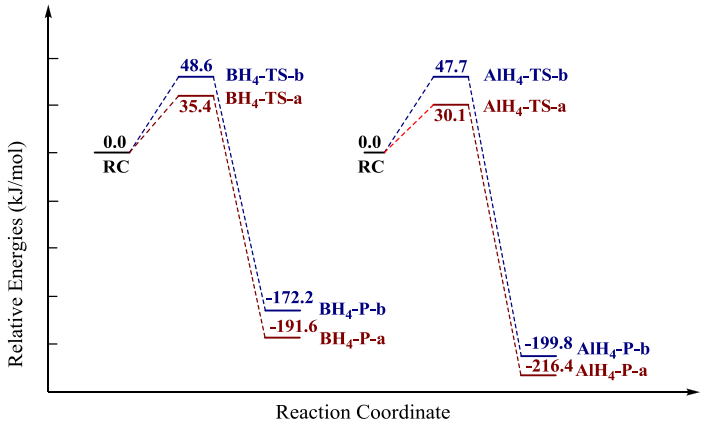


Scheme 59

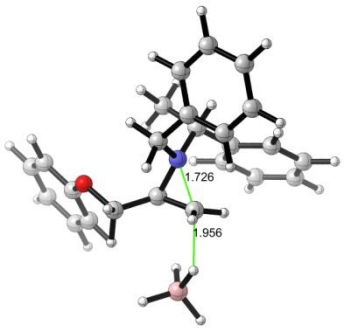
In the case of hydride donors (BH_4^- and AlH_4^-), the attack at the unhindered ring carbon of the 1-benzyl-1-(α(*R*)-methylbenzyl)-2(*S*)-(phenoxymethyl)aziridinium ion, was shown to be the kinetic route

and incidentally led to the thermodynamically favourable product (Figure 6),[96,102b] as observed experimentally.

i)



ii)



BH_4-TS-a

Figure 6. i) Free energy profile for the hydride-induced ring opening of the 1-benzyl-1-(α(*R*)-methylbenzyl)-2(*S*)-(phenoxymethyl)aziridinium ion at the unhindered (pathway a) and hindered (pathway b) ring carbons. ii) Transition state geometry for borohydride attack at unhindered aziridine carbon.
(SCS-MP2/6-31++G(d,p))//B3LYP/6-31++G(d,p) at 298 K and 1 atm)
BH_4-Ts-a, BH_4-Ts-b – transition states for hydride (from $NaBH_4$) attack via pathways a and b, respectively
AlH_4-Ts-a, AlH_4-Ts-b – transition states for hydride (from $LiAlH_4$) attack via pathways a and b, respectively

The overall picture for halide-induced ring opening showed that the unhindered route (pathway a) is always kinetically preferred, yet the hindered route leads to the thermodynamic product (Figure 7). 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 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.

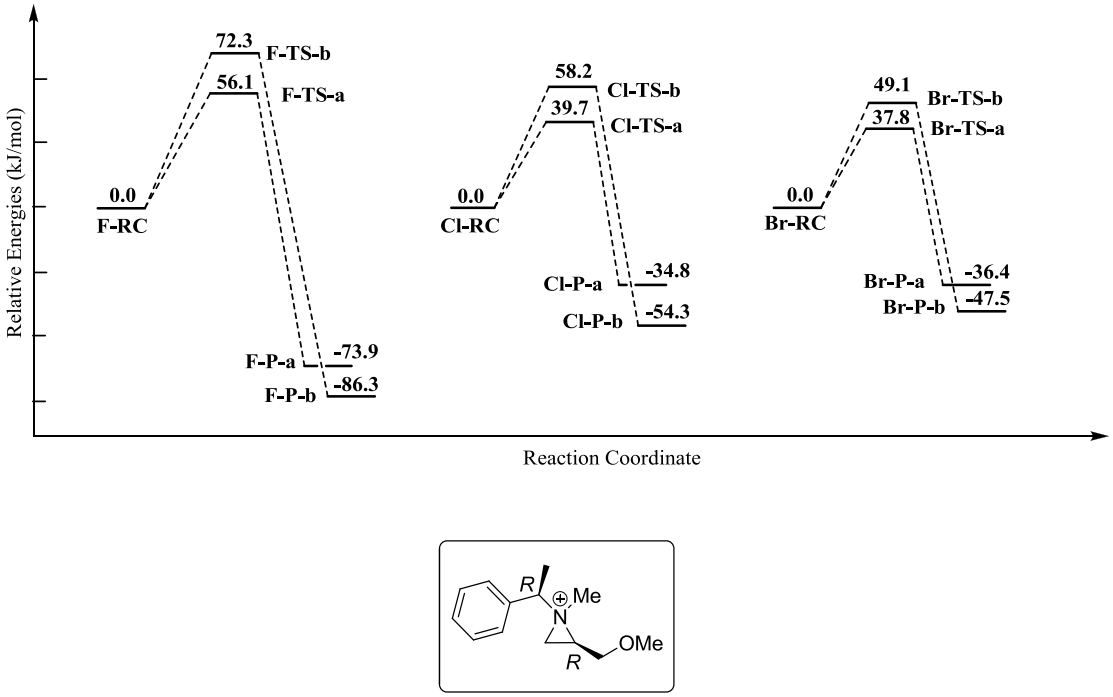


Figure 7. Free energy profile for the halide-induced ring opening of the 1-methyl-1-(α(*R*)-methylbenzyl)-2(*R*)-(methoxymethyl)aziridinium ion at the unhindered (pathway a) and hindered (pathway b) ring carbons. (MPW1B95/6-31++G(d,p)//B3LYP/6-31++G(d,p) at 298 K and 1 atm)

F-Ts-a, F-Ts-b – transition states for fluoride attack via pathways a and b, respectively; F-P-a, F-P-b-products of fluoride attack via pathways a and b, respectively. Cl-Ts-a, Cl-Ts-b – transition states for chloride attack via pathways a and b, respectively; Cl-P-a, Cl-P-b-products of chloride attack via pathways a and b, respectively. Br-Ts-a, Br-Ts-b – transition states for bromide attack via pathways a and b, respectively; Br-P-a, Br-P-b-products of bromide attack via pathways a and b, respectively

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 bromide, 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 (Figure 8, acetonitrile molecules) was used to stabilize ionic species, as this was proven to significantly influence the energy landscape of S_N2 reactions.[31,96]

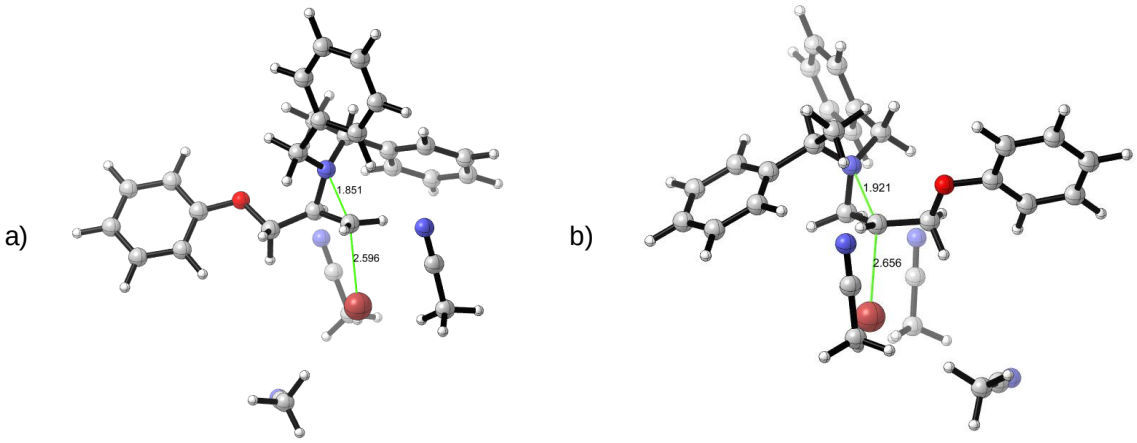
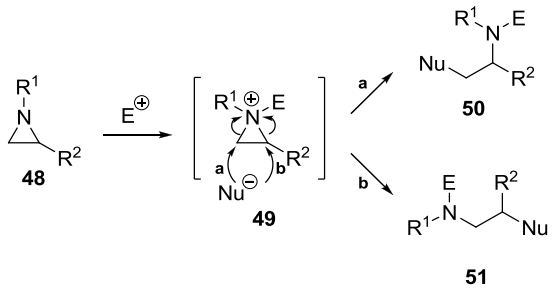


Figure 8. Transition state geometries for bromide attack on the a) unhindered b) hindered carbon atom of the 1-methyl-1-(α(*R*)-methylbenzyl)-2(*R*)-(methoxymethyl)aziridinium ion. (MPW1B95/6-31++G(d,p)//B3LYP/6-31++G(d,p))

2.7 Conclusion

The ring-opening reactions of non-activated 2-substituted aziridines **48** 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 **49**, which are then opened at the more (path **a**) or/and the less substituted carbon atom (path **b**) toward amines **50** and **51**, respectively (Scheme 8). 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.



Scheme 8.

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

E^+ / R^2	LA	$RC^+=O$	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)

In this PhD thesis, the ring opening of non-activated aziridines (via intermediate aziridinium salts) will be employed as a powerful tool for the transformation of these strained species into a wide range of synthetically and biologically interesting nitrogen-containing scaffolds.

3 Results and Discussion

3.1 Microwave-assisted regioselective ring opening of non-activated aziridines by lithium aluminium hydride[103]

The aziridine moiety represents a valuable three-membered ring system in organic chemistry due to its versatility as a building block for the preparation of a large variety of amines via ring opening and ring expansion.[3a,4a,b,5a,35b,e,104,105] In the chapter 'Literature Review', the regioselectivity of the ring opening of 2-substituted non-activated aziridines was discussed, showing this class of aziridines to be fruitful synthons for further chemical transformation.

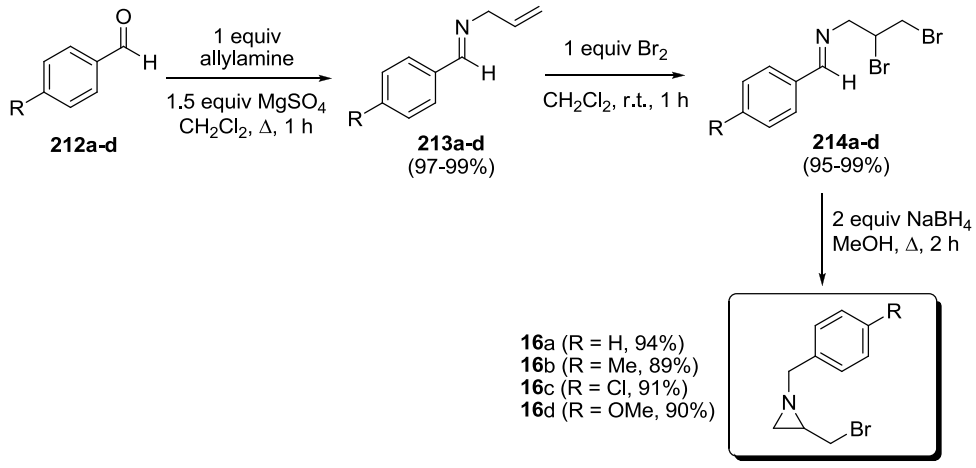
In comparison to the huge number of reports on the ring opening of aziridines by other nucleophiles, their ring opening by hydrides has received very limited interest in the literature despite the synthetic potential of this approach. The intermediacy of aziridines in direct, non-regioselective ring-opening reactions by $LiAlH_4$ has been proposed in an early paper, in which the reduction of *N*-(1,1-dichloro-2-alkylidene)anilines was investigated,[106] and has also been deduced indirectly from the experiments of Suzuki.[107] In addition, in one recent report,[108] the reduction of 2-methyl-1-phenylaziridine with $LiAlH_4$ in THF yielded a mixture of ring-opened amines (derived from hydride attack at both the more and the less hindered aziridine carbon atom in a 1:2 ratio, respectively) yet showed to be slow and not complete after heating under reflux for 20 hours. Furthermore, the contribution of the electron-withdrawing effect of the phenyl group at nitrogen, facilitating ring opening of the aziridine moiety, should not be neglected in this particular case. In addition to the above-mentioned reports, the ring opening of reactive 2-chloroaziridine intermediates by $LiAlH_4$ has also been described.[109]

It should be stressed that several syntheses of aziridines have been reported in the literature based on the reduction of suitable substrates, such as α-halo imines,[110] vinyl azides,[111] oximes[112] and azirines,[113] by nucleophilic complex hydrides. Recently, the reductive ring opening of highly electrophilic aziridinium salts by hydrides has been reported to afford 2-aminopropanes through regiospecific ring opening at the unsubstituted position.[102] However, up to now, $LiAlH_4$ has been mainly used to reduce functional groups in compounds incorporating an aziridine unit without affecting the three-membered ring itself,[26] and the hydride-promoted ring opening of non-activated aziridines has not been described in the literature so far. The lack of studies concerning the reduction of aziridines by $LiAlH_4$ is remarkable in view of the large number of papers on the reductive ring opening of their oxygen counterparts, oxiranes.

Therefore, in this section, special attention was devoted to the $LiAlH_4$-promoted ring opening of non-activated 2-subtituted aziridines toward biologically and synthetically relevant species.

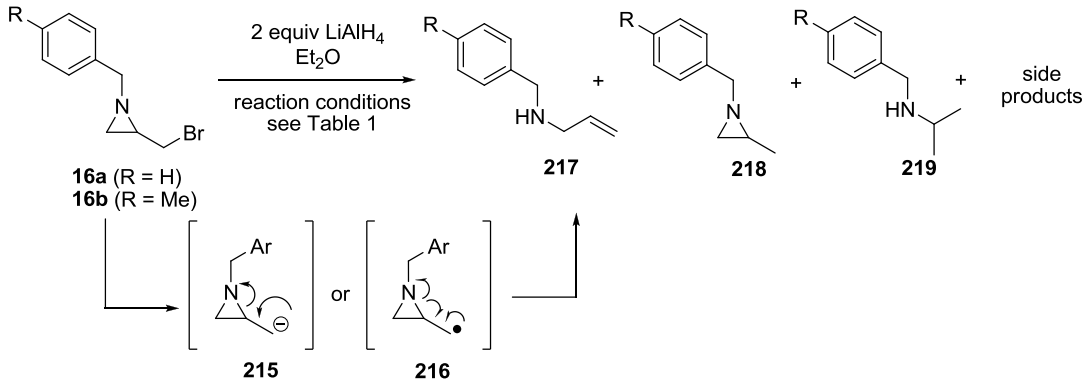
3.1.1 Ring opening of 2-(bromomethyl)aziridines with $LiAlH_4$

As mentioned in the section 1 "Introduction and goals", 1-arylmethyl-2-(bromomethyl)aziridines **16** have proven to be valuable synthons for the preparation of wide variety of azaheterocyclic compounds and amines derived from their ring opening.[24c,92,93,114] These substrates were prepared by an efficient three-step procedure, comprising the initial imination of benzaldehydes **212a-d** with 1 equiv of allylamine in the presence of 1.5 equiv of $MgSO_4$ in CH_2Cl_2 for 1 hour under reflux. Subsequent bromination of imines **213a-d** with 1 equiv of Br_2 in CH_2Cl_2 at room temperature for 1 hour furnished dibromoimines **214a-d** in nearly quantitative yields (95-99%, Scheme 60). Finally, the reductive cyclization of brominated imines **214a-d** with 2 molar equiv of $NaBH_4$ in MeOH under reflux for 2 hours resulted in the formation of aziridines **16a-d** in high yields (89-94%) and excellent purity.[22,25b,115]



Scheme 60

In order to evaluate the unexplored reactivity of 2-(bromomethyl)aziridines **16** toward $LiAlH_4$, aziridines **16a,b** were treated with two molar equivalents of $LiAlH_4$ in dry Et_2O under reflux for 2-15 hours. The reaction resulted in complex mixtures, in which signals pertaining to the corresponding allylamines **217**, 2-methylaziridines **218** and isopropylamines **219** were detected (based on NMR and LC-MS) (Scheme 61). Changing the reaction conditions, i.e., the temperature and the reaction time, resulted in a different and sometimes unpredictable reaction outcome (Table 2).



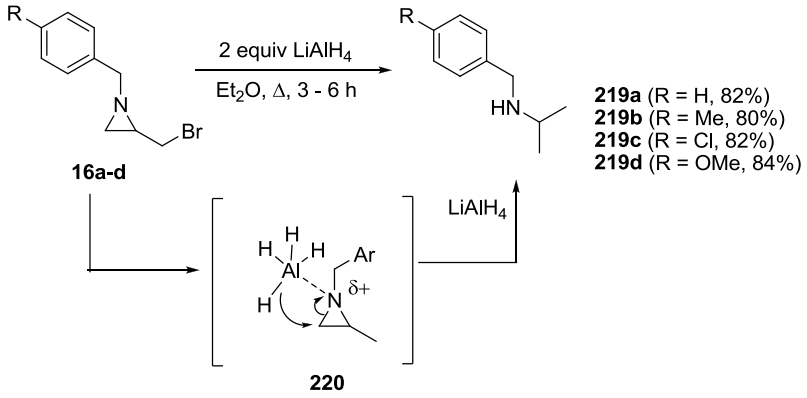
Scheme 61

Table 2. Treatment of 2-(bromomethyl)aziridines **16a,b** with 2 molar equiv $LiAlH_4$

Compound	Reaction conditions	Result
16a	Et_2O, r.t., 15 h	15-20% of **217** + side products
16a	Et_2O, Δ, 15 h	**217** (12%)/**218** (48%) : 1/4 + side products
16b	Et_2O, Δ, 2 h	**217** (15%)/**218** (45%) : 1/3 + side products
16b	Et_2O, Δ, 2.5 h	**218** (52%)/**219** (30%) : 1.7/1 + side products

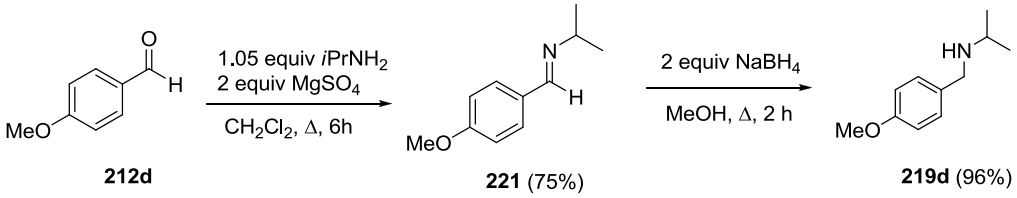
The formation of amines **217** can be explained by a $LiAlH_4$-induced debromination of aziridines **16** via a nucleophilic or a radical reaction,[116] followed by ring opening of the intermediate aziridinylmethyl anion **215** or aziridinylmethyl radical **216** to give the corresponding amines **217** after aqueous work up (Scheme 61).

After a number of attempts to optimize the reaction conditions, the reaction of aziridines **16a-d** with 2 molar equiv of $LiAlH_4$ in dry Et_2O under reflux for 3-6 hours afforded *N*-arylmethyl-*N*-isopropylamines **219** as the sole reaction products quite unexpectedly in high yields (80-84%) (Scheme 62). Again, the suggested mechanistic pathway for this transformation consists of an initial reductive debromination of 2-(bromomethyl)aziridines **16** toward 2-methylaziridines **218** through the action of $LiAlH_4$, either via a nucleophilic or a radical reaction.[116] Subsequently, reductive ring opening takes place via nucleophilic attack of a hydride ion (from $LiAlH_4$) at the less substituted carbon atom of the aziridine moiety in intermediates **220**. Apparently, the reducing agent acts both as the activator of the aziridine ring (through coordination of aluminium with nitrogen)[68,108] and as the provider of the nucleophile (hydride) which opens up the ring at the less hindered position (Scheme 62). However, the alternative mechanistic pathway comprising an initial hydride attack at the less hindered position of the aziridine moiety of 2-(bromomethyl)aziridines **16** yielding the corresponding ring-opened intermediates, and their subsequent ring closure toward 2-methylaziridines **218**, should not be neglected. Although attempts to isolate 2-methylaziridine **218**[117] by column chromatography on silica gel failed, their intermediacy was acknowledged by ^{1}H NMR, ^{13}C NMR and MS analysis of some of the crude reaction mixtures.



Scheme 62

Additionally, in order to confirm the structure of *N*-arylmethyl-*N*-isopropylamines **219**, an independent synthesis of *N*-(4-methoxybenzyl)-*N*-isopropylamine **219d** was performed. Condensation of 4-methoxybenzaldehyde **212d** with 1.05 equiv of $iPrNH_2$ in CH_2Cl_2 in the presence of $MgSO_4$ afforded the corresponding imine **221** in 75% yield after six hours under reflux, which was then reduced using two molar equiv of $NaBH_4$ in MeOH for two hours under reflux, furnishing *N*-(4-methoxybenzyl)-*N*-isopropylamine **219d** in 96% yield (Scheme 63). The spectral data of amine **219d** obtained via both routes were judged to be identical.



Scheme 63

Apart from amines **219**, which can of course easily be prepared via other routes, this methodology holds significant synthetic potential for the preparation of a large variety of amines in a convenient way through reductive ring opening of the appropriate aziridine derivatives, which will be the topic of the following paragraphs.

3.1.2 Ring opening of 2-(acetoxymethyl)aziridines with $LiAlH_4$

The utility of this $LiAlH_4$-promoted ring opening of non-activated aziridines was also demonstrated by the synthesis of versatile β-amino alcohols starting from 2-(acetoxymethyl)aziridines.

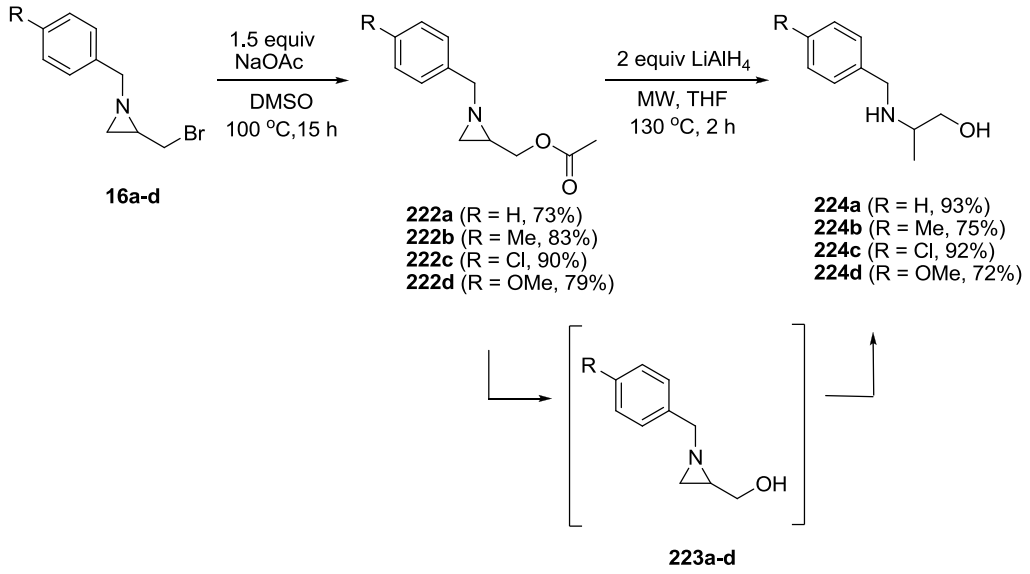
1-Arylmethyl-2-(acetoxymethyl)aziridines **222** were smoothly prepared upon treatment of 2-(bromomethyl)aziridines **16a-d** with an excess (1.5 equiv) of sodium acetate in DMSO at 100 °C for 15 hours (Scheme 64). The reaction provided almost pure acetates **222a-d** suitable for further elaboration without prior purification. However, for full characterization, aziridines **222** were purified by column chromatography on silica gel, affording analytically pure samples.

Further treatment of 2-(acetoxymethyl)aziridines **222** with two molar equiv of $LiAlH_4$ in Et_2O and heating for six hours under reflux provided crude mixtures containing mainly aziridinyl alcohols **223**, and no traces of ring opened β-amino alcohols **224** were detected. Increasing the reaction time to 24-62 hours led to partial formation of β-amino alcohols **224** (~50%). It was shown that, in order to obtain β-amino alcohols **224** in reasonable yields, a reflux time of several days (4-5) was required (Table 3).

Table 3. Treatment of 2-(acetoxymethyl)aziridines **222** with 2 molar equiv $LiAlH_4$

Compound	Reaction conditions	Result
222b	Et_2O, Δ, 15 h	70% of **223b** + side products
222a	Et_2O, Δ, 20 h	76% of **223a** + side products
222a	Et_2O, Δ, 1.5 h	15% of **224a** + side products
222c	Et_2O, Δ, 7 d	85% of **224c** + side products
222d	Et_2O, Δ, 4 d	**223d** + **224d** + side products
222d	THF, Δ, 6 d	90% of **224d** + side products
222c	Et_2O, Δ, 5 d	85% of **224c** + side products
222b	Et_2O, Δ, 5 d	65% of **224b** + side products

In order to overcome this major drawback, the reaction mixture was subjected to microwave irradiation (CAUTION!). Gratifyingly, after heating aziridines **222** in THF at 130 °C for two hours (220 W_{max}) in the presence of two molar equiv of $LiAlH_4$, only the corresponding β-amino alcohols **224** were formed in high purity without traces of 2-(hydroxymethyl)aziridines **223** (Scheme 64). Thus, the nucleophilic attack of hydride at the less substituted carbon atom of aziridines **223** was confirmed and, as a result, β-amino alcohols **224** were obtained in high yields after purification by column chromatography on silica gel. In this way, 2-aminopropan-1-ols **224** were formed selectively through complete regio- and stereoselective conversion of 2-(hydroxymethyl)aziridines **223**. Although several useful routes for the synthesis of β-amino alcohols are available in the literature,[28a,40a,118] some of these approaches suffer from (minor) drawbacks such as low regioselectivity, cumbrous substrate synthesis or low substrate stability. The synthesis of β-amino alcohols **224** through microwave-assisted ring opening of aziridines **222** utilizing $LiAlH_4$ satisfies the requirements for a generally applicable route, i.e., the use of commercially available starting compounds, complete regio- and stereoselectivity and high energy efficiency. Thus, the presented methodology can be regarded as a complementary approach or a worthy alternative for other known routes. β-Amino alcohols are applied extensively in organic synthesis as a building blocks in designing natural and biologically active substances,[27,28a,39,119] and their chiral versions are also used in catalytic asymmetric synthesis.[28]

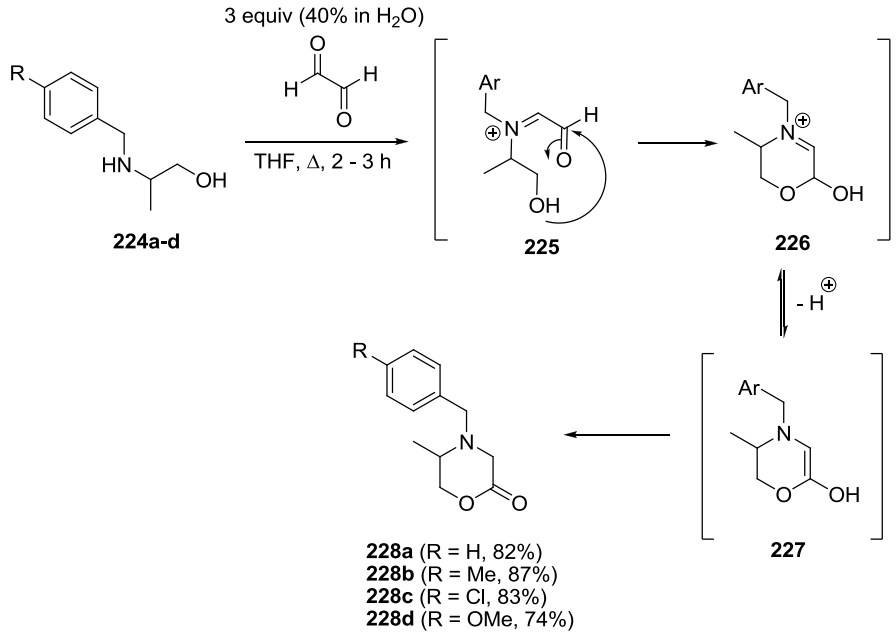


Scheme 64

3.1.3 Synthesis of 5-methylmorpholin-2-ones from β-amino alcohols

The reactivity of β-amino alcohols toward the synthesis of the corresponding 1,4-oxazin-2-ones upon the condensation with glyoxal was a subject of a number of literature reports.[120] In the next part, 2-aminopropan-1-ols **224** were also shown to be suitable intermediates for the construction of 5-methylmorpholin-2-ones,[29] which are known as fruitful substrates for the synthesis of biologically relevant compounds.[121]

Thus, 2-(arylmethylamino)propan-1-ols **224a-d** were dissolved in THF and treated with three equiv of glyoxal. After heating these mixtures for 2-3 hours, 5-methylmorpholin-2-ones **228a-d** were obtained in good yields (Scheme 65), and column chromatography on silica gel provided analytically pure compounds suitable for full characterization. The mechanism of the formation of morpholin-2-ones **228** could be explained by the initial formation of iminium salt **225**, which undergoes an intramolecular nucleophilic addition of the hydroxyl group to the carbonyl group to give the cyclic iminium intermediate **226**, which rearranges to the more stable enamine **227** to provide morpholin-2-one **228** as the final product.

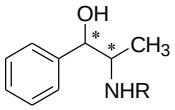


Scheme 65

3.1.4 Synthesis of enantiopure β-amino alcohols and 5-methylmorpholin-2-ones

Given the intermediacy of 2-(hydroxymethyl)aziridines **223** in the conversion of acetates **222** into alcohols **224**, efforts were devoted to the evaluation of chiral 2-(hydroxymethyl)aziridines as substrates for a $LiAlH_4$-promoted reductive ring opening. In the literature, only a few studies have been made on ring-opening reactions of non-activated enantiomerically pure 2-(hydroxymethyl)aziridines.[79,84,85,118a,122] For example, the catalytic hydrogenation of 2-(aziridinyl)methanols **229a** and **229b** in EtOH using $Pd(OH)_2$ has provided β-amino alcohols **230a** and **230b** in good yields.[122] Recently, the preparation of chiral β-amino alcohols via regio- and stereocontrolled ring-opening reactions of chiral aziridines has been examined.[74] This approach comprised the reaction of 2-alkylaziridines with acetic acid to yield the ring-opening products with excellent regioselectivity, which were then treated with $LiAlH_4$ or $Pd(OH)_2$ to provide the corresponding β-amino alcohols. On the other hand, the reaction of the same chiral aziridines with acetyl chloride followed by treatment with water gave isomeric β-amino alcohols through oxazoline intermediates.[74] In addition, the reaction of the latter chiral aziridines with benzyl bromide followed by the treatment with sulfuric acid gave secondary β-amino alcohols via ring opening at the substituted aziridine carbon atom.

Many β-amino alcohols are biologically active and play very important roles in living organisms.[123] Therefore, the syntheses of enantiomerically pure amino alcohols are becoming important areas of research. Among those, *Ephedra* alkaloids (Figure 9) are attractive targets because of their biological and medicinal activities. These compounds have long been used in China to treat bronchial asthma, hay fever, and other allergic reactions, and large quantities are produced in Western countries to relieve mucous membrane congestion.[124]



R = CH_3 ((1*R*,2*S*)-(-)-ephedrine)
R = H ((1*R*,2*S*)-(-)-norephedrine)
R = CH_3 ((1*S*,2*S*)-(+)-pseudoephedrine)
R = H ((1*S*,2*S*)-(-)-norpseudoephedrine)

Figure 9

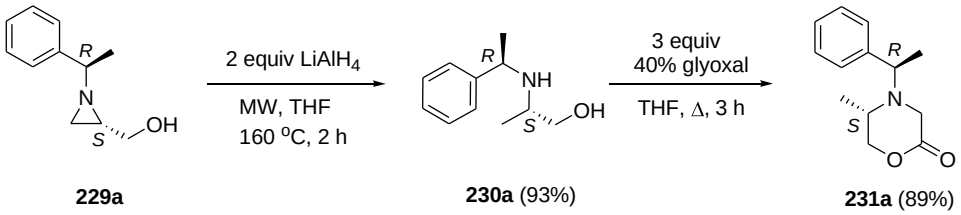
In this part, the synthesis of enantiopure 2-aminopropan-1-ols by means of $LiAlH_4$-promoted reduction of chiral 2-(hydroxymethyl)aziridines **229a** and **229b** was successfully examined. After failing to prepare amines **230a** and **230b** upon treatment with two molar equiv of $LiAlH_4$ under reflux for several days in THF and toluene (Table 4), the mixture of aziridines **229** and two molar equiv of $LiAlH_4$ in THF was subjected to microwave conditions (160 °C, 220 W_{max}, two hours). Fortunately, full and selective conversion of aziridines **229a** and **229b** into enantiopure 2-aminopropan-1-ols **230a** and **230b** as single stereoisomers was obtained (Scheme 66).

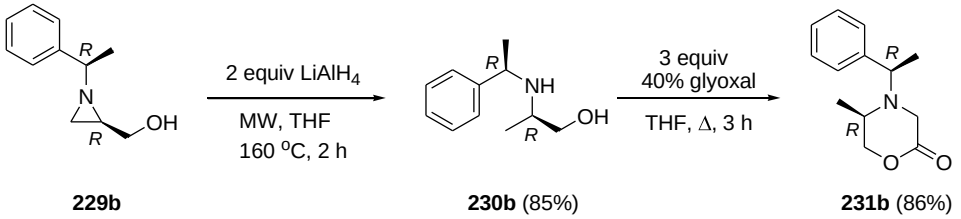
Table 4. Treatment of 2-(hydroxymethyl)aziridines **229** with 2 molar equiv $LiAlH_4$

Compound	Reaction conditions	Result
229a	Et_2O, Δ, 6 h	no reaction
229a	THF, Δ, 10 d	no reaction
229a	toluene, Δ, 3 h	no reaction
229b	THF, Δ, 2 d	no reaction
229b	toluene, Δ, 5-10 d	complex mixture

Again, the mechanism comprises coordination of aluminium with the aziridine nitrogen atom, enabling C(3)-N bond cleavage induced by nucleophilic attack of a hydride ion to furnish the corresponding ring-opened product. The bond cleavage showed to be highly regioselective, since hydride attack only occured at the less hindered position. Furthermore, the ring opening reaction of chiral aziridines **229** proceeded not only with high regioselectivity, as it also furnished the corresponding enantiopure amino alcohols **230a** and **230b** with full retention of configuration.

The preparation of enantiopure six-membered oxazaheterocycles has received significant attention, for example due to their high potential as chiral substrates. In particular, chiral morpholin-2-ones have been used in the asymmetric synthesis of α-amino acids[121a,b] and other natural products.[121c,d,e] In the present study, enantiopure 5-methylmorpholin-2-ones were prepared by condensation of the corresponding chiral amino alcohols with glyoxal. Thus, chiral β-amino alcohols **230a** and **230b** were treated with three equiv of glyoxal (40%), affording enantiopure morpholin-2-ones **231a** and **231b** upon reflux for three hours in THF (Scheme 66). The reaction showed high stereoselectivity since no diastereomers were detected in the crude ^1H NMR spectra, which is in accordance with previously reported analogous condensation reactions.[29]

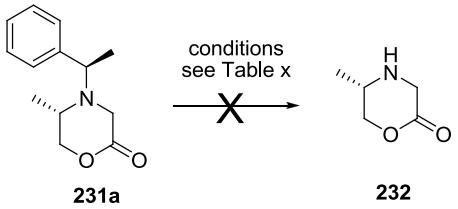




Scheme 66

Attempts to convert enantiopure amino alcohols **230** into chiral 2-methylaziridines were not successful. For this purpose, β-amino alcohols **230a** and **230b** were subjected to Mitsunobu conditions using 1.2 equiv of PPh_3 and 1.2 equiv of diisopropyl azodicarboxylate (or 1.2 equiv of *N*-bromosuccinimide) in THF for 18 hours, or were treated with 1.05 equiv of MsCl and 1.1 equiv of Et_3N (or 1.05 equiv of TsCl and 0.1 equiv of DMAP) in CH_2Cl_2 for 4 hours, although in all cases only complex mixtures were obtained.

In addition, the efforts to cleave the 1-phenylethyl group at the nitrogen atom in morpholinone **231a** by means of hydrogenation using $Pd(OH)_2$ (5-15 mol%) at 5 bar, were not successful, even after prolonged reaction times (3 days) (Table 5, Scheme 67).



Scheme 67

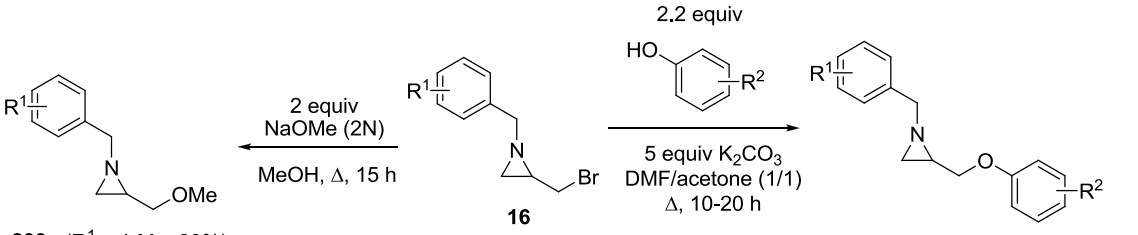
Table 5. Attempts to deprotect nitrogen in morpholinone **231a**

Compound	Reaction conditions	Result
231a	5mol% $Pd(OH)_2$, EtOAc, 4 bar, 1 d	no reaction
231a	15mol% $Pd(OH)_2$, EtOAc, 5 bar, 3 d	no reaction

3.1.5 Ring opening of 2-(methoxymethyl)- and 2-(phenoxymethyl)aziridines with $LiAlH_4$

In addition to the use of 2-(acetoxymethyl)- and 2-(hydroxymethyl)aziridines, the $LiAlH_4$-promoted ring opening of 2-(methoxymethyl)- and 2-(phenoxymethyl)aziridines **233** and **234** was evaluated applying microwave conditions (Scheme 68).

2-(Methoxymethyl)aziridines **233a,b** were prepared through conversion of 2-(bromomethyl)aziridines **16** upon treatment with two equiv of sodium methoxide in methanol (2M) under reflux for 15 hours,[125] whereas 2-(phenoxymethyl)aziridines **234a-d** were obtained by treatment of 2-(bromomethyl)aziridines **16** with 2.2 equiv of phenol and 5 equiv of K_2CO_3 in a mixture of DMF and acetone (1/1) under reflux for 10-20 hours.[92]

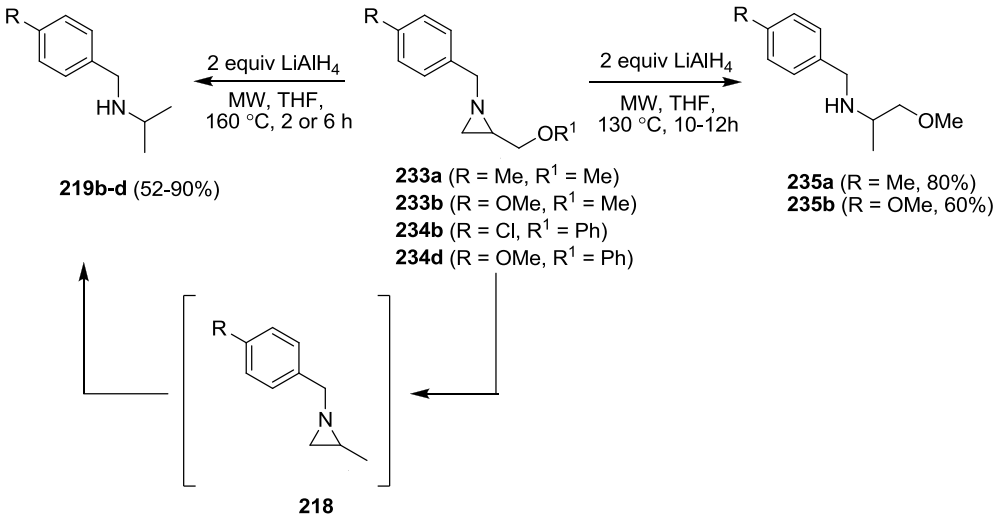


233a (R^1 = 4-Me, 89%)
233b (R^1 = 4-OMe, 87%)

234a (R^1 = 2-Cl, R^2 = H, 72%)
234b (R^1 = 4-Cl, R^2 = H, 85%)
234c (R^1 = 4-Cl, R^2 = 4-Cl, 82%)
234d (R^1 = 4-OMe, R^2 = H, 87%)

Scheme 68

Remarkably, treatment of aziridines **233** with two equiv of $LiAlH_4$ under microwave conditions resulted in different reaction products depending on the temperature used. Indeed, treatment of aziridine **233a,b** for 2 hours at 160 °C yielded isopropylamines **219**, whereas mainly β-methoxyamines **235a**,**b** were obtained after 12 hours at 130 °C (Scheme 69, Table 6). The formation of isopropylamines **219b-d** can be explained considering the initial replacement of the methoxy group by means of $LiAlH_4$ (via a nucleophilic or radical pathway) furnishing 2-methylaziridines **218**, which subsequently underwent reductive ring opening via nucleophilic attack of a hydride ion (from $LiAlH_4$) at the less substituted carbon atom of the aziridine moiety. Again, spectroscopic evidence for the intermediacy of 2-methylaziridines **218** was obtained through careful analysis of the reaction mixtures. Apparently, at 130 °C nucleophilic aziridine ring opening by hydride took place prior to replacement of the methoxy group, and β-methoxyamines **235a,b** were obtained as the major components in the reaction mixtures (Scheme 69). The reaction of 2-(phenoxymethyl)aziridines **234b,d** with two equiv of $LiAlH_4$ surprisingly furnished isopropylamines **219** after 6 hours at 160 °C under microwave irradiation. However, when these aziridines **234b,d** were heated at 130 °C (or 140 °C) for 10-15 hours, 2-methylaziridines **218** were obtained in a mixture together with starting compounds **234b,d**. Increasing the temperature to 160 °C led to the full conversion of aziridines **234b,d** into isopropylamines **219**. These observations can be explained considering the better leaving group capacities of the phenoxy substituent as compared to the methoxy group, resulting in a more rapid formation of intermediate 2-methylaziridines **218**. The unexpected behaviour of the phenoxy group as a leaving group is remarkable, as no other reports on the conversion of phenoxyalkanes into the corresponding alkanes using hydride reagents have been reported in the literature. Thus, attempts were made to convert *n*-decylphenyl ether into *n*-decane using $LiAlH_4$ under microwave conditions. However, the reaction showed to be potentially dangerous under microwave irradiation at 160 °C, leading to an explosive reaction outcome. Therefore, this method cannot to be regarded as a general synthetic approach for alkane formation as such.



Scheme 69

Table 6. $LiAlH_4$-promoted ring opening of aziridines **233** and **234** using microwave irradiation

Compound	Reaction conditions	Result
233a	2 equiv $LiAlH_4$, THF, 130 °C, 30 min	no reaction
233a	2 equiv $LiAlH_4$, THF, 130 °C, 10 h	80% of **235a**
233b	2 equiv $LiAlH_4$, THF, 130 °C, 12 h	60% of **235b**
234d	2 equiv $LiAlH_4$, THF, 120 °C, 15 h	no reaction
234d	2 equiv $LiAlH_4$, THF, 130 °C, 12 h	complex mixture
234b	2 equiv $LiAlH_4$, THF, 120 °C, 15 h	no reaction
234b	2 equiv $LiAlH_4$, THF, 140 °C, 10 h	complex mixture
234d	2 equiv $LiAlH_4$, THF, 160 °C, 6 h	52% of **219d**
234b	2 equiv $LiAlH_4$, THF, 160 °C, 6 h	54% of **219c**

In conclusion, the microwave-assisted reductive ring opening of 2-substituted non-activated aziridines utilizing $LiAlH_4$ proceeded smoothly in a highly regio- and stereoselective way, not requiring the presence of additional Lewis acids. 2-(Acetoxymethyl)aziridines provided β-amino alcohols upon treatment with $LiAlH_4$ under microwave irradiation, which were then used to produce synthetically relevant 5-methylmorpholin-2-ones in a straightforward way. Besides, the microwave-assisted conversion of chiral aziridine substrates by means of $LiAlH_4$ furnished the corresponding enantiopure β-amino alcohols, which were then exposed to glyoxal to give chiral 5(*R*)- and 5(*S*)-morpholin-2-ones. In addition, 2-(methoxymethyl)aziridines provided isopropylamines or β-methoxyamines upon treatment with $LiAlH_4$ under microwave irradiation, depending on the temperature applied. Thus, $LiAlH_4$ can be regarded as a useful reagent for a new type of reductive aziridine ring opening in a

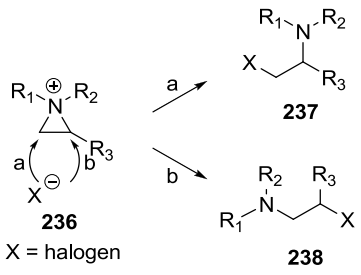
selective way under microwave conditions, paving the way for a variety of novel applications in organic chemistry.

3.2 Systematic study of halide-induced ring opening of 2-substituted aziridinium salts[126]

The regio-controlled ring opening of C-substituted aziridines constitutes a powerful approach toward the preparation of a large variety of functionalized nitrogen-containing target compounds. In the chapter 'Literature review' the issue of regioselectivity in the ring opening of 2-substituted aziridinium salts, obtained by *N*-functionalization of neutral aziridines, by different nucleophiles was thoroughly discussed. Therein, 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 was disclosed.

The ring opening of aziridinium salts by halides constitutes a convenient approach toward β-halo amines, which are generally recognized as useful building blocks in organic chemistry[22,115,127] and valuable targets in medicinal chemistry (nitrogen mustards – chemotherapy agents).[128]

As seen in the previous chapter, intermediate aziridinium salts **236** can be ring opened at the unsubstituted (path a) or the substituted aziridine carbon atom (path b), leading either to primary halides **237** (path a) or to secondary halides **238** (path b) (Scheme 70).



Scheme 70

In the literature, a number of reports are available on the synthesis of β-halo amines through ring opening of aziridinium salts by halides.[31a,39,68,74,129] In most cases, 2-vinyl- and 2-arylaziridinium salts have been evaluated, in which the regioselectivity is substrate-dictated due to the presence of a pronounced electrophilic centre at the substituted aziridine carbon atom. The use of 2-alkyl-substituted aziridinium ions has somewhat been neglected in that respect, probably because of the potential influence of different parameters such as the type of nucleophile, substrate and solvent on the reaction outcome. Whereas the issue of regioselectivity has been addressed in a number of literature reports, no systematic study has been performed up to now in which aziridinium substrates are subjected to ring opening by fluoride, chloride, bromide and iodide.

Therefore, in this part, *in situ* generated 2-substituted aziridinium salts have been used as electrophiles for ring opening by fluoride, chloride, bromide and iodide in acetonitrile in a systematic way.

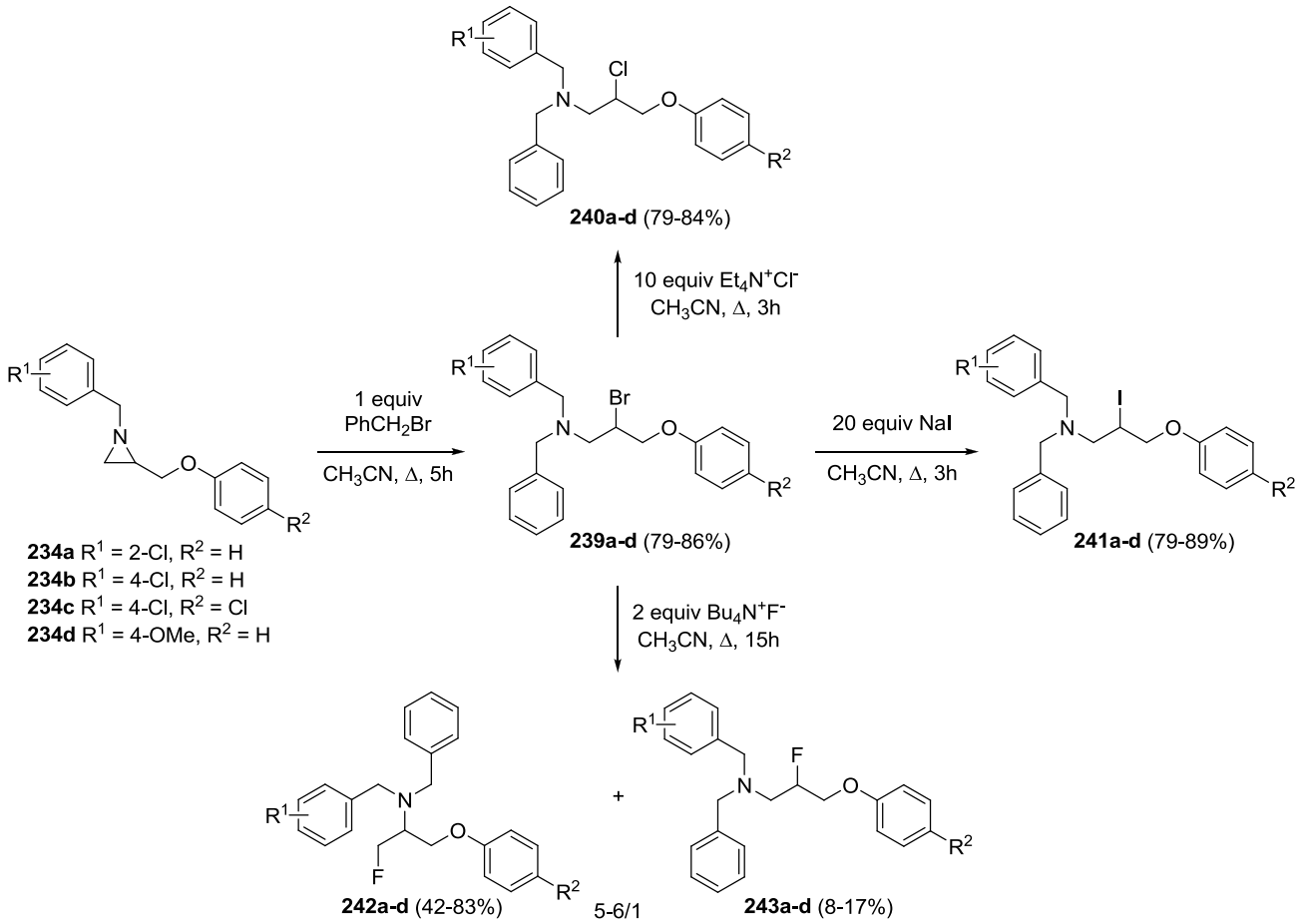
3.2.1 Ring opening of 2-aryloxymethyl-1,1-di(arylmethyl)aziridinium salts by halides

In this part, halide-induced ring opening of intermediate 2-aryloxymethyl-1,1-di(arylmethyl)aziridinium salts was contemplated. As reported before, 2-(aryloxymethyl)aziridines **234** can be prepared in high yields and purity upon treatment of the corresponding 2-(bromomethyl)aziridines **16**[22,115a,b] with two equiv of the appropriate potassium phenolate in a DMF/acetone (1/1) solvent system under reflux for 10-20 hours (Scheme 68).[92]

Treatment of the aziridines **234** with one equiv of benzyl bromide in acetonitrile is known to afford secondary bromides **239** as the sole reaction products in high yields after reflux for five hours (Scheme 11, Table 7).[92] In order to provide an entry into the corresponding fluorides, chlorides and iodides as well, β-bromo amines **239** were treated with different halide sources. Thus, both novel β-chloro amines **240** and β-iodo amines **241** were prepared as the sole reaction products by the use of either 10 equiv of tetraethylammonium chloride or 20 equiv of sodium iodide, respectively, in acetonitrile after reflux for three hours (Scheme 11, Table 7). The formation of the other regioisomers was excluded based on detailed spectroscopic analysis.

The conversion of β-bromo amines **239** into β-chloro amines **240** using 20 equiv of NaCl instead of tetraethylammonium chloride in acetonitrile proceeded very sluggishly, as no conversion occurred after heating under reflux for 4 hours and only partial conversion was observed after reflux for 60 hours. On the other hand, the reaction of β-bromo amines **239** with 10 equiv of tetrabutylammonium iodide in acetonitrile appeared to be less successful as compared to the use of sodium iodide, as only 50% conversion took place after reflux for 7 hours. If 15 equiv of sodium iodide were used instead of 20 equiv, a longer reaction time (5 hours) was required in order to drive the reaction to completion.

When β-bromo amines **239** were treated with two equiv of tetrabutylammonium fluoride in acetonitrile, however, a mixture of regioisomeric fluorides **242** and **243** were obtained after reflux for 15 hours (Scheme 71, Table 7).[94] In this case, primary fluorides **242** were formed as the major reaction products, besides minor amounts of secondary fluorides **243** (ratio **242**/**243** 5-6/1). In order to test the reaction outcome as a function of reaction time and temperature, prolonged and elevated reaction times were also evaluated. In particular, heating under reflux for 3 days instead of 15 hours did not affect the isomeric distribution (ratio **242**/**243**: 5-6/1), and the same conclusion was drawn after heating under reflux for 25 hours in DMF. These observations point to the fact that the product distribution between primary and secondary fluorides **242** and **243** is not under thermodynamic control.



Scheme 71

Table 7. Synthesis of β-bromo amines **239**, β-chloro amines **240**, β-iodo amines **241** and β-fluoro amines **242** and **243**.

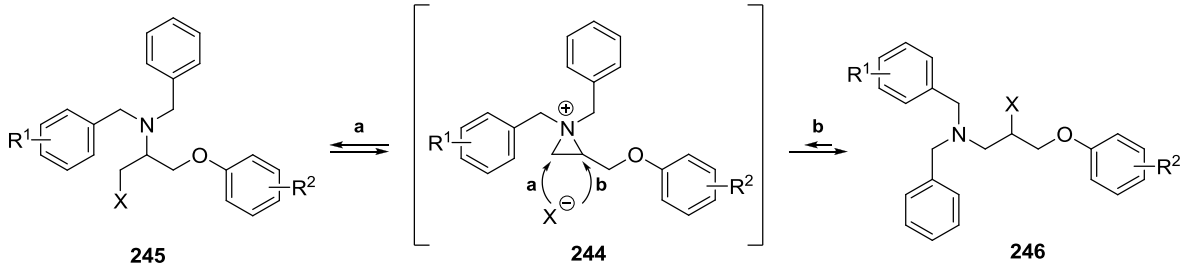
Entry	R^1	R^2	**239** (yield)	**240** (yield)	**241** (yield)	**242** (yield)	**243** (yield)	Ratio[a] **242**/**243**
1	2-Cl	H	**239a** (71%)	**240a** (82%)	**241a** (89%)	**242a** (54%)	**243a** (10%)	5/1
2	4-Cl	H	**239b** (86%)	**240b** (79%)	**241b** (88%)	**242b** (42%)	**243b** (8%)	5/1
3	4-Cl	Cl	**239c** (85%)	**240c** (83%)	**241c** (82%)	**242c** (60%)	**243c** (10%)	6/1
4	4-OMe	H	**239d** (84%)	**240d** (84%)	**241d** (79%)	**242d** (61%)	**243d** (14%)	6/1

[a] Ratio determined by ^{1}H NMR analysis

As observed and investigated before, quaternization and subsequent ring opening of 2-(aryloxymethyl)aziridines **234** using benzyl bromide produces β-bromo amines **246** through regiospecific ring opening of aziridinium salts **244** at the substituted aziridine carbon atom (X = Br, path b, Scheme 72).[42,94,102a] Furthermore, in addition to preliminary findings using other types of substrates,[94] the ring opening of aziridinum intermediates **244** by fluoride afforded a mixture of regioisomers in which primary fluorides **245** are predominant (X = F, path a, Scheme 72), pointing to a change in regioselectivity as compared to bromide. In previous theoretical studies, it was

demonstrated that product stabilities seem to dictate the outcome of the reaction through thermodynamic control in the bromide case, whereas difference in barriers for the fluoride case were shown to be mainly due to the difference in interaction energies, pointing to the fact that sterics dictate the outcome.[102a]

In this study, the formation of β-bromo amines **239**, β-chloro amines **240**, β-iodo amines **241** and β-fluoro amines **242** and **243** proceeds through ring opening of the same intermediate aziridinium salts **244** by different halides (Scheme 72). Apparently, the chloride-[130] and iodide-promoted ring opening of aziridinium ions **244** is controlled by the same factors as compared to bromide-induced ring opening, involving attack at the substituted position (X = Cl and I, path b, Scheme 72). Thus, it can be concluded that chloride-, bromide- and iodide-promoted ring openings of aziridinium ions **244** are under thermodynamic control, eventually leading to the more stable secondary halides **246** as the final reaction products. On the other hand, ring opening by fluoride is kinetically controlled, which can be rationalized considering the poor leaving group capacity of fluoride as compared to the other halides, preventing thermodynamic equilibration.



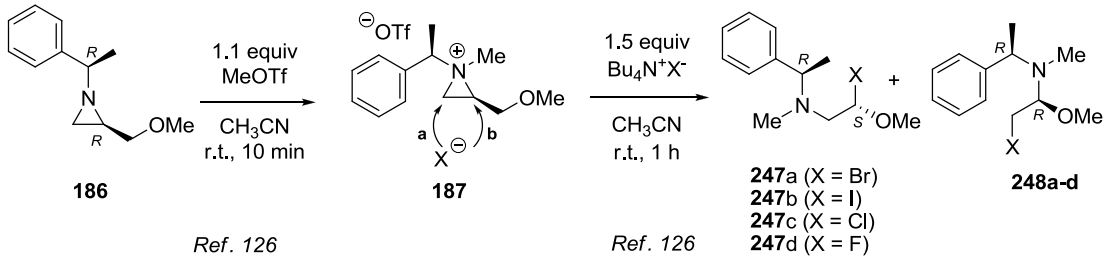
Scheme 72

3.2.2 Ring opening of stable 1-methylaziridinium triflates by halides

In order to provide an insight into the potential role of the substrate in the above-described ring opening reactions, the synthesis of another type of aziridinium salts has been performed by the group of H.-J. Ha (Hankuk University of Foreign studies, Yongin, Korea). Therein, for example, stable 1-methylaziridinium triflates **187** were prepared through *N*-methylation of chiral 2-(methoxymethyl)aziridines **186** upon treatment with 1.1 equiv of methyl trifluoromethanesulfonate in acetonitrile for 10 minutes (Scheme 73), and were then evaluated as electrophiles for halide-induced ring opening reactions.

For this purpose, in the group of H.-J. Ha, different tetrabutylammonium halides have been used as halide sources for the ring opening of aziridinium triflates **187**. First, the reaction of 2-(methoxymethyl)aziridinium ions **187** with 1.5 equiv of tetrabutylammonium fluoride, chloride, bromide or iodide in acetonitrile at room temperature for one hour afforded the corresponding β-halo amines in good yields. Interestingly, the same conclusions were drawn as described above, involving the selective synthesis of secondary bromide **247a**, iodide **247b** and chloride **247c** as the sole reaction products, besides a regioisomeric mixture of primary and secondary fluoride **248d** and **247d** (3/1)

(Scheme 73, Table 8). These observations further consolidate the nucleophile-dependency of ring opening reactions of 1,1,3-trialkylaziridinium ions by halides, pointing to a chloride-, bromide- and iodide-mediated ring opening under thermodynamic control and a fluoride-induced ring opening under kinetic control.



Scheme 73

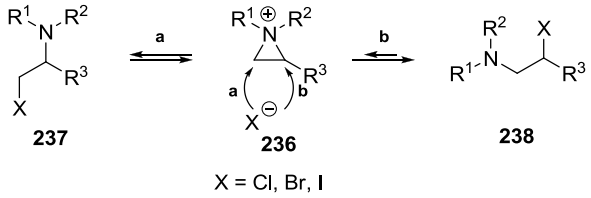
Table 8. Ring opening of 1-methylaziridinium triflates **187** by tetrabutylammonium halides.[126]

Entry	Substrate	X	Product	Yield(%)
1	**187**	Br^-	**247a**	47%
2	**187**	I^-	**247b**	52%
3	**187**	Cl^-	**247c**	73%
4	**187**	F^-	**248d + 247d**	77% (3/1)

Interestingly, when aziridinium triflate **187** was treated with 1.5 equiv of NaCl in acetonitrile (20 hours, rt) instead of $Bu_4N^+Cl^-$, the initial formation of a different reaction product has been observed upon chromatographic analysis (TLC), which slowly underwent conversion into secondary β-chloro amine **247c** upon standing at the room temperature (research group of H.-J. Ha). Although purification by column chromatography on silica gel failed, the initially formed reaction product could be identified as 2-amino-3-chloro-1-methoxypropane **248c** by ^1H NMR analysis. Obviously, the latter primary chloride comprises the kinetically controlled reaction product obtained through ring opening of aziridinium ion **187** at the unsubstituted position (route a, Scheme 73), which then rearranges into the more stable secondary chloride via a thermodynamic equilibrium. The same observation was made through careful analysis of the reaction outcome after treatment of aziridinium triflate **187** with 1.5 equiv of $Me_4N^+Cl^-$. It should be noted that these findings made by the research group of Prof. Ha comprised the first experimental proof for the occurrence of a thermodynamic equilibrium in the halide-induced ring opening of 2-alkyl-substituted aziridinium salts.[126]

From these data, it can be concluded that the ring opening of 2-alkyl-substituted aziridinium salts **236** by chloride, bromide and iodide proceeds under thermodynamic control, where product stabilities dictate the outcome of the reaction. Thus, the initially formed kinetic primary halides **237** undergo rearrangement into the thermodynamically more stable secondary halides **238** (Scheme 74). Fluoride-

mediated ring opening, however, is under kinetic control, where the reaction outcome is only dictated by steric interactions.



Scheme 74

3.2.3 Evaluation of halide-induced ring opening of 2-substituted aziridinium salts by computational methods

In order to elucidate the factors causing the differences in regioselectivity, a thorough computational analysis on the halide-mediated ring opening of **187** has been performed in the Center for Molecular Modeling of Ghent University (Prof. V. Van Speybroeck and Prof. M. Waroquier).[126]

The potential energy surfaces (PES) for the halide-induced nucleophilic ring opening of **187** through pathways *a* (unhindered) and *b* (hindered) (see Scheme 74) for all three halides are illustrated in Figure 10.

The overall picture for halide-induced ring opening shows that the unhindered route (*pathway a*) is always kinetically preferred, however, the hindered route leads to the thermodynamic product. The eventual outcome depends on the softness and leaving group ability of the nucleophile (halide). If the nucleophile is a good leaving group (soft 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.[126] Theoretical results are in perfect agreement with experimental findings, also pointing to the well-known trend in nucleophile strength and leaving group ability throughout the halide series.

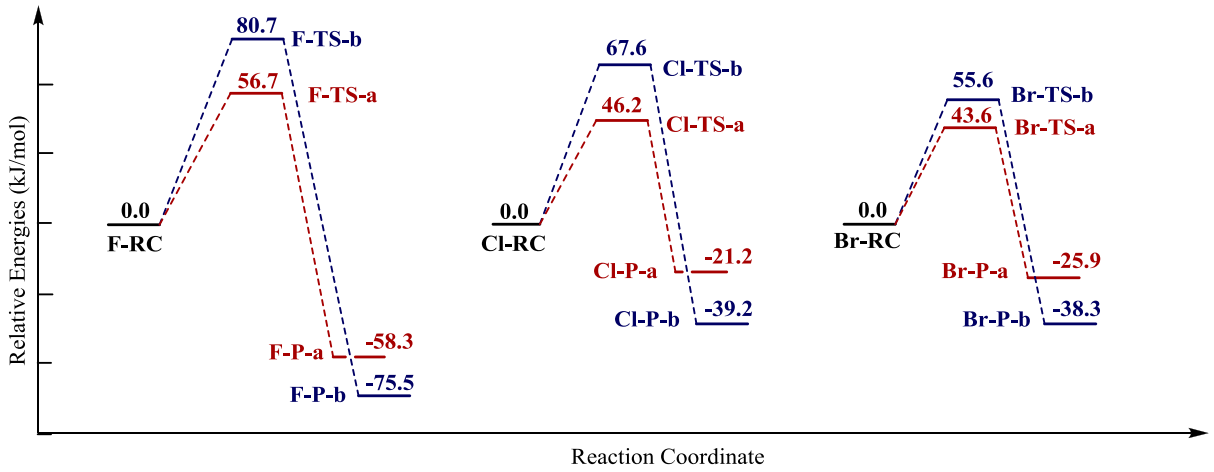


Figure 10. Potential Energy Surfaces (PES) for the halide-induced nucleophilic ring opening of **187** *via* pathways *a* (unhindered) and *b* (hindered). (MPW1B95/6-31++G(d,p)//B3LYP/6-31++G(d,p)). Relative energies are given in kJ/mol.

F-Ts-a, F-Ts-b – transition states for fluoride attack via pathways a and b, respectively; F-P-a, F-P-b-products of fluoride attack via pathways a and b, respectively. Cl-Ts-a, Cl-Ts-b – transition states for chloride attack via pathways a and b, respectively; Cl-P-a, Cl-P-b-products of chloride attack via pathways a and b, respectively. Br-Ts-a, Br-Ts-b – transition states for bromide attack via pathways a and b, respectively; Br-P-a, Br-P-b-products of bromide attack via pathways a and b, respectively

In summary, the ring opening of 2-alkyl-substituted aziridinium salts by fluoride, chloride, bromide and iodide was studied for the first time in a systematic way, pointing to an inherent difference in reactivity between fluoride on the one hand and chloride, bromide and iodide on the other. Both experimental and computational evidence was provided for the fact that product stabilities dictate the reaction outcome through thermodynamic control in the chloride, bromide and iodide case, involving rearrangement of the initially formed primary halides to the more stable secondary halides via a thermodynamic equilibrium. The ring opening of the same aziridinium salts by fluoride, however, was shown to be mediated by steric interactions (kinetic control), as the difference in barriers were mainly due to the difference in interaction energies.

3.3 Synthesis of 3-methoxyazetidines via an aziridine to azetidine rearrangement[131]

Imines carrying halogens in their side chain display a high intrinsic reactivity, and the selective introduction of halogens in imino substrates has led to building blocks with high synthetic potential, as shown amply for the useful class of α-haloimines.[110a,c,f-i,132] The halogen can be introduced in the aldehyde- (or ketone-) derived part, either before or after imination.[110f-i,132] On the other hand,

examples are known regarding halogenated imines in which the halogen is present in the amine-derived part.[110e,133] The latter type of imines is usually accessed through imination of carbonyl compounds by means of halogenated (and thus reactive) amines, or via electrophilic addition of, e.g., bromine, across *N*-alkenyl imines. As a subclass, *N*-alkylidene- and *N*-arylmethylidene-(2,3-dibromopropyl)amines comprise useful intermediates for the preparation of azaheterocyclic compounds such as aziridines and azetidines.[22,25b,92,115,134]

Next to the diverse utility of aziridines, also their four-membered ring analogues, azetidines, represent an extraordinary class of strained compounds with diverse synthetic and biological applications. In addition to their synthetic relevance,[10a-d,f,g,135] compounds containing an azetidine moiety have been shown to possess a wide range of biological activities.[5a,9a,b,136] In particular, 3-alkoxy- and 3-aryloxyazetidines (Figure 11) have been described as for example G-protein coupled receptor agonists **249**,[137] inhibitors of stearoyl-coenzyme d-9 desaturase **250** and **251**,[138] and antibacterial agents **252**.[139]

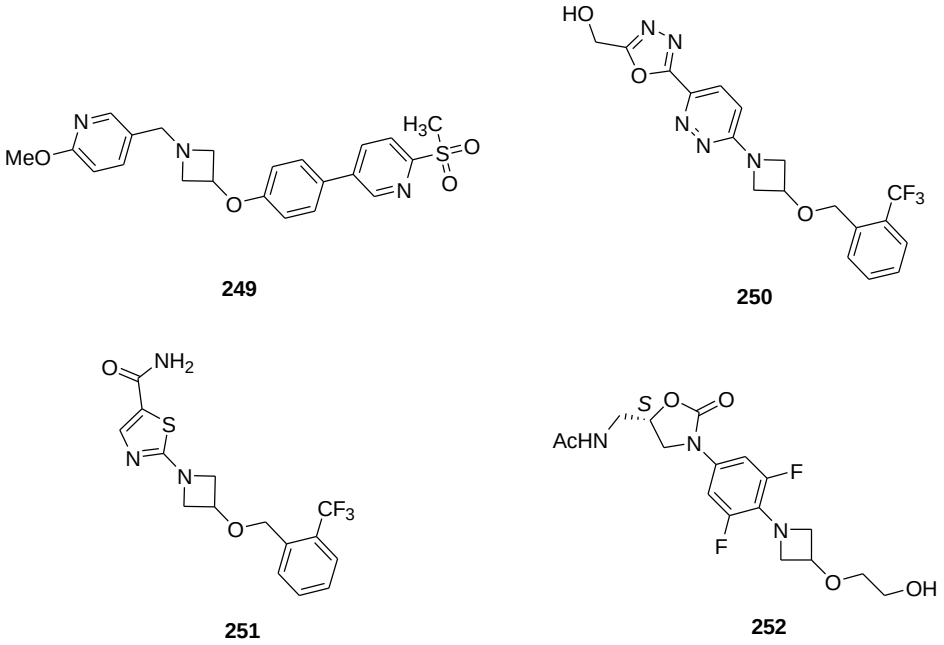
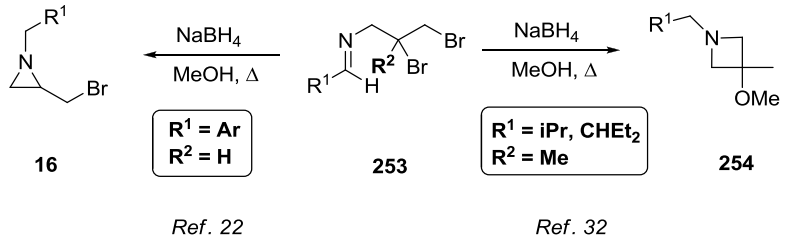


Figure 11

In the previous chapters, the utility of 2-(bromomethyl)aziridines **16** as versatile building blocks to provide an entry into functionalized β-amino alcohols, morpholinones and wide range of functionalized amines was elaborated. The synthesis of these aziridines **16** was performed by the $NaBH_4$-mediated reduction of the corresponding *N*-alkylidene-(2,3-dibromopropyl)amines **253** (R^1 = Ar, R^2 = H) in methanol under reflux (Scheme 75). On the other hand, in a preliminary study at the Department of Sustainable Organic Chemistry and Technology (UGent), it has been shown that structurally similar *N*-alkylidene-(2,3-dibromo-2-methylpropyl)amines **253** (R^1 = iPr, $CHEt_2$, R^2 = Me) afforded 3-methoxyazetidines **254** under the same reaction conditions (Scheme 75).

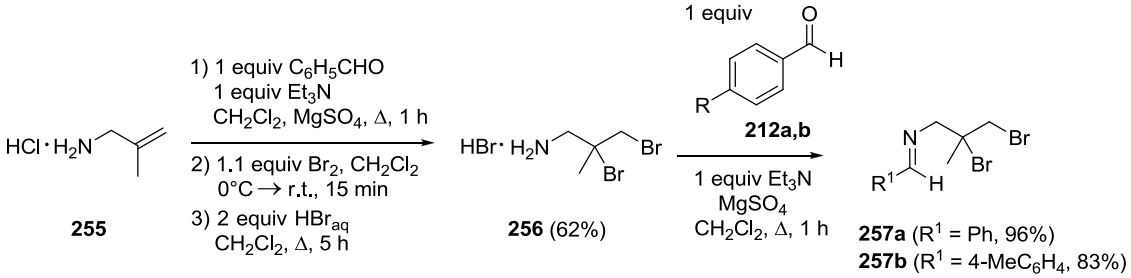
It is clear that this unexpected reactivity of imines **253** (R^1 = iPr, $CHEt_2$, R^2 = Me) to form azetidines **254**, raised a lot of questions regarding the mechanism of the latter reaction. For this purpose, in the next part, the kinetically controlled synthesis of 2-bromomethyl-2-methylaziridines, as potential intermediates in this reaction, and their conversion to 3-methoxyazetidines will be discussed thoroughly.



Scheme 75

3.3.1 Evaluation of the synthesis of 3-methoxyazetidines from *N*-arylmethylidene-(2,3-dibromo-2-methylpropyl)amines

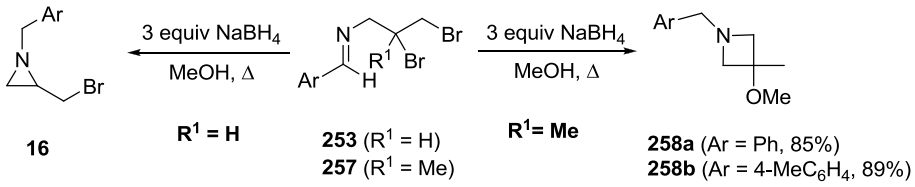
N-Arylmethylidene-(2,3-dibromo-2-methylpropyl)amines **257a,b** were prepared by a procedure comprising condensation of 2,3-dibromo-2-methylpropylamine hydrobromide **256** with different benzaldehydes **212a,b** in the presence of 1 molar equiv of triethylamine and magnesium sulfate in dichloromethane after reflux for 1 hour (Scheme 76). The synthesis of 2,3-dibromo-2-methylpropylamine hydrobromide **256** commenced with the imination of benzaldehyde using 2-methylallylamine hydrochloride **255** in dichloromethane in the presence of triethylamine and magnesium sulfate, followed by bromination of the alkene moiety in the resulting *N*-(2-methyl-2-propenyl)imine in dichloromethane and subsequent treatment with 2 equiv of hydrogen bromide (48% solution in water) in dichloromethane (two-phase system). In this way, the desired 2,3-dibromo-2-methylpropylamine **256** was obtained as the corresponding hydrobromide salt in 62% overall yield.



Scheme 76

Despite their reactive nature, imines **257a** and **257b** were judged to be pure enough to be used in further reactions without prior purification (purity >95% based on ^{1}H NMR). As already mentioned, *N*-alkylidene- and *N*-arylmethylidene-(2,3-dibromopropyl)amines **253** (R^1 = H, Scheme 77) have been

used as intermediates for the straightforward preparation of 2-(bromomethyl)aziridines **16** via reductive 3-*exo*-*tet*-cyclization using sodium borohydride in methanol under reflux.[22,25b,92,115] However, when the same methodology was applied to *N*-arylmethylidene-(2,3-dibromo-2-methylpropyl)amines **257** (R^1 = Me, Scheme 77) with the intention to prepare 2-bromomethyl-2-methylaziridines as a novel class of substrates, only 3-methoxy-3-methylazetidines **258a,b** were obtained instead. Apparently, the presence of an additional methyl group (R^2 = Me) in imines **257** has a profound influence on the reaction outcome. In a previous study, treatment of *N*-alkylidene-(2,2,3-tribromopropyl)amines with $NaBH_4$ in methanol has been reported to furnish 3,3-dimethoxyazetidines via double methanolysis,[134] although in that case the direct formation of azetidines was foreseen, as nucleophilic substitution at the dibrominated carbon atom toward aziridines is unlikely.

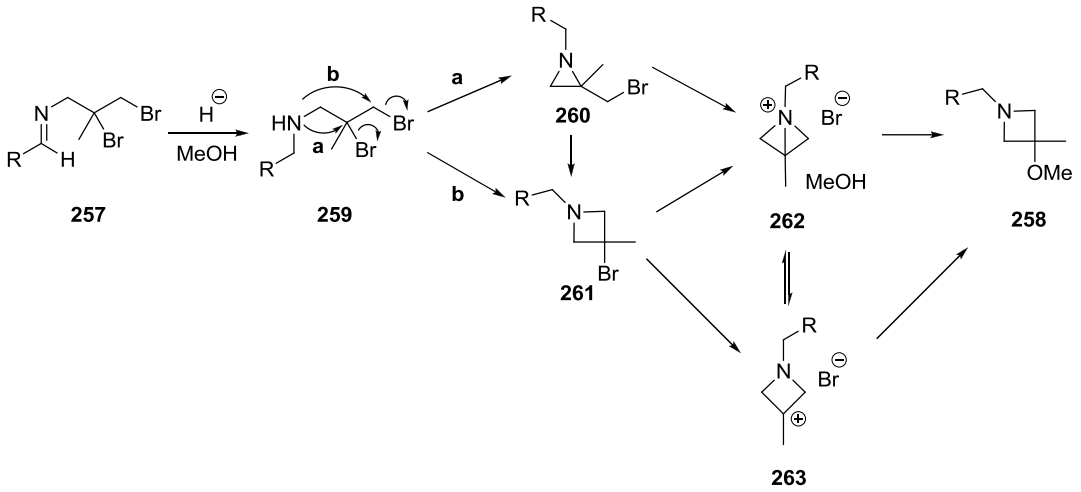


Scheme 77

From a mechanistic point of view, different pathways can be considered to explain the observed reactivity (Scheme 78). Reduction of imines **257** in methanol via hydride addition across the imino bond toward amines **259** can either be followed by a 3-*exo*-*tet*-cyclization affording 2-bromomethyl-2-methylaziridines **260** (pathway a) or a 4-*exo*-*tet*-cyclization toward 3-bromoazetidines **261** (pathway b). Subsequently, both types of β-bromo amines (**260** and **261**) can be transformed into bicyclic aziridinium salts **262** through intramolecular displacement of bromide by the nucleophilic nitrogen atom, which stand in equilibrium with the nonbridged carbenium ions **263**. Alternatively, the formation of carbenium species **263** can be the result of spontaneous expulsion of bromide in 3-bromoazetidines **261**. Ring opening of intermediates **262** by methanol at the more hindered position or solvolysis of carbenium species **263** by methanol finally affords 3-methoxyazetidines **258**.

On the basis of previous findings,[140] the 3-*exo*-*tet*-cyclization of amines **259** toward 2-bromomethyl-2-methylaziridines **260** (pathway a) will probably prevail (kinetic effect). The cyclization of 2-bromomethyl-2-methylaziridines **260** to strained intermediates **262** stands in contrast with the well-known chemistry of 2-(bromomethyl)aziridines bearing no additional substituent at the 2-position, as in this case the intramolecular cyclization and further transformation has never been observed.[22,24c,25b,92,93,114,115,141] The spontaneous cyclization of 2-bromomethyl-2-methylaziridines **260** under thermodynamic conditions can be rationalized considering the Thorpe-Ingold effect due to the *gem*-disubstitution at the aziridine carbon atom, resulting in a more favorable geometric positioning of the nucleophilic nitrogen atom with respect to the halogenated carbon atom. Alternatively, 2-bromomethyl-2-methylaziridines **260** can first be transformed into 3-bromoazetidines **261** via a concerted mechanism, which comprises simultaneous cleavage and formation of a carbon-nitrogen bond along with bromide migration. Furthermore, 3-bromoazetidines **261** can be converted into 3-

methoxyazetidines **258** either via bicyclic aziridinium salts **262** or via carbenium ions **263**. The presence and formation of strained intermediates **262** is regarded as reasonable in view of various reports involving this type of intermediates. For example, the formation of a bicyclic aziridinium intermediate has been suggested in the literature based on the stereospecific transformation of 3-tosyloxy- and 3-haloazetidines after hydrolysis and substitution reactions, and ring contraction to aziridinylmethyl derivatives.[142] Moreover, it has been established that the substitution of 3-chloroazetidines with different nucleophiles occurs via formation of an analogous bicyclic intermediate, which is then regioselectively opened at the C3 position.[10i] In light of these reports, the ring opening of bicyclic aziridinium salts **262** by methanol is expected to proceed in a regiospecific way at the more hindered carbon atom, furnishing 3-methoxyazetidines **258**. However, the formation of intermediate carbenium species **263** and their subsequent solvolysis by methanol should not be neglected as an alternative pathway toward azetidines **258**. It is worth mentioning that the isomerization of 2-(halomethyl)aziridines to 3-haloazetidines has been observed in the literature in only three cases,[143] and that isolated examples are known in which ring opening of strained bicyclic intermediates does not occur in a regiospecific way.[142c]



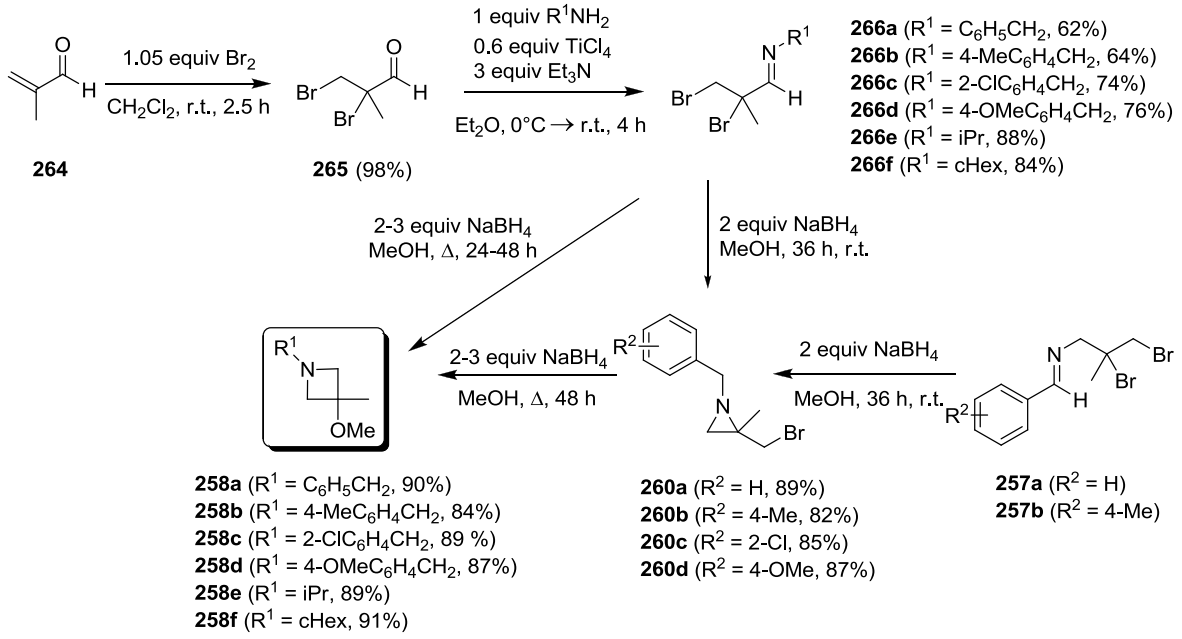
Scheme 78

3.3.2 Synthesis and ring expansion of 2-bromomethyl-2-methylaziridines

In the next part, a stepwise experimental approach was applied in order to shed more light on the underlying reaction mechanism. At first, a kinetically controlled synthesis of 1-arylmethyl-2-bromomethyl-2-methylaziridines **260** was envisaged starting from α,β-dibromoaldimines **266** (Scheme 79). The synthesis of 2-bromomethyl-2-methylaziridine **260a**, deriving from the corresponding α,β-dibromoaldimine has previously been performed,[33] yet this aziridine **260a** was present as a minor component in a mixture with the corresponding β,γ-dibromoamine. Optimization of the reaction conditions was required to furnish aziridines **260** as sole reaction products.

Bromination of 2-methylpropenal **264** using 1.05 equiv of bromine in dichloromethane afforded the corresponding 2,3-dibromopropanal **265** in nearly quantitative yield, which was subsequently

condensed with 1 equiv of different *N*-alkylamines by means of 0.6 equiv of titanium(IV) chloride and 3 equiv of triethylamine in diethyl ether,[140] furnishing α,β-dibromoimines **266** in good yields (Scheme 79). The latter imines **266** were reduced by means of 2 molar equiv of sodium borohydride in methanol, resulting in 2-bromomethyl-2-methylaziridines **260** after 36 h at room temperature. Alternatively, imines **266** were reduced toward aziridines **260a-d** utilizing two molar equiv of sodium cyanoborohydride in methanol in the presence of 1 equiv of acetic acid, however, without providing better yields. In addition, 2-bromomethyl-2-methylaziridines **260a,b** were also obtained through reaction of *N*-arylmethylidene-(2,3-dibromo-2-methylpropyl)-amines **257a** and **257b** with 2 molar equiv of $NaBH_4$ in methanol after 36 h at room temperature. The formation of 2-bromomethyl-2-methylaziridines **260** from both *N*-(2,3-dibromo-2-methylpropylidene)amines **266** and *N*-arylmethylidene-(2,3-dibromo-2-methylpropyl)amines **257** is rationalized by the intermediacy of the same amines **259** (Scheme 78) obtained upon reduction of imines **257** and **266** with $NaBH_4$. From these findings, it is clear that aziridines **260** are the kinetic products obtained through $NaBH_4$-mediated reduction of imines **257** and **266** in methanol under reflux (Scheme 79).

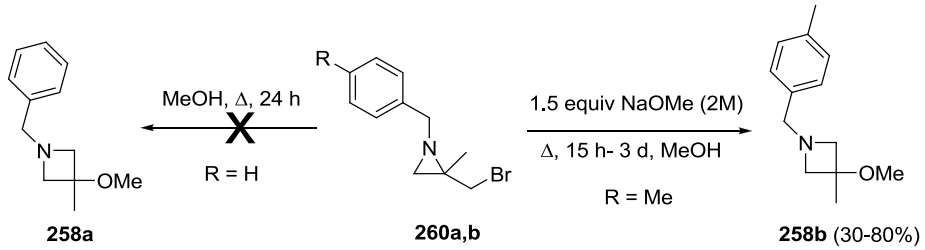


Scheme 79

Non-activated 2-bromomethyl-2-methylaziridines **260** represent a novel class of synthons suitable for further elaboration to a variety of nitrogen-containing compounds.

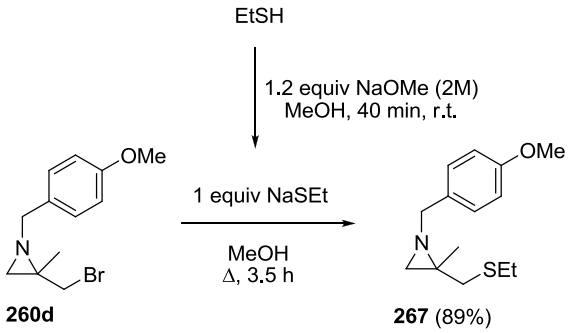
Under thermodynamic conditions, i.e., treatment of aziridines **260a-d** with sodium borohydride in methanol under reflux for 48 h, 3-methoxy-3-methylazetidines **258a-d** were formed in high yields as the sole reaction products (Scheme 79). This prolonged reaction time appeared to be necessary in order to drive the reaction to completion. Again, it should be remarked that applying the same reaction conditions to 2-(bromomethyl)aziridines **16** without a 2-methyl substituent is known to result in full recovery of the starting material. Heating of aziridines **260a** in methanol under reflux for 24 h resulted

in a complex reaction mixture, pointing to the necessity of a basic environment for this aziridine to azetidine rearrangement process. Furthermore, treatment of aziridines **260b** with 1.5 equiv of NaOMe in MeOH (2 M) furnished azetidine **258b**, although a prolonged reaction time was required (72 instead of 48 h) (Scheme 80).



Scheme 80

In an attempt to investigate the reactivity of 2-bromomethyl-2-methylaziridines toward thiolates, aziridine **260d** was treated with 1 equiv of sodium thioethylate (obtained from the reaction of ethanethiol with 1.2 equiv of sodium methoxide (2M), in methanol for 3.5 hours under reflux, affording 2-ethylthiomethyl-2-methylaziridine **267** as the sole product, without traces of the corresponding azetidine (Scheme 81). Apparently, in this case, a direct nucleophilic displacement of bromide by the highly reactive thiolate happens faster than intramolecular expulsion of bromide by the less nucleophilic nitrogen atom.

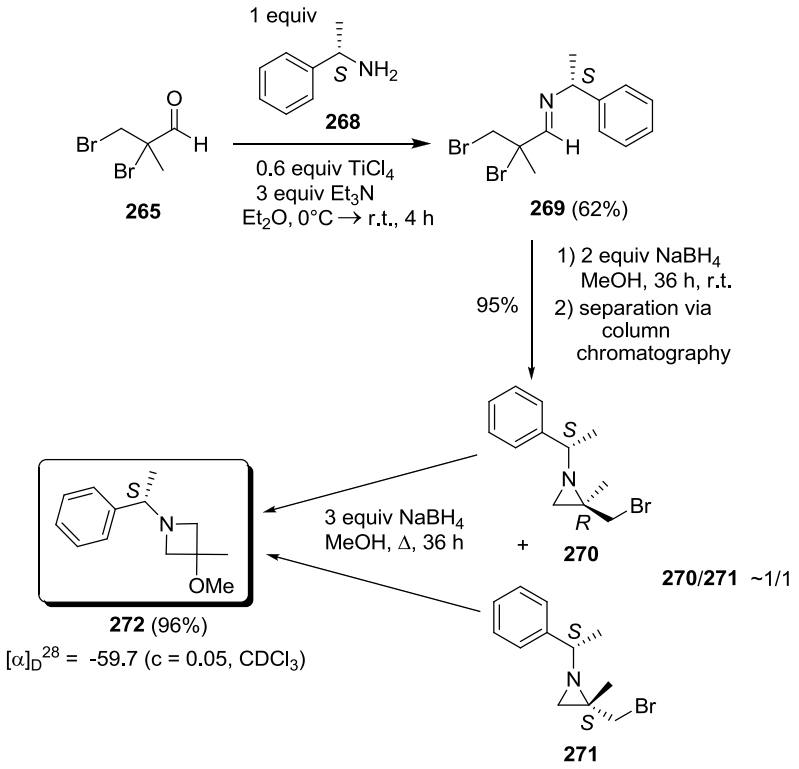


Scheme 81

3.3.3 Synthesis of chiral 2-bromomethyl-2-methylaziridines and a 3-methoxyazetidine

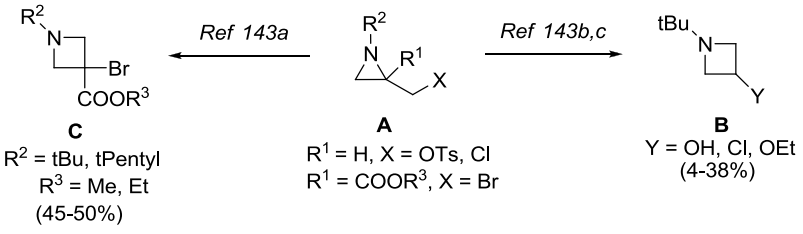
The above-described synthetic route was also applied for a straightforward synthesis of chiral 2-bromomethyl-2-methylaziridines. For this purpose, *N*-(2,3-dibromo-2-methylpropylidene)-1(*S*)-phenylethylamine **269** was prepared by imination of 2,3-dibromopropanal **265** with one equiv of (*S*)-α-methylbenzylamine **268** in the presence of titanium(IV) choride and triethylamine. Next, imine **67** was reduced utilizing two molar equiv of sodium borohydride in methanol, resulting in a mixture of two diastereomeric 2-bromomethyl-2-methylaziridines **270** and **271** (~1/1) after 36 hours at room temperature (Scheme 82). After successful separation by column chromatography on silica gel, chiral

aziridines **270** and **271** were separately subjected to three molar equiv of $NaBH_4$ under reflux in methanol for 36 hours. As expected, both reactions provided the same chiral azetidine **272**, which can be explained considering the loss of chirality of the azetidine carbon atom due to C_2-symmetry (Scheme 82).

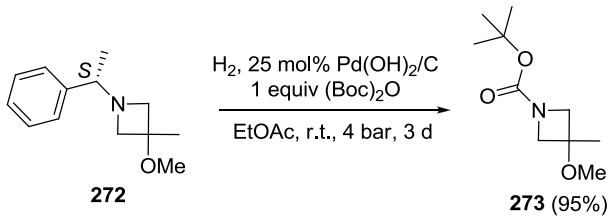


Scheme 82

Once again, it should be stressed that only three reports are available in the literature describing the ring expansion of aziridines toward azetidines,[143] pointing to the peculiar nature of this type of rearrangements (see Scheme below). In these reports, it has been suggested that even some monosubstituted aziridines i.e., 2-(chloromethyl)- and 2-(tosyloxymethyl)aziridines **A** (R^1 = H, R^2 = tBu, X = OTs, Cl) can undergo ring rearrangement to furnish the corresponding azetidines **B** (Y = OH, Cl, OEt), yet in low yields (4-38%).[143b,c] In another study, which is more consistent with the findings described in this PhD thesis, a facile ring expansion of alkyl 2-(bromomethyl)aziridine-2-carboxylates **A** (R^1 = $COOR^3$, X = Br) to different 3-bromoazetidines **C** (45-50%) has been reported.[143a]



Deprotection of nitrogen in azetidine **272** by hydrogenation at 3-5 bar using $Pd(OH)_2$ (5-25mol%) in EtOAc resulted only in the recovery of the starting material even after 6 days. However, upon addition of 1 equiv of $(Boc)_2O$, the Boc-protected azetidine **273** (95%) was obtained as the sole product after 3 days at 4 bar (Scheme 83).

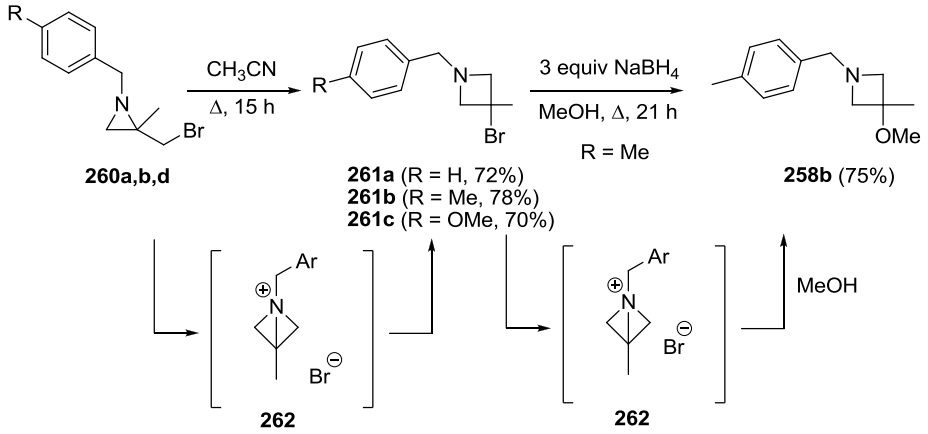


272 **273** (95%)

Scheme 83

3.3.4 Ring expansion of 2-bromomethyl-2-methylaziridines to 3-bromo-3-methylazetidines

In order to evaluate the intrinsic reactivity of 2-bromomethyl-2-methylaziridines **260** toward ring expansion, aziridines **260a,b,d** were subjected to heating in acetonitile under reflux for 15 hours, affording 3-bromoazetidines **261a-c** in acceptable yields (70-78%, Scheme 84). It should be mentioned that the formation of 3-bromoazetidines **261** was not always straightforward, since this azetidine was often present in a mixture with the starting aziridine. Attempts to effect full conversion of aziridine **260b** in the presence of $AgBF_4$ or KBr resulted in more complex reaction outcomes (Table 9). Nevertheless, azetidines **261** were isolated in pure form by column chromatography on silica gel.
The unprecedented transformation of aziridines **260** into azetidines **261** as the thermodynamic product further illustrates the relevance of this aziridine to azetidine ring expansion and can be explained by formation of bicyclic aziridinium salt **262** followed by attack of bromide at the more hindered carbon atom. Moreover, when 3-bromoazetidine **261b** was treated with $NaBH_4$ in methanol under reflux, 3-methoxy-3-methylazetidine **258b** was formed via solvolysis of the same bicyclic intermediate **262** through ring opening (Scheme 84).[10i,142] The direct replacement of bromide by methanol in azetidine **261** via an S_N2 protocol should be neglected as an alternative reaction pathway due to the steric hindrance at the tertiary carbon center, although S_N1 reaction through solvolysis of a tertiary carbenium ion might involve a plausible alternative.



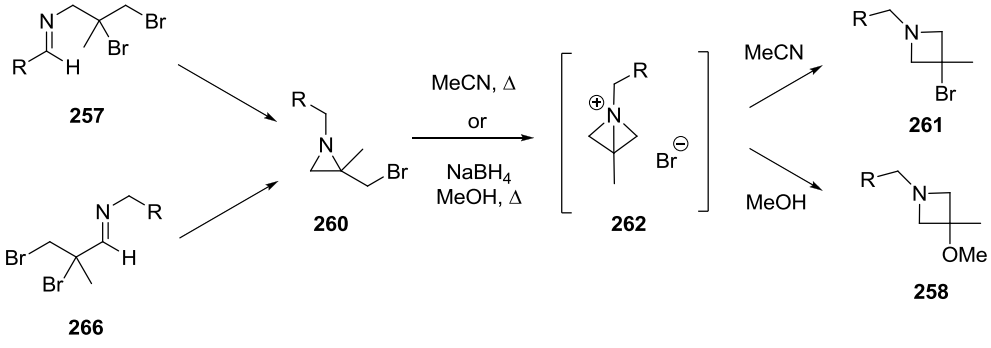
Scheme 84

Table 9. Synthesis of 3-bromo-3-methylazetidines **260b**

compound	conditions	result
260b (R = Me)	0.1-1 equiv $AgBF_4$, Δ, 15 h	complex mixture
260b (R = Me)	0.2-1 equiv KBr, Δ, 15 h	**261b** + side products
260b (R = Me)	Δ, 15 h	**260b** + **261b**
260b (R = Me)	Δ, 20 h	complex mixture

It should be mentioned that experiments to prepare 3-bromoazetidine **261b**, through $LiAlH_4$- or $NaBH_4$-mediated reduction of *N*-(2,3-dibromo-2-methylpropylidene)amine **266b** were unsuccessful and provided different reaction products such as 3-bromo-2-methyl-propylamine, 2-bromo-1,1-dimethyl-ethylamine and/or 2-bromomethyl-2-methylaziridine **260b**, and no traces of azetidine **261b** were present.

In summary, a novel aziridine to azetidine rearrangement protocol was established involving the conversion of 2-bromomethyl-2-methylaziridines **260**, obtained via reductive cyclization of halogenated imines **257** or **266**, into 3-methoxy-3-methylazetidines **258** through ring opening of bicyclic intermediates **262** by methanol upon treatment with $NaBH_4$ in methanol under reflux (Scheme 85). Furthermore, the ring expansion of aziridines **260** in acetonitrile under reflux provided a facile entry to novel 3-bromoazetidines **261**, which can be considered as versatile synthons for further derivatization.

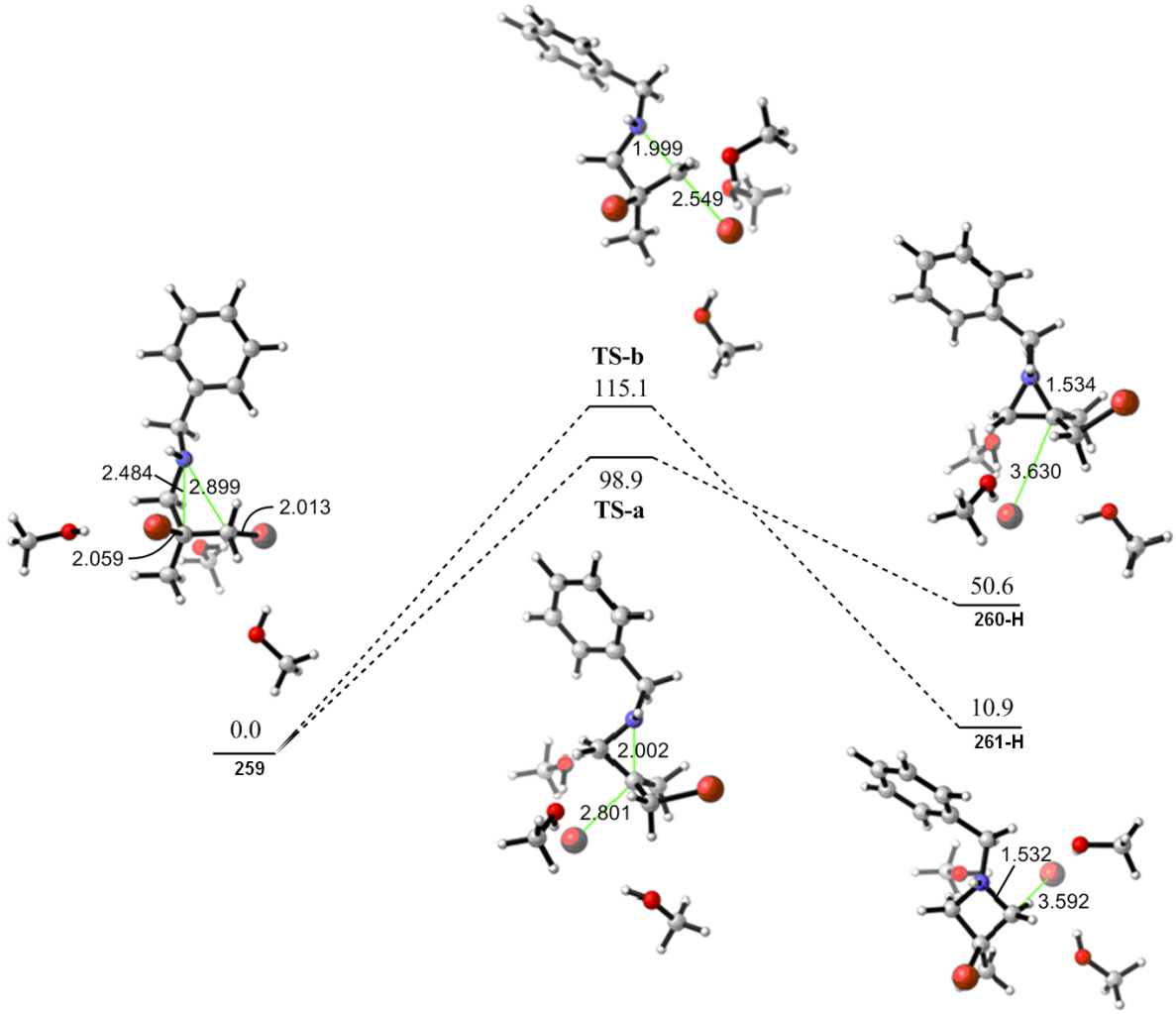


Scheme 85

The above-described experimental results were also supported by means of high-level molecular modeling calculations, performed at the Center for Molecular Modeling of Ghent University. In the next part, the most important results and conclusions of this study are highlighted.

3.3.5 Evaluation of the synthesis of 3-methoxyazetidines by computational methods

In Figure 12, free energy profiles and relative energies along the reaction coordinate for the cyclization of *N*-benzyl-*N*-(2,3-dibromo-2-methylpropyl)amine **259** (R = Ph) to aziridine **260** (pathway a, Scheme 78), or to azetidine **261** (pathway b, Scheme 78) was depicted. Free energies of activation show that pathway **a** is the kinetically preferred route ($\Delta G^{\ddagger}$ = 16.2 kJ/mol MPW1B95/6-31++G**), which is in accordance with experimental findings. Although the azetidinium ion (denoted as **261-H** in Figure 12) is the thermodynamically preferred product, thermodynamic equilibration is not feasible as the aziridinium ion (denoted as **260-H** in Figure 12) is immediately deprotonated toward the neutral, non-activated aziridine **260** (which is thus not able to undergo ring opening by bromide at C2). Therefore, aziridine **260** is the preferred product for the cyclization, as observed experimentally.



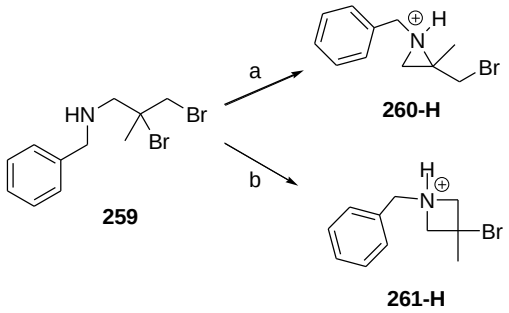
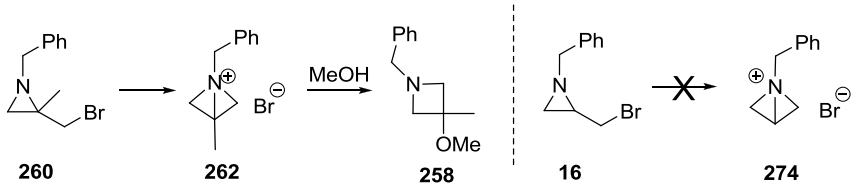


Figure 12. Gibbs free energy profiles for the conversion of *N*-benzyl-*N*-(2,3-dibromo-2-methylpropyl)amine **259** (R = Ph) via pathways **a** and **b** (kJ/mol, MPW1B95/6-31++G**). B3LYP/6-31++G** geometries. Critical distances in Å.

As previously described in Scheme 78, aziridine **260** is suggested to undergo further cyclization to yield the bicyclic aziridinium ion **262**, a bicyclic intermediate that will undergo nucleophilic ring opening to form azetidine **258**. However, as mentioned earlier, 2-(bromomethyl)aziridines **16** were not able to undergo ring expansion to form the corresponding azetidines (Scheme 86). The comparison of the cyclization pathways (transition state geometries and relative energies) for the formation of the bicyclic aziridinium ion **262** and **274** explains the preference of aziridine **260** to undergo ring rearrangement as compared to aziridine **16**. As mentioned before, this difference can be rationalized considering the Thorpe-Ingold effect due to the *gem*-disubstitution at the aziridine carbon atom, resulting in a more favorable geometry for nucleophilic attack.[144]



Scheme 86

Replacement of the methyl group at the 2-position of aziridine **260** by a hydrogen atom increases the distance between the nucleophilic nitrogen atom and the halogenated carbon atom in aziridine **16**, as shown in Figure 13, which in turn gives rise to a reduced reactivity.

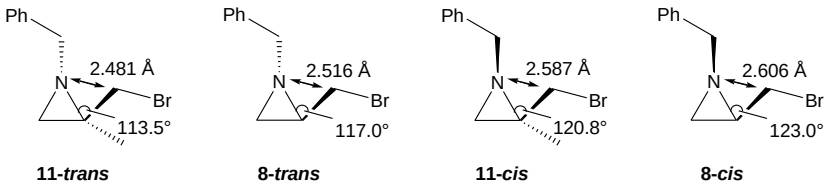
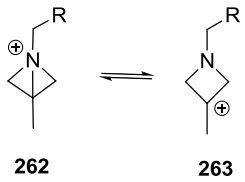


Figure 13. Invertomers of **260** and **16**

As suggested earlier, bicyclic aziridinium ion **262** can be in equilibrium with its non-bridged carbenium ion counterpart **263** (Scheme 87, Figure 14). The difference in relative stabilities of bicyclic aziridinium ion **262** and cyclic carbenium ion **263** shows that the former, where all atoms have full octet structure is far more stable than the latter.



Scheme 87

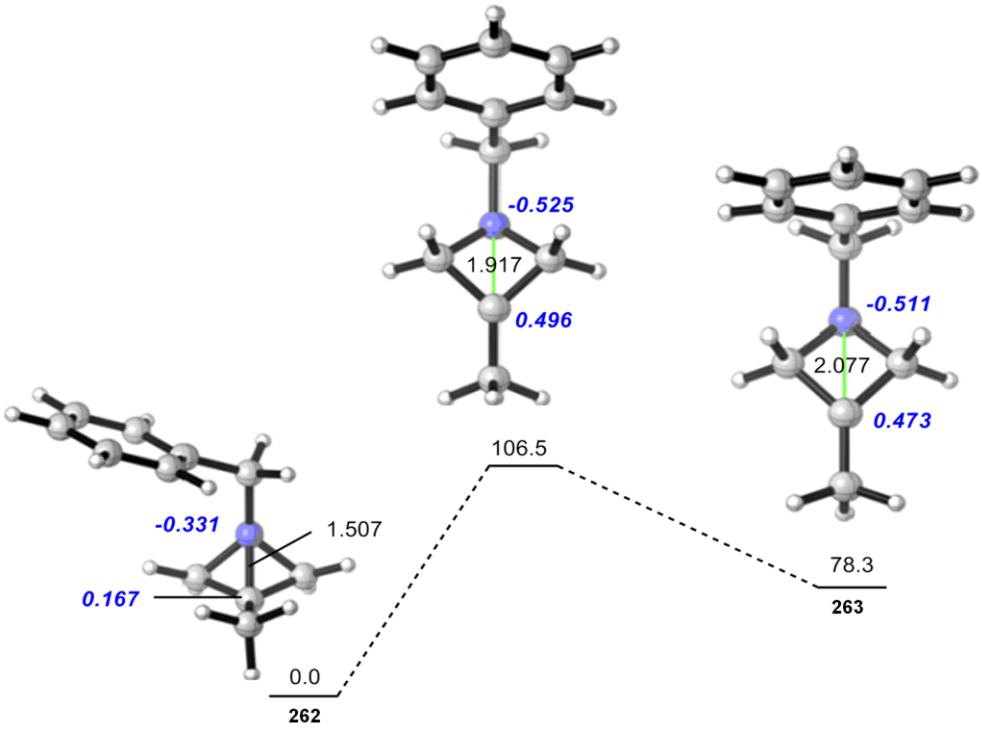


Figure 14. Gibbs free energy profile for the **58** to **59** equilibration (kJ/mol, CPCM (ε = 32.6) MPW1B95/6-31++G**).
B3LYP/6-31++G** geometries. Critical distances in Å. Atomic charges in italic.

Therefore, the reaction is expected to proceed through the bicyclic aziridinium ion **262**, and the carbenium species **263** is less likely to be formed or will be short-lived. Next, the computational study also showed that the bicyclic intermediates **262** easily undergoes ring opening to form azetidines **258** and **261**.

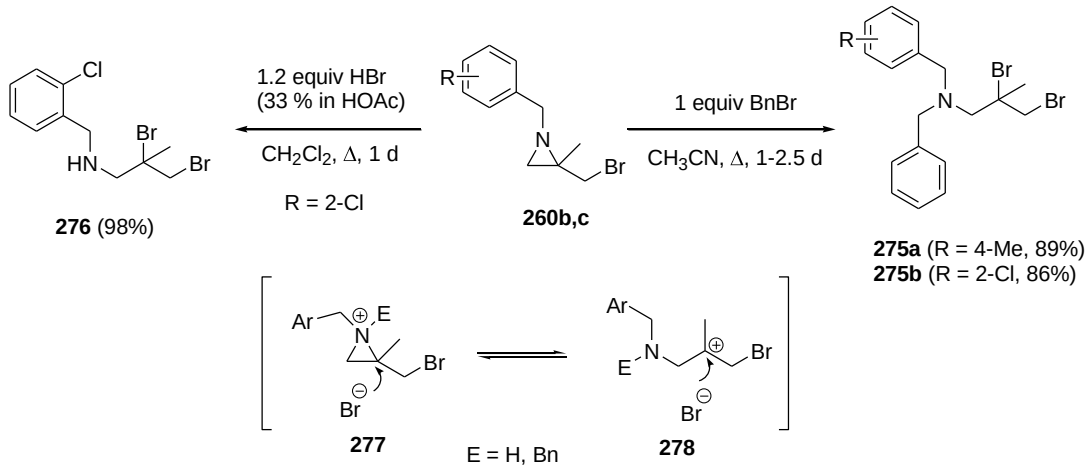
The transformation of **262** to azetidines **261** is energetically more favorable (ΔΔG = 38.9 kJ/mol MPW1B95/ 6-31þþG**), since the bromide anion — solvated or not — is a stronger nucleophile than neutral methanol. However, the reaction conditions highly favor the formation of 3-methoxyazetidines **258** since the concentration of methanol is much higher than that of bromide. In the absence of methanol, azetidine **261** should be the observed product, as was experimentally shown (Scheme 84).

Computational analysis of the possible reaction pathways proposed in Scheme 78 (R = Ph) has revealed that pathway **a** is the kinetically preferred route and aziridine **260** is the subsequent product for the cyclization, as observed experimentally. Unlike aziridines **16**, which lack an additional substituent at the 2-position, aziridine **260** then undergoes further cyclization to yield the bicyclic aziridinium ion **262**, a strained intermediate, which can undergo nucleophile-induced ring opening to form azetidines **258** or **261**, depending on the relative abundance of the nucleophilic entity.

3.3.6 Ring opening of 2-bromomethyl-2-methylaziridines

As seen before, ring opening of aziridines provides an efficient and easy approach toward a variety of amines via regio- and stereoselective ring-opening reactions with nucleophiles. Therefore, in order to gain insights into the reactivity of 2-bromomethyl-2-methylaziridines toward ring opening with different halides (bromide and chloride), a number of reactions were performed.

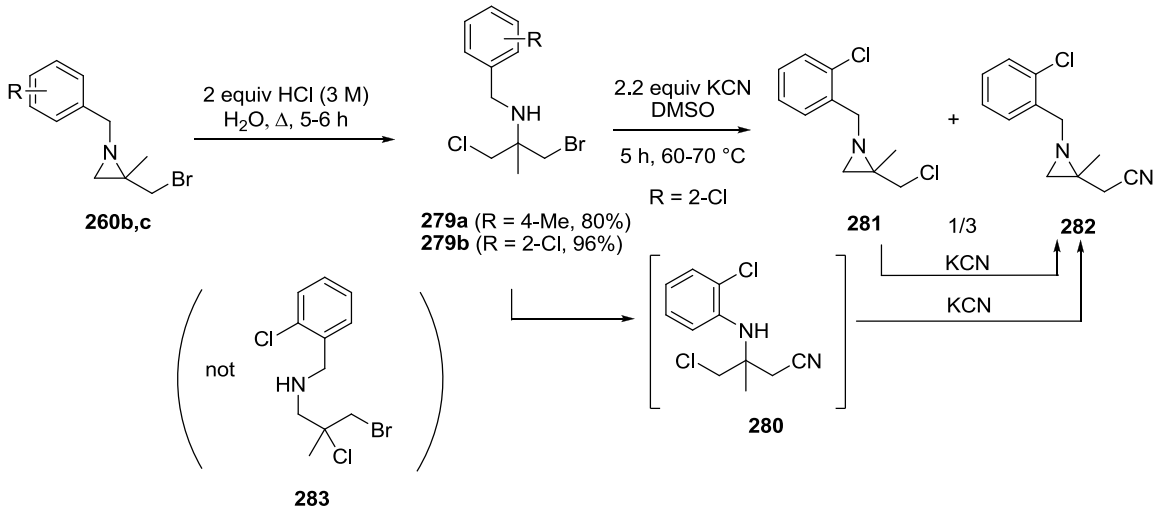
First, treatment of 2-bromomethyl-2-methylaziridines **260b,c** with 1 equiv of benzyl bromide in acetonitrile for 1-2.5 days under reflux afforded the corresponding amines **275a,b** in high yields (86-89%). The regioselectivity in this reaction was in accordance with the previously observed ring opening of 2-substituted non-activated aziridines with benzyl bromide through ring opening at the substituted aziridine carbon.[31b,c,35,92,93,94] Furthermore, the reaction of aziridine **260c** with 1.2 equiv of HBr (33% in HOAc) in CH_2Cl_2 for 1 day under reflux furnished the amine **276**, again as a consequence of the ring opening of the aziridine moiety at the more substituted carbon atom in aziridinium ions **277** (Scheme 88). This result showed, however, the opposite regioselectivity with respect to the ring opening of 2-(cyanomethyl)aziridines with HBr.[31a] The preference for the attack of bromide at the more substituted carbon atom of aziridines **260** in both cases (with HBr and benzyl bromide) could be explained considering a more pronounced development of a positive charge in the intermediate aziridinium ions **277** as compared to the corresponding monosubstituted aziridinium ions. This leads to an increased electrophilicity of the more substituted carbon atom of the aziridine moiety, which is then attacked by the approaching nucleophile. In fact, the ring opening of aziridines **260b,c** could also occur via a clean S_N1 mechanism as well through neutralization of a tertiary carbenium ions **278**.



Scheme 88

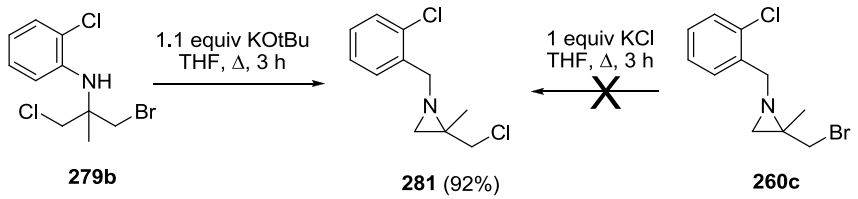
Next, the ring opening of aziridines **260b,c** with 2 equiv of HCl (3M) in water for 3 hours under reflux resulted in the formation of a single regioisomer. Close inspection of ^{13}C NMR data suggested the formation of amines **279a,b** instead of isomer **283**, which was surprising bearing in mind the opposite regioselectivity in case of ring opening with HBr. In order to confirm the proposed structure, the resulted mixture was subjected to a number of experiments.

Treatment of amine **279b** with 1 equiv of TosCl and 3 equiv of Et_3N in CH_2Cl_2 for 2 hours at room temperature gave a complex mixture for further elucidation. Furthermore, the reaction of amine **279b** with 2.2 equiv of KCN in DMSO for 5 hours at 60-70°C provided a mixture of 2-chloromethyl-2-methylaziridine **281** and 2-(cyanomethyl)aziridine **282** (**281**/**282** = 1/3, Scheme 89). The presence of aziridine **282** could be explained either by a direct displacement of chloride by the cyanide ion in aziridine **281**, or by a ring closure of the initially formed 4-chloro-3-(2-chlorophenylamino)-3-methylbutyronitrile **280** (Scheme 89).



Scheme 89

Finally, amine **279b** was subjected to 1.1 equiv of KOtBu in THF for 3 hours under reflux to furnish aziridine **281**, confirmed by means of NMR and MS analysis (Scheme 90). Alternatively, aziridine **281** could also be formed by nucleophilic substitution of bromide by chloride in initially formed aziridine **260c**, which could derive from the other regioisomer **283**. In order to exclude this possibility, aziridine **260c** was treated with 1 equiv of KCl in THF for 3 hours under reflux, furnishing a complex mixture in which no signs of aziridine **281** were detected.



279b **281** (92%) **260c**

Scheme 90

From the above-described reactions, it can be deduced that the regioselectivity in the ring opening of 2-bromomethyl-2-methylaziridines **63** is not always straightforward and strongly dependent on both the type of activation (protonation or alkylation) and the type of nucleophile (chloride or bromide) used. Although these reactions are not the subject of further elaboration within this PhD thesis, it is clear that the factors governing the regioselectivity in these aziridinium ion ring openings should be inspected in more detail in order to use these transformations in a predictive way.

3.4 Solvent-controlled selective transformation of 2-bromomethyl-2-methylaziridines to functionalized aziridines and azetidines[145]

In the course of this thesis, the synthetic relevance of 2-(bromomethyl)aziridines as starting synthons for the preparation of α-branched and β-branched amines, β-amino alcohols and morpholinones was described. Moreover, a high synthetic potential of 2-bromomethyl-2-methylaziridines with respect to their ring expansion to 3-substituted azetidines was shown, making these substrates valuable for further elaboration. In particular, examples of the ring rearrangement of 2-bromomethyl-2-methylaziridines to the corresponding 3-bromo-3-methylazetidines upon heating in acetonitrile were highlighted. The isomerization of 2-(halomethyl)aziridines to 3-haloazetidines has been observed in the literature in only a few exceptional cases,[140,146] pointing to the peculiar nature of this type of rearrangement.

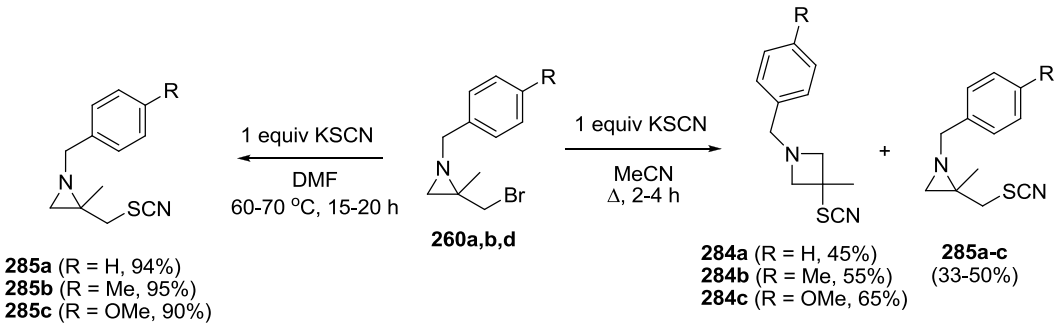
The limited number of reports regarding aziridine to azetidine ring expansions[143] and the mainly unexplored synthetic potential of 2-bromomethyl-2-methylaziridines creates opportunities to access different classes of 3-functionalized azetidines in an efficient way. As already mentioned, 3-substituted azetidines represent valuable class of compounds with diverse biological activities.[5a,9]

Therefore, in this part, the reactivity of 2-bromomethyl-2-methylaziridines toward different oxygen, sulfur and carbon nucleophiles in different solvent systems will be envisaged.

3.4.1 Synthesis of functionalized aziridines and azetidines

In light of above-described aziridine ring expansion, the intrinsic reactivity of 2-bromomethyl-2-methylaziridines **63** to undergo a ring rearrangement was further investigated utilizing a variety of different nucleophiles such as thiocyanate, cyanide, phenoxide and acetate in order to assess the scope of this transformation with respect to carbon and heteroatom nucleophiles.

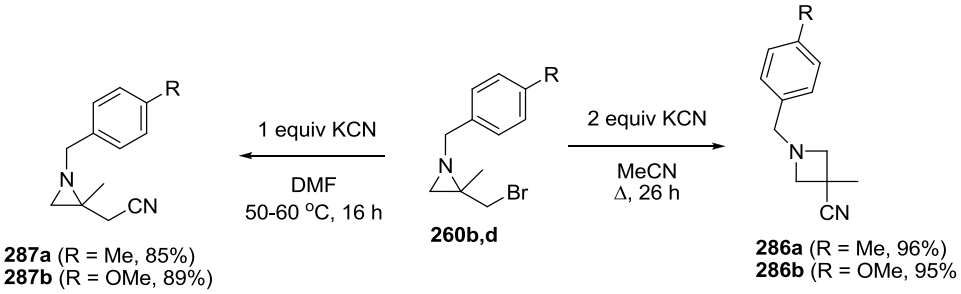
First, aziridines **260a,b,d** were treated with 1 equiv of potassium thiocyanate (KSCN) in acetonitrile at reflux temperature for 2-4 hours, furnishing mixtures of 3-methyl-3-thiocyanatoazetidines **284a-c** and 2-methyl-2-(thiocyanatomethyl)aziridines **285a-c**, with azetidines **284a-c** being the major products (ratio **284**/**285 =** 50-67/50-33, Scheme 91). From these mixtures, azetidines **284a-c** were isolated in pure form by preparative TLC chromatography on silica gel. Several experiments were performed to optimize the reaction conditions. Surprisingly, when aziridines **260a,b,d** were treated with 1 equiv of KSCN in DMF at 60-70 °C for 15-20 hours aziridines **285a-c** were obtained as the sole reaction products, giving rise to a new and straightforward synthetic methodology for the selective preparation of either aziridines in DMF and azetidines in acetonitrile. Aziridines **285a-c** were then successfully purified by means of column chromatography on silica gel in order to obtain analytically pure samples. It should be noted that aziridines **285a-c** were susceptible to partial decomposition during the chromatographic purification process.



Scheme 91

Bearing in mind the different reactivity profile of aziridines **260** toward KSCN in different solvents (MeCN *versus* DMF), 2-bromomethyl-2-methylaziridines **260b,d** were then treated with other nucleophiles such as cyanide, phenoxide and acetate both in MeCN and DMF as the solvent medium.

After treatment of aziridines **260b,d** with 2 equiv of KCN in MeCN for 26 hours at reflux temperature, only 3-cyano-3-methylazetidines **286a,b** were obtained, whereas the same reaction in DMF gave exclusively 2-cyanomethyl-2-methylaziridines **287a,b** after 16 hours at 50-60 °C (Scheme 92). As in the case of thiocyanate (Nu = SCN), the reaction outcome was shown to be dictated by the solvent used in these reactions, providing an efficient method for the synthesis of new functionalized aziridines and azetidines in a selective way. Azetidines **286a,b** and aziridines **287a,b** were purified by means of column chromatography on silica gel in order to provide analytically pure samples.



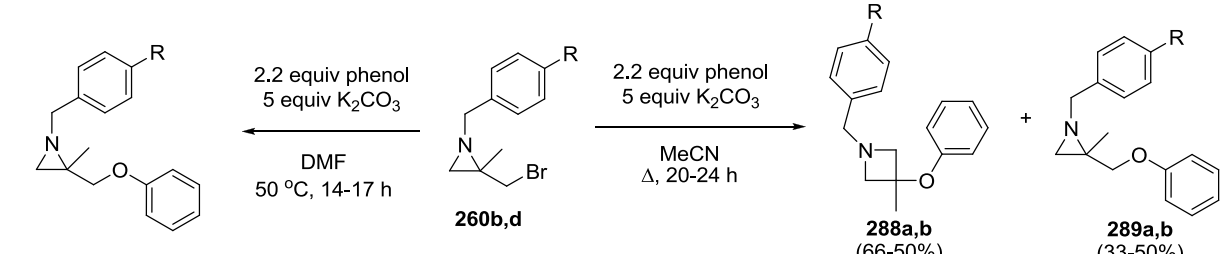
287a (R = Me, 85%)
287b (R = OMe, 89%)

260b,d

286a (R = Me, 96%)
286b (R = OMe, 95%

Scheme 92

The reaction of aziridines **260b,d** with 2.2 equiv of phenol and 5 equiv of K_2CO_3 in MeCN for 20-24 hours was not so straightforward and gave mixtures of 3-methyl-3-phenoxyazetidines **288a,b** and 2-methyl-2-(phenoxymethyl)aziridines **289a,b**, in which azetidines **288a,b** were present as the major isomers (ratio **288/289** = 57-67/43-33, Scheme 93). These compounds were separated and isolated by means of column chromatography (SiO_2). On the other hand, treatment of aziridines **260b,c** with 2.2 equiv of phenol and 5 equiv of K_2CO_3 in DMF for 14-17 hours at 50 °C provided 2-methyl-2-(phenoxymethyl)aziridines **289a,b** as the major products, and only small amounts (~10%) of azetidine **288a,b** were observed. However, the purification by silica gel column chromatography did not provide completely pure products due to co-elution of an unidentified side product in small quantities (10-15%).



289a (R = Me, 85%)
289b (R = OMe, 90%)

260b,d

288a,b
(66-50%)

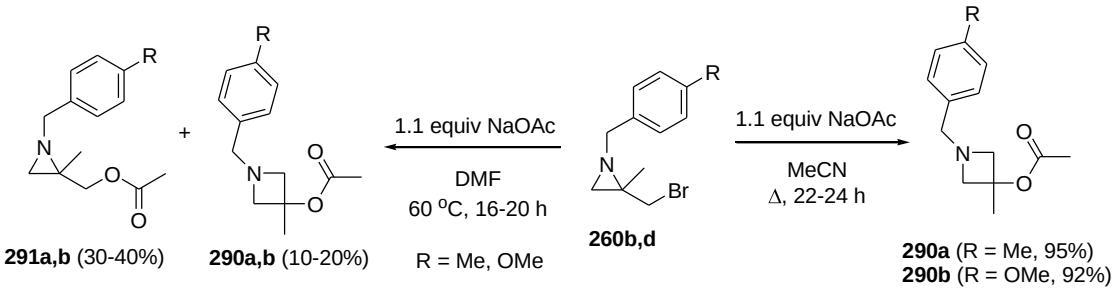
289a,b
(33-50%)

288a/289a 1.3 : 1
288b/289b 2 : 1

Scheme 93

Finally, when aziridines **260b,d** were subjected to 1.1 equiv of NaOAc in MeCN for 22-24 hours at reflux temperature, 3-acetoxy-3-methylazetidines **290a,b** were produced without traces of the corresponding aziridines (Scheme 94). On the other hand, the reaction of the same aziridines **260b,d**

with 1.1 equiv of NaOAc in DMF for 16-20 hours resulted in complex mixtures, in which the presence of 2-acetoxymethyl-2-methylaziridines **291a,b** (30-40%) as well as 3-acetoxy-3-methylazetidines **290a,b** (10-20%) was acknowledged by means of ^{1}H NMR analysis. It should be mentioned that the reaction with NaOAc provided a unique case of noteworthy amounts of azetidine formation in DMF as the solvent, while in all other cases (except in the case of a small amount of azetidine **288b**) the formation of azetidines using DMF as the solvent was not observed.

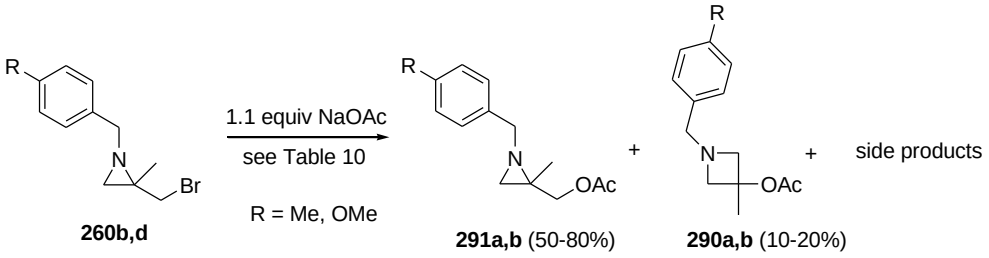


291a,b (30-40%) **290a,b** (10-20%) **260b,d**

290a (R = Me, 95%)
290b (R = OMe, 92%)

Scheme 94

After several attempts to optimize the reaction conditions in different solvents (DMF and DMSO), at different temperatures (r.t. to 100 °C), and by using additional reagents (such as $AgBF_4$), aziridines **291a,b** were finally obtained as the major compounds (ratio **290**/**291 =** 20-25/80-75) after treatment of aziridines **260b,d** with 1.1 equiv of NaOAc in DMSO at room temperature for 3-5 days (Scheme 95, Table 10). Higher temperatures (>30 °C) yielded complete conversion of the starting aziridines **260b,d** only after a few hours, however at the expense of the selectivity of this reaction (ratio **290**/**291** = 40-50/60-50). From these mixtures, aziridines **291a,b** could not be isolated in completely pure form by means of column chromatography on silica gel due to co-elution of azetidines **290a,b** and small amounts of some side products (10-15%).



260b,d

291a,b (50-80%) **290a,b** (10-20%)

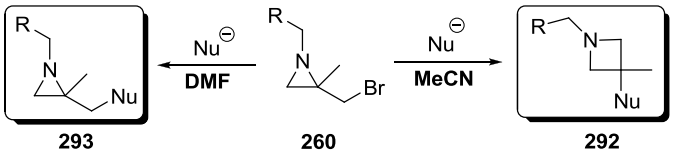
Scheme 95

Table 10. Synthesis of 2-acetoxymethyl-2-methylaziridines **291a,b**

compound	conditions	result
260b	1 equiv $AgBF_4$, DMF, 60 °C, 3 h	complex mixture
260d	0.1 equiv $AgBF_4$, DMSO, r.t., 2 days	**290b+ 291b** + side products
260d	1 equiv $AgNO_3$, DMSO, r.t., 31 h	complex mixture
260b	DMSO, 50 °C, 1 h	**290**/**291 =** 40/60
260d	DMSO, 60 °C, 2 h	**290**/**291 =** 50/50
260b	DMSO, r.t., 5 d	**290**/**291 =** 20/80
260d	DMSO, r.t., 3 d	**290**/**291 =** 25/75

It should be mentioned that the ratio aziridine/azetidine in all cases was determined by detailed spectroscopic analysis (^{1}H NMR) of the crude reaction mixtures. After purification, the structures of the pure azetidines and aziridines were then confirmed by means of different characterization methods (^{1}H NMR, ^{13}C NMR, IR, MS).

In summary, the selective transformation of aziridines **260** toward either azetidines **292** in acetonitrile or aziridines **293** in dimethylformamide (Scheme 96) provides interesting opportunities for further elaboration to valuable azaheterocycles.



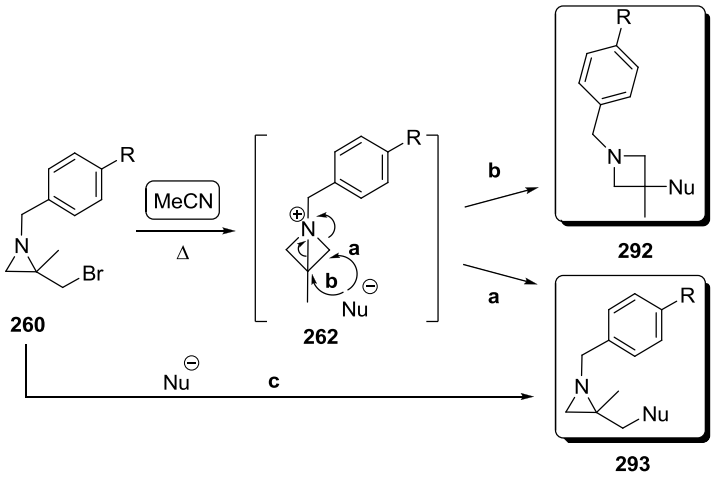
Nu = CN, OAc, OPh, SCN

Scheme 96

3.4.2 Evaluation of the reaction mechanisms for the formation of aziridines and azetidines

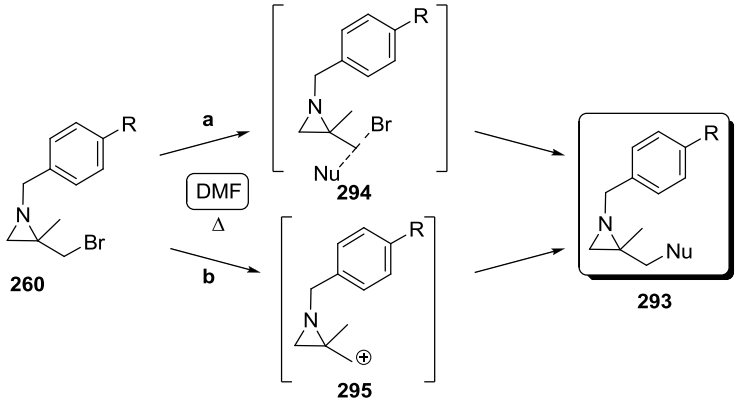
From a mechanistic point of view, different pathways can be considered to explain the synthesis of functionalized aziridines and azetidines starting from 2-bromomethyl-2-methylaziridines **260**. An overview of possible reactivity profiles of aziridines **260** in MeCN is presented in Scheme 97. Bearing in mind the previously described intermediacy of bicyclic aziridinium ions in the synthesis of 3-methoxy-3-methylazetidines starting from 2-bromomethyl-2-methylaziridines, the nucleophilic attack at the more hindered carbon atom of the strained intermediates **262** (path b, Scheme 97) is considered to be the most plausible route for the formation of 3-substituted azetidines **292** in MeCN. This fact is also in accordance with the ring transformation of 2-bromomethyl-2-methylaziridines **260a-c** in MeCN at reflux temperature (Scheme 84). It should be noted that in some cases the formation of aziridines (**285a-c** and **289a,b**) was observed as well (33-50%). The presence of these aziridines in MeCN-mediated reactions can be attributed to nucleophilic attack at the less-hindered carbon atom of the

bicyclic aziridinium ions **262** (path a, Scheme 97), taking into account a few isolated literature examples on the ring opening of strained bicyclic intermediates.[142c] However, direct nucleophilic displacement of bromide in 2-bromomethyl-2-methylaziridines **260** by the nucleophile (path c, Scheme 97) will most probably prevail as the pathway toward substituted aziridines **293**.



Scheme 97

The proposed mechanistic pathways for the selective formation of aziridines **293** in DMF are depicted in Scheme 98. Herein, two different routes can be considered, involving either direct S_N2 displacement of bromide by the approaching nucleophile (path a, intermediate **294**, Scheme 98) or via the formation of primary carbenium ions **295** (S_N1 mechanism, path b, Scheme 98), which might be stabilized by the nitrogen lone pair through anchimeric assistance. The formation of aziridines **293** via nucleophilic attack at the less-substituted carbon atom of bicyclic aziridinium intermediates **262** (path a, Scheme 97) in DMF should not be completely neglected, although the fact that aziridines **260** do not rearrange into azetidines **261** upon heating in DMF for several hours suggests that no bicyclic aziridinium species **262** are formed in these reactions.



Scheme 98

In order to shed more light on the remarkable preference for the formation of azetidines in MeCN and aziridines in DMF (Schemes 97 and 98), some computational analyses were performed at the Center of Molecular Modeling of Ghent University.[145]

In this study, a different close-packing (as a measure to indicate how free the nucleophiles are to attack and how willing the nucleophuge is to leave) of the nucleophiles (CN^- and SCN^-), the nucleophuge Br^- or even the bicyclic aziridinium intermediate **262** by DMF and MeCN was investigated by calculating and comparing their coordination solvation energies (CSE's).

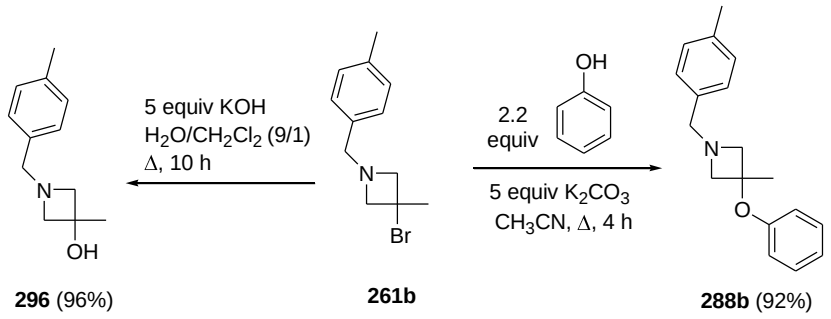
The high-level molecular modeling calculations showed that the stronger coordination and better stabilization of CN^- by MeCN as compared to DMF can point to a lower reactivity, hence allowing the formation of azetidine **292** via formation of the bicyclic intermediate **262**. Since CN^- is less stabilized in DMF, it will be more reactive and hence, nucleophilic substitution of aziridine **260** will lead to aziridine **293**. The weaker coordination of SCN^- by MeCN, compared to CN^-, could explain why both the formation of the bicyclic intermediate **262** and nucleophilic substitution in the aziridine **260** are possible for SCN^- in MeCN. Finally, the stronger coordination of Br^- by MeCN can improve its leaving group capacity and thus help in the formation of the bicyclic intermediate **262**.

3.4.3 Reactivity of 3-bromo-3-methylazetidines[147]

As discussed before (section 3.3.4), a peculiar, thermodynamically controlled rearrangement of 2-bromomethyl-2-methylaziridines in acetonitrile provided a general access to novel 3-bromo-3-methylazetidines. The broad synthetic potential of 3-haloazetidines has been demonstrated in the literature in terms of their nucleophilic substitution with different nucleophiles.[148]

However, the reactivity profile of 3-bromo-3-methylazetidines as useful synthons in organic chemistry has not been studied so far. Therefore, a number of reactions were performed in order to assess the propensity of azetidines **261** to undergo nucleophilic substitution at the 3-position to access a window of novel 3-functionalized azetidines.

Thus, treatment of azetidine **261b** with 2.2 equiv of phenol and 5 equiv of K_2CO_3 in MeCN for 4 hours under reflux afforded the corresponding 3-aryloxyazetidine **288b** in high yield (Scheme 99). In a similar manner, the reaction of azetidine **261b** with 5 equiv of KOH in H_2O/CH_2Cl_2 (9/1) mixture for 10 hours under reflux resulted in the formation of 3-hydroxyazetidine **296**. The above-described findings support the suitability of 3-bromo-3-methylazetidines as substrates for nucleophilic substitutions by oxygen-centered nucleophiles.



296 (96%) **261b** **288b** (92%)

Scheme 99

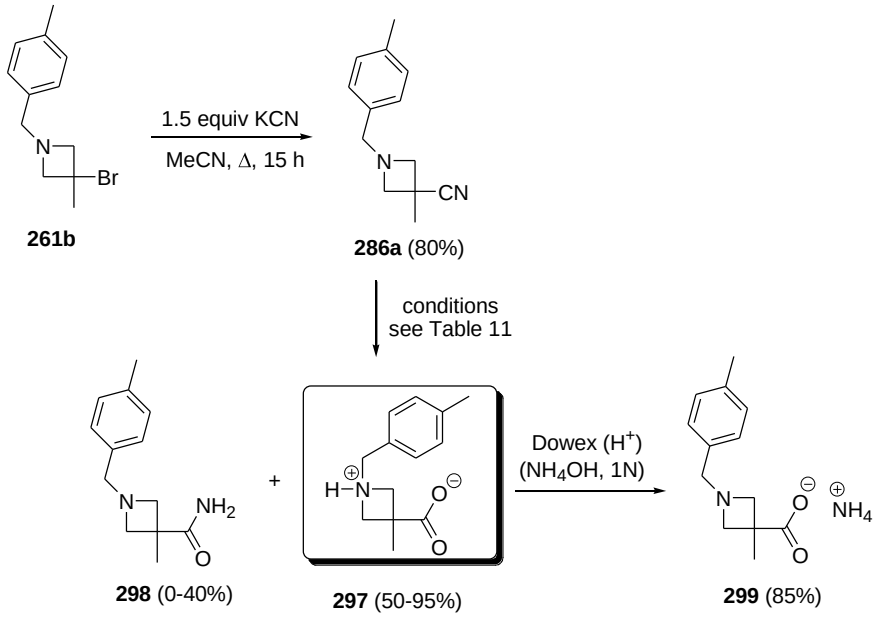
In the literature, it is known that azetidine-3-carbonitriles can be prepared via nucleophilic substitution of 3-mesyloxy- and 3-tosyloxyazetidines.[15,142c,149] In that respect, 3-bromo-3-methylazetidine **261b** was also shown to be a good substrate for the synthesis of azetidine-3-carbonitrile **286b** upon treatment with 1.5 equiv of KCN in acetonitrile under reflux for 15 hours (Scheme 100). Azetidine **286b** was purified by means of column chromatography on silica gel to obtain an analytically pure sample. The hydrolysis of the cyano group in azetidine **286b** can provide an access toward cyclic amino acids which can be considered as analogues of azetidine-2-carboxylic acid, a natural molecule isolated from *Convallaria majalis* (lily of the valley) and endowed with impressive biological activities such as the inhibition of the proliferation of Escherichia coli, alteration of the structure of collagen, keratin and hemoglobin in human proteins, and teratogenic effects and various malformations in animals.[10d]

Therefore, a number of experiments were performed for the hydrolysis of the cyano group in 1-(4-methylbenzyl)azetidine-3-carbonitrile **286a** (Table 11). The reaction of azetidine **286a** with 4 equiv of HCl (3M) in water for 2 days under reflux resulted in the recovery of the starting product. Heating the mixture under microwave conditions (150 °C, 1h, 150 W) gave a complex mixture, probably as the result of the ring opening of the azetidine moiety. The treatment of azetidine **286a** in basic conditions using 5 equiv of $Ba(OH)_2$ in dioxane for 15 hours at 100 °C, or microwave-induced irradiation (150 °C, 1 h), again afforded only the starting material **286a**.

Finally, treatment of azetidine **286a** with 5 equiv of KOH in $EtOH/H_2O$ (5/1) under microwave irradiation (150 °C, 10 min, 150 W) and subsequent neutralization with a solution of hydrochloric acid (1 M) gave a mixture of amino acid **297** and the corresponding amide **298** (**297**/**298** = 3/2, Scheme 100). Prolonging the reaction time in the latter case (150 °C, 20 min, 150 W), gave amino acid **297** as the sole product (96%, based on NMR). Both the amide **298** and acid **297** could be isolated by means of a suitable extraction procedure with CH_2Cl_2.

Interestingly, two isomeric structures (ratio 3/2) of azetidine **297** were observed upon NMR analysis (CD_3OD), which can be attributed to the zwitterionic nature of this compound providing two diastereomeric counterparts. The purification of amino acid **297** on Dowex H^+ (NH_4OH) afforded ammonium 3-methyl-1-(4-methylbenzyl)azetidine-3-carboxylate **299** as a single isomer in pure form (Scheme 100). These observations further support the synthetic utility of 3-bromo-3-methylazetidines

as substrates for nucleophilic displacements, i.e., toward the synthesis of versatile 3-methylazetidine-3-carbonitriles.



Scheme 100

Table 11. Hydrolysis of the cyano group in azetidine **286a**

Conditions 286a → 297	**result**
4 equiv HCl (3M), H_2O, Δ, 2 days	no reaction
4 equiv HCl (3M), H_2O, MW, 1h, 150 °C	complex mixture
5 equiv $Ba(OH)_2$, dioxane, MW, 1 h, 150 °C + neutralization	no reaction
5 equiv KOH, EtOH/H_2O (5/1), MW, 10 min, 150 °C + neutralization	**297** (55%) + **298** (40%)
5 equiv KOH, EtOH/H_2O (5/1), MW, 20 min, 150 °C + neutralization	**297** (96%)

In conclusion, 3-bromo-3-methylazetidines **261** were shown to easily undergo nucleophilic substitution with different nucleophiles, providing a convenient method for the preparation of new synthetically and biologically attractive 3-substituted azetidines such as 3-aryloxy-, 3-hydroxy-, 3-cyanoazetidines.

3.5 Synthesis and reactivity of 3-ethylideneazetidines

Next to the synthetic utility of 3-bromo-3-methylazetidines as building blocks for the preparation of 3-functionalized azetidines, this type of azetidines can also be considered as synthons for the preparation of the corresponding 3-methyleneazetidines as versatile synthetic intermediates. In preliminary research performed at the Department of Sustainable Organic Chemistry and Technology

(UGent), similar substrates, i.e., 1-*t*-butyl-3-methylene- and 1-*t*-butyl-3-ethylideneazetidine, were prepared starting from the corresponding 3-bromoazetidines,[33] although the reactivity of these species has not been explored so far.

3-Alkylideneazetidines are strained cyclic allylamines, and only limited information on the reactivity of this class of compounds is available in the literature.[150] In most cases, the 3-alkylideneazetidine moiety was incorporated in the structure of more complex molecules,[151] and no special attention has been devoted to the chemical nature of this strained system. In addition, the introduction of conformational constraint at the 3-position of azetidine rings is known to increase the potency of human and rat FAAH inhibitors[152] and showed to be an important structural feature of some drugs.[153] Two main approaches to produce 3-alkylideneazetidines comprise the Wittig olefination of the corresponding azetidin-3-ones[150b,d,e] and dehalogenation of different 3-halo-3-(1-haloalkyl)azetidines.[150d]

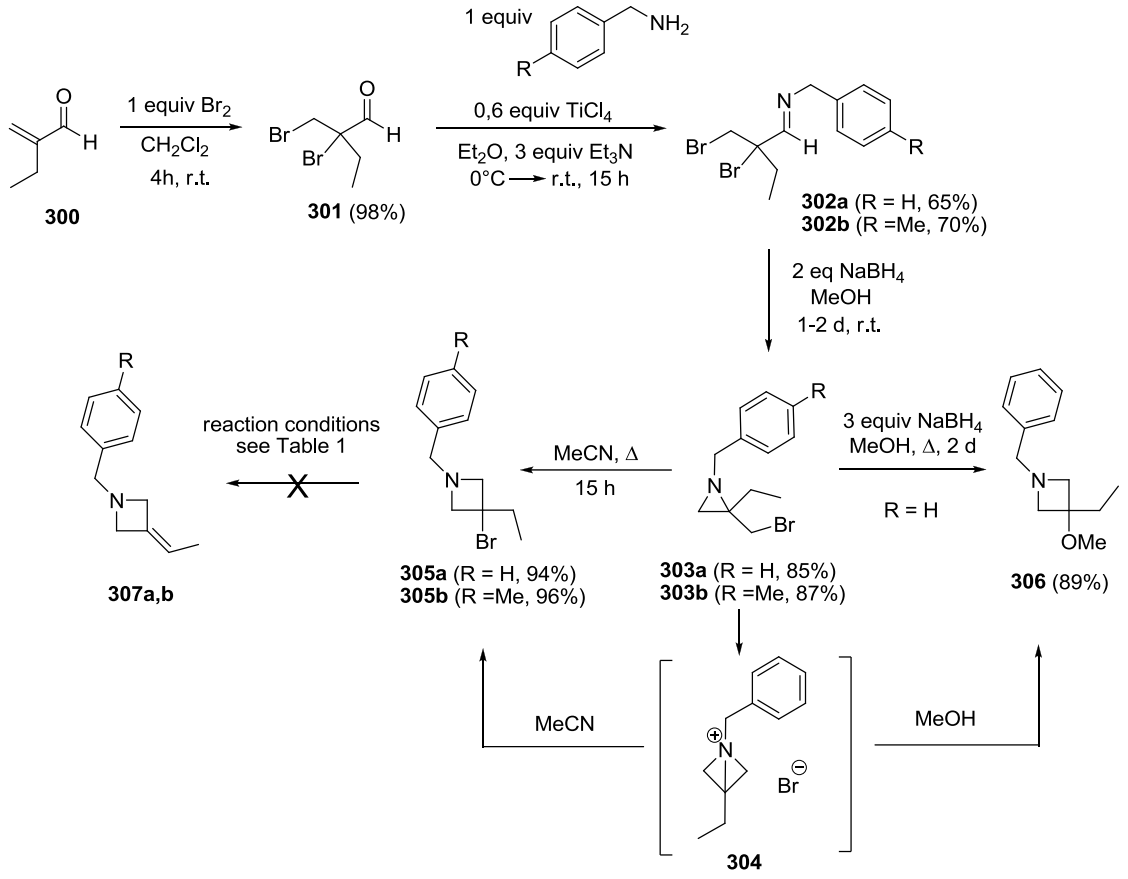
In this section, a facile and efficient synthesis of novel 3-ethylideneazetidines is reported starting from the corresponding 3-bromo-3-ethylazetidines. Although the combination of two functionalities, i.e., an azetidine moiety and an exocyclic double bond, might result in unstable structures, this type of substrates are considered to be valuable for further elaboration. In this part of this PhD thesis, two aspects of the reactivity of 3-ethylideneazetidines were separately studied, i.e., the activation and subsequent ring opening of the azetidine moiety on the one hand, and functionalization of the exocyclic double bond on the other.

The synthesis and reactivity of structurally similar 2-alkylideneazetidines (cyclic enamines) has been the subject of previous studies.[10k,154] These azetidines were shown to be good substrates in various cycloaddition reactions[154d] and ring rearrangements.[154a,c,155] However, it is expected that 3-alkylideneazetidines bearing an less reactive and sterically hindered double bond exhibit a different reactivity profile as compared to 2-alkylideneazetidines, which display the chemical properties of strained cyclic enamines. Therefore, in addition to the development of an efficient synthesis of 3-ethylideneazetidines, the main objective of this study was to elaborate the hitherto unexplored reactivity of these azetidines, which, in spite of their poor intrinsic reactivity, can still be regarded as versatile synthetic intermediates in heterocyclic chemistry.

3.5.1 Synthesis of 3-ethylideneazetidines

Thus, 3-bromo-3-ethylazetidines **305** were selected as potentially eligible substrates for the preparation of novel 3-ethylideneazetidines, and these azetidines **305** were obtained following the procedure reported for the synthesis of 3-bromo-3-methylazetidines **261**. In that respect, bromination of 2-ethylpropenal **300** using 1 equiv of bromine in dichloromethane afforded the corresponding 2,3-dibromopropanal **301** in nearly quantitative yield, which was subsequently condensed with 1 equiv of different *N*-(arylmethyl)amines using 0.6 equiv of titanium(IV) chloride and 3 equiv of triethylamine in

diethyl ether, furnishing α,β-dibromoimines **302a,b** in good yields (Scheme 101). The latter imines **302** were reduced by means of 2 molar equiv of sodium borohydride in methanol, resulting in 2-bromomethyl-2-ethylaziridines **303a,b** as a mixture of invertomers after 1-2 days at room temperature. Subsequently, heating of aziridines **303** in acetonitrile under reflux for 15 hours afforded 3-bromo-3-ethylazetidines **305a,b** in nearly quantitative yields. In analogy with the synthesis of 3-bromo-3-methylazetidines **261**, the aziridine **303** to azetidine **305** ring expansion can be explained by intermediacy of bicyclic aziridinium species **304**, which were attacked at the more hindered carbon atom to provide azetidines **305**. Furthermore, in analogy with the previously reported synthesis of 3-methoxy-3-methylazetidines **258** (Scheme 79), treatment of aziridine **303a** with 3 molar equiv of $NaBH_4$ in MeOH for 2 days under reflux furnished 3-ethyl-3-methoxyazetidine **306** as the single product through the formation of the same intermediates **304** (Scheme 101).



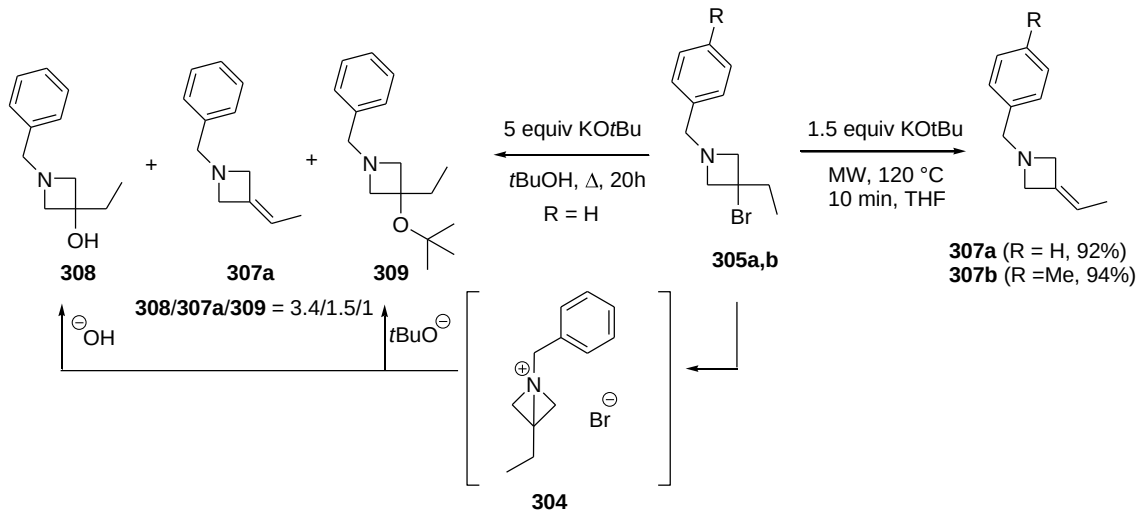
Scheme 101

The synthesis of 3-ethylideneazetidines **307a,b** starting from 3-bromo-3-ethylazetidines **305**, however, was not as straightforward as initially anticipated, and several attempts were performed to optimize the reaction conditions. Treatment of azetidine **305a** with different bases such as KOtBu, LDA and NaH in tetrahydrofuran at room temperature or under reflux gave no reaction after stirring for one day, resulting in the recovery of the substrate (Table 12).

Table 12. Treatment of 3-bromo-3-ethylazetidines **305a** with different bases

Compound	Base	Reaction conditions	Conversion
305a	1 equiv KOtBu	THF, r.t., 15 h	No reaction
305a	1 equiv KOtBu	THF, Δ, 15 h	No reaction
305a	1 equiv LDA	THF, Δ, 15 h	No reaction
305a	1 equiv NaH	THF, Δ, 15 h	No reaction
305a	5 equiv KOtBu	tBuOH, Δ, 20 h	**308**/**307a**/**309** = 3.4/1.5/1

The reaction of 3-bromo-3-ethylazetidine **305a** with 5 equiv of KOtBu in tBuOH (instead of THF) under reflux for 20 hours gave a mixture of 1-benzyl-3-ethylazetidin-3-ol **308**, 1-benzyl-3-ethylideneazetidine **307a** and 3-(*tert*-butoxy)-3-ethylazetidine **309** (**308**/**307a**/**309** = 3.4/1.5/1) (Scheme 102). The presence of azetidines **309** and **308** could be explained by the nucleophilic attack of either *tert*-butoxide or hydroxide (due to the presence of adventitious water) at the bicyclic aziridinium intermediate **304**. Finally, using 1.5 equiv of KOtBu in THF and heating under microwave irradiation for 10 min at 120 °C selectively provided 3-ethylideneazetidines **307a,b** in excellent yields (Scheme 102).



Scheme 102

3.5.2 Reactivity study of 3-ethylideneazetidines

A small number of literature reports reveal the potential of spiro azetidines[156] to acquire a prominent place within the class of bioactive spiro heterocycles. In particular, the biological activity of spiro azetidines **310** containing a piperidine moiety as blockers of voltage-gated calcium channels has been reported.[157] Furthermore, adamantane-based spiro azetidines **311** and **312** (Figure 15) have been evaluated as potential anti-influenza A drugs.[158] In that respect, next to the reactivity of azetidines **307** toward ring opening, the preparation of new classes of spiro azaheterocycles starting from 3-ethylideneazetidines **307** will be evaluated in the following section.

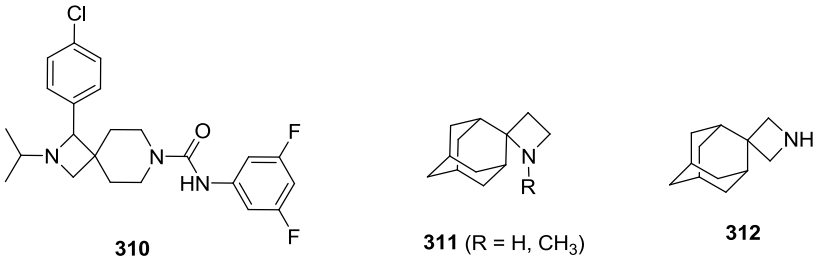
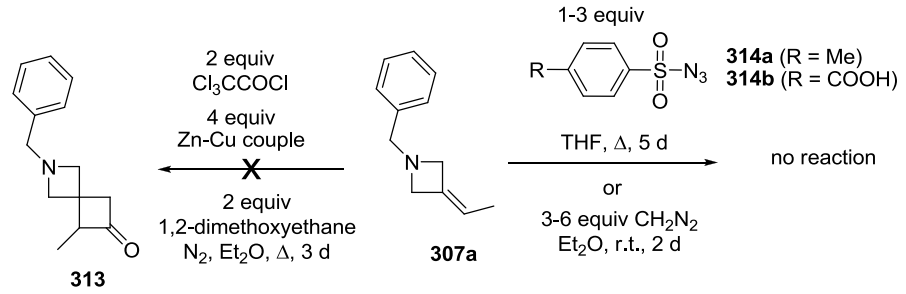


Figure 15

As already mentioned, the study of the reactivity of 3-ethylideneazetidines was expected to be a quite challenging task bearing in mind the sterically hindered and poorly reactive double bond. This feature was evidenced by many attempts to directly functionalize the olefinic moiety and to provide an access toward different biologically interesting spiro compounds. For example, the treatment of 3-ethylideneazetidine **307a** with 2 equiv of trichloroacetyl chloride, 4 equiv of Zn-Cu couple and 2 equiv of 1,2-dimethoxyethane in Et_2O under nitrogen atmosphere[159] resulted in the full recovery of the starting material after 3 days, and no traces of the corresponding cyclobutanone **313** were observed. The reaction with 3-6 equiv of diazomethane in Et_2O at room temperature for several hours[160] or the reaction with 1-3 equiv of tosylazides **314a,b** in THF at room temperature or under reflux[115b] for 5 days gave no conversion of the starting azetidine **307a**. Azetidine **307a** was also shown to be unreactive toward [*N*-(*p*-nitrophenylsulfonyl)imino]phenyliodinane (Ph=INNs) in the presence of a catalytic amount of $Cu(OTf)_2$ in acetonitrile under reflux for 1 day (Scheme 103, Table 13).[161]

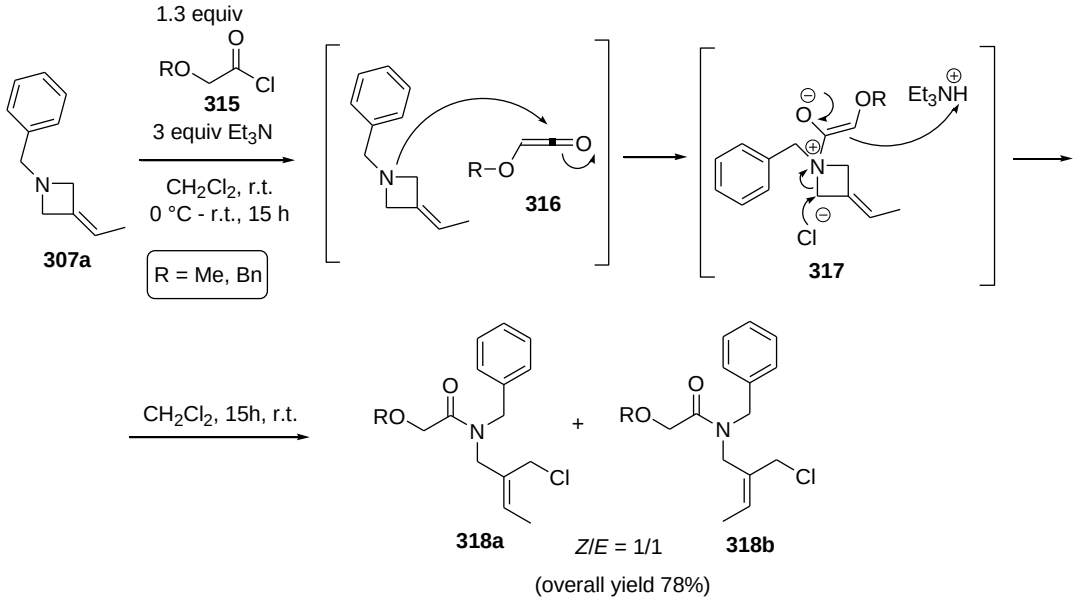


Scheme 103

Table 13. Attempts to functionalize 3-ethylideneazetidine **307a**

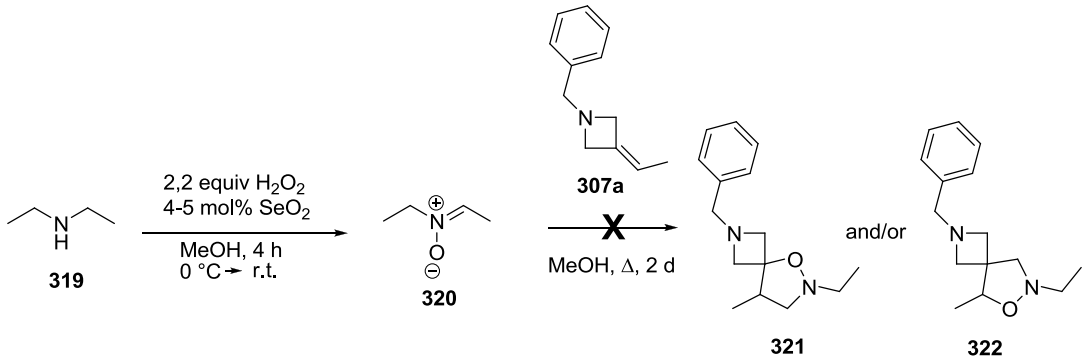
Compound	Reaction conditions	Conversion
307a	2 equiv Cl_3CCOCl, 4 equiv Zn-Cu couple 2 equiv 1,2-dimethoxyethane, N_2, Et_2O, Δ, 3d	No reaction
307a	1 equiv **314a**, THF, r.t., 5d	No reaction
307a	1 equiv **314a**, THF, Δ, 5d	No reaction
307a	1 equiv **314b**, THF, Δ, 5d	No reaction
307a	3 equiv CH_2N_2, Et_2O, r.t., 2d	No reaction
307a	1.5 equiv Ph=INNs, 0.15 equiv $Cu(OTf)_2$, MeCN, Δ, 1d	No reaction

When azetidine **307a** was added to a mixture of 1.3 equiv of benzyloxy- or methoxyacetyl chloride **315** and 3 equiv of Et_3N in CH_2Cl_2 and stirred at room temperature for 15 hours in an attempt to effect cycloaddition, the corresponding ring-opened amides **318a,b** were formed instead (ratio **318a**/**318b** = 1/1, based on ^1H NMR) (Scheme 104). Apparently, the initial attack of the nucleophilic nitrogen to the *in situ* formed ketene **316** and subsequent ring opening of the azetidine moiety prevailed over the premised cycloaddition reaction due to the presence of a less reactive and sterically hindered double bond in azetidine **307a**.



Scheme 104

In order to evaluate a possible nitrone-olefin [3+2]-cycloaddition, *N*-oxide **320** was synthesized by treatment of diethylamine **319** with 2.2 equiv of H_2O_2 (30% in H_2O) and a catalytic amount (4-5 mol%) of SeO_2 in methanol at room temperature for 4 hours. Addition of 2 equiv of this nitrone **320** to a methanolic solution of azetidine **307a** and heating under reflux for 2 days, however, did not result in the corresponding spiroisoxazolidines **321** and/or **322** (Scheme 105, Table 14). The failure to perform this reaction showed that azetidines **307** do not exhibit the same reactivity behaviour with respect to [3+2]-cycloadditions as their structurally related 3-methylidene-β-lactams.[162]



Scheme 105

In addition, also the Diels-Alder reaction of azetidines **307a,b** with cyclopentadiene or with the highly reactive Danishefsky's diene ((*E*)-1-methoxy-3-trimethylsilyloxy-1,3-butadiene) resulted in full recovery of the substrate (Table 14).

Table 14. Reactivity of 3-ethylideneazetidine **307a,b** toward [2+2]- and [3+2]- cycloadditions

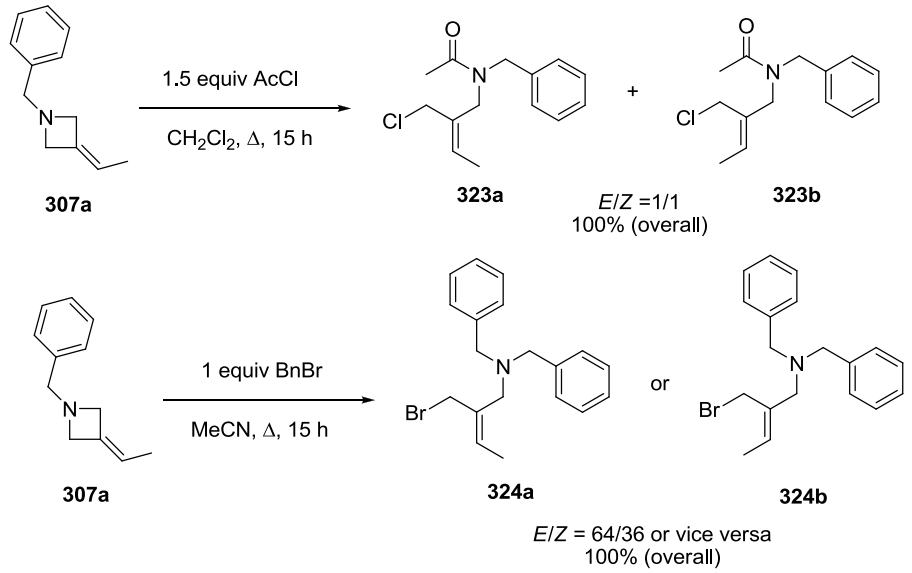
Compound	Reaction conditions	Conversion
307a	1 equiv **320**, MeOH, r.t., 2d	No reaction
307a	1 equiv **320**, MeOH, Δ, 2d	No reaction
307a	3 equiv cyclopentadiene, CH_2Cl_2, 0 °C, 5h	No reaction
307b	3 equiv cyclopentadiene, CH_2Cl_2, r.t., 5d	No reaction
307b	3 equiv Danishefsky's diene ((*E*)-1-methoxy-3-trimethylsilyloxy-1,3-butadiene), CH_2Cl_2, r.t., 2d	No reaction

Furthermore, the electron-poor double bond of azetidine **307** was, as expected, not able to react with soft electrophiles such as benzaldehyde or methyl vinyl ketone. It is clear that the peculiar nature of the alkenyl functionality in 3-ethylideneazetidines represents a limiting factor to functionalize these azetidines through standard types of double bond transformations.

However, in spite of the limited reactivity of 3-ethylideneazetidines **307**, many additional efforts were made to prove this class of compounds interesting for further elaboration. For this purpose, the reactivity profile of azetidines **307a,b** was assessed from two approaches, i.e., evaluation of the reactivity of the strained azetidine moiety toward ring opening and evaluation of electrophilic additions to the exocyclic double bond.

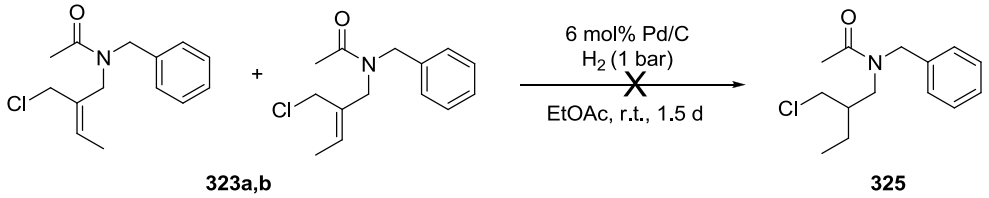
Bearing in mind the presence of an electron-donating substituent at the azetidine nitrogen atom, these species had to be activated in order to effect ring opening. Acetylation of nitrogen with 1.5 equiv of acetyl chloride in CH_2Cl_2 and subsequent ring opening of the azetidine moiety by the expelled chloride ion afforded a mixture of *E* and *Z* ring-opened amines **323a,b** (*E*/*Z* = 1/1) after 15 hours under reflux (Scheme 106). In a similar way, the reaction of **307a** with 1 equiv benzyl bromide in acetonitrile gave a mixture of the corresponding unsaturated amines **324a,b** after 15 hours under reflux. These reactions

were straightforward and resulted in a complete conversion of the starting material, although inseparable mixtures of amines were obtained.



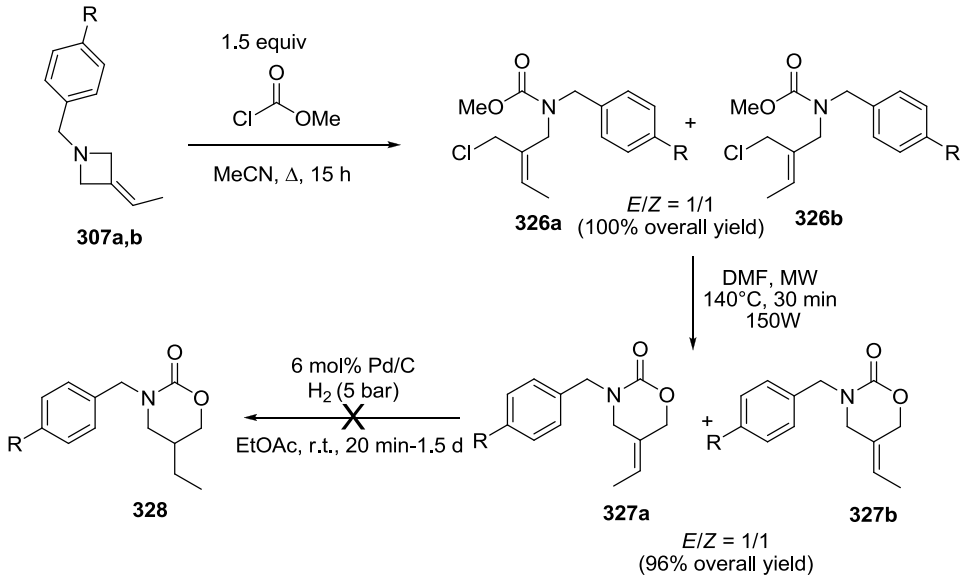
Scheme 106

Although it was expected that these reactions would give rise to mixtures of geometrical isomers, the presence of different chemical shift in NMR could also be explained by hindered rotation around the amide bond in acetamides **318** and **323**. Therefore, the mixture of amines **323a,b** was subjected to the hydrogenation reaction with 6 mol% of Pd/C at 1 bar for 1.5 days, yet only a complex mixture was obtained, without the presence of the corresponding amine **325** (Scheme 107).



Scheme 107

In addition, the treatment of azetidine **307a,b** with 1.5 equiv of methyl chloroformate in acetonitrile for 15 hours under reflux resulted in a mixture of amines **326a,b** (Scheme 108). Upon heating of this mixture under microwave irradiation (140 °C, 30 min, 150 W) in DMF, a mixture of the corresponding cyclic carbamates **327a,b** was obtained through 6-*exo*-*tet* cyclization.[163] These cyclic carbamates can be regarded as interesting compounds with a variety of applications, most notably as precursors for 1,3-amino alcohols,[164] as chiral auxiliaries,[165] and as the core substructure in a number of biologically active compounds.[166] The subsequent hydrogenation of the double bond in **327a,b** (H_2, 1 bar, 20 min-1.5 d) gave a complex mixture in which no traces of 1,3-oxazinan-2-one **328** were detected (Scheme 108).

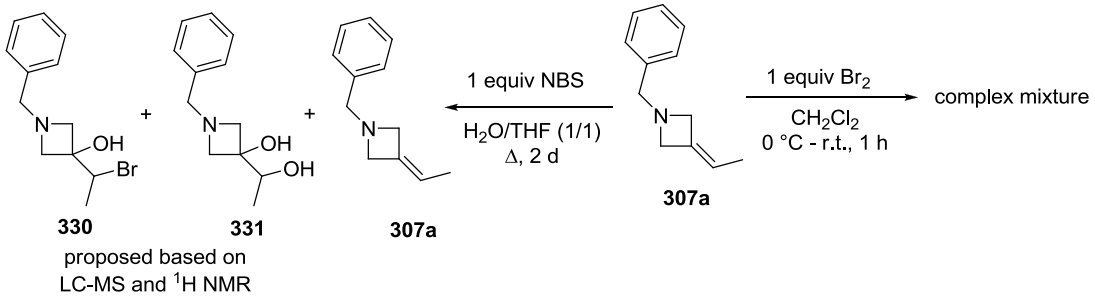


Scheme 108

It should be mentioned that the hydrogenation of azetidine **307b** in ethyl acetate in the presence of 6 mol% of Pd/C (10% wt) at 5 bar for 3 days at room temperature afforded 1-benzyl-3-ethylazetidine **329** as the single product (Scheme 109).

Scheme 109

In the second part of this work, the reactivity of the double bond in azetidines **307** toward different electrophilic reagents was investigated. At first, azetidine **307a** was subjected to 1 equiv of Br_2 in CH_2Cl_2 for 5 min to 1 hour, yet only complex mixtures were obtained (Table 15). The attempts to prepare halohydrines **330** by treatment of azetidine **307a** with 1 equiv of NBS in a water/THF (1/1) solution for 10 min to 2 days proceeded sluggishly and gave mixtures of multiple products, in which halohydrine **330** and 3-hydroxy-3-(hydroxymethyl)azetidine **331** could be detected based on LC-MS and ^{1}H NMR analysis (Scheme 110, Table 15). The outcome of this reaction was shown to be hardly controllable and also dependent on the purity of NBS.

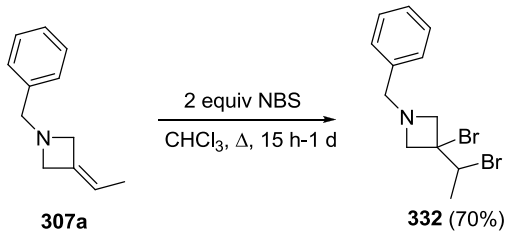


Scheme 110

Table 15. Reactions of 3-ethylideneazetidine **307a** with Br_2 and NBS

Compound	Reaction conditions	Conversion
307a	1 equiv Br_2, CH_2Cl_2, r.t., 1 h	Complex mixture
307a	1 equiv Br_2, CH_2Cl_2, r.t., 10 min	Complex mixture
307a	1 equiv NBS, H_2O/THF (1/1), r.t., 2 d	No reaction
307a	1 equiv NBS, H_2O/THF (1/1), Δ, 2 d	Complex mixture

On the other hand, selective access to the functionalized dibrominated azetidine **332** was achieved by the reaction of azetidine **307a** with 2 equiv of NBS in $CHCl_3$ or CH_2Cl_2 under reflux for 15 hours to 1 day. Apparently, the small amount of bromine - released from NBS - was able to react with azetidine **307a** to afford 3-bromo-3-(1-bromoethyl)azetidine **332**, however, in variable yields dependent on the purity of NBS (Scheme 111).



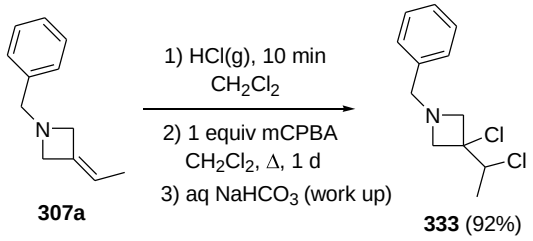
Scheme 111

After the unsuccessful attempt to prepare halohydrines as precursors of the corresponding spiranic epoxy azetidines, a direct epoxidation of the double bond in azetidine **307a** with *m*CPBA in CH_2Cl_2 could provide an alternative route toward these strained spirocyclic compounds. For this purpose, two reaction conditions were initially investigated (Table 16). Upon treatment of azetidine **307a** with 1 or 2 equiv of *m*CPBA in CH_2Cl_2 at room temperature or under reflux, the starting azetidine or complex mixtures were obtained. This can be explained by the propensity of the nucleophilic nitrogen to react with *m*CPBA to form the corresponding *N*-oxides, which then underwent further reactions.

Table 16. Reaction of azetidine **307a** with *m*CPBA

Compound	Reaction conditions	Conversion
307a	1 equiv *m*CPBA, CH_2Cl_2, r.t., 1 d	No reaction
307a	1 equiv *m*CPBA, CH_2Cl_2, Δ, 1 d	Complex mixture

In order to prevent the formation of *N*-oxides, the azetidine nitrogen atom was protonated by introducing gaseous HCl to the solution of azetidine **307a** in CH_2Cl_2 for 10 min, after which 1 equiv of *m*CPBA was added. Instead of the expected spirocyclic azetidinyl epoxide, 3-chloro-3-(1-chloroethyl)azetidine **333** was obtained instead (Scheme 112), probably as the result of the electrophilic addition of *in situ* formed Cl_2 [167] to the double bond.



307a **333** (92%)

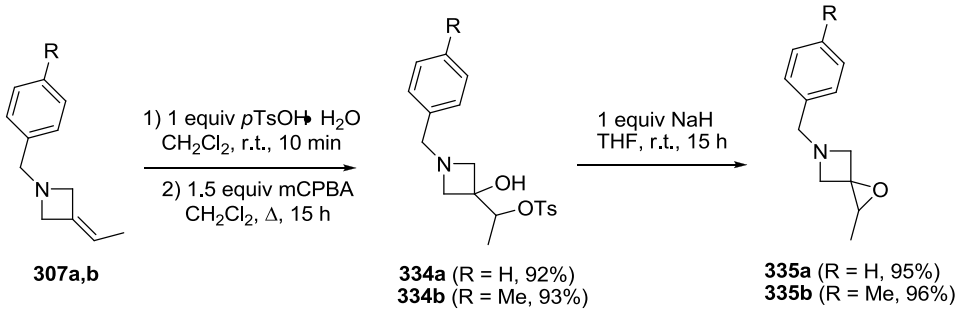
Scheme 112

The vicinally dihalogenated azetidines **332** and **333** were subsequently subjected to nucleophilic substitution reactions with benzylamine and KCN in acetonitrile under reflux or applying microwave irradiation and in the presence of a catalytic amount of silver salts (Ag_2CO_3) or NaI. Unfortunately, these reactions resulted in the recovery of the starting materials or gave complex mixtures as a result of decomposition (Table 17).

Table 17. Reaction of azetidines **332** and **333**

Compound	Reaction conditions	Conversion
332	1 equiv $BnNH_2$, 0.5 equiv NaI, MeCN, Δ, 3 d	No reaction
332	1 equiv $BnNH_2$, 1 equiv Ag_2CO_3, MeCN, Δ, 3 d	Complex mixture
333	2 equiv KCN, 0.1 equiv Ag_2CO_3, MeCN, Δ, 15 h	No reaction
333	2 equiv KCN, 1 equiv Ag_2CO_3, MeCN, MW, 150 °C, 15 min	Complex mixture

In a final attempt, the azetidine nitrogen atom was protected by addition of 1 equiv of *p*TsOH in CH_2Cl_2. Subsequent addition of 1.5 equiv of *m*CPBA and heating under reflux for 15 hours afforded very unstable azetidine-3-ols **334a,b**. However, immediate treatment of these azetidines **334** with 1 equiv of NaH in THF for 15 hours at room temperature provided the target 1-oxa-5-azaspiro[2,3]hexanes **335a,b** in very high yields (Scheme 113).



307a,b

334a (R = H, 92%)
334b (R = Me, 93%)

335a (R = H, 95%)
335b (R = Me, 96%)

Scheme 113

These novel strained spirocyclic systems showed a considerable stability as they were purified by means of column chromatography on basic Al_2O_3 to provide analytically pure samples. As expected, the purification on slightly acidic silica gel column resulted in decomposition. This reaction can be considered as a very useful and efficient synthetic approach toward interesting new aza-spirocyclic building blocks. The synthesis of the spiranic azetidinyl epoxide moiety has received only limited attention in the literature.[168] These compounds were shown to be very useful intermediates for the preparation of different biologically active molecules.[169] In general, the synthesis and reactivity of different azaspirocyclic scaffolds represent a challenging task for organic chemists and has lately been the subject of significant interest.[168a,170]

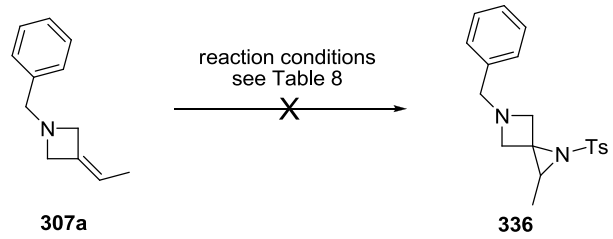
Bearing in mind that a number of azaspirocyles containing an azetidine moiety can be considered as structural surrogates of commonly employed saturated heterocycles with beneficial inherent structural features, further efforts were devoted to expand the family of novel spiroazetidine building blocks.

Attempts to perform a cyclopropanation of the double bond in azetidine **307a** under Simmons-Smith conditions (4 equiv Et_2Zn, 2 equiv CH_2I_2, 2 equiv TFA)[171] in CH_2Cl_2 gave complex mixtures (Table 18).

Table 18. Cyclopropanation of azetidines **307a** under the Simmons-Smith conditions

Compound	Reaction conditions	Conversion
307a	4 equiv Et_2Zn, 2 equiv CH_2I_2, CH_2Cl_2, r.t., 3.5 h	Complex mixture
307a	4 equiv Et_2Zn, 2 equiv CH_2I_2, 2 equiv TFA, CH_2Cl_2, r.t., 3.5 h	Complex mixture

In analogy with the epoxidation of azetidine **307a**, the direct aziridination of the double bond could provide an access to novel spirocyclic 1,5-diazaspiro[2.3]hexanes **336** (Scheme 114). Treatment of azetidine **307a** with 1 equiv of NBS and 1-2 equiv of Chloramine-T, a nitrene precursor,[172] in acetonitrile under reflux for 1-2 days afforded only small amounts of 3-bromo-3-(1-bromoethyl)azetidine **332**, and no traces of the corresponding spiro compounds were detected. A complex mixture was also obtained with 0.1 equiv of phenyltrimethylammonium tribromide (PTAB) and 1.1 equiv of Chloramine-T in acetonitrile[173] at room temperature for 1 day (Table 19).



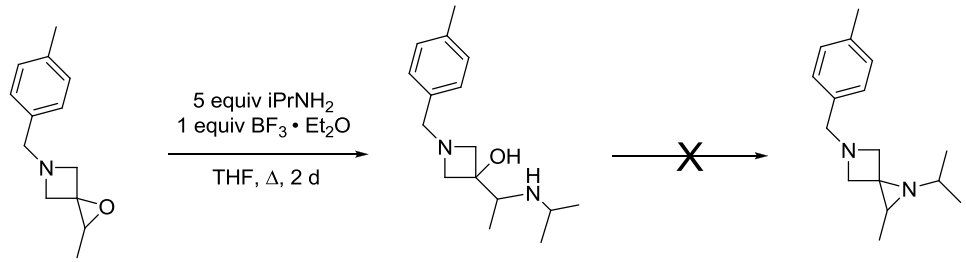
307a **336**

Scheme 114

Table 19. Attempted aziridination of the double bond in azetidine **307a** with Chloramine-T

Compound	Reaction conditions	Conversion
307a	1 equiv NBS, 1 equiv Chloramine-T, MeCN, r.t., 5 h	No reaction
307a	1 equiv NBS, 1 equiv Chloramine-T, MeCN, r.t., 2 d	No reaction
307a	1 equiv NBS, 2 equiv Chloramine-T, MeCN, Δ, 2 d	Azetidine **332** (32%)
307a	0.1 equiv PTAB, 1.1 equiv Chloramine-T, MeCN, r.t., 2 d	Complex mixture

An alternative route to the synthesis of the spiranyl aziridinyl azetidine core structure could comprise the ring opening of epoxides **335b** with an appropriate amine ($iPrNH_2$) in the presence of $BF_3{\cdot}Et_2O$, followed by subsequent ring closure of the resulting amino alcohols under the Mitsunobu conditions. Although the epoxide ring opening was shown to be successful, the drawback of this procedure for the preparation of 1,5-diazaspiro[2.3]hexane **338** involved a very low stability of thus obtained β-amino alcohol **337**, which underwent immediate decomposition (Scheme 115, Table 20).



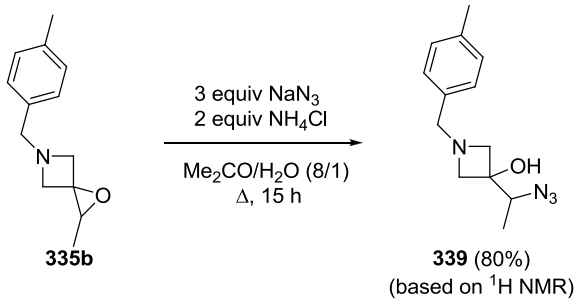
335b **337** (70%) (based on ^1H NMR) **338**

Scheme 115

Table 20. Attempts to synthesize β-amino alcohol **337** from epoxide **335b**

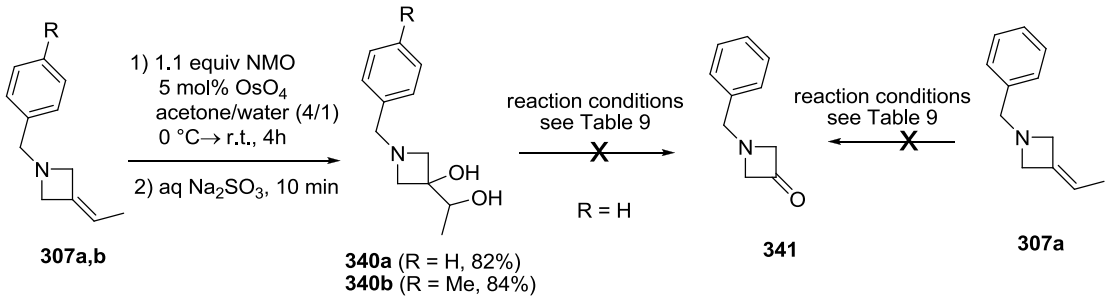
Compound	Reaction conditions	Conversion
335b	1 equiv $BnNH_2$, 0.1 equiv $BF_3{\cdot}Et_2O$, THF, r.t., 1 d	Complex mixture
335b	3 equiv $iPrNH_2$, 1 equiv $BF_3{\cdot}Et_2O$, THF, r.t., 1 d	No reaction
335b	5 equiv $iPrNH_2$, 1 equiv $BF_3{\cdot}Et_2O$, THF, Δ, 1 d	**337** (70%)
335b	1.5 equiv $nPrNH_2$, 1 equiv $BF_3{\cdot}Et_2O$, THF, Δ, 1 d	Complex mixture

On the other hand, the ring opening of epoxide **335b** with 3 equiv of NaN_3 and 2 equiv of NH_4Cl in a acetone/water (8/1) mixture afforded the corresponding azide **339** after 15 hours under reflux (Scheme 116). However, the subsequent ring closure of **339** with 1.2 equiv of Ph_3P in THF under reflux gave a complex mixture after 17 hours.



Scheme 116

In a final part, dihydroxylation of the double bond in azetidines **307a,b** with 1.1 equiv of *N*-methylmorpholine-*N*-oxide (NMO) and a catalytic amount of OsO_4 (5-6 mol%) in acetone/water (4/1) for 4 hours at room temperature, followed by an aqueous work up, furnished dihydroxyazetidines **340a,b** in good yields (Scheme 117). These new azetidines were purified by means of column chromatography on silica gel (CH_2Cl_2/MeOH = 9/1) to provide analytically pure samples. Unfortunately, glycol cleavage in azetidine **340a** with 1-1.5 equiv of $NaIO_4$ in THF/H_2O (3/1) in order to prepare azetidine-3-one **341** resulted in complex reaction mixtures, and ozonolysis of the double bond in 3-etylideneazetidine **307a** did not provide a suitable alternative in that respect (Table 21).

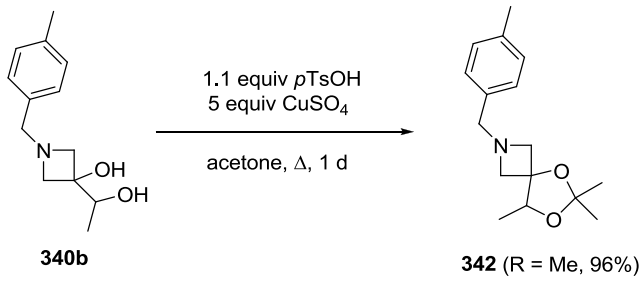


Scheme 117

Table 21. Attempts to synthesize azetidine-3-one **341** from diol **340a** or azetidine **307a**

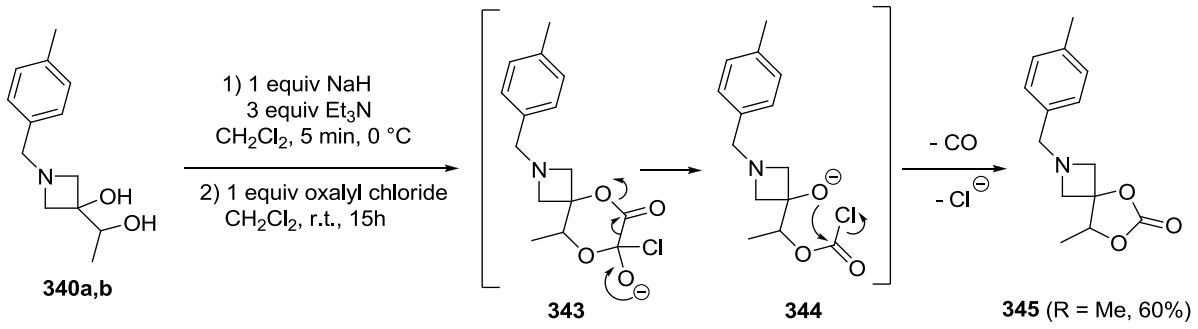
Compound	Reaction conditions	Conversion
340a	1 equiv $NaIO_4$, THF/H_2O (3/1), r.t., 1h	Complex mixture
340a	1 equiv $NaIO_4$, THF/H_2O (3/1), r.t., 1h	Complex mixture
307a	O_3, CH_2Cl_2, -78 °C, 10 min, then 5 equiv $(CH_3)_2S$	Complex mixture
307a	O_3, CH_2Cl_2, -78 °C, 10 min, then 5 equiv $(CH_3)_2S$	Complex mixture

In order to provide an entry to a different class of azaspirocyclic building blocks, azetidines **340b** were treated with 1.1 equiv of *p*TsOH and 5 equiv of $CuSO_4$ in acetone to successfully afford the corresponding novel 5,7-dioxa-2-azaspiro[3.4]octane **342** after stirring for 1 day under reflux (Scheme 118). This spirocyclic core structure was found to be present in a number of spiro lactames, suitable for the further chemical transformations.[174]



Scheme 118

Furthermore, treatment of azetidines **340b** with 1 equiv of NaH and 3 equiv of Et_3N in CH_2Cl_2 for 5 min at 0 °C followed by addition of 1 equiv of oxalyl chloride furnished new 5,7-dioxa-2-azaspiro[3,4]octane-6-one **345** after 15 hours at room temperature (Scheme 119). The formation of these cyclic carbonate could be explained by the initial formation of intermediate **343**, which was then rearranged to azetidine **345** after expulsion of carbon monoxide and chloride.[175]



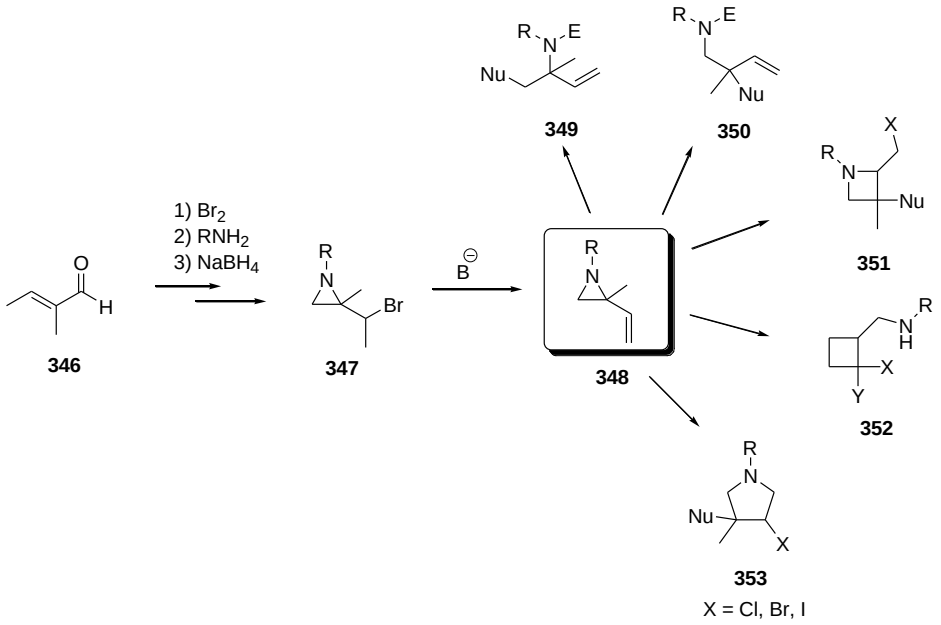
Scheme 119

It can be concluded that, in spite of a significant number of unsuccessful reactions, 3-ethylideneazetidines can still be regarded as versatile synthons to access a window of novel ring-opened amines, cyclic carbamates, functionalized azetidines and different spirocyclic building blocks.

4 Perspectives

In this PhD thesis, the efficient synthesis of 2-bromomethyl-2-methylaziridines as versatile building blocks was reported starting from 2-methylpropenal. In light of the broad synthetic potential of these synthons, the reactivity study of structurally related 2-(bromomethyl)aziridines **347** bearing an additional methyl group could provide a fruitful research area.

In analogy with the preparation of 2-bromomethyl-2-methylaziridines, the synthesis of 2-(1-bromoethyl)-2-methylaziridines **347** starting from the corresponding 2-methylbut-2-enal **346** could be performed. The treatment of these aziridines with an appropriate base (KOtBu, LDA..) could provide an access to 2-vinylaziridines **348**, being suitable substrates for further conversions through interception of highly reactive strained intermediates obtained by means of double bond functionalization. Given the increasing number of reports concerning the reactivity of 2-vinylaziridines,[43,176] these substrates are regarded as promising species for further elaboration. In this way, a novel strategy toward the synthesis of other relevant target compounds such as α-branched and β-branched amines **349** and **350**, functionalized azetidines **351**, cyclobutanes **352**, pyrrolidines **353**, recognized as potential fungicides, antidepressants and β-blockers, could be devised (Scheme 120).

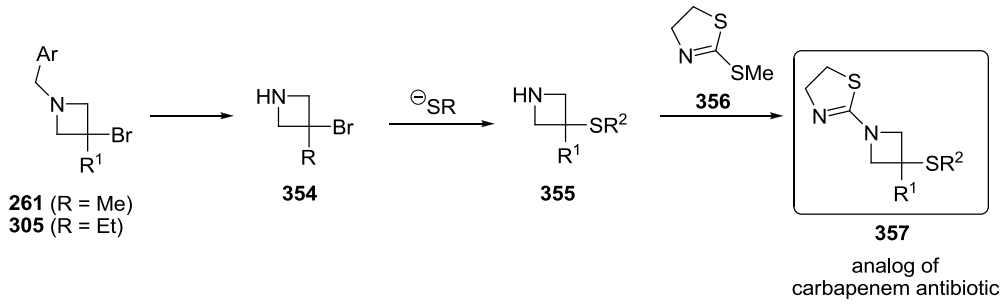


Scheme 120

As mentioned before, 3-substituted azetidines represent versatile building blocks in heterocyclic chemistry with diverse synthetic and biological properties. Next to a high number of biologically

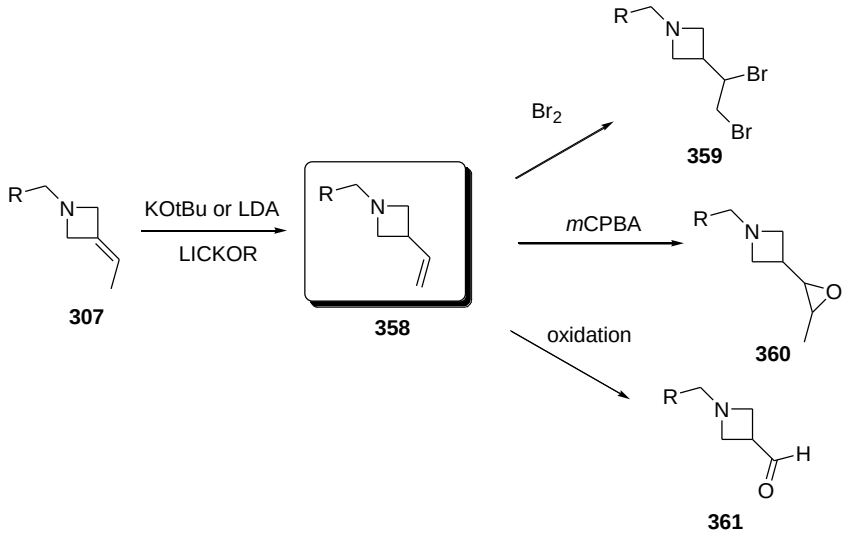
relevant 3-functionalized azetidines,[148] the introduction of an azetidine moiety into the structure of a molecule can also result in an increased biological activity. For example, different 3-sulfenylazetidine and 3-aminoazetidine derivatives have been introduced into fluoroquinolone carboxylic acids to afford the corresponding fluoroquinolone antibiotics with improved biological properties.[177] In addition, the importance of 3-sulfenylazetidines can be also seen in the development of new carbapenem antibiotics, where the synthesis of 3-mercapto-1-(1,3-thiazolin-2-yl)azetidine, starting from benzylamine and epichlorohydrin, has been reported.[178]

In order to provide an efficient access to a novel class of 3-sulfenylazetidines **357**, deprotection of the benzyl group in 3-bromoazetidines **261** or **305**, nucleophilic replacement of bromide in azetidine **354** with different *S*-centered nucleophiles, and subsequent condensation of azetidines **355** with 2-methylthio-2-thiazoline **356** could be performed. In this way, 3-sulfenyl-1-(1,3-thiazolin-2-yl)azetidines **357** could be obtained as analogs of carbapenem antibiotics (Scheme 121)



Scheme 121

Furthermore, 3-ethylideneazetidines **307** might be suitable synthons for the preparation of the corresponding 3-vinylazetidines **358** by treatment with strong base (LDA, Schlosser's base). Further functionalization of azetidine **358** could afford 3-(1,2-dibromoethyl)azetidines **359** upon reaction with Br_2, 3-(oxiran-2-yl)azetidines **360** in the reaction with *m*CPBA and azetidine-3-carboxaldehydes **361** *via* oxidation of the double bond (Scheme 122). These substrates could then be used to access a range of novel synthetically and biologically interesting molecules pertaining to the oxetane, tetrahydrofuran and pyran family.


R
N
KOtBu or LDA
LICKOR
307
358
Br2
359
Br
Br
mCPBA
360
O
oxidation
361
H
O

Scheme 122

5 Experimental part

5.1 General methods

Diethyl ether, tetrahydrofuran and toluene were distilled from sodium or sodium benzophenone ketyl, while dichloromethane was distilled from calcium hydride prior to use. Commercially available solvents and reagents were purchased from Sigma-Aldrich or Acros and used as such without further purification unless stated otherwise.

The purification of reaction mixtures was performed by column chromatography using a glass column filled with silica gel (Fluka, pore size 60 Å, 70-230 mesh, particle size 63-200 µm). Solvent systems were determined via initial TLC analysis on glass plates, coated with silica gel (Merck, Kieselgel 60F254, precoated 250 µm) using UV light or coloring with a potassium permanganate solution as detection methods. Preparative TLC analyses were performed on preparative TLC plates (Analtech, precoated 2000 µm). The compounds to be separated are applied as long streaks and after development recovered by scraping the adsorbent layers from the plate in the region of interest and eluting the separated material from the adsorbent using a CH_2Cl_2/MeOH (9/1) solvent mixture.

High resolution ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) were recorded on a Jeol Eclipse FT 300 NMR spectrometer at room temperature unless stated otherwise. Peak assignments were made with the aid of DEPT, HSQC and/or 2D-COSY experiments. The compounds were diluted in a deuterated solvent, while tetramethylsilane (TMS) was used as an internal standard.

IR spectra were recorded on a Perkin-Elemer Spectrum BX FT-IR spectrometer. All compounds were analysed in neat form with an ATR (Attenuated Total Reflectance) accessory.

Low resolution mass spectra were recorded via direct injection on an Agilent 1100 series LC-MSD type SL mass spectrometer with Electron Spray Ionization Geometry (ESI 70 eV) and using a Mass Selective Detector (quadrupole).

HPLC analyses used for the follow-up of reactions were performed on an Agilent 1200 Series with UV/DAD detector. The column was of the type Eclipse Plus C18 (4,6x50 mm, particle size 3,5 µm) or Phenomenex Kinetex C18 (4,6x50 mm, particle size 2,6 µm). A general method for these analyses uses a gradient-based solvent mixture (MeCN/H_2O, from 30% to 100% MeCN), which is suitable for good separation and resolution of all peaks. This HPLC apparatus was coupled with an Agilent 1100 series LC-MSD type VL mass spectrometer with Electron Spray Ionization Geometry (ESI 70 eV) and using a Mass Selective Detector (quadrupole).

Gas chromatography analyses were performed on an Agilent 6890 Series. The column was of the type Alltech EC-5 with a film thickness of 0.25 µm (length 30.0 m, i.d. 250 µm) with He as carrier gas. The GC was connected to a FID detector (H_2 gas).

Melting points of crystalline compounds were measured using a Büchi B-540 apparatus.

Elemental analyses were obtained by means of a Perkin Elmer series II CHNS/O analyzer 2400.

High resolution electro spray (ES) mass spectra were obtained with an Agilent Technologies 6210 Series Time-of-Flight.

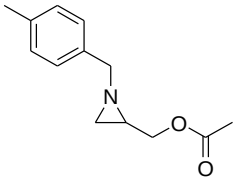
Optical rotations were determined using an JASCO P-2000 series polarimeter.

All microwave reactions were performed in a CEM Discover Benchmate with a continuous power output from 0 to 300 Watt and a self-adjusting, single mode MW cavity. The reactions were performed in a 10 mL thick walled Pyrex reaction vessels closed with a 'snap-on' septa cap and equipped with a small stirring bar, or in a 80 mL thick walled Pyrex reaction vessel connected with the locking cover assembly equipped with the thermowell nut. The temperature control uses either a non-contact infrared sensor to measure the temperature on the bottom of the vessel or a Fiber Optic temperature sensor (Model Discover, 314307), which were used in a feedback loop with the on-board computer to regulate the temperature from 25-250 °C by adjusting the power output (1 Watt increments). The pressure control, IntelliVent$_{TM}$ Pressure Control System, uses an indirect measurement of the pressure by sensing changes in the external deflection of the septa on the top of the sealed pressure vessel. Stirring is performed by a rotating magnetic plate located below the floor of microwave cavity. Cooling of the vessel after the reaction is performed by a stream of clean air onto the vessel which decreases the temperature of a 2 mL solution from 150 °C to 40 °C in less than 120 s. A ramp time of maximum 5 min is used during which the temperature increases from room temperature to the desired one. This temperature is maintained during the course of the reaction for the indicated time.

5.2 Synthesis of 2-acetoxymethyl-1-(arylmethyl)aziridines 222

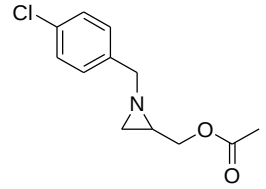
As a representative example, the synthesis of 2-acetoxymethyl-1-(4-chlorobenzyl)aziridine **222c** is described here. 2-(Bromomethyl)-1-(4-chlorobenzyl)aziridine **16c** (2.60 g, 10 mmol) was added to a stirred solution of NaOAc (1.23 g, 1.5 equiv) in DMSO (20 mL) at room temperature, and the mixture was heated at 100 °C for 15 h. The reaction mixture was poured into water (20 mL) and extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with H_2O (2 x 15 mL) and brine (20 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded 2-(acetoxymethyl)-1-(4-chlorobenzyl)aziridine **222c** (2.16 g, 90%), which was purified by filtration through silica gel (hexane/ethyl acetate 2:1) in order to obtain an analytically pure sample.

2-(Acetoxymethyl)-1-(4-methylbenzyl)aziridine 222b



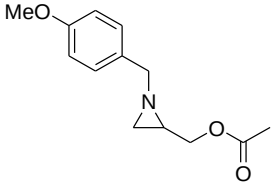
Light-yellow oil, R_f = 0.15 (hexane/ethyl acetate 2/1), Yield 83 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.51 (1H, d, J = 6.0 Hz, (H_{cis}CH)CHN), 1.77 (1H, d, J = 3.3 Hz, (HCH_{trans})CHN), 1.81–1.89 (1H, m, NCH), 1.97 (3H, s, CH_3CO), 2.34 (3H, s, CH_3Ar), 3.30 and 3.54 (2H, 2 x d, J = 13.2 Hz, (HCH)Ar), 3.82 and 4.17 (2H, 2 x d x d, J = 11.5, 7.2, 4.4 Hz, (HCH)O), 7.13-7.25 (4H, m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.7 (CH_3CO), 21.1 (CH_3Ar), 31.8 (NCH_2CH), 36.9 (NCH), 64.0 (NCH_2Ar), 66.6 (CH_2O), 128.0 and 129.0 (4 x CH_{arom}), 135.7 and 136.6 (2 x $C_{arom,quat}$), 170.9 (CO). IR (neat, cm^{-1}): ν_{CO} = 1737, ν_{max} = 2924, 1370, 1230, 1032, 802. MS (70 eV): *m/z* (%): 220 (M^+ + 1, 100). Anal. Calcd for $C_{13}H_{17}NO_2$: C 71.21, H 7.81, N 6.39. Found: C 71.35, H 8.03, N 6.44.

2-(Acetoxymethyl)-1-(4-chlorobenzyl)aziridine 222c



Light-yellow oil, R_f = 0.12 (hexane/ethyl acetate 2/1), Yield 90%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.51 (1H, d, J = 6.6 Hz, (H_{cis}CH)CHN), 1.79 (1H, d, J = 3.9 Hz, (HCH_{trans})CHN), 1.80–1.90 (1H, m, NCH), 1.98 (3H, s, CH_3CO), 3.26 and 3.56 (2H, 2 x d, J = 13.8 Hz, (HCH)Ar), 3.79 and 4.20 (2H, 2 x d x d, J = 11.6, 7.4, 4.4 Hz, (HCH)O), 7.24-7.32 (4H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 20.9 (CH_3CO), 32.0 (NCH_2CH), 37.2 (NCHCH_2), 63.5 (NCH_2Ar), 66.6 (CH_2O), 128.5 and 129.5 (4 x CH_{arom}), 132.9 and 137.4 (2 x $C_{arom,quat}$), 171.0 (CO). IR (neat, cm^{-1}): ν_{CO} = 1737, ν_{max} = 2986; 2832, 1491, 1370, 1231, 1087, 1033, 806. MS (70 eV): *m/z* (%): 240/2 (M^+ + 1, 100). Anal. Calcd for $C_{12}H_{14}ClNO_2$: C 60.13, H 5.89, N 5.84. Found: C 60.28, H 6.12, N 5.79.

2-(Acetoxymethyl)-1-(4-methoxybenzyl)aziridine 222d

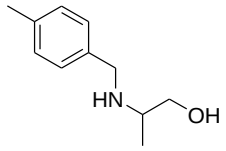


Light-yellow oil, R_f = 0.08 (hexane/ethyl acetate 2/1), Yield 79%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.51 (1H, d, J = 6.6 Hz, (H_{cis}CH)CHN), 1.77 (1H, d, J = 3.3 Hz, (HCH_{trans})CHN), 1.79–1.89 (1H, m, NCH), 1.97 (3H, s, CH_3CO), 3.26 and 3.52 (2H, 2 x d, J = 13.0 Hz, (HCH)Ar), 3.80 (3H, s, OCH_3), 3.86 and 4.17 (2H, 2 x d x d, J = 11.6, 7.7, 4.7 Hz, (HCH)O), 6.85-6.88 and 7.25-7.28 (4H, 2 x m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.8 (CH_3CO), 31.8 (NCH_2CH), 36.9 (NCHCH$_2$), 55.3 (OCH_3), 63.6 (NCH_2Ar), 66.6 (CH_2O), 113.7 and 129.3 (4 x CH_{arom}), 131.0 ($C_{arom,quat}$), 158.8 (C_{arom}O), 170.9 (CO). IR (neat, cm^{-1}): ν_{CO} = 1736, ν_{max} = 2952, 2835, 1511, 1234, 1031, 818. MS (70 eV): *m/z* (%): 236 (M^+ + 1, 100). Anal. Calcd for $C_{13}H_{17}NO_3$: C 66.36, H 7.28, N 5.95. Found: C 66.45, H 7.57, N 5.81.

5.3 Synthesis of 2-(arylmethylamino)propan-1-ols 224

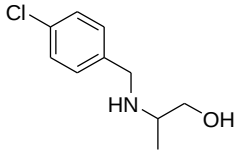
As a representative example, the synthesis of 2-{[(4-chlorophenyl)methyl]amino}propan-1-ol **224c** is described here. 2-(Acetoxymethyl)-1-(4-chlorobenzyl)aziridine **222c** (1.20 g, 5 mmol) was dissolved in dry THF (50 mL), after which $LiAlH_4$ (0.38 g, 2 molar equiv) was added in small portions at 0 °C. The resulting mixture was then placed in 80 mL sealed vessel, provided with appropriate stirrer bar and subjected to microwave conditions (130 °C, 220 W_{max}, two hours). Afterward, the reaction mixture was poured into water (20 mL) and extracted with Et_2O (3 x 20 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded 2-{[(4-chlorophenyl)methyl]amino}propan-1-ol **224c** (0.92 g, 92%), which was purified by filtration through a silica gel column (dichloromethane/methanol 9:1) in order to obtain an analytically pure sample. CAUTION: strict safety measurements have to be applied for $LiAlH_4$-promoted reactions under microwave irradiation in order to cover the risk of explosion.

2-{[(4-Methylphenyl)methyl]amino}propan-1-ol 224b



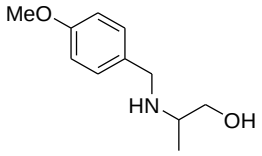
Light-yellow crystals, R_f = 0.17 (dichloromethane/methanol 9/1), Yield 75%. Mp = 71.7-72.2 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07 (3H, d, *J* = 6.6 Hz, C*H*$_3$CH), 2.33 (3H, s, C*H*$_3$Ar), 2.74 (2H, br s, OH, NH), 2.77–2.88 (1H, m, NHC*H*), 3.27 and 3.57 (2H, 2 x d x d, *J* = 11.0, 6.9, 3.9 Hz, (*HCH*)OH), 3.68 and 3.83 (2H, 2 x d, *J* = 12.9 Hz, (HCH)Ar), 7.07-7.25 (4H, m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.7 (*C*H$_3$CH), 21.2 (CH_3Ar), 50.5 (NCH_2Ar), 53.9 (CHNH), 65.2 (CH_2OH), 128.4 and 129.3 (4 x CH_{arom}), 136.0 and 137.1 (2 x $C_{arom,quat}$). IR (neat, cm^{-1}): $\nu_{NH,OH}$ = 3277, ν_{max} = 2846, 1460, 1063, 886, 812. MS (70 eV): *m/z* (%): 180 (M^+ + 1, 100). Anal. Calcd for $C_{11}H_{17}NO$: C 73.70, H 9.56, N 7.81. Found: C 73.92, H 9.48, N 9.47.

2-{[(4-Chlorophenyl)methyl]amino}propan-1-ol 224c



Light-yellow crystals, R_f = 0.19 (dichloromethane/methanol 9/1), Yield 92%. Mp = 64.6-65.6 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06 (3H, d, *J* = 6.6 Hz, C*H*$_3$CH), 2.31 (2H, br s, OH, NH), 2.75-2.85 (1H, m, NHC*H*), 3.27 and 3.56 (2H, 2 x d x d, *J* = 10.8, 7.2, 3.8 Hz, (*HCH*)OH), 3.68 and 3.83 (2H, 2 x d, *J* = 13.2 Hz, (HCH)Ar), 7.23-7.33 (4H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 17.2 (*C*H$_3$CH), 50.4 (NCH_2Ar), 53.9 (CHNH), 65.6 (CH_2OH), 128.7 and 129.5 (2 x CH_{arom}), 132.9 and 138.8 (2 x $C_{arom,quat}$). IR (neat, cm^{-1}): $\nu_{NH,OH}$ = 3312, ν_{max} = 2927, 1491, 1256, 1043, 730. MS (70 eV): *m/z* (%): 200/2 (M^+ + 1, 100). Anal. Calcd for $C_{10}H_{14}ClNO$: C 60.15, H 7.07, N 7.01. Found: C 60.05, H 7.18, N 7.10.

2-{[(4-Methoxyphenyl)methyl]amino}propan-1-ol 224d

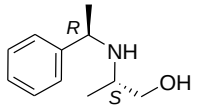


Light-yellow crystals, R_f = 0.08 (dichloromethane/methanol 9/1), Yield 72%. Mp = 59.4-60.4 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.02 (3H, d, *J* = 7.2 Hz, C*H*$_3$CH), 1.95 (2H, br s, OH, NH), 2.72–2.81 (1H, m, NHC*H*), 3.20 and 3.52 (2H, 2 x d x d, *J* = 10.5, 6.6, 3.9 Hz, (*HCH*)OH), 3.61 and 3.74 (2H, 2 x d, *J* = 12.9 Hz, (HCH)Ar), 3.72 (3H, s, OCH_3), 6.78-6.81 and 7.15-7.19 (4H, 2 x m, CH_{arom}). ^{13}C NMR (75 MHz, ref= $CDCl_3$) δ 17.1 (*C*H_3CH), 50.6 (NCH_2Ar), 53.7 (CHNH), 55.4 (OCH_3), 65.6 (CH_2OH), 113.9 and 129.4 (2 x CH_{arom}), 132.4 ($C_{arom,quat}$), 158.8 (C_{arom}O). IR (neat, cm^{-1}): $\nu_{NH,OH}$ = 3294, ν_{max} = 2834, 1511, 1245, 1034, 819. MS (70 eV): *m/z* (%): 196 (M^+ + 1, 100). Anal. Calcd for $C_{11}H_{17}NO_2$: C 67.66, H 8.78, N 7.17. Found: C 67.76, H 8.91, N 7.14.

5.4 Synthesis of optically active 2-aminopropan-1-ols 230

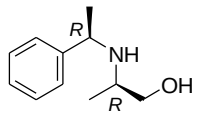
As a representative example, the synthesis of (*S*)-[1(*R*)-phenylethylamino]propan-1-ol **230a** is described here. Aziridine alcohol **229a** (0.88 g, 5 mmol) was diluted in dry THF (50 mL), and $LiAlH_4$ (0.38 g, 2 molar equiv) was added in small portions at 0 °C. The resulting mixture was then placed in 80 mL sealed vessel, provided with appropriate stirrer bar and subjected to microwave conditions (160 °C, 220 W_{max}, two hours). The resulting reaction mixture was subsequently poured into water (15 mL) and extracted with Et_2O (3 x 20 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded 2(*S*)-[1(*R*)-phenylethylamino]propan-1-ol **230a** (0.83 g, 93%), which was purified by filtration through silica gel (dichloromethane/methanol 9:1) in order to obtain an analytically pure sample.

2(*S*)-[1(*R*)-Phenylethylamino]propan-1-ol 230a



Colorless liquid, R_f = 0.18 (dichloromethane/methanol 9/1), Yield 93%. $[\alpha]_D^{28}$ = + 115.6 (c = 0.41, $CDCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.98 (d x d, *J* = 6.9, 1.4 Hz, C*H*$_3$CHCH$_2$OH), 1.36 (3H, d, *J* = 6.6 Hz, C*H*$_3$CHPh), 2.51–2.61 (1H, m, NHC*H*CH$_2$OH), 2.55 (2H, br s, OH, NH), 3.16-3.23 (1H, m, (*H*CH)OH), 3.40 (1H, d x d, *J* = 10.8, 4.2 Hz, (HC*H*)OH), 3.93 (1H, q, *J* = 6.6 Hz, CH$_3$C*H*Ar), 7.19-7.34 (5H, m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.6 (*C*H$_3$CHCH$_2$OH), 25.2 (*C*H$_3$CHPh), 51.4 (NH*C*HCH$_2$OH), 54.9 (CH$_3$*C*HAr), 66.5 (*C*H$_2$OH), 126.6, 127.1 and 128.6 (5 x CH_{arom}) and 145.1 ($C_{arom,quat}$). IR (neat, cm^{-1}): $\nu_{NH,OH}$ = 3292, ν_{max} = 2965, 1452, 1044, 762, 731, 699. MS (70 eV): *m/z* (%): 180 (M^+ + 1, 100). Anal. Calcd for $C_{11}H_{17}NO$: C 73.70, H 9.56, N 7.81. Found: C 73.94, H 9.84, N 7.69.

2(*R*)-[1(*R*)-Phenylethylethylamino]propan-1-ol 230b

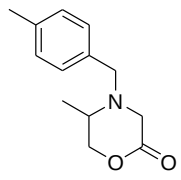


White crystals. R_f = 0.08 (dichloromethane/methanol 9/1), Yield 85%. Mp = 49.5-51.1 °C, $[\alpha]_D^{28}$ = - 2.3 (c = 0.36, $CDCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.98 (3H, d, *J* = 6.6 Hz, C*H*$_3$CHCH$_2$OH), 1.35 (3H, d, *J* = 6.4 Hz, C*H*$_3$CHPh), 2.30 (2H, br s, OH, NH), 2.68–2.80 (1H, m, NHC*H*CH$_2$OH), 3.20 and 3.59 (2H, 2 x d x d, *J* = 10.5, 6.1, 3.8 Hz, (*HCH*)OH), 3.87 (1H, q, *J* = 6.4 Hz, CH$_3$C*H*Ar), 7.22-7.36 (5H, m, CH$_{arom}$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.2 (*C*H$_3$CHCH$_2$OH), 24.1 (*C*H$_3$CHPh), 51.6 (NH*C*HCH$_2$OH), 55.4 (CH$_3$*C*HAr), 64.9 (*C*H$_2$OH), 126.4, 127.1 and 128.6 (5 x CH$_{arom}$) and 145.9 (C$_{arom,quat}$). IR (neat, cm^{-1}): $\nu_{NH,OH}$ = 3292, ν_{max} = 2965, 1452, 1045, 761, 700. MS (70 eV): *m/z* (%): 180 (M$^+$ + 1, 100). Anal. Calcd for $C_{11}H_{17}NO$: C 73.70, H 9.56, N 7.81. Found: C 73.78, H 9.72, N 7.82.

5.5 Synthesis of 5-methylmorpholin-2-ones 228

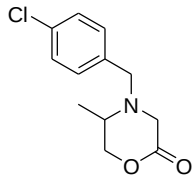
As a representative example, the synthesis of 4-(4-methylphenyl)methyl-5-methylmorpholin-2-one **228b** is described here. To a solution of 2-{[(4-methylphenyl)methyl]amino}propan-1-ol **224b** (0.72 g, 4 mmol) in THF (30 mL) an aqueous solution of glyoxal (40%, 1.74 g, 3 equiv) was added, and the resulting mixture was heated for 2.5 h under reflux. The reaction mixture was then poured into water (20 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried with anhydrous Na_2SO_4, filtered and evaporated. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate 7/1) in order to obtain an analytically pure sample (0.76 g, 87%).

4-(4-Methylphenyl)methyl-5-methylmorpholin-2-one 228b



Yellow liquid, R_f = 0.07 (petroleum ether/ethyl acetate 7/1), Yield 87%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.17 (3H, d, *J* = 6.1 Hz, C*H*$_3$CH), 2.34 (3H, s, C*H*$_3$Ar), 2.82–2.92 (1H, m, C*H*CH$_3$), 3.11 and 3.43 (2H, 2 x d, *J* = 18.2 Hz, (HCH)CO), 3.27 and 3.88 (2H, 2 x d, 12.9 Hz, (HCH)Ar), 4.09 and 4.34 (2H, 2 x d x d, *J* = 11.0, 7.7, 3.6 Hz, (HCH)O), 7.09-7.19 (4H, m, CH$_{arom}$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.4 (*C*H$_3$CH), 21.1 (CH$_3$Ar), 51.1 (*C*HCH$_3$), 52.5 (*C*H$_2$CO), 57.3 (NCH$_2$Ar), 73.7 (CH$_2$O), 128.8 and 129.3 (4 x CH$_{arom}$), 133.6 and 137.3 (2 x C$_{arom,quat}$), 168.2 (CO). IR (neat, cm^{-1}): ν_{CO} = 1742, ν_{max} = 2923, 1227, 1055, 807. MS (70 eV): *m/z* (%): 220 (M$^+$ + 1, 100). Anal. Calcd for $C_{13}H_{17}NO_2$: C 71.21, H 7.81, N 6.39. Found: C 71.47, H 8.06, N 6.27.

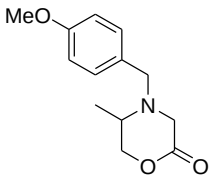
4-(4-Chlorophenyl)methyl-5-methylmorpholin-2-one 228c



Yellow solid, R_f = 0.05 (petroleum ether/ethyl acetate 7/1), Yield 83%. Mp = 55.5-58.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.16 (3H, d, *J* = 6.0 Hz, C*H*$_3$CH), 2.84–2.93 (1H, m, C*H*CH$_3$), 3.11 and 3.41 (2H, 2 x d, *J* = 17.6 Hz, (HCH)CO), 3.29 and 3.88 (2H, 2 x d, 13.2 Hz, (HCH)Ar), 4.09 and 4.35 (2H, 2 x d x d, *J* = 11.0, 7.7, 3.6 Hz, (HCH)O), 7.23-7.35 (4H, m, CH$_{arom}$). ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 12.5 (*C*H$_3$CH), 51.4 (*C*HCH$_3$), 52.6 (*C*H$_2$CO), 57.1 (NCH$_2$Ar), 73.7 (CH$_2$O), 128.8 and 130.2 (4 x

CH_{arom}), 133.4 and 135.6 (2 x $C_{arom,quat}$), 168.0 (CO). IR (neat, cm^{-1}): ν_{CO} = 1741, ν_{max} = 2969, 1490, 1227, 1056, 810. MS (70 eV): *m/z* (%): 240/2 (M^+ + 1, 100). Anal. Calcd for $C_{12}H_{14}ClNO_2$: C 60.13, H 5.89, N 5.84. Found: C 60.27, H 6.11, N 5.98.

4-(4-Methoxyphenyl)methyl-5-methylmorpholin-2-one 228d

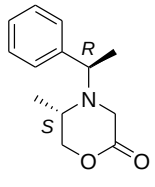


Yellow solid, R_f = 0.05 (petroleum ether/ethyl acetate 7/1), Yield 74%. Mp = 48.3–51.3 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.17 (3H, d, *J* = 6.6 Hz, C*H*$_3$CH), 2.82–2.92 (1H, m, C*H*CH_3), 3.11 and 3.43 (2H, 2 x d, *J* = 17.6 Hz, (HCH)CO), 3.26 and 3.86 (2H, 2 x d, *J* = 12.6 Hz, (HCH)Ar), 3.81 (3H, s, CH_3O), 4.09 and 4.34 (2H, 2 x d x d, *J* = 11.0, 7.7, 3.3 Hz, (HCH)O), 6.84-6.89 and 7.18-7.25 (4H, 2 x m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.4 (*C*H_3CH), 51.1 (*C*HCH$_3$), 52.4 (*C*H_2CO), 55.3 (OCH_3), 57.0 (NCH_2Ar), 73.7 (CH_2O), 114.0 and 130.1 (4 x CH_{arom}), 128.6 ($C_{arom,quat}$), 161.3 ($C_{arom}O$), 167.9 (CO). IR (neat, cm^{-1}): ν_{CO} = 1739, ν_{max} = 2965, 1511, 1243, 1031, 822. MS (70 eV): *m/z* (%): 236 (M^+ + 1, 100). Anal. Calcd for $C_{13}H_{17}NO_3$: C 66.36, H 7.28, N 5.95. Found: C 66.31, H 7.24, N 5.88.

5.6 Synthesis of chiral 5-methylmorpholin-2-ones 231

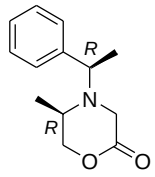
As a representative example, the synthesis of 5(*S*)-methyl-4-[1(*R*)-phenylethyl]morpholin-2-one **231a** is described here. To a solution of 2(*S*)-[1(*R*)-phenylethylamino]propan-1-ol **230a** (0.72 g, 4 mmol) in THF (30 mL) an aqueous solution of glyoxal (40%, 1.74 g, 3 equiv) was added, and the resulting mixture was heated for 3 h under reflux. The reaction mixture was then poured into water (20 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried with anhydrous Na_2SO_4, filtered and evaporated. The crude product was purified by column chromatography on silica gel (hexane/ethyl acetate 3:1) in order to obtain an analytically pure sample (0.78 g, 89%).

5(*S*)-Methyl-4-[1(*R*)-phenylethyl]morpholin-2-one 231a



Light-yellow solid, R_f = 0.25 (hexane/ethyl acetate 3/1), Yield 89%. Mp = 37.1–40.2 °C, $[\alpha]_D^{28}$ = + 25.0 (c = 0.44, $CDCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.04 (3H, d, *J* = 6.6 Hz, C*H*$_3$CHCH$_2$), 1.35 (3H, d, *J* = 6.8 Hz, C*H*$_3$CHAr), 2.82–2.91 (1H, m, CH_2C*H*CH_3), 3.38 and 3.74 (2H, 2 x d, *J* = 17.9 Hz, (HCH)CO), 3.66 (1H, q, *J* = 6.8 Hz, CH_3C*H*Ar), 4.00 and 4.37 (2H, 2 x d x d, *J* = 11.0, 3.3, 3.3 Hz, (HCH)O), 7.24-7.34 (5H, m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.0 (*C*H_3CHCH$_2$), 21.0 (*C*H_3CHAr), 47.2 (CH_2*C*HCH$_3$), 48.3 (*C*H_2CO), 60.2 (Ar*C*HCH$_3$), 74.1 (CH_2O), 127.3, 127.6 and 128.7 (5 x CH_{arom}), 142.7 ($C_{arom,quat}$), 168.6 (CO). IR (neat, cm^{-1}): ν_{CO} = 1737, ν_{max} = 2973, 1224, 1004, 701. MS (70 eV): *m/z* (%): 220 (M^+ + 1, 100). Anal. Calcd for $C_{13}H_{17}NO_2$: C 71.21, H 7.81, N 6.39. Found: C 71.27, H 7.93, N 6.33.

5(*R*)-Methyl-4-[1(*R*)-phenylethyl]morpholin-2-one 231b

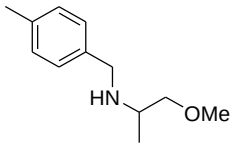


Light-yellow liquid, R_f = 0.18 (hexane/ethyl acetate 3/1), Yield 86%. $[\alpha]_D^{28}$ = + 9.6 (c = 0.37, $CDCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.16 (3H, d, *J* = 6.6 Hz, C*H*$_3$CHCH$_2$), 1.34 (3H, d, *J* = 6.6 Hz, C*H*$_3$CHAr), 3.11 and 3.28 (2H, 2 x d, *J* = 18.2 Hz, (HCH)CO), 3.26–3.36 (1H, m, CH$_2$C*H*CH$_3$), 3.74 (1H, q, *J* = 6.6 Hz, CH$_3$C*H*Ar), 4.14 and 4.47 (2H, 2 x d x d, *J* = 10.8, 5.2, 3.6 Hz, (HCH)O), 7.22-7.39 (5H, m, CH$_{arom}$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.6 (*C*H$_3$CHCH$_2$), 16.6 (*C*H$_3$CHAr), 47.6 (CH$_2$*C*HCH$_3$), 48.3 (*C*H$_2$CO), 59.1 (Ar*C*HCH$_3$), 73.9 (CH$_2$O), 127.38, 127.44 and 128.6 (5 x CH$_{arom}$), 142.8 (C$_{arom,quat}$), 168.8 (CO). IR (neat, cm^{-1}): ν_{CO} = 1740, ν_{max} = 2972, 1206, 1050, 700. MS (70 eV): *m/z* (%): 220 (M$^+$ + 1, 100). Anal. Calcd for $C_{13}H_{17}NO_2$: C 71.21, H 7.81, N 6.39. Found: C 71.01, H 8.00, N 6.52.

5.7 Synthesis of 1-methoxypropan-2-amines 235

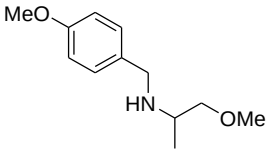
As a representative example, the synthesis of *N*-(1-methoxyprop-1-yl)-*N*-(4-methylbenzyl)amine **235a** is described here. 2-(Methoxymethyl)-1-(4-methylbenzyl)aziridine **233a** (0.96 g, 5 mmol) was dissolved in dry THF (25 mL), after which $LiAlH_4$ (0.38 g, 2 molar equiv) was added in small portions at 0 °C. The resulting mixture was then placed in 80 mL sealed vessel, provided with appropriate stirrer bar and subjected to microwave conditions (130 °C, 250 W$_{max}$, 12 h). Afterward, the reaction mixture was poured into water (20 mL) and extracted with Et_2O (3 x 20 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded *N*-(1-methoxyprop-1-yl)-*N*-(4-methylbenzyl)amine **235a** (0.27 g, 80%), which was purified by filtration through silica gel column (dichloromethane/methanol 9:1) in order to obtain an analytically pure sample.

***N*-(1-Methoxyprop-1-yl)-*N*-(4-methylbenzyl)amine 235a**



Light-yellow oil, R_f = 0.23 (dichloromethane/methanol 9/1), Yield 80%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06 (3H, d, *J* = 6.1 Hz, C*H*$_3$CH), 2.33 (3H, s, CH$_3$Ar), 2.08 (1H, br s, NH), 2.89–2.99 (1H, m, NHC*H*), 3.27 and 3.34 (2H, 2 x d x d, *J* = 9.4, 7.7, 4.4 Hz, (*HCH*)OCH$_3$), 3.32 (3H, s, OCH$_3$), 3.69 and 3.86 (2H, 2 x d, *J* = 12.9 Hz, (HCH)Ar), 7.12-7.26 (4H, m, CH$_{arom}$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.9 (*C*H$_3$CH), 21.1 (CH$_3$Ar), 50.9 (NCH$_2$Ar), 51.8 (CHNH), 58.9 (OCH$_3$), 77.1 (*C*H$_2$OCH$_3$), 128.2 and 129.1 (4 x CH$_{arom}$), 136.5 and 137.2 (2 x C$_{arom,quat}$). IR (neat, cm^{-1}): ν_{NH} = 3325, ν_{max} = 2923, 2875, 2826, 1514, 1450, 1373, 1197, 1162, 1106, 805. MS (70 eV): *m/z* (%): 194 (M$^+$ + 1, 100). Anal. Calcd for $C_{12}H_{19}NO$: C 74.57, H 9.91, N 7.25. Found: C 74.68, H 9.48, N 7.47.

_N_-(4-Methoxylbenzyl)-_N_-(1-methoxyprop-1-yl)amine 235b

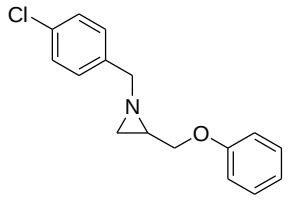


Dark-yellow oil, R_f = 0.21 (dichloromethane/methanol 9/1), Yield 60%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07 (3H, d, J = 6.1 Hz, CH_3CH), 2.24 (1H, br s, NH), 2.89–2.99 (1H, m, NHCH), 3.25-3.36 (2H, m, CH_2OCH$_3$), 3.67 and 3.83 (2H, 2 x d, J = 12.7 Hz, (HCH)Ar), 3.80 (3H, s, OCH_3), 6.85-6.88 (4H, m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.8 (CH_3CH), 50.7 (NCH_2Ar), 51.8 (CHNH), 55.3 (OCH_3Ar), 58.8 (CH_2OCH_3), 77.0 (CH_2OCH$_3$), 113.8 and 129.4 (4 x CH_{arom}), 132.4 ($C_{arom,quat}$), 158.6 (C_{arom}O). IR (neat, cm^{-1}): ν_{NH} = 3324, ν_{max} = 2928, 2877, 2832, 1612, 1511, 1462, 1244, 1105, 1035, 822. MS (70 eV): *m/z* (%): 210 (M^+ + 1, 100). Anal. Calcd for $C_{12}H_{19}NO_2$: C 68.87, H 9.15, N 6.69. Found: C 68.61, H 9.48, N 6.47.

5.8 Synthesis of 1-arylmethyl-2-(aryloxymethyl)aziridines 234

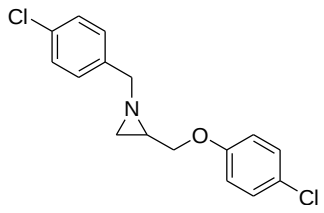
As a representative example, the synthesis of 1-[(4-methoxyphenyl)methyl]-2-(phenoxymethyl)aziridine **234d** is described here. 2-Bromomethyl-1-[(4-methoxyphenyl)methyl]aziridine **16d** (1.28 g, 5 mmol) was added to a mixture of phenol (1.03 g, 2.2 equiv) and K_2CO_3 (3.45 g, 5 equiv) in a solvent mixture containing acetone and DMF (50 mL, 1:1 v/v), and the resulting mixture was heated at reflux for 15 h. Afterward, the reaction mixture was poured into brine (50 mL) and extracted with Et_2O (3 x 50 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded 1-[(4-methoxyphenyl)methyl]-2-(phenoxymethyl)aziridine **234d**, which was purified by column chromatography on silica gel (hexane/ethyl acetate 4/1) to give an analytically pure sample (1.17 g, 87%).

1-[(4-Chlorophenyl)methyl]-2-(phenoxymethyl)aziridine 234b



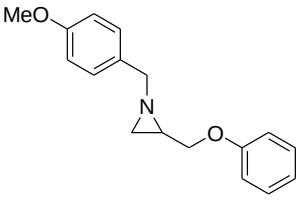
Yellow liquid, R_f = 0.28 (hexane/ethyl acetate 4/1), Yield 85%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.55 (1H, d, J = 6.6 Hz, (H_{cis}CH)CHN), 1.85 (1H, d, J = 3.3 Hz, (HCH_{trans})CHN), 1.94–2.03 (1H, m, NCH), 3.43 and 3.49 (2H, 2 x d, J = 13.8 Hz, N(HCH)Ar), 3.89 and 3.99 (2H, 2 x d x d, J = 10.3, 6.3, 5.0 Hz, (HCH)O), 6.86–6.96 and 7.22–7.33 (9H, 2 x m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.8 (NCH_2CH), 38.0 (NCH), 63.5 (NCH_2Ar), 70.0 (CH_2O), 114.6, 120.9, 128.5, 129.3 and 129.4 (9 x CH_{arom}), 132.8, 137.4 and 158.6 (3 x $C_{arom,quat}$). IR (neat): ν_{max} = 2921, 1599, 1491, 1240, 1086, 1034, 1015, 805, 752, 691 cm^{-1}. MS (70 eV): *m/z* (%) = 274/6 (M^+ + 1, 100). $C_{16}H_{16}ClNO$ (273.76): calcd. C 70.20, H 5.89, N 5.12; found C 70.31, H 6.04, N 5.21.

2-[(4-Chlorophenoxy)methyl]-1-[(4-chlorophenyl)methyl]aziridine 234c



Yellow liquid, R_f = 0.10 (hexane/ethyl acetate 4/1), Yield 82%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.55 (1H, d, *J* = 6.6 Hz, (H_{cis}CH)CHN), 1.84 (1H, d, *J* = 3.3 Hz, (HCH_{trans})CHN), 1.91–1.98 (1H, m, NCH), 3.42 and 3.48 (2H, 2 x d, *J* = 13.2 Hz, N(HCH)Ar), 3.83 and 3.99 (2 H, 2 x d x d, *J* = 10.4, 6.6, 4.4 Hz, (HCH)O), 6.77–6.80, 7.18–7.21 and 7.27–7.32 (8H, 3 x m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.7 (NCH_2CH), 37.9 (NCH), 63.5 (NCH_2Ar), 70.4 (CH_2O), 115.9, 128.5, 129.29, 129.34 (8 x CH_{arom}), 125.8, 133.0, 137.3 and 157.3 (4 x $C_{arom,quat}$). IR (neat): ν_{max} = 2986, 2923, 2830, 1596, 1489, 1284, 1240, 1171, 1089, 1015, 822, 806, 668 cm^{-1}. MS (70 eV): *m*/*z* (%) = 308/10/12 (M^+ + 1, 100). $C_{16}H_{15}Cl2NO$ (308.21): calcd. C 62.35, H 4.91, N 4.54; found C 62.42, H 5.23, N 4.45.

1-[(4-Methoxyphenyl)methyl]-2-(phenoxymethyl)aziridine 234d

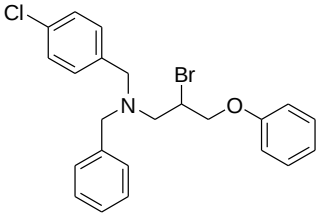


Light-yellow crystals, R_f = 0.11 (hexane/ethyl acetate 4/1), Yield 87 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.52 (1H, d, *J* = 6.6 Hz, (H_{cis}CH)CHN), 1.79 (1H, d, *J* = 3.3 Hz, (HCH_{trans})CHN), 1.86–1.97 (1H, m, NCH), 3.37 and 3.44 (2H, 2 x d, *J* = 13.2 Hz, N(HCH)Ar), 3.76 (3H, s, OCH_3), 3.91 (2H, d, *J* = 5.5 Hz, (HCH)O), 6.81–6.93 and 7.19–7.28 (9H, 2 x m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.8 (NCH_2CH), 37.8 (NCH), 55.2 (OCH_3), 63.6 (NCH_2Ar), 70.1 (CH_2O), 113.8, 114.6, 120.8, 129.3 and 129.4 (9 x CH_{arom}), 130.0 ($C_{arom,quat}$), 158.7 and 158.8 (2 x C_{arom}O). IR (neat): ν_{max} = 2933, 2836, 1609, 1511, 1457, 1243, 1173, 1030, 1018, 809, 760 cm^{-1}. MS (70 eV): *m*/*z* (%) = 270 (M^+ + 1, 100). $C_{17}H_{19}NO_2$ (269.34): calcd. C 75.81, H 7.11, N 5.20; found C 75.67, H 7.27, N 5.08.

5.9 Synthesis of *N*-(3-aryloxy-2-bromopropyl)amines 239

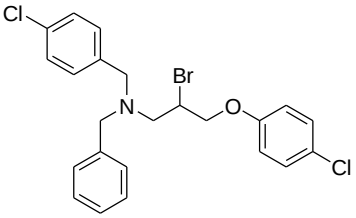
As a representative example the synthesis of *N*-benzyl-*N*-(2-bromo-3-phenoxypropyl)-*N*-(4-chlorobenzyl)amine **239b** is described here. Benzyl bromide (1.71 g, 1 equiv) was added to a solution of 1-[(4-chlorophenyl)methyl]-2-(phenoxymethyl)aziridine **234b** (2.73 g, 10 mmol) in acetonitrile (50 mL) at room temperature whilst stirring, and the resulting mixture was heated at reflux for 5 h. Afterward, the reaction mixture was poured into water (50 mL) and extracted with Et_2O (3 x 50 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded *N*-benzyl-*N*-(2-bromo-3-phenoxypropyl)-*N*-(4-chlorobenzyl)amine **239b**, which was purified by column chromatography on silica gel (hexane/ethyl acetate 1/1) to obtain an analytically pure sample (3.83 g, 86%).

_N_-Benzyl-_N_-(2-bromo-3-phenoxypropyl)-_N_-(4-chlorobenzyl)amine 239b



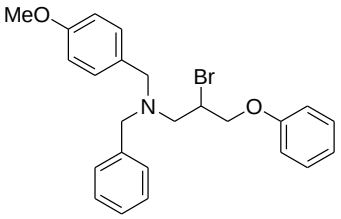
Colourless oil, R_f = 0.76 (hexane/ethyl acetate 1/1), Yield 86%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.91 and 3.10 (2H, 2 x d x d, J = 13.8, 7.2, 5.5 Hz, N(*HCH*)CH), 3.53–3.71 (4H, m, 2 x NCH_2Ar), 4.07–4.23 (3H, m, BrCH and (HCH)O), 6.77–6.80, 6.94–6.99 and 7.22–7.36 (14H, 3 x m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$) δ 48.9 (CHBr), 57.8 (NCH_2), 58.5 (NCH_2), 59.2 (NCH_2), 70.0 (CH_2O), 114.6, 121.2, 127.4, 128.4, 128.5, 129.0, 129.5 and 130.3 (14 x CH_{arom}), 132.9, 137.3, 138.5 and 158.1 (4 x $C_{arom,quat}$). IR (neat): ν_{max} = 2925, 2826, 1736, 1598, 1587, 1491, 1453, 1240, 1088, 801, 752, 692 cm^{-1}. MS (70 eV): *m*/*z* (%) = 364/6 (100), 444/6/8 (M^+ + 1, 15). $C_{23}H_{23}BrClNO$ (444.80): calcd. C 62.11, H 5.21, N 3.15; found C 62.29, H 5.41, N 3.04.

_N_-Benzyl-_N_-[2-bromo-3-(4-chlorophenoxy)propyl]-_N_-(4-chlorobenzyl)amine 239c



Colourless oil, R_f = 0.74 (hexane/ethyl acetate 1/1), Yield 85%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.90 and 3.08 (2H, 2 x d x d, J = 13.8, 7.4, 5.8 Hz, N(*HCH*)CH), 3.52–3.72 (4H, m, 2 x NCH_2Ar), 4.02–4.14 (3H, m, BrCH and (HCH)O), 6.67–6.71 and 7.20–7.38 (13H, 2 x m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$) δ 48.5 (CHBr), 57.7 (NCH_2), 58.6 (NCH_2), 59.4 (NCH_2), 70.2 (CH_2O), 115.9, 127.4, 128.45, 128.53, 129.0, 129.4 and 130.3 (13 x CH_{arom}), 133.0, 137.3, 138.5, 156.8 and 126.2 (5 x $C_{arom,quat}$). IR (neat): ν_{max} = 2920, 2826, 1596, 1490, 1453, 1240, 1090, 821, 801, 740, 697 cm^{-1}. MS (70 eV): *m*/*z* (%) = 398/400/402 (M^+ + 1, 100). $C_{23}H_{22}BrCl_2NO$ (479.24): calcd. C 57.64, H 4.63, N 2.92; found C 57.79, H 4.95, N 2.81.

_N_-Benzyl-_N_-(2-bromo-3-phenoxypropyl)-_N_-(4-methoxybenzyl)amine 239d



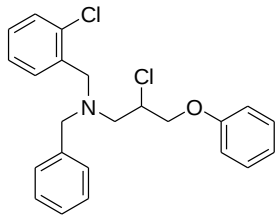
Colourless oil, R_f = 0.76 (hexane/ethyl acetate 1/1), Yield 84%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.91 and 3.08 (2H, 2 x d x d, J = 13.8, 8.3, 5.4 Hz, N(*HCH*)CH), 3.49–3.74 (4H, m, 2 x NCH_2Ar), 3.77 (3H, s, OCH_3), 4.01–4.24 (3H, m, BrCH and (HCH)O), 6.78–6.83, 6.92–6.97 and 7.15–7.39 (14H, 3 x m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$) δ 49.3 (CHBr), 55.2 (NCH_2), 57.8 (NCH_2), 58.6 (NCH_2), 59.3 (OCH_3), 70.2 (CH_2O), 113.7, 114.7, 121.1, 127.2, 128.3, 129.0, 129.4 and 130.2 (14 x CH_{arom}), 130.8 and 138.9, (2 x $C_{arom,quat}$) 158.3 and 158.9 (2 x $C_{arom}O$). IR (neat): ν_{max} = 2932, 2833, 1599, 1509, 1495, 1453, 1241, 1172, 1034, 813, 752, 691 cm^{-1}. MS (70 eV): *m*/*z* (%) = 360 (100), 440/2 (M^+ + 1, 30). $C_{24}H_{26}BrNO_2$ (440.38): calcd. C 65.46, H 5.95, N 3.18; found C 65.62, H 6.13, N 3.14.

5.10 Synthesis of _N_-(2-chloro-3-aryloxypropyl)amines 240

As a representative example the synthesis of *N*-benzyl-*N*-(2-chloro-3-phenoxypropyl)-*N*-(4-methoxybenzyl)amine **240d** is described here. Tetraethylammonium chloride (1.66 g, 10 equiv) was

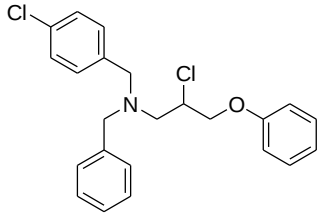
added to a solution of *N*-benzyl-*N*-(2-bromo-3-phenoxypropyl)-*N*-(4-methoxybenzyl)amine **239d** (0.44 g, 1 mmol) in acetonitrile (20 mL) at room temperature whilst stirring, and the resulting mixture was heated at reflux for 3 h. Afterward, the reaction mixture was poured into water (50 mL) and extracted with Et_2O (3 x 50 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded *N*-benzyl-*N*-(2-chloro-3-phenoxypropyl)-*N*-(4-methoxybenzyl) amine **240d**, which was purified by column chromatography on silica gel (hexane/ethyl acetate 1/1) to obtain an analytically pure sample (0.33 g, 84%).

_N_-Benzyl-_N_-(2-chlorobenzyl)-_N_-(2-chloro-3-phenoxypropyl)amine 240a



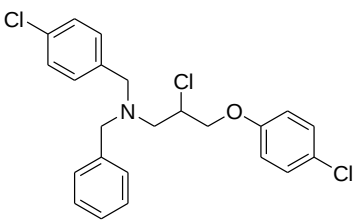
Colourless oil, R_f = 0.78 (hexane/ethyl acetate 1/1), Yield 82%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.87 and 3.06 (2H, 2 x d x d, *J* = 13.8, 7.2, 5.5 Hz, N(*HCH*)CH), 3.61–3.84 (4H, m, 2 x NCH_2Ar), 3.90–3.96 (1H, m, ClCH), 4.10–4.18 (2H, m, (HCH)O), 6.76–6.78, 6.92–6.97, 7.13–7.39 and 7.51–7.54 (14H, 4 x m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$) δ 56.5 (CHCl), 57.0 (NCH_2), 57.5 (NCH_2), 59.6 (NCH_2), 69.9 (CH_2O), 114.6, 121.1, 126.7, 127.3, 128.3, 128.4, 129.1, 129.4, 129.6 and 131.0 (14 x CH_{arom}), 134.3, 136.4 and 138.5 (3 x $C_{arom,quat}$), 158.3 ($C_{arom}O$). IR (neat): ν_{max} = 2923, 2849, 1599, 1495, 1453, 1241, 1037, 749, 690 cm^{-1}. MS (70 eV): *m*/*z* (%) = 400/2/4 (M^+ + 1, 100), 364/6 (75). $C_{23}H_{23}Cl_2NO$ (400.35): calcd. C 69.00, H 5.79, N 3.50; found C 69.17, H 5.97, N 3.72.

_N_-Benzyl-_N_-(4-chlorobenzyl)-_N_-(2-chloro-3-phenoxypropyl)amine 240b



Colourless oil, R_f = 0.79 (hexane/ethyl acetate 1/1), Yield 79%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.81 and 3.02 (2H, 2 x d x d, *J* = 13.8, 7.2, 6.0 Hz, N(*HCH*)CH), 3.55 and 3.68 (2H, 2 x d, *J* = 13.5 Hz, N(HCH)Ar), 3.59 and 3.64 (2H, 2 x d, *J* = 13.8 Hz, N(HCH)Ar), 3.96–4.01 (1H, m, ClCH), 4.05–4.18 (2H, m, CH_2O), 6.76–6.79, 6.93–6.98 and 7.21–7.38 (14H, 3 x m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$) δ 57.1 (CHCl), 57.4 (NCH_2), 58.7 (NCH_2), 59.4 (NCH_2), 70.0 (CH_2O), 114.7, 121.3, 127.5, 128.5, 128.6, 129.1, 129.6 and 130.4 (14 x CH_{arom}), 133.0, 137.5 and 138.7 (3 x $C_{arom,quat}$), 158.3 ($C_{arom}O$). IR (neat): ν_{max} = 2924, 2828, 1599, 1588, 1491, 1453, 1241, 1088, 801, 751, 691 cm^{-1}. MS (70 eV): *m*/*z* (%) = 400/2/4 (M^+ + 1, 100), 364/6 (60). $C_{23}H_{23}Cl_2NO$ (400.35): calcd. C 69.00, H 5.79, N 3.50; found C 68.92, H 5.94, N 3.55.

_N_-Benzyl-_N_-(4-chlorobenzyl)-_N_-[2-chloro-3-(4-chlorophenoxy)propyl]amine 240c

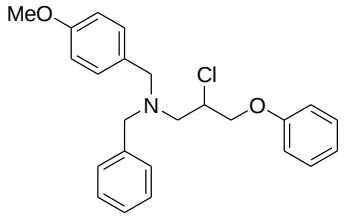


Colourless oil, R_f = 0.80 (hexane/ethyl acetate 1/1), Yield 83%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.80 and 3.00 (2H, 2 x d x d, *J* = 13.6, 7.4, 5.5 Hz, N(*HCH*)CH), 3.51–3.71 (4H, m, 2 x NCH_2Ar), 3.91–3.96 (1H, m, ClCH), 4.02–4.13 (2H, m, CH_2O), 6.65–6.68 and 7.18–7.31 (13H, 2 x m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$) δ 56.7 (CHCl), 57.1 (NCH_2), 58.7 (NCH_2), 59.4 (NCH_2), 70.0 (CH_2O), 115.8, 127.4, 128.4, 128.5, 128.9, 129.3 and 130.2 (13 x CH_{arom}), 126.1, 132.9, 137.3 and 138.5 (4 x $C_{arom,quat}$), 156.8 ($C_{arom}O$). IR (neat): ν_{max} = 2925, 2828, 2359, 1596, 1490, 1453, 1285, 1241,

1090, 821, 801, 740, 698 cm^{-1}. MS (70 eV): *m*/*z* (%) = 434/36/38/40 (M^+ + 1, 100), 398/400 (90). $C_{23}H_{22}Cl_3NO$ (434.79): calcd. C 63.54, H 5.10, N 3.22; found C 63.78, H 5.41, N 3.38.

_N_-Benzyl-_N_-(2-chloro-3-phenoxypropyl)-_N_-(4-methoxybenzyl)amine 240d

Colourless oil, R_f = 0.75 (hexane/ethyl acetate 1/1), Yield 84%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.80 and 3.00 (2H, 2 x d x d, *J* = 13.6, 8.0, 5.5 Hz, N(*HCH*)CH), 3.48–3.75 (4H, m, 2 x NCH_2Ar), 3.77 (3H, s, OCH_3), 3.86–3.95 (1H, m, ClCH), 4.09–4.17 (2H, m, CH_2O), 6.78–6.84, 6.92–6.97 and 7.21–7.32 (14H, 3 x m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.2 (CHCl), 57.2 (NCH_2), 58.7 (NCH_2), 59.3 (NCH_2), 70.0 (CH_2O), 113.7, 114.7, 121.1, 127.2, 128.3, 129.0, 129.4 and 130.1 (14 x CH_{arom}), 130.8 and 138.9 (2 x $C_{arom,quat}$), 158.3 and 158.8 (2 x $C_{arom}O$). IR (neat): ν_{max} = 2932, 2833, 2342, 1599, 1510, 1495, 1454, 1241, 1172, 1035, 813, 752, 741, 691 cm^{-1}. MS (70 eV): *m*/*z* (%) = 360 (100), 396/8 (M^+ + 1, 49). $C_{24}H_{26}ClNO_2$ (395.93): calcd. C 72.81, H 6.62, N 3.54; found C 72.94, H 6.82, N 3.40.

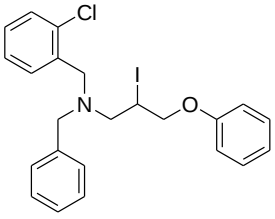


5.11 Synthesis of *N*-(2-iodo-3-aryloxypropyl)amines 241

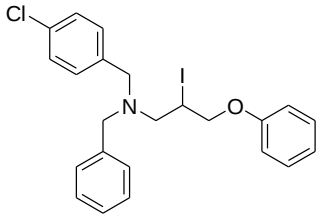
As a representative example the synthesis of *N*-benzyl-*N*-(2-chlorobenzyl)-*N*-(2-iodo-3-phenoxypropyl)amine **241a** is described here. Sodium iodide (3.00 g, 20 equiv) was added to a solution of *N*-benzyl-*N*-(2-chlorobenzyl)-*N*-(2-bromo-3-phenoxypropyl)amine **239a** (0.44 g, 1 mmol) in acetonitrile (20 mL) at room temperature whilst stirring, and the resulting mixture was heated at reflux for 3 h. Afterward, the reaction mixture was poured into water (50 mL) and extracted with Et_2O (3 x 50 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded *N*-benzyl-*N*-(2-chlorobenzyl)-*N*-(2-iodo-3-phenoxypropyl)amine **241a**, which was purified by column chromatography on silica gel (hexane/ethyl acetate 1/1) to obtain an analytically pure sample (0.40 g, 89%).

_N_-Benzyl-_N_-(2-chlorobenzyl)-_N_-(2-iodo-3-phenoxypropyl)amine 241a

Colourless oil, R_f = 0.76 (hexane/ethyl acetate 1/1), Yield 89%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.01 and 3.07 (2H, 2 x d x d, *J* = 14.0, 8.5, 6.9 Hz, N(*HCH*)CH), 3.63 and 3.70 (2H, 2 x d, *J* = 13.2 Hz, N(HCH)Ar), 3.74 and 3.81 (2H, 2 x d, *J* = 14.1 Hz, N(HCH)Ar), 4.05–4.18 (2H, m, CH_2O), 4.22–4.30 (1H, m, ICH), 6.76–6.79, 6.93–6.97, 7.12–7.41 and 7.54–7.57 (14H, 4 x m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.7 (CHI), 56.1 (NCH_2), 59.4 (NCH_2), 59.6 (NCH_2), 71.0 (CH_2O), 114.8, 121.1, 126.7, 127.3, 128.3, 128.4, 129.2, 129.4, 129.5 and 131.2 (14 x CH_{arom}), 134.2, 136.3 and 138.4 (3 x $C_{arom,quat}$), 158.1 ($C_{arom}O$). IR (neat): ν_{max} = 2921, 2849, 1598, 1494, 1453, 1239, 1029, 749, 690 cm^{-1}. MS (70 eV): *m*/*z* (%) = 364/6 (100), 492/4 (M^+ + 1, 5). $C_{23}H_{23}ClINO$ (491.80): calcd. C 56.17, H 4.71, N 2.85; found C 55.96, H 4.83, N 3.01.

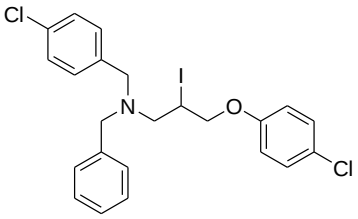


_N_-Benzyl-_N_-(4-chlorobenzyl)-_N_-(2-iodo-3-phenoxypropyl)amine 241b



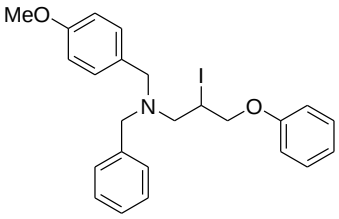
Colourless oil, R_f = 0.77 (hexane/ethyl acetate 1/1), Yield 88%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.93 and 3.00 (2H, 2 x d x d, J = 13.8, 7.7, 7.2 Hz, N(*HCH*)CH), 3.54 and 3.63 (2H, 2 x d, J = 13.8 Hz, N(HCH)Ar), 3.59 (2H, d, J = 7.7 Hz, N(HCH)Ar), 4.08–4.20 (2H, m, CH_2O), 4.22–4.32 (1H, m, ICH), 6.77–6.81, 6.94–6.99 and 7.21–7.42 (14H, 3 x m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.7 (CHI), 58.3 (NCH_2), 59.0 (NCH_2), 59.3 (NCH_2), 71.1 (CH_2O), 114.8, 121.3, 127.5, 128.5, 128.6, 129.1, 129.6 and 130.4 (14 x CH_{arom}), 133.0, 137.4 and 138.5 (3 x $C_{arom,quat}$), 158.1 ($C_{arom}O$). IR (neat): ν_{max} = 2924, 2803, 1598, 1587, 1491, 1453, 1239, 1088, 800, 751, 690 cm^{-1}. MS (70 eV): *m/z* (%) = 364/6 (100), 492/4 (M^+ + 1, 8). $C_{23}H_{23}ClINO$ (491.80): calcd. C 56.17, H 4.71, N 2.85; found C 56.19, H 4.88, N 3.04.

_N_-Benzyl-_N_-(4-chlorobenzyl)-_N_-[3-(4-chlorophenoxy)-2-iodopropyl]amine 241c



Colourless oil, R_f = 0.77 (hexane/ethyl acetate 1/1), Yield 82 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.92 and 2.99 (2H, 2 x d x d, J = 14.0, 8.0, 6.9 Hz, N(*HCH*)CH), 3.52 and 3.64 (2H, 2 x d, J = 13.5 Hz, N(HCH)Ar), 3.58 (2H, s, PhCH_2N), 4.03–4.14 (2H, m, CH_2O), 4.18–4.26 (1H, m, ICH), 6.67–6.70 and 7.18–7.38 (13H, 2 x m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.0 (CHI), 58.3 (NCH_2), 59.0 (NCH_2), 59.1 (NCH_2), 71.1 (CH_2O), 115.9, 127.4, 128.4, 128.5, 129.0, 129.3 and 130.3 (13 x CH_{arom}), 126.1, 132.9, 137.2 and 138.4 (4 x $C_{arom,quat}$), 156.6 ($C_{arom}O$). IR (neat): ν_{max} = 2924, 2804, 2361, 1596, 1489, 1452, 1238, 1090, 821, 800, 737, 698 cm^{-1}. MS (70 eV): *m/z* (%) = no [M]+, 398/400/402 (M^+ – I, 100). $C_{23}H_{22}Cl_2INO$ (526.24): calcd. C 52.49, H 4.21, N 2.66; found C 52.36, H 4.18, N 2.53.

_N_-Benzyl-_N_-(2-iodo-3-phenoxypropyl)-_N_-(4-methoxybenzyl)amine 241d

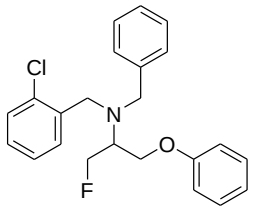


Colourless oil, R_f = 0.77 (hexane/ethyl acetate 1/1), Yield 79%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.95 and 3.01 (2H, 2 x d x d, J = 13.9, 8.5, 6.6 Hz, N(*HCH*)CH), 3.48–3.72 (4H, m, 2 x NCH_2Ar), 3.76 (3H, s, OCH_3), 4.01–4.29 (3H, m, ICH and (HCH)O), 6.78–6.83, 6.92–6.97 and 7.22–7.35 (14H, 3 x m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.1 (CHI), 55.2 (OCH_3), 58.3 (NCH_2), 58.9 (NCH_2), 59.3 (NCH_2), 71.1 (CH_2O), 113.7, 114.7, 121.1, 127.2, 128.3, 129.0, 129.4 and 130.2 (14 x CH_{arom}), 130.7 and 138.8 (2 x $C_{arom,quat}$), 158.2 and 158.8 (2 x $C_{arom}O$). IR (neat): ν_{max} = 2928, 2833, 1598, 1509, 1495, 1240, 1171, 1033, 812, 752, 734, 691 cm^{-1}. MS (70 eV): *m/z* (%) = 360 (100), 488 (M^+ + 1, 10). $C_{24}H_{26}INO_2$ (487.38): calcd. C 59.14, H 5.38, N 2.87; found C 59.30, H 5.62, N 3.00.

5.12 Synthesis of 2-amino-3-aryloxy-1-fluoropropanes 242 and *N*-(2-fluoro-3-aryloxypropyl)amines 243

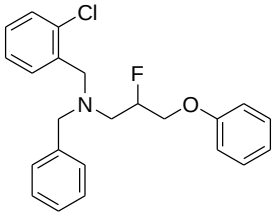
As a representative example the synthesis of 2-[*N*-benzyl-*N*-(2-chlorobenzyl)amino]-1-fluoro-3-phenoxypropane **242a** and *N*-benzyl-*N*-(2-chlorobenzyl)-*N*-(2-fluoro-3-phenoxypropyl)amine **243a** is described here. TBAF (2.61 g, 2 equiv) was added to a solution of *N*-benzyl-*N*-(2-chlorobenzyl)-*N*-(2-bromo-3-phenoxypropyl)amine **239a** (2.22 g, 5 mmol) in acetonitrile (30 mL) at room temperature whilst stirring, and the resulting mixture was heated at reflux for 15 h. Extraction with Et_2O (3 x 50 mL), drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded a mixture of 2-[*N*-benzyl-*N*-(2-chlorobenzyl)amino]-1-fluoro-3-phenoxypropane **242a** and *N*-benzyl-*N*-(2-chlorobenzyl)-*N*-(2-fluoro-3-phenoxypropyl)amine **243a** in a ratio of 5:1. The two isomers were separated by column chromatography (hexane/ethyl acetate 97:3) to furnish compounds **242a** (1.04 g, 54%) and **243a** (0.19 g, 10%) as analytically pure samples.

2-[*N*-Benzyl-*N*-(2-chlorobenzyl)amino]-1-fluoro-3-phenoxypropane 242a



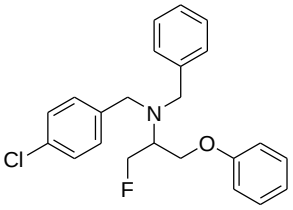
Colourless oil, R_f = 0.17 (hexane/ethyl acetate 97/3), Yield 54%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.31–3.44 (1H, m, NCH), 3.88 and 4.01 (4H, 2 x s, 2 x NCH_2Ar), 4.20 (2H, d, J = 6.1 Hz, (HCH)O), 4.77 (2H, d x d, J = 47.4, 5.5 Hz, (HCH)F), 6.86–6.89, 6.91–6.97, 7.12–7.38 and 7.61–7.63 (14H, 4 x m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.2 (NCH_2Ar), 55.5 (NCH_2Ar), 57.2 (d, J = 18.4 Hz, CHN), 65.3 (d, J = 5.8 Hz, CH_2O), 82.4 (d, J = 170.7 Hz, CHF), 114.4, 121.0, 126.8, 127.1, 128.1, 128.3, 128.7, 129.4, 129.5 and 130.5 (14 x CH_{arom}), 134.0, 137.1 and 139.6 (3 x $C_{arom,quat}$), 158.5 ($C_{arom}O$). ^{19}F NMR (CCl_3F): δ -227.32 (t x d, J = 48.0, 23.7 Hz, CH_2F). IR (neat): ν_{max} = 3062, 3029, 2954, 1599, 1495, 1470, 1241, 1037, 751, 734, 691 cm^{-1}. MS (70 eV): *m*/*z* (%) = 384/6 (M^+ + 1, 100). $C_{23}H_{23}ClFNO$ (383.89): calcd. C 71.96, H 6.04, N 3.65; found C 71.82, H 6.19, N 3.56.

N-Benzyl-*N*-(2-chlorobenzyl)-*N*-(2-fluoro-3-phenoxypropyl)amine 243a



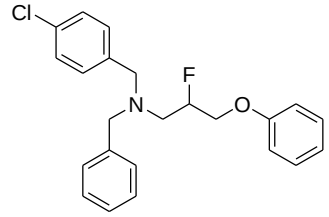
Colourless oil, R_f = 0.10 (hexane/ethyl acetate 97/3), Yield 10%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.84–2.93 (2H, m, N(*HCH*)CHF), 3.71 (2H, s, NCH_2Ar), 3.82 (2H, s, NCH_2Ar), 3.92–4.06 (2H, m, (HCH)O), 4.80–4.87 and 4.96–5.03 (1H, 2 x m, CHF), 6.78–6.81, 6.92–6.97, 7.15–7.40 and 7.52–7.55 (14H, 4 x m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$) δ 54.0 (d, J = 21.9 Hz, NCH_2CHF), 56.5 and 59.6 (2 x NCH_2Ar), 68.3 (d, J = 23.1 Hz, CH_2O), 90.9 (d, J = 174.2 Hz, CHF), 114.6, 121.2, 126.8, 127.4, 128.5, 129.1, 129.5, 129.6, 129.7 and 131.0 (14 x CH_{arom}), 134.3, 136.7 and 138.9 (3 x $C_{arom,quat}$), 158.5 ($C_{arom}O$). ^{19}F NMR (CCl_3F): δ -188.68 to -188.2 (m, CHF). IR (neat): $\underline{\nu}_{max}$ = 2923, 2850, 1598, 1588, 1494, 1443, 1242, 1049, 1037, 750, 690 cm^{-1}. MS (70 eV): *m*/*z* (%) = 384/6 (M^+ + 1, 82).

2-[*N*-Benzyl-*N*-(4-chlorobenzyl)amino]-1-fluoro-3-phenoxypropane 242b



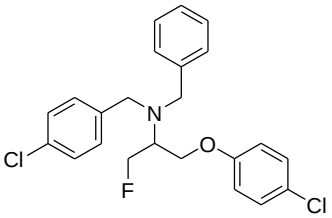
Colourless oil, R_f = 0.35 (hexane/ethyl acetate 96/4), Yield 42%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.28–3.43 (1H, m, NCH), 3.82 (2H, s, NCH_2Ar), 3.83 (2H, s, NCH_2Ar), 4.16 (2H, d, J = 6.1 Hz, (HCH)O), 4.72 (2H, d x d, J = 47.4, 5.0 Hz, (HCH)F), 6.85–6.88, 6.94–6.99 and 7.22–7.38 (14H, 3 x m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$) δ 54.7 (NCH_2Ar), 55.3 (NCH_2Ar), 56.4 (d, J = 18.5 Hz, CHN), 65.4 (d, J = 6.9 Hz, CH_2O), 82.5 (d, J = 172.0 Hz, CHF), 114.4, 121.0, 127.2, 128.4, 128.5, 128.6, 129.5 and 130.0, (14 x CH_{arom}), 132.7, 138.4 and 139.6 (3 x $C_{arom,quat}$), 158.4 ($C_{arom}O$). ^{19}F NMR (CCl_3F): δ -227.30 (t x d, J = 47.3, 22.3 Hz, CH_2F). IR (neat): ν_{max} = 2928, 2833, 1599, 1588, 1491, 1470, 1241, 1088, 1014, 907, 753, 730, 691 cm^{-1}. MS (70 eV): *m*/*z* (%) = 364/6 (100), 384/6 (M^+ + 1, 77). $C_{23}H_{23}ClFNO$ (383.89): calcd. C 71.96, H 6.04, N 3.65; found C 71.89, H 6.18, N 3.67.

***N*-Benzyl-*N*-(4-chlorobenzyl)-*N*-(2-fluoro-3-phenoxypropyl)amine 243b**



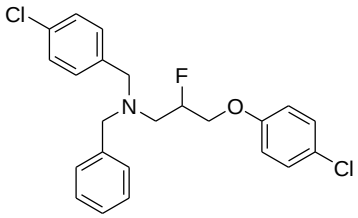
Colourless oil, R_f = 0.28 (hexane/ethyl acetate 96/4), Yield 8%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.75–2.95 (2H, m, N(*HCH*)CHF), 3.65 (2H, s, NCH_2Ar), 3.67 (2H, s, NCH_2Ar), 3.91–4.06 (2H, m, CH_2O), 4.80–4.86 and 4.93–5.02 (1H, 2 x m, CHF), 6.79–6.82, 6.94–6.99 and 7.22–7.38 (14H, 3 x m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 53.7 (d, J = 21.9 Hz, NCH_2CHF), 58.7 (NCH_2Ar), 59.4 (NCH_2Ar), 68.2 (d, J = 23.1 Hz, CH_2O), 90.9 (d, J = 174.3 Hz, CHF), 114.6, 121.3, 127.4, 128.5, 128.6, 129.0, 129.6 and 130.3 (14 x CH_{arom}), 132.9, 137.7 and 138.9 (3 x $C_{arom,quat}$), 158.4 ($C_{arom}O$). ^{19}F NMR (CCl_3F): δ -188.58 to -188.18 (m, CHF). IR (neat): ν_{max} = 2924, 2829, 1598, 1588, 1490, 1453, 1242, 1088, 1014, 801, 752, 691 cm^{-1}. MS (70 eV): *m*/*z* (%) = 364/6 (100), 384/6 (M^+ + 1, 55).

2-[*N*-Benzyl-*N*-(4-chlorobenzyl)amino]-3-(4-chlorophenoxy)-1-fluoropropane 242c



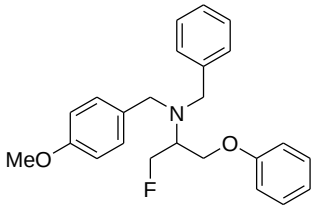
Colourless oil, R_f = 0.33 (hexane/ethyl acetate 96/4), Yield 60%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.25–3.40 (1H, m, NCH), 3.81 (2H, s, NCH_2Ar), 3.82 (2H, s, NCH_2Ar), 4.11 (2H, d, J = 6.0 Hz, (HCH)O), 4.71 (2H, d x d, J = 47.3, 4.9 Hz, (HCH)F), 6.75–6.80 and 7.19–7.37 (13H, 2 x m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$) δ 54.7 (NCH_2Ar), 55.3 (NCH_2Ar), 56.4 (d, J = 18.5 Hz, CHN), 66.0 (d, J = 7.0 Hz, CH_2O), 82.3 (d, J = 171.9 Hz, CHF), 115.7, 127.2, 128.4, 128.5, 128.6, 129.4 and 129.9, (13 x CH_{arom}), 125.9, 132.7, 138.3 and 139.4 (4 x $C_{arom,quat}$), 157.0 ($C_{arom}O$). ^{19}F NMR (CCl_3F): δ -227.31 (t x d, J = 47.3, 22.3 Hz, CH_2F). IR (neat): ν_{max} = 2930, 2831, 1596, 1588, 1490, 1470, 1241, 1090, 1014, 1006, 821, 737, 698 cm^{-1}. MS (70 eV): *m*/*z* (%) = 418/20/22 (M^+ + 1, 100). $C_{23}H_{22}Cl_2FNO$ (418.34): calcd. C 66.04, H 5.30, N 3.35; found C 66.11, H 5.54, N 3.57.

_N_-Benzyl-_N_-(4-chlorobenzyl)-_N_-[3-(4-chlorophenoxy)-2-fluoropropyl]amine 243c



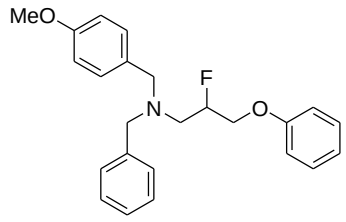
Colourless oil, R_f = 0.27 (hexane/ethyl acetate 96/4), Yield 10%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.74–2.96 (2H, m, N(*HCH*)CHF), 3.64 (2H, s, NCH_2Ar), 3.66 (2H, s, NCH_2Ar), 3.90–4.05 (2H, m, CH_2O), 4.75–4.82 and 4.91–5.03 (1H, 2 x m, CHF), 6.69–6.72 and 7.20–7.37 (13H, 2 x m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$) δ 53.4 (d, J = 21.9 Hz, NCH_2CHF), 58.7 (NCH_2Ar), 59.4 (NCH_2Ar), 68.5 (d, J = 24.2 Hz, CH_2O), 90.7 (d, J = 175.4 Hz, CHF), 115.7, 128.4, 128.5, 128.9, 129.3, 129.6 and 130.2, (13 x CH_{arom}), 127.3, 132.9, 137.5 and 138.7 (4 x $C_{arom,quat}$), 156.9 ($C_{arom}O$). ^{19}F NMR (CCl_3F): δ –188.96 to –188.73 (m, CHF). IR (neat): ν_{max} = 2925, 2828, 1594, 1488, 1452, 1240, 1090, 1014, 907, 822, 732, 698 cm^{-1}. MS (70 eV): *m*/*z* (%) = 418/20/22 (M^+ + 1, 100).

2-[_N_-Benzyl-_N_-(4-methoxybenzyl)amino]-1-fluoro-3-phenoxypropane 242d



Colourless oil, R_f = 0.13 (hexane/ethyl acetate 97/3), Yield 61%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.29–3.44 (1H, m, NCH), 3.78 (5H, s, NCH_2Ar and OCH_3), 3.84 (2H, s, NCH_2Ar), 4.15 (2H, d, J = 6.6 Hz, (HCH)O), 4.71 (2H, d x d, J = 47.6, 5.2 Hz, (HCH)F), 6.83–6.87, 6.92–6.97 and 7.20–7.39 (14H, 3 x m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$) δ 54.7 (NCH_2Ar), 55.1 (NCH_2Ar), 55.2 (OCH_3), 56.2 (d, J = 18.5 Hz, CHN), 65.5 (d, J = 7.0 Hz, CH_2O), 82.6 (d, J = 171.9 Hz, CHF), 113.7, 114.4, 120.9, 127.0, 128.3, 128.6, 129.5 and 129.8 (14 x CH_{arom}), 131.8 and 140.0 (2 x $C_{arom,quat}$), 158.5 and 158.7 (2 x $C_{arom}O$). ^{19}F NMR (CCl_3F): δ –227.27 (t x d, J = 47.4, 23.7 Hz, CH_2F). IR (neat): ν_{max} = 2917, 2849, 1599, 1510, 1495, 1454, 1241, 1171, 1035, 831, 819, 753, 737, 691 cm^{-1}. MS (70 eV): *m*/*z* (%) = 380 (M^+ + 1, 100). $C_{24}H_{26}FNO_2$ (379.47): calcd. C 75.96, H 6.91, N 3.69; found C 75.77, H 7.03, N 3.51.

_N_-Benzyl-_N_-(2-fluoro-3-phenoxypropyl)-_N_-(4-methoxybenzyl)amine 243d

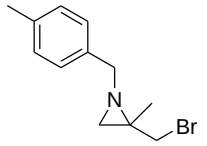


Colourless oil, R_f = 0.09 (hexane/ethyl acetate 97/3), Yield 14 %. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.73–2.94 (2H, m, N(*HCH*)CHF), 3.61 (2H, s, NCH_2Ar), 3.67 (2H, s, NCH_2Ar), 3.78 (3H, s, OCH_3), 3.94–4.04 (2H, m, (HCH)O), 4.77–4.83 and 4.93–5.00 (1H, 2 x m, CHF), 6.78–6.85, 6.93–6.98 and 7.22–7.36 (14H, 3 x m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$) δ 53.6 (d, J = 23.1 Hz, NCH_2CHF), 55.3 (OCH_3), 58.8 (NCH_2Ar), 59.4 (NCH_2Ar), 68.5 (d, J = 23.1 Hz, CH_2O), 91.0 (d, J = 174.2 Hz, CHF), 113.8, 114.6, 121.1, 127.2, 128.4, 129.0, 129.5 and 130.2 (14 x CH_{arom}), 131.1 and 139.3 (2 x $C_{arom,quat}$), 158.5 and 158.8 (2 x $C_{arom}O$). ^{19}F NMR (CCl_3F): δ –188.52 to –188.05 (m, CHF). IR (neat): ν_{max} = 2951, 2834, 1599, 1510, 1495, 1453, 1243, 1172, 1035, 812, 752, 742, 691 cm^{-1}. MS (70 eV): *m*/*z* (%) = 380 (M^+ + 1, 100).

5.13 Synthesis of 2-bromomethyl-2-methylaziridines 260

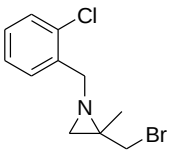
As a representative example, the synthesis of 2-bromomethyl-1-(4-methoxybenzyl)-2-methylaziridine **260d** is described here. *N*-(2,3-Dibromo-2-methylpropylidene)-4-methoxybenzylamine **266d**[131] (3.49 g, 10 mmol) was dissolved in methanol (30 mL), after which $NaBH_4$ (0.76 g, 2 molar equiv) was added in small portions at 0 °C and the mixture was stirred for 36 hours at room temperature. The reaction mixture was poured into water (20 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were washed with H_2O (2 x 15 mL) and brine (20 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded 2-bromomethyl-1-(4-methoxybenzyl)-2-methylaziridine **260d** (2.36 g, 87%), which was purified by filtration through silica gel (hexane/ethyl acetate 7/1) in order to obtain an analytically pure sample.

2-Bromomethyl-1-(4-methylbenzyl)-2-methylaziridine 260b



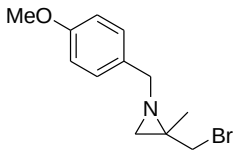
Yellow oil, R_f = 0.16 (hexane/ethyl acetate 9/1), Yield 82%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43 (3H, s, CCH_3), 1.50 (1H, s, (*H*CH)CN), 1.98 (1H, s, (HC*H*)CN), 2.33 (3H, s, CH_3Ar), 3.28 and 3.36 (2H, 2 x d, *J* = 9.9 Hz, (HCH)Br), 3.50 and 3.71 (2H, 2 x d, *J* = 13.7 Hz, N(HCH)Ar), 7.13-7.15 and 7.24-7.26 (4H, 2 x m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.6 (CCH_3), 21.1 (CH_3Ar), 40.2 (CCH_3), 41.7 (CH_2CN), 44.1 (CH_2Br), 57.1 (NCH_2Ar), 127.7 and 129.1 (4 x CH_{arom}), 136.5 (2 x $C_{arom,quat}$). IR (neat): ν_{max} = 3024, 2962, 2922, 2851, 1671, 1515, 1451, 1384, 1348, 1216, 1167, 1046, 798, 647 cm^{-1}. MS *m/z* (%) 254/6 (M^+ + 1, 100).

2-Bromomethyl-1-(2-chlorobenzyl)-2-methylaziridine 260c



Yellow oil, R_f = 0.24 (hexane/ethyl acetate 9/1), Yield 85%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44 (3H, s, CCH_3), 1.58 (1H, s, (*H*CH)CN), 2.07 (1H, s, (HC*H*)CN), 3.35 and 3.40 (2H, 2 x d, *J* = 10.2 Hz, (HCH)Br), 3.63 and 3.85 (2H, 2 x d, *J* = 15.7 Hz, N(HCH)Ar), 7.20-7.36 and 7.66-7.69 (4H, 2 x m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.6 (CCH_3), 40.2 (CCH_3), 42.0 (CH_2CN), 43.9 (CH_2Br), 54.3 (NCH_2Ar), 126.9, 128.0, 129.0 and 129.1 (4 x CH_{arom}), 132.8 (NCH_2C), 137.3 (*C*Cl). IR (neat) ν_{max} = 3035, 2964, 1470, 1443, 1386, 1348, 1218, 1171, 1037, 748, 644 cm^{-1}. MS *m/z* (%) 274/6/8 (M^+ + 1, 100).

2-Bromomethyl-1-(4-methoxybenzyl)-2-methylaziridine 260d

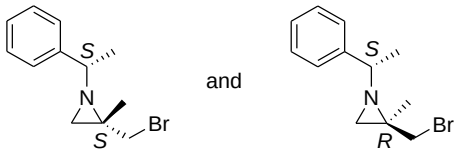


Yellow oil, R_f = 0.10 (hexane/ethyl acetate 7/1), Yield 87%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43 (3H, s, CCH_3), 1.50 (1H, s, (*H*CH)CN), 1.97 (1H, s, (HC*H*)CN), 3.29 and 3.34 (2H, 2 x d, *J* = 10.2 Hz, (HCH)Br), 3.47 and 3.69 (2H, 2 x d, *J* = 13.8 Hz, N(HCH)Ar), 3.80 (3H, s, OCH_3), 6.86-6.89 and 7.27-7.29 (4H, 2 x m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.6 (CCH_3), 40.2 (CCH_3), 41.7 (CH_2CN), 44.2 (CH_2Br), 55.3 (OCH_3), 56.8 (NCH_2Ar), 113.8 and 129.0 (4 x CH_{arom}), 131.7 ($C_{arom,quat}$), 158.6 (C_{arom}O); IR (neat) ν_{max} = 3030, 2959, 2933, 2834, 1612, 1511, 1463, 1244, 1172, 1034, 819, 644 cm^{-1}. MS *m/z* (%) 270/2 (M^+ + 1, 100).

5.14 Synthesis of optically active 2-bromomethyl-2-methylaziridines 270 and 271

N-(2,3-Dibromo-2-methylpropylidene)-1(*S*)-phenylethylamine **269** (3.33 g, 10 mmol) was dissolved in methanol (30 mL), after which $NaBH_4$ (0.76 g, 2 molar equiv) was added in small portions at 0 °C and the mixture was stirred for 36 hours at room temperature. The reaction mixture was poured into water (20 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were washed with H_2O (2 x 15 mL) and brine (20 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded a mixture of 2(*R*)-2-bromomethyl-1-[1(*S*)-phenylethyl]-2-methylaziridine and 2(*S*)-2-bromomethyl-1-[1(*S*)-phenylethyl]-2-methylaziridine **270** and **271** (2.42 g, 95%), which were separated by silica gel column chromatography (petroleum ether/ethyl acetate 9:1) in order to obtain analytically pure samples.

2(*R*)-2-Bromomethyl-1-[1(*S*)-phenylethyl]-2-methylaziridine 270 and 2(*S*)-2-bromomethyl-1-[1(*S*)-phenylethyl]-2-methylaziridine 271



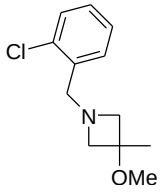
Light yellow oil, R_f = 0.28 (petroleum ether/ethyl acetate 9/1), Yield 45%. $[\alpha]_D^{28}$ = -48.4 (c = 0.05, $CDCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) 1.38 (1H, s, (*H*CH)CN), 1.43 (3H, d, *J* = 6.6 Hz, CHC*H*$_3$), 1.51 (3H, s, CH_3Ar), 1.79 (1H, s, (HC*H*)CN), 3.10 (1H, q, *J* = 6.6 Hz, C*H*CH_3), 3.25 and 3.46 (2H, 2 x d, *J* = 9.9 Hz, (HCH)Br), 7.25-7.40 (5H, m, CH_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.4 (C*C*H$_3$), 24.6 (CH*C*H$_3$), 40.6 (*C*H_2CN), 41.1 (*C*CH_3), 44.9 (CH_2Br), 61.6 (NCH_2Ar), 127.0 and 128.3 (5 x CH_{arom}), 145.0 ($C_{arom,quat}$). IR (neat) ν_{max} = 3027, 2969, 2927, 2866, 1449, 1348, 1222, 1172, 755, 699, 646 cm^{-1}. MS *m/z* (%) 254/6 (M^+ + 1, 100). Anal. Calcd for $C_{12}H_{16}BrN$: C, 56.71; H, 6.35; N, 5.51. Found: C, 56.35; H, 6.63; N, 5.44.

Light yellow oil, R_f = 0.15 (petroleum ether/ethyl acetate 9/1), Yield 42%. $[\alpha]_D^{28}$ = -44.2 (c = 0.06, $CDCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) 1.21 (3H, s, CCH_3), 1.40 (3H, d, *J* = 6.6 Hz, CHC*H*$_3$), 1.48 (1H, s, (*H*CH)CN), 2.00 (1H, s, (HC*H*)CN), 3.16 (1H, q, *J* = 6.6 Hz, C*H*CH_3), 3.22 and 3.34 (2H, 2 x d, *J* = 9.9 Hz, CH_2Br), 7.23-7.39 (5H, m, CH_{arom}); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.6 (C*C*H$_3$), 24.7 (CH*C*H$_3$), 40.3 (*C*H_2CN), 41.0 (*C*CH_3), 43.6 (CH_2Br), 62.8 (NCH_2Ar), 126.5, 126.8 and 128.3 (5 x CH_{arom}), 145.4 ($C_{arom,quat}$). IR (neat) ν_{max} = 3028, 2967, 2926, 2866, 1450, 1349, 1217, 1173, 757, 699, 646 cm^{-1}. MS *m/z* (%) 254/6 (M^+ + 1, 100). Anal. Calcd for $C_{12}H_{16}BrN$: C, 56.71; H, 6.35; N, 5.51. Found: C, 56.62; H, 6.55; N, 5.46.

5.15 Synthesis of 3-methoxy-3-methylazetidines 258 from 2-bromomethyl-2-methylaziridines

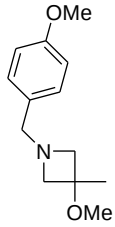
As a representative example, the synthesis of 1-(2-chlorobenzyl)-3-methoxy-3-methylazetidine **258c** is described here. 2-Bromomethyl-1-(2-chlorobenzyl)-2-methylaziridine **260c** (2.76 g, 10 mmol) was dissolved in methanol (30 mL), after which $NaBH_4$ (1.13 g, 3 molar equiv) was added in small portions at 0 °C and the mixture was heated for 48 hours under reflux. The reaction mixture was poured into water (20 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were washed with H_2O (2 x 15 mL) and brine (20 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded 1-(2-chlorobenzyl)-3-methoxy-3-methylazetidine **258c** (2.01 g, 89%), which was purified by filtration through silica gel (ether/hexane 10:1) in order to obtain an analytically pure sample.

1-(2-Chlorobenzyl)-3-methoxy-3-methylazetidine 258c



Yellow oil, R_f = 0.15 (ether/hexane 10/1); Yield 89%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.51 (3H, s, CCH_3), 3.16 (2H, d, J = 8.3 Hz, 2 x (HCH)C_{quat}), 3.31 (2H, d, J = 8.3 Hz, 2 x (HCH)C_{quat}), 3.21 (3H, s, $C(CH_3)OCH_3$), 3.79 (2H, s, NCH_2Ar), 7.14-7.42 (4H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 21.8 (CCH_3), 50.6 ($C(CH_3)OCH_3$), 60.2 (NCH_2Ar), 65.0 (CH_2NCH_2), 73.0 ($C(CH_3)OCH_3$), 126.8, 127.8, 129.3 and 129.4 (4 x CH_{arom}), 133.5 and 136.3 (2 x $C_{arom,quat}$). IR (neat) ν_{max} = 2968, 2930, 2827, 1469, 1443, 1371, 1359, 1232, 1067, 1050, 1038, 748 cm^{-1}. MS *m/z* (%) 226/8 (M^+ + 1, 100).

1-(4-Methoxybenzyl)-3-methoxy-3-methylazetidine 258d



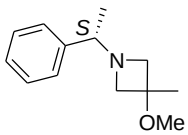
Yellow oil, R_f = 0.17 (ether/hexane 10/1), Yield 87%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.47 (3H, s, CCH_3), 3.04 (2H, d, J = 7.7 Hz, 2 x (HCH)C_{quat}), 3.21 (2H, d, J = 7.7 Hz, 2 x (HCH)C_{quat}), 3.18 (3H, s, $C(CH_3)OCH_3$), 3.60 (2H, s, NCH_2Ar), 3.79 (3H, s, OCH_3Ar), 6.83-6.86 and 7.19-7.22 (4H, 2 x m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.6 (CCH_3), 50.4 ($C(CH_3)OCH_3$), 55.2 (OCH_3Ar), 63.1 (NCH_2Ar), 64.5 ($CH_2C_{quat}CH_2$), 72.8 ($C(CH_3)OCH_3$), 113.7 and 129.6 (4 x CH_{arom}), 130.4 ($C_{arom,quat}$), 158.7 ($C_{arom}O$). IR (neat) ν_{max} = 2933, 2833, 1611, 1511, 1463, 1241, 1173, 1065, 1034, 820 cm^{-1}. MS *m/z* (%) 222 (M^+ + 1, 100).

5.16 Synthesis of 3-methoxy-3-methyl-1-[1(*S*)-phenylethyl]azetidine 272

The mixture of 2(*R*)-2-bromomethyl-1-[1(*S*)-phenylethyl]-2-methylaziridine and 2(*S*)-2-bromomethyl-1-[1(*S*)-phenylethyl]-2-methylaziridine **270** and **271** (2.55 g, 10 mmol) was dissolved in methanol (30 mL), after which $NaBH_4$ (1.13 g, 3 molar equiv) was added in small portions at 0 °C and the mixture was heated for 36 hours under reflux. Afterward, the reaction mixture was poured into water (20 mL)

and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were washed with H_2O (2 x 15 mL) and brine (20 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded 3-methoxy-3-methyl-1-[1(*S*)-phenylethyl]azetidine **272** (1.97 g, 96%), which was purified by filtration through silica gel (ether/hexane 10:1) in order to obtain an analytically pure sample.

3-Methoxy-3-methyl-1-[1(*S*)-phenylethyl]azetidine 272

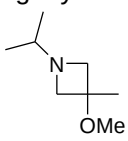


Light yellow oil, R_f = 0.23 (ether/hexane 10:1), Yield 96%. $[\alpha]_D^{28}$ = -51.6 (c = 0.05, $CDCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22 (3H, d, *J* = 6.6 Hz, C*H*CH_3), 1.46 (3H, s, CCH_3), 2.93 and 2.99 (2H, 2 x d, *J* = 7.5 Hz, CH_2N), 3.05 and 3.27 (2H, 2 x d, *J* = 7.4 Hz, CH_2N), 3.18 (3H, s, OCH_3), 3.33 (1H, q, *J* = 6.6 Hz, C*H*CH_3), 7.20-7.33 (5H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 21.6 ($CHCH_3$), 21.8 (CCH_3), 50.5 (OCH_3), 63.7 and 63.8 (CH_2NCH_2), 68.9 ($CH(CH_3)Ph$), 71.9 ($C(CH_3)OCH_3$), 127.1, 127.3 and 128.4 (5 x CH_{arom}), 143.8 ($C_{arom,quat}$). IR (neat) ν_{max} = 2966, 2929, 2825, 1451, 1370, 1235, 1067, 762, 700 cm^{-1}. MS *m/z* (%) 206 (M^+ + 1, 100). Anal. Calcd for $C_{13}H_{19}NO$: C, 76.06; H, 9.33; N, 6.82. Found: C, 76.15; H, 9.60; N, 6.69.

5.17 Synthesis of 3-methoxy-3-methylazetidines 258 starting from imines 266

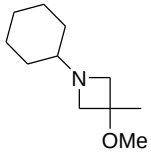
As a representative example, the synthesis of *N*-cyclohexyl-3-methoxy-3-methylazetidine **258f** is described here. *N*-Cyclohexyl-(2,3-dibromo-2-methyl-propylidene)amine **266f**[131] (3.08 g, 10 mmol) was dissolved in methanol (30 mL), after which $NaBH_4$ (0.95 g, 2.5 molar equiv) was added in small portions at 0 °C and the mixture was heated for 24 hours under reflux. The reaction mixture was poured into water (20 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were washed with H_2O (2 x 15 mL) and brine (20 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded *N*-cyclohexyl-3-methoxy-3-methylazetidine **258f** (1.67 g, 91%).

***N*-Isopropyl-3-methoxy-3-methylazetidine 258e**



Light yellow oil, Yield 89%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (6H, d, *J* = 6.0 Hz, $(CH_3)_2CH$), 1.42 (3H, s, CCH_3), 2.28 (1H, quintet, *J* = 6.0 Hz, $CH(CH_3)_2$), 2.95 (2H, d, *J* = 8.0 Hz, 2 x (*H*CH)C_{quat}), 3.15 (2H, d, *J* = 8.0 Hz, 2 x (HC*H*)C_{quat}), 3.14 (3H, s, OCH_3). ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 19.8 ($(CH_3)_2CH$), 21.7 (CCH_3), 50.4 (OCH_3), 59.0 ($(CH_3)_2CH$), 63.5 (CH_2NCH_2), 71.5 (CCH_3). IR (neat) ν_{max} = 2972, 2930, 2824, 1453, 1368, 1337, 1240, 1070 cm^{-1}. MS *m/z* (%) 144 (M^+ + 1, 100).

***N*-Cyclohexyl-3-methoxy-3-methylazetidine 258f**



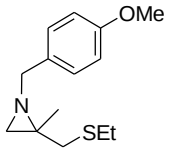
Light yellow oil, Yield 91%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.46 (3H, s, CCH_3), 0.88-1.03, 1.10-1.25, 1.59-1.62 and 1.71-1.82 and (10H, 2 x m, $(CH_2)_5$), 1.92-2.01 (1H, m, CH), 3.01 (2H, d, *J* = 8.0 Hz, 2 x (*H*CH)C_{quat}), 3.19 (2H, d, *J* = 8.0 Hz, 2 x (HC*H*)C_{quat}), 3.19

(3H, s, OCH_3). ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 21.7 (CCH_3), 24.6 (2 x CH_2), 25.2 (CH_2), 29.9 (2 x CH_2), 50.4 (OCH_3), 63.0 (*2 x* CH_2N), 67.4 (CH), 72.3 (CCH_3). IR (neat) ν_{max} = 2925, 2853, 2824, 1448, 1370, 1248, 1227, 1069 cm^{-1}. MS *m/z* (%) 184 (M^+ + 1, 100).

5.18 Synthesis of 2-ethylthiomethyl-2-methylaziridine 267

To a solution of NaOMe in methanol (2M, 2.22 mL, 4,4 mmol) ethanethiol (0.23 g, 1 equiv) was added and the resulting mixture was stirred for 40 min at room temperature. After this time 1 equiv of 2-bromomethyl-1-(4-methoxybenzyl)-2-methylaziridine **260d** (1.00 g, 0.0037 mol) was added and the mixture was heated for 3.5 hours under reflux. The reaction mixture was poured into water (20 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were washed with H_2O (2 x 15 mL) and brine (20 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded 2-ethylthiomethyl-2-methylaziridine **267** (0.99 g, 89%).

2-Ethylthiomethyl-2-methylaziridine 267

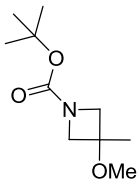


Yellow oil, Yield 89%. ^1H NMR (300 MHz, $CDCl_3$) δ 1.22 (3H, t, *J* = 7.4 Hz, CH_3CH_2), 1.31 (1H, s, (HCH)$C_{quat}N$), 1.40 (3H, s, CCH_3), 1.87 (1H, s, (HCH)$C_{quat}N$), 2.51-2.66 (4H, m, 2 x CH_2S), 3.46 and 3.67 (2H, 2 x d, *J* = 13.2 Hz, N(HCH)Ar), 3.80 (3H, s, OCH_3), 6.85-6.89 and 7.26-7.29 (4H, 2 x m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 14.3 (CCH_3), 15.0 (CH_3CH_2), 26.5 (SCH_2CH_3), 39.8 (CCH_3), 40.2 ($CH_2C_{quat}N$), 42.9 (CCH_2S), 55.4 (OCH_3), 56.6 (NCH_2Ar), 113.9 and 129.1 (4 x CH_{arom}), 132.3 ($C_{arom,quat}$), 158.6 ($C_{arom}O$). IR (neat) ν_{max} = 2960, 2927, 1612, 1511, 1454, 1244, 1172, 1035, 820 cm^{-1}. MS *m/z* (%) 252 (M^+ + 1, 100).

5.19 Synthesis of *N*-tert-butoxycarbonyl-3-methoxy-3-methylazetidine 273

3-Methoxy-3-methyl-1-[1(*S*)-phenylethyl]azetidine **272** (0.10 g, 0.49 mmol) was dissolved in EtOAc (15 mL), after which 20 wt% $Pd(OH)_2$ (25 mol%, 0.09 g) and Boc_2O (0.11 g, 1 equiv) were added in small portions at 0 °C and the mixture was subjected to hydrogenation for 72 hours (4 bar, H_2) at room temperature. The reaction mixture was first filtered through a small sintered funnel and thoroughly washed with ethyl acetate (30 mL). Subsequently, this filtrate was poured into water (20 mL) and extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with H_2O (2 x 15 mL) and brine (20 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded *N*-butoxycarbonyl-3-methoxy-3-methylazetidine **273** (0.09 g, 95%), which was described based on the crude mixture.

***N-tert*-Butoxycarbonyl-3-methoxy-3-methylazetidine 273**

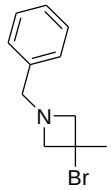


Light yellow oil, Yield 95%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44 (9H, s, $(CH_3)_3C$), 1.53 (3H, s, CCH_3), 3.23 (3H, s, OCH_3), 3.66 (2H, d, J = 9.1 Hz, 2 x (*H*CH)C_{quat}), 3.91 (2H, d, J = 9.1 Hz, 2 x (HC*H*)C_{quat}); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.4 (C(*C*$H_3)_3$), 27.4 (C*C*H_3), 50.8 (OCH_3), 60.5 (*C*H_2N*C*H_2), 72.6 (*C*$(CH_3)OCH_3$). IR (neat) ν_{CO} = 1703; ν_{max} = 2977, 1809, 1395, 1370, 1114, 1065, cm^{-1}. MS *m/z* (%) 202 (M^+ + 1, 100).

5.20 Synthesis of 3-bromo-3-methylazetidines 261

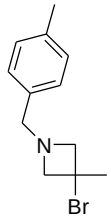
As a representative example, the synthesis of 1-benzyl-3-bromo-3-methylazetidine **261a** is described here. 1-Benzyl-2-bromomethyl-2-methylaziridine **260a** (1.20 g, 5 mmol) was dissolved in acetonitrile (30 mL), and the mixture was heated at reflux temperature for 15 h. The reaction mixture was cooled to room temperature, poured into water (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with H_2O (2 × 15 mL) and brine (20 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent in vacuo afforded 1-benzyl-3-bromo-3-methylazetidine **261a** (0.86 g, 72%), which was purified by silica gel column chromatography (petroleum ether/ethyl acetate 7/1) to obtain an analytically pure sample.

1-Benzyl-3-bromo-3-methylazetidine 261a



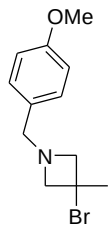
Yellow oil, R_f = 0.30 (petroleum ether/ethyl acetate 7/1), Yield 72%, isolated yield 62% (after purification). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.00 (3H, s, CCH_3), 3.52 (2H, d, J = 9.1 Hz, 2 x (*H*CH)C_{quat}), 3.69 (2H, d, J = 9.1 Hz, 2 x (HC*H*)C_{quat}), 3.71 (2H, s, NCH_2Ar), 7.21−7.33 (5H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 31.6 (C*C*H_3), 51.9 (C(CH_3)Br), 63.2 (NCH_2Ar), 70.9 (*C*H_2C_{quat}*C*H_2), 127.3 (2 × CH_{arom}), 128.5 (3 × CH_{arom}), 137.8 ($C_{arom,quat}$). IR (neat) vmax = 2924, 2844, 1495, 1453, 1362, 1245, 1208, 1181, 746, 696 cm^{-1}. MS m/z (%) 240/2 (M^+ + 1, 100).

3-Bromo-1-(4-methylbenzyl)-3-methylazetidine 261b



Light-yellow oil, R_f = 0.41 (petroleum ether/ethyl acetate 7/1), Yield 78%. ^{1}H NMR (300 MHz, ref = $CDCl_3$) δ 1.99 (3H, s, CCH_3), 2.33 (3H, s, CH_3Ar), 3.51 (2H, d, J = 8.2 Hz, 2 x (*H*CH)C_{quat}), 3.69 (2H, d, J = 8.2 Hz, 2 x (HC*H*)C_{quat}), 3.67 (2H, s, NCH_2Ar), 7.10-7.18 (4H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 21.2 (CH_3Ar), 31.6 (C*C*H_3), 52.0 (C(CH_3)Br), 63.0 (NCH_2Ar), 70.8 (*C*H_2C_{quat}*C*H_2), 128.5 and 129.2 (4 x CH_{arom}), 134.6 and 136.9 (2 x $C_{arom,quat}$). IR (neat) ν_{max} = 2922, 2848, 2807, 1514, 1440, 1360, 1244, 1206, 1178, 806, 734 cm^{-1}. MS *m/z* (%) 254/6 (M^+ + 1, 100). Anal. Calcd for $C_{12}H_{16}BrN$: C, 56.71; H, 6.35; N, 5.51. Found: C, 56.55; H, 6.54; N, 5.37.

3-Bromo-1-(4-methoxybenzyl)-3-methylazetidine 261c



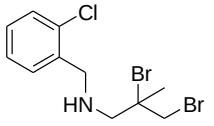
Yellow oil, R_f = 0.22 (petroleum ether/ethyl acetate 7/1), Yield 70%, isolated yield 59% (after purification). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.99 (3H, s, CCH_3), 3.49 (2H, d, J = 9.1 Hz, 2 x (*H*CH)C_{quat}), 3.67 (2H, d, J = 9.1 Hz, 2 x (HC*H*)C_{quat}), 3.64 (2H, s, NCH_2Ar), 3.79 (3H, s, OCH_3), 6.83−6.86 and 7.18−7.20 (4H, 2 × m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 31.6 (C*C*H_3), 52.0 (*C*(CH_3)Br), 55.3 (OCH_3), 62.6 (NCH_2Ar) 70.7 ($CH_2C_{quat}CH_2$), 113.8 (2 × CH_{arom}), 129.7 (2 × CH_{arom}), 129.1 ($C_{arom,quat}$), 158.9 (C_{arom}O). IR (neat) ν_{max} = 2930, 2835, 1612, 1511, 1243, 1171, 1034, 819, 738, 696 cm^{-1}. MS m/z (%) 240/2 (M^+ + 1, 100).

5.21 Synthesis of *N*-(2-chlorobenzyl)-*N*-(2,3-dibromo-2-methylpropyl)amine 276

2-Bromomethyl-1-(2-chlorobenzyl)-2-methylaziridine **260c** (2.75 g, 10 mmol) was dissolved in CH_2Cl_2 (30 mL), after which HBr (33% in AcOH) (3.24 g, 1.2 equiv) was added and the mixture was heated for 24 hours under reflux. The reaction mixture was first neutralized with saturated aqueous solution of $NaHCO_3$ (5 mL) and then poured into water (20 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were washed with H_2O (2 x 15 mL) and brine (20 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded *N*-(2-chlorobenzyl)-*N*-(2,3-dibromo-2-methylpropyl)amine **276** (3.47 g, 98%).

***N*-(2-Chlorobenzyl)-*N*-(2,3-dibromo-2-methylpropyl)amine 276**

Dark-yellow oil, Yield 98%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.70 (1H, br s, NH), 1.85 (3H, s, CCH_3), 2.91 and 2.96 (2H, 2 x d, J = 13.5 Hz, N(HCH*)*CBr), 3.79 (1H, d, J = 9.6 Hz, (*H*CH)Br), 4.00 (2H, s, NCH_2Ar), 4.23 (1H, d, J = 9.6 Hz, (HC*H)*Br), 7.18–7.48 (4H, m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.4 (CH_3), 40.4 (CH_2Br), 51.2 (NCH_2Ar), 57.4 (CH_2CBr), 68.3 (CBr), 126.8, 128.4, 129.5 and 130.0 (4 x CH_{arom}), 133.7 and 137.4 ($C_{arom,quat}$). IR (neat): ν_{max} = 2839, 1443, 1050, 749 cm^{-1}. MS (70 eV): *m*/*z* (%) = 354/356/358 (100) (M^+ + 1, 100).

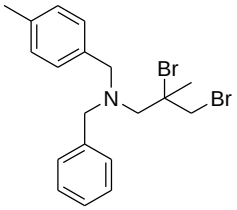


5.22 Synthesis of *N*,*N*-dibenzyl-*N*-(2,3-dibromo-2-methylpropyl)amines 275

As a representative example the synthesis of *N*-benzyl-*N*-(2,3-dibromo-2-methylpropyl)-*N*-(4-methylbenzyl)amine **275a** is described here. Benzyl bromide (1.71 g, 1 equiv) was added to a solution of 2-bromomethyl-2-methyl-1-(4-methylbenzyl)aziridine **260b** (2.54 g, 10 mmol) in acetonitrile (30 mL) at room temperature whilst stirring, and the resulting mixture was heated at reflux for 1 day. Afterward, the reaction mixture was poured into water (30 mL) and extracted with Et_2O (3 x 30 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded *N*-benzyl-*N*-(2,3-

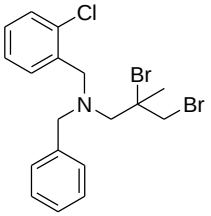
dibromo-2-methylpropyl)-*N*-(4-methylbenzyl)amine **275a**, which was purified by column chromatography on silica gel (hexane/ethyl acetate 4/1) to obtain an analytically pure sample (3.78 g, 89%).

_N_-Benzyl-(2,3-dibromo-2-methylpropyl)-_N_-(4-methylbenzyl)amine 275a



Yellow oil, R_f = 0.78 (hexane/ethyl acetate 4/1), Yield 89%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.74 (3H, s, CH_3CBr), 2.36 (3H, s, CH_3Ar), 3.06-3.18 (2H, m, NCH_2CBr), 3.78 and 3.98 (2H, 2 x d, J = 10.5 Hz, (HCH)Br), 3.82 (2H, s, NCH_2Ar), 3.85 (2H, s, NCH_2Ar), 7.14–7.35 (9H, m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.1 (CH_3Ar), 28.6 (CH_3CBr), 41.8 (CH_2Br), 58.2 ($C_{arom}CH_2N$), 58.5 ($C_{arom}CH_2N$), 62.2 (NCH_2CBr), 68.8 (CBr), 127.1, 128.3, 129.0 and 129.2 (9 x CH_{arom}), 135.4, 136.7 and 138.8 (3 x $C_{arom,quat}$). IR (neat): ν_{max} = 2924, 1737, 1452, 1373, 1240, 1041, 801, 737, 696 cm^{-1}. MS (70 eV): *m*/*z* (%) = 344/6 (100), 424/6/8 (10) (M^+ + 1, 100).

_N_-Benzyl-(2-chlorobenzyl)-_N_-(2,3-dibromo-2-methylpropyl)amine 275b

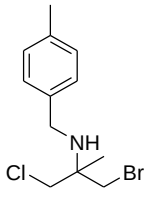


Yellow oil. R_f = 0.62 (hexane/ethyl acetate 4/1), Yield 86%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.70 (3H, s, CH_3CBr), 3.15 and 3.22 (2H, 2 x d, J = 15.1 Hz, N(HCH)CBr), 3.75 and 3.90 (2H, 2 x d, J = 10.5 Hz, (HCH)Br), 3.87 and 3.93 (2H, 2 x d, J = 14.3 Hz, C_{arom}(HCH)N), 3.98 and 4.03 (2H, 2 x d, J = 15.4 Hz, C_{arom}(HCH)N), 7.16–7.35 and 7.59-7.62 (9H, 2 x m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.4 (CH_3CBr), 41.7 (CH_2Br), 56.3 (NCH_2Ar), 59.5 (NCH_2Ar), 62.8 (NCH_2CBr), 68.5 (CBr), 126.7, 127.3, 128.2, 128.3, 129.4, 129.5 and 130.7 (9 x CH_{arom}), 134.0, 136.6 and 138.2 (3 x $C_{arom,quat}$). IR (neat): ν_{max} = 2834, 1443, 1377, 1038, 751, 698 cm^{-1}. MS (70 eV): *m*/*z* (%) = 364/6 (100), 444/6/8 (10) (M^+ + 1, 100).

5.23 Synthesis of *N*-(1-bromo-3-chloro-2-methylprop-2-yl)amines 279

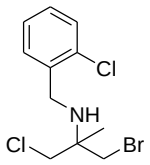
As representative example the synthesis of *N*-(1-bromo-3-chloro-2-methylprop-2-yl)-*N*-(2-chlorobenzyl)amine **279b** was described here. 2-Bromomethyl-1-(2-chlorobenzyl)-2-methylaziridine **260c** (2.75 g, 10 mmol) was dissolved in CH_2Cl_2 (30 mL), after which HCl (3M) (6.7 mL, 2 equiv) was added and the mixture was heated for 6 hours under reflux. The reaction mixture was first neutralized with saturated aqueous solution of $NaHCO_3$ (5 mL) and then poured into water (20 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were washed with H_2O (2 x 15 mL) and brine (20 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded *N*-(1-bromo-3-chloro-2-methylprop-2-yl)-*N*-(2-chlorobenzyl)amine **279b** (2.99 g, 96%), which was considered as analytically pure and described without prior purification.

_N_-(1-Bromo-3-chloro-2-methylprop-2-yl)-_N_-(4-methylbenzyl)amine 279a



Light yellow oil, Yield 80%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (3H, s, CCH_3), 2.33 (3H, s, CH_3Ar), 3.62 (2H, s, CH_2Br), 3.63 (2H, s, CH_2Cl), 3.67 (2H, s, NCH_2Ar), 7.12-7.15 and 7.22-7.26 (4H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 20.5 (CCH_3), 21.2 (CH_3Ar), 46.3 (CH_2N), 48.9 (CH_2Br and CH_2Cl), 54.4 (CCH_3), 127.7, 128.3, 129.2 and 129.3 (4 x CH_{arom}), 132.2 and 137.0 ($C_{arom,quat}$). IR (neat): ν_{max} = 2959, 1443, 1377, 1049, 748 cm^{-1}. MS (70 eV): *m*/*z* (%) = 266/268/270 (100), 310/312/314 (M^+ + 1, 23).

_N_-(1-Bromo-3-chloro-2-methylprop-2-yl)-_N_-(2-chlorobenzyl)amine 279b

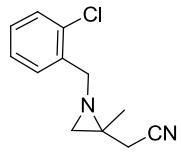


Light yellow oil, Yield 96%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34 (3H, s, CCH_3), 1.82 (1H, br s, NH), 3.63 and 3.68 (4H, 2 x d, *J* = 11.6 Hz, CH_2Br and CH_2Cl), 3.84 (2H, s, CH_2N), 7.19–7.28, 7.35-7.38 and 7.45-7.48 (4H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 20.4 (CCH_3), 43.9 (CH_2N), 49.1 (CH_2Br and CH_2Cl), 57.3 (CCH_3), 127.2, 128.6, 129.7 and 130.2 (4 x CH_{arom}), 133.7 and 137.6 ($C_{arom,quat}$). IR (neat): ν_{max} = 2959, 1443, 1377, 1049, 748 cm^{-1}. MS (70 eV): *m*/*z* (%) = 266/268/270 (100), 310/312/314 (M^+ + 1, 23).

5.24 Synthesis of 1-(2-chlorobenzyl)-2-(cyanomethyl)aziridine 282

N-(1-Bromo-3-chloro-2-methylprop-2-yl)-*N*-(2-chlorobenzyl)amine **279b** (2.75 g, 10 mmol) was dissolved in DMSO (20 mL), after which KCN (1.43 g, 2.2 equiv) was added and the mixture was heated for 5 hours at 60-70 °C. The reaction mixture was poured into water (20 mL) and extracted with Et_2O (3 x 20 ml). The combined organic extracts were washed with H_2O (2 x 15 mL) and brine (20 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded a mixture 1-(2-chlorobenzyl)-2-(cyanomethyl)aziridine **282** and 2-(chloromethyl)-2-methylaziridine **281** (**282**/**281** = 3/1). 2-(1-(2-1-(2-Chlorobenzyl)-2-(cyanomethyl)aziridine **282** was described based on the crude mixture.

1-(2-Chlorobenzyl)-2-(cyanomethyl)aziridine 282



Light-yellow oil, Yield 60%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (1H, s, (*H*CH)CN), 1.44 (3H, s, CCH_3), 2.06 (1H, s, (HC*H*)C_{quat}), 2.51 and 2.60 (2H, 2 x s, (HCH)CN), 3.63 and 3.84 (2H, 2 x d, *J* = 15.4 Hz, NCH_2Ar), 7.18–7.35 and 7.62-7.65 (4H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 14.8 (CCH_3), 29.3 ($C_{quat}CH_2CN$), 36.7 ($CH_2C_{quat}N$), 39.7 (NCH_2C_{quat}), 53.9 (NCH_2Ar), 117.6 (CN), 127.1, 128.2, 129.0 and 129.2 (4 x CH_{arom}), 132.8 and 137.2 (2 x $C_{arom,quat}$). IR (neat): ν_{max} = 2916, 1469, 1443, 1350, 1048, 1038, 751 cm^{-1}. MS (70 eV): *m*/*z* (%) 221/3 (M^+ + 1, 100).

5.25 Synthesis of *N*-(2-chlorobenzyl)-2-chloromethyl-2-methylaziridine 281

N-(1-Bromo-3-chloro-2-methylprop-2-yl)-*N*-(2-chlorobenzyl)amine **279b** (1.56 g, 5 mmol) was dissolved in dry THF (15 mL), after which KOtBu (0.62 g, 1.1 equiv) was added and the mixture was heated for 3 hours under reflux. The reaction mixture was poured into water (20 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were washed with H_2O (2 x 15 mL) and brine (20 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded *N*-(2-chlorobenzyl)-2-chloromethyl-2-methylaziridine **281** (1.06 g, 92%).

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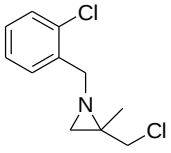
_N_-(2-Chlorobenzyl)-2-chloromethyl-2-methylaziridine 281

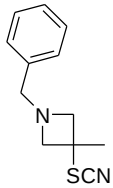


Yellow oil, Yield 92%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34 (3H, s, CCH_3), 1.41 (1H, s, (*H*CH)CN), 1.97 (1H, s, (HC*H*)CN), 3.37 and 3.44 (2H, 2 x d, *J* = 11.0 Hz, (HCH)Cl), 3.58 and 3.74 (2H, 2 x d, *J* = 15.7 Hz, N(HCH)Ar), 7.09-7.27 and 7.59-7.62 (4H, 2 x m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.9 (C*C*H_3), 40.5 (*C*CH_3), 40.7 (*C*H_2CN), 54.1 and 54.3 (CH2Cl and NCH_2Ar), 127.0, 128.0, 129.07 and 129.12 (4 x CH_{arom}), 132.8 and 137.5 (2 x $C_{arom,quat}$). IR (neat) ν_{max} = 2965, 1469, 1443, 1349, 1257, 1048, 1038, 749, 698 cm^{-1}. MS *m/z* (%) 230/2/4 (M^+ + 1, 100).

5.26 Synthesis of 3-methyl-3-thiocyanatoazetidines 284

As a representative example, the synthesis of 1-(4-methoxybenzyl)-3-methyl-3-thiocyanatoazetidine **284c** is described here. 2-Bromomethyl-1-(4-methoxybenzyl)-2-methylaziridine **260d** (1.35 g, 5 mmol) was dissolved in acetonitrile (30 mL), after which KSCN (0.49 g, 1 equiv) was added and the mixture was heated at reflux temperature for 4 h. The reaction mixture was cooled to room temperature, poured into water (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with H_2O (2 × 15 mL) and brine (20 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded a mixture of 1-(4-methoxybenzyl)-3-methyl-3-thiocyanatoazetidine **284c** and 2-methyl-2-(thiocyanatomethyl)aziridine **285c** (**284c**/**285c** = ratio 67/33), from which 1-(4-methoxybenzyl)-3-methyl-3-thiocyanatoazetidine **284c** (0.94 g, 65%) was isolated in pure form by preparative thin layer chromatography on silica gel (hexane/ethyl acetate/triethylamine 1/1/0.01) to obtain an analytically pure sample.

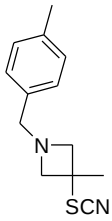
1-Benzyl-3-methyl-3-thiocyanatoazetidine 284a



Yellow oil, R_f = 0.20 (hexane/ethyl acetate/triethylamine 1/1/0.01), Yield 45%, isolated yield 36% (after purification). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.79 (3H, s, CCH_3), 3.35 (2H, d, *J* = 8.8 Hz, 2 x (*H*CH)C_{quat}), 3.47 (2H, d, *J* = 8.8 Hz, 2 x (HC*H*)C_{quat}), 3.69 (2H, s, NCH_2Ar), 7.24−7.35 (5H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 26.4 (CCH_3), 47.5

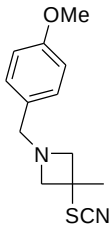
(CCH_3), 62.5 (NCH_2Ar), 66.3 ($CH_2C_{quat}CH_2$), 111.5 (SCN), 127.5, 128.5 and 128.6 (5 × CH_{arom}), 137.2 ($C_{arom,quat}$). IR (neat) ν_{SCN} = 2151 cm^{-1}. MS m/z (%) 219 (M^+ + 1, 100).

3-Methyl-1-(4-methybenzyl)-3-thiocyanatoazetidine 284b



Yellow oil, R_f = 0.22 (hexane/ethyl acetate/triethylamine 1/1/0.01), Yield 55%, isolated yield 47% (after purification). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.78 (3H, s, CCH_3), 2.33 (3H, s, CH_3Ar), 3.33 (2H, d, J = 8.8 Hz, 2 x (HCH)C_{quat}), 3.46 (2H, d, J = 8.8 Hz, 2 x (HCH)C_{quat}), 3.64 (2H, s, NCH_2Ar), 7.11−7.18 (4H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 21.2 (CH_3Ar), 26.4 (CCH_3), 47.5 (CCH_3), 62.3 (NCH_2Ar), 66.2 ($CH_2C_{quat}CH_2$), 111.5 (SCN), 128.5 and 129.2 (4 × CH_{arom}), 134.1 and 137.1 (2 x $C_{arom,quat}$). IR (neat) ν_{SCN} = 2151 cm^{-1}. MS m/z (%) 233 (M^+ +1, 100).

1-(4-Methoxybenzyl)-3-methyl-3-thiocyanatoazetidine 284c



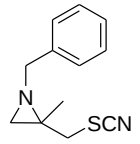
Yellow oil, R_f = 0.18 (hexane/ethyl acetate/triethylamine 1/1/0.01), Yield 65%, isolated yield 52% (after purification). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.78 (3H, s, CCH_3), 3.32 (2H, d, J = 9.4 Hz, 2 x (HCH)C_{quat}), 3.44 (2H, d, J = 9.4 Hz, 2 x (HCH)C_{quat}), 3.62 (2H, s, NCH_2Ar), 3.80 (3H, s, OCH_3), 6.84−6.87 and 7.18−7.20 (4H, 2 × m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 26.4 (CCH_3), 47.5 (CCH_3), 55.4 (OCH_3), 61.9 (NCH_2Ar), 66.1 ($CH_2C_{quat}CH_2$), 111.5 (SCN), 113.9 (2 × CH_{arom}), 129.2 ($C_{arom,quat}$), 129.8 (2 × CH_{arom}), 159.0 ($C_{arom}O$). IR (neat) ν_{SCN} = 2151 cm^{-1}. MS m/z (%) 249 (M^+ + 1, 100). HRMS m/z (ESI) calculated for $C_{13}H_{16}N_2OS$ $[MH]^+$ 249.1062, found 249.1059.

5.27 Synthesis of 2-methyl-2-(thiocyanatomethyl)aziridines 285

As a representative example, the synthesis of 2-methyl-1-(4-methylbenzyl)-2-(thiocyanatomethyl)aziridine **285b** is described here. 2-Bromomethyl-2-methyl-1-(4-methylbenzyl)aziridine **260b** (1.27 g, 5 mmol) was dissolved in DMF (30 mL), after which KSCN (0.49 g, 1 equiv) was added and the mixture was stirred at 60−70 °C for 15 h. The reaction mixture was cooled to room temperature, poured into water (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with H_2O (2 × 15 mL) and brine (20 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded 2-methyl-1-(4-methylbenzyl)-2-(thiocyanatomethyl)aziridine **285b** (0.91 g, 95%), which was purified by silica gel column chromatography (hexane/ethyl acetate/triethylamine 1/1/0.1) to obtain an analytically pure sample. It should be mentioned that aziridines **285a−c** showed to be rather unstable on silica gel column during the purification process.

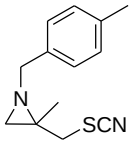
1-Benzyl-2-methyl-2-(thiocyanatomethyl)aziridine 285a

Light-yellow oil, R_f = 0.43 (hexane/ethyl acetate/triethylamine 1/1/0.1), Yield 94%, isolated yield 41% (after purification). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.47 (1H and 3H, s, (*H*CH)CCH_3 and CH_3C), 2.08 (1H, s, (HC*H*)CCH_3), 3.02 (H, d, *J* = 12.9 Hz, (*H*CH)S), 3.14 (H, d, *J* = 12.9 Hz, (HC*H*)S), 3.53 (H, d, *J* = 13.8 Hz, (*H*CH)Ar), 3.78 (H, d, *J* = 13.8 Hz, (HC*H*)Ar), 7.26−7.35 (5H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 14.0 (CCH_3), 38.8 (*C*CH_3), 40.3 (*C*H_2NCH_2C_{arom}), 45.1 (CH_2S), 57.1 (CH_2C_{arom}), 113.1 (SCN), 127.2, 128.0 and 128.6 (5 × CH_{arom}), 139.3 ($C_{arom,quat}$). IR (neat) ν_{SCN} = 2152 cm^{-1}. MS m/z (%) 219 (M^+ + 1, 100). HRMS m/z (ESI) calculated for $C_{12}H_{14}N_2S$ $[MH]^+$ 219.0956, found 219.0952.



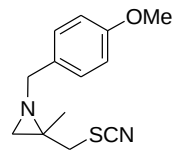
2-Methyl-1-(4-methylbenzyl)-2-(thiocyanatomethyl)aziridine 285b

Light-yellow oil, R_f = 0.44 (hexane/ethyl acetate/triethylamine 1/1/0.1), Yield 95%, isolated yield 64% (after purification). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.46 (1H and 3H, s, (*H*CH)CCH_3 and CH_3C), 2.05 (1H, s, (HC*H*)CCH_3), 2.34 (3H, s, CH_3Ar), 3.02 (H, d, *J* = 12.7 Hz, (*H*CH)S), 3.13 (H, d, *J* = 12.7 Hz, (HC*H*)S), 3.49 (H, d, *J* = 13.2 Hz, (*H*CH)Ar), 3.73 (H, d, *J* = 13.2 Hz, (HC*H*)Ar), 7.13−7.24 (4H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 14.0 (CCH_3), 21.2 (CH_3Ar), 38.8 (*C*CH_3), 40.2 (*C*H_2NCH_2C_{arom}), 45.2 (CH_2S), 56.8 (CH_2C_{arom}), 113.1 (SCN), 127.9 and 129.2 (4 × CH_{arom}), 136.3 and 136.8 (2 x $C_{arom,quat}$). IR (neat) ν_{SCN} = 2151 cm^{-1}. MS m/z (%) 233 (M^+ + 1, 100). HRMS m/z (ESI) calculated for $C_{13}H_{16}N_2S$ $[MH]^+$ 233.1112, found 233.1110.



1-(4-Methoxybenzyl)-2-methyl-2-(thiocyanatomethyl)aziridine 285c

Light-yellow oil, R_f = 0.36 (hexane/ethyl acetate/triethylamine 1/1/0.1), Yield 90%, isolated yield 37% (after purification). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.46 (1H and 3H, s, (*H*CH)CCH_3 and CH_3C), 2.04 (1H, s, (HC*H*)CCH_3), 3.00 (H, d, *J* = 12.9 Hz, (*H*CH)S), 3.12 (H, d, *J* = 12.9 Hz, (HC*H*)S), 3.45 (H, d, *J* = 13.2 Hz, (*H*CH)Ar), 3.71 (H, d, *J* = 13.2 Hz, (HC*H*)Ar), 3.81 (3H, s, OCH_3), 6.86−6.89 and 7.25−7.28 (4H, 2 × m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 14.0 (CCH_3), 38.8 (*C*CH_3), 40.2 (*C*H_2NCH_2C_{arom}), 45.2 (CH_2S), 55.4 (OCH_3), 56.5 (CH_2C_{arom}), 113.1 (SCN), 114.0 and 129.2 (4 × CH_{arom}), 131.4 ($C_{arom,quat}$), 158.8 (C_{arom}O). IR (neat) ν_{SCN} = 2153 cm^{-1}. MS m/z (%) 249 (M^+ + 1, 100). HRMS m/z (ESI) calculated for $C_{13}H_{16}N_2OS$ $[MH]^+$ 249,1062, found 249.1058.

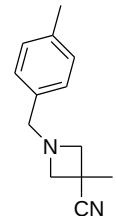


5.28 Synthesis of azetidine-3-carbonitriles 286

As a representative example, the synthesis of 1-(4-methoxybenzyl)-3-methylazetidine-3-carbonitrile **286b** is described here. 2-Bromomethyl-1-(4-methoxybenzyl)-2-methylaziridine **260d** (1.35 g, 5 mmol) was dissolved in acetonitrile (30 mL), after which KCN (0.64 g, 2 equiv) was added in small portions and the mixture was heated at reflux temperature for 26 h. The reaction mixture was cooled to room temperature, poured into water (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic

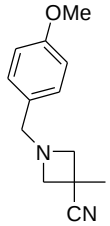
extracts were washed with H_2O (2 × 15 mL) and brine (20 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded 1-(4-methoxybenzyl)-3-methylazetidine-3-carbonitrile **286b** (0.96 g, 95%), which was purified by silica gel column chromatography (dichloromethane/methanol 10/1) to obtain an analytically pure sample.

3-Methyl-1-(4-methylbenzyl)azetidine-3-carbonitrile 286a



Yellow oil, R_f = 0.28 (dichloromethane), Yield 96%, isolated yield 88% (after purification). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.64 (3H, s, CCH_3), 2.33 (3H, s, CH_3Ar), 3.19 (2H, d, *J* = 6.9 Hz, 2 x (*H*CH)C_{quat}), 3.48 (2H, d, *J* = 6.9 Hz, 2 x (HC*H*)C_{quat}), 3.58 (2H, s, NCH_2Ar), 7.04−7.24 (4H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 21.2 (CH_3Ar), 22.9 (CCH_3), 27.1 (CCH_3), 62.5 (NCH_2Ar), 63.4 ($CH_2C_{quat}CH_2$), 123.5 (CN), 128.4 and 129.2 (4 × CH_{arom}), 133.9 and 137.1 (2 x $C_{arom,quat}$). IR (neat) ν_{CN} = 2238 cm^{-1}. MS m/z (%) 201 (M^+ + 1, 100). HRMS m/z (ESI) calculated for $C_{13}H_{16}N_2$ $[MH]^+$ 201.1392, found 201.1389.

1-(4-Methoxybenzyl)-3-methylazetidine-3-carbonitrile 286b

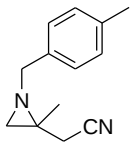


Yellow oil, R_f = 0.60 (dichloromethane/methanol 10/1), Yield 95%, isolated yield 89% (after purification). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.64 (3H, s, CCH_3), 3.18 (2H, d, *J* = 7.2 Hz, 2 x (*H*CH)C_{quat}), 3.48 (2H, d, *J* = 7.2 Hz, 2 x (HC*H*)C_{quat}), 3.56 (2H, s, NCH_2Ar), 3.80 (3H, s, OCH_3), 6.84−6.87 and 7.16−7.19 (4H, 2 × m, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.7 (CCH_3), 27.0 (CCH_3), 55.3 (OCH_3), 62.1 (CH_2Ar), 63.2 ($CH_2C_{quat}CH_2$), 113.8 (2 × CH_{arom}), 123.4 (CN), 128.9 ($C_{arom,quat}$), 129.6 (2 × CH_{arom}), 158.9 ($C_{arom}O$). IR (neat) ν_{CN} = 2238 cm^{-1}. MS m/z (%) 217 (M^+ + 1, 100). HRMS m/z (ESI) calculated for $C_{13}H_{16}N_2O$ $[MH]^+$ 217.1341, found 217.1340.

5.29 Synthesis of 2-cyanomethyl-2-methylaziridines 287

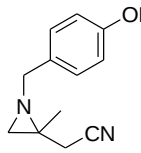
As a representative example, the synthesis of 2-cyanomethyl-2-methyl-1-(4-methylbenzyl)aziridine **287a** is described here. 2-Bromomethyl-2-methyl-1-(4-methylbenzyl)aziridine **260b** (1.27 g, 5 mmol) was dissolved in DMF (30 mL), after which KCN (0.33 g, 1 equiv) was added and the mixture was stirred at 50−60 °C for 16 h. The reaction mixture was cooled to room temperature, poured into water (20 mL) and extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with H_2O (2 × 15 mL) and brine (20 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded 2-cyanomethyl-2-methyl-1-(4-methylbenzyl)aziridine **287a** (0.85 g, 85%), which was purified by silica gel column chromatography (hexane/ethyl acetate 1/1) to obtain an analytically pure sample. Aziridines **287a,b** showed to be rather unstable on silica gel column during the purification process.

2-Cyanomethyl-2-methyl-1-(4-methylbenzyl)aziridine 287a



Yellow oil, R_f = 0.29 (hexane/ethyl acetate 1/1), Yield 85%, isolated yield 36% (after purification). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.39 (1H, s, (*H*CH)CCH_3), 1.43 (3H, s, CH_3C), 1.96 (1H, s, (HC*H*)CCH_3), 2.33 (3H, s, CH_3Ar), 2.40 (H, d, *J* = 16.8 Hz, (*H*CH)CN), 2.49 (H, d, *J* = 16.8 Hz, *(*HC*H*)CN), 3.52 (H, d, *J* = 13.8 Hz, (*H*CH)Ar), 3.69 (H, d, *J* = 13.8 Hz, (HC*H*)Ar), 7.13−7.25 (4H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 14.8 (CCH_3), 21.2 (CH_3Ar), 29.4 (CH_2CN), 36.7 (CCH_3), 39.4 ($CH_2NCH_2C_{arom}$), 56.7 (CH_2C_{arom}), 117.8 (CN), 127.7 and 129.3 (4 × CH_{arom}), 136.4 and 136.8 (2 x $C_{arom,quat}$). IR (neat) ν_{CN} = 2250 cm^{-1}. MS m/z (%) 201 (M^+ + 1, 100). HRMS m/z (ESI) calculated for $C_{13}H_{16}N_2$ $[MH]^+$ 201.1392, found 201.1386.

2-Cyanomethyl-1-(4-methoxybenzyl)-2-methylaziridine 287b

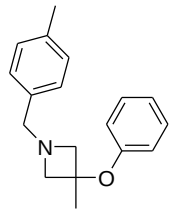


Yellow oil, R_f = 0.21 (hexane/ethyl acetate 1/1), Yield 89%, isolated yield 42% (after purification). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.39 (1H, s, (*H*CH)CCH_3), 1.44 (3H, s, CH_3C), 1.96 (1H, s, (HC*H*)CCH_3), 2.41 (1H, d, *J* = 17.1 Hz, (*H*CH)CN), 2.49 (1H, d, *J* = 17.1 Hz, (HC*H*)CN), 3.49 (1H, d, *J* = 13.5 Hz, (*H*CH)Ar), 3.68 (1H, d, *J* = 13.5 Hz, (HC*H*)Ar), 3.81 (3H, s, OCH_3), 6.86−6.90 and 7.26−7.28 (4H, 2 × m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 14.8 (CCH_3), 29.4 (CH_2CN), 36.7 (CCH_3), 39.4 ($CH_2NCH_2C_{arom}$), 55.4 (OCH_3), 56.4 (CH_2C_{arom}), 114.0 (2 × CH_{arom}), 117.8 (CN), 128.9 (2 × CH_{arom}), 131.5 ($C_{arom,quat}$), 158.8 ($C_{arom}O$). IR (neat) ν_{CN} = 2249 cm^{-1}. MS m/z (%) 217 (M^+ + 1, 100). HRMS m/z (ESI) calculated for $C_{13}H_{16}N_2O$ $[MH]^+$ 217.1341, found 217.1344.

5.30 Synthesis of 3-methyl-3-phenoxyazetidines 288

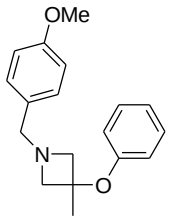
As a representative example, the synthesis of 1-(4-methoxybenzyl)-3-methyl-3-phenoxyazetidine **288b** is described here. 2-Bromomethyl-1-(4-methoxybenzyl)-2-methylaziridine **260d** (1.35 g, 5 mmol) was added to a mixture of phenol (1.04 g, 2.2 equiv) and K_2CO_3 (3.46 g, 5 equiv) dissolved in acetonitrile (30 mL), and the resulting suspension was heated at reflux temperature for 24 h. The reaction mixture was cooled to room temperature, poured into a NaOH solution (30 mL, 0.5M) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with H_2O (2 × 15 mL) and brine (20 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded a mixture of 1-(4-methoxybenzyl)-3-methyl-3-phenoxyazetidine **288b** and 1-(4-methoxybenzyl)-2-methyl-2-(phenoxymethyl)aziridine **289b** (**288b**/**289b** = ratio 67/33), from which 1-(4-methoxybenzyl)-3-methyl-3-phenoxyazetidine **288b** (0.93 g, 65%) was isolated in pure form by silica gel column chromatography (petroleum ether/ethyl acetate 4/1).

3-Methyl-1-(4-methylbenzyl)-3-phenoxyazetidine 288a



Yellow oil, R_f = 0.25 (petroleum ether/ethyl acetate 4/1), Yield, 47%, isolated yield 37% (after purification). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.60 (3H, s, CCH_3), 2.33 (3H, s, CH_3Ar), 3.29 (2H, d, J = 8.3 Hz, 2 x (*H*CH)C_{quat}), 3.55 (2H, d, J = 8.3 Hz, 2 x (HC*H*)C_{quat}), 3.66 (2H, s, NCH_2Ar), 6.67−6.70, 6.91−6.95 and 7.11−7.31 (9H, 3 × m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 21.2 (CH_3Ar), 22.0 (CCH_3), 63.4 (NCH_2Ar), 66.3 ($CH_2C_{quat}CH_2$), 73.6 (CCH_3), 116.8, 120.9, 128.5, 129.1 and 129.5 (9 × CH_{arom}), 136.8 and 137.0 (2 x $C_{arom,quat}$), 155.3 ($C_{arom,quat}$). IR (neat) ν_{max} = 2927, 2838, 1599, 1587, 1514, 1494, 1456, 1241, 1223, 1170, 1034, 959, 803, 752, 692 cm^{-1}. MS m/z (%) 268 (M^+ + 1, 100). HRMS m/z (ESI) calculated for $C_{18}H_{21}NO$ $[MH]^+$ 268.1701, found 268.1698.

1-(4-Methoxybenzyl)-3-methyl-3-phenoxyazetidine 288b

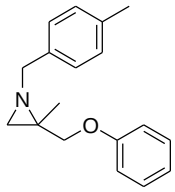


Yellow oil, R_f = 0.07 (petroleum ether/ethyl acetate 4/1), Yield 65%, isolated yield 42% (after purification). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.67 (3H, s, CCH_3), 3.28 (2H, d, J = 8.3 Hz, 2 x (*H*CH)C_{quat}), 3.53 (2H, d, J = 8.3 Hz, 2 x (HC*H*)C_{quat}), 3.63 (2H, s, NCH_2Ar), 3.79 (3H, s, OCH_3), 6.67−6.70, 6.84−6.95 and 7.20−7.26 (9H, 3 × m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 22.0 (CCH_3), 55.3 (OCH_3), 63.0 (NCH_2Ar), 66.2 ($CH_2C_{quat}CH_2$), 73.6 (CCH_3), 113.8, 116.8, 121.0, 129.5 and 129.8 (9 × CH_{arom}), 130.2 ($C_{arom,quat}$), 155.3 ($C_{arom,quat}$), 158.9 ($C_{arom}O$). IR (neat) ν_{max} = 2932, 2834, 2364, 1611, 1586, 1511, 1493, 1242, 1223, 1204, 1171, 1034, 958, 818, 752, 693 cm^{-1}. MS m/z (%) 284 (M^+ + 1, 100). HRMS m/z (ESI) calculated for $C_{18}H_{21}NO_2$ $[MH]^+$ 284.1651, found 284.1645.

5.31 Synthesis of 2-methyl-2-(phenoxymethyl)aziridines 289

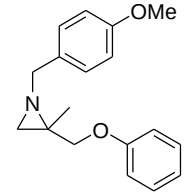
As a representative example, the synthesis of 1-(4-methoxybenzyl)-2-methyl-2-(phenoxymethyl)aziridine **289b** is described here. 2-Bromomethyl-1-(4-methoxybenzyl)-2-methylaziridine **260d** (1.35 g, 5 mmol) was added to a mixture of phenol (1.04 g, 2.2 equiv) and K_2CO_3 (3.46 g, 5 equiv) in DMF (30 mL), and the resulting suspension was heated at 50 °C for 14 h. The reaction mixture was cooled to room temperature, poured into a NaOH solution (30 mL, 0.5 M) and extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with H_2O (2 × 15 mL) and brine (20 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded 1-(4-methoxybenzyl)-2-methyl-2-(phenoxymethyl)aziridine **289b** (1.27 g, 76%), which was purified by silica gel column chromatography (petroleum ether/ethyl acetate 4/1) to obtain an analytically pure sample.

2-Methyl-1-(4-methylbenzyl)-2-(phenoxymethyl)aziridine 289a



Yellow oil, R_f = 0.17 (petroleum ether/ethyl acetate 4/1), Yield 85%, isolated yield 70% (after purification). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (1H, s, (*H*CH)CCH_3), 1.44 (3H, s, CH_3C), 2.00 (1H, s, (HC*H*)CCH_3), 2.34 (3H, s, CH_3Ar), 3.60 (1H, d, *J* = 14.0 Hz, (*H*CH)Ar), 3.73 (1H, d, *J* = 14.0 Hz, (HC*H*)Ar), 3.75 (1H, d, *J* = 9.8 Hz, (*H*CH)O), 3.90 (1H, d, *J* = 9.8 Hz, (HC*H*)O), 6.88−6.96 and 7.11−7.30 (9H, 2 × m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 13.0 (C*C*H_3), 21.2 (CH_3Ar), 38.9 (*C*H_2NCH_2C_{arom}), 39.2 (*C*CH_3), 56.3 (CH_2C_{arom}), 75.8 (CH_2O), 114.7, 120.8, 127.7, 129.1, 129.5 (9 × CH_{arom}), 136.4 and 137.0 (2 x $C_{arom,quat}$), 159.1 ($C_{arom}O$). IR (neat) ν_{max} = 3030, 2922, 1599, 1586, 1495, 1456, 1241, 1171, 1034, 1020, 798, 752, 691 cm^{-1}; MS m/z (%) 268 (M^+ + 1, 100). HRMS m/z (ESI) calculated for $C_{18}H_{21}NO$ $[MH]^+$ 268.1701, found 268.1689.

1-(4-Methoxybenzyl)-2-methyl-2-(phenoxymethyl)aziridine 289b

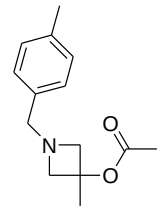


Yellow oil, R_f = 0.31 (petroleum ether/ethyl acetate 4/1), Yield 90%, isolated yield 76% (after purification). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41 (1H, s, (*H*CH)CCH_3), 1.45 (3H, s, CH_3C), 2.00 (1H, s, (HC*H*)CCH_3), 3.56 (1H, d, *J* = 13.8 Hz, (*H*CH)Ar), 3.71 (1H, d, *J* = 13.8 Hz, (HC*H*)Ar), 3.76 (1H, d, *J* = 9.4 Hz, (*H*CH)O), 3.81 (3H, s, OCH_3), 3.89 (1H, d, *J* = 9.4 Hz, (HC*H*)O), 6.84−6.96 and 7.24−7.33 (9H, 2 × m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 13.0 (C*C*H_3), 38.9 (*C*H_2NCH_2C_{arom}), 39.2 (*C*CH_3), 55.4 (OCH_3), 56.0 (*C*H_2C_{arom}), 75.9 (CH_2O), 113.9, 114.8, 120.8, 128.9 and 129.5 (9 × CH_{arom}), 132.2 ($C_{arom,quat}$), 158.6 and 159.1 (2 x $C_{arom}O$). IR (neat) ν_{max} = 3038, 2930, 2835, 1599, 1586, 1511, 1496, 1463, 1300, 1241, 1172, 1033, 819, 753, 691 cm^{-1}. MS m/z (%) 284 (M^+ + 1, 100). HRMS m/z (ESI) calculated for $C_{18}H_{21}NO_2$ $[MH]^+$ 284.1651, found 284.1659.

5.32 Synthesis of 3-acetoxy-3-methylazetidines 290

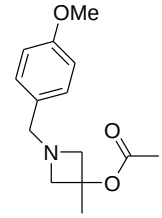
As a representative example, the synthesis of 3-acetoxy-3-methyl-1-(4-methylbenzyl)azetidine **290a** is described here. 2-Bromomethyl-2-methyl-1-(4-methylbenzyl)aziridine **260b** (1.27 g, 5 mmol) was dissolved in acetonitrile (30 mL), after which NaOAc (0.45 g, 1.1 equiv) was added and the mixture was heated at reflux temperature for 24 h. The reaction mixture was cooled to room temperature, poured into water (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with H_2O (2 × 15 mL) and brine (20 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded 3-acetoxy-3-methyl-1-(4-methylbenzyl)azetidine **290a** (1.10 g, 87%), which was purified by silica gel column chromatography (petroleum ether/ethyl acetate 4/1) to obtain an analytically pure sample.

3-Acetoxy-3-methyl-1-(4-methylbenzyl)azetidine 290a



Yellow oil, R_f = 0.11 (petroleum ether/ethyl acetate 4/1), Yield 95%, isolated yield 87% (after purification). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.64 (3H, s, CCH_3), 2.01 (3H, s, CH_3CO), 2.32 (3H, s, CH_3Ar), 3.13 (2H, d, J = 9.1 Hz, 2 x (HCH)C_{quat}), 3.46 (2H, d, J = 9.1 Hz, 2 x (HCH)C_{quat}), 3.61 (2H, s, NCH_2Ar), 7.09−7.17 (4H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 21.2 (CH_3Ar), 21.6 (CH_3CO), 22.7 (CCH_3), 63.3 (NCH_2Ar), 65.8 ($CH_2C_{quat}CH_2$), 74.3 (CCH_3), 128.5 and 129.1 (4 × CH_{arom}), 135.0 and 136.8 (2 x $C_{arom,quat}$), 169.7 (CO). IR (neat) ν_{CO} = 1737 cm^{-1}. MS m/z (%) 234 (M^+ + 1, 100). HRMS m/z (ESI) calculated for $C_{14}H_{19}NO_2$ $[MH]^+$ 234.1494, found 234.1490.

3-Acetoxy-1-(4-methoxybenzyl)-3-methylazetidine 290b

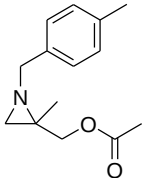


Yellow oil, R_f = 0.06 (hexane/ethyl acetate 2/1) Yield 92%, isolated yield 84% (after purification). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.64 (3H, s, CCH_3), 2.02 (3H, s, CH_3CO), 3.12 (2H, d, J = 9.4 Hz, 2 x (HCH)C_{quat}), 3.45 (2H, d, J = 9.4 Hz, 2 x (HCH)C_{quat}), 3.59 (2H, s, NCH_2Ar), 3.79 (3H, s, OCH_3), 6.83−6.86 and 7.17−7.20 (4H, 2 × m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 21.6 (CH_3CO), 22.6 (CCH_3), 55.3 (OCH_3), 62.9 (NCH_2Ar), 65.6 ($CH_2C_{quat}CH_2$), 74.2 (CCH_3), 113.8 and 129.7 (4 × CH_{arom}), 130.0 ($C_{arom,quat}$), 158.8 ($C_{arom}O$), 169.8 (CO). IR (neat) ν_{CO} = 1736 cm^{-1}. MS m/z (%) 250 (M^+ + 1, 100). HRMS m/z (ESI) calculated for $C_{14}H_{19}NO_3$ $[MH]^+$ 250.1443, found 250.1444.

5.33 Synthesis of 2-acetoxymethyl-2-methylaziridines 291

As a representative example, the synthesis of 2-acetoxymethyl-2-methyl-1-(4-methylbenzyl)aziridine **291a** is described here. 2-Bromomethyl-2-methyl-1-(4-methylbenzyl)aziridine **260b** (1.27 g, 5 mmol) was dissolved in DMSO (30 mL), after which NaOAc (0.45 g, 1.1 equiv) was added and the mixture was stirred at room temperature for 5 days. The reaction mixture was poured into water (20 mL) and extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with H_2O (2 × 15 mL) and brine (20 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded a mixture of 3-acetoxy-3-methyl-1-(4-methylbenzyl)azetidine **290a** and 2-acetoxymethyl-2-methyl-1-(4-methylbenzyl)aziridine **291a** (**290a**/**291a** = ratio 20/80), from which 2-acetoxymethyl-2-methyl-1-(4-methylbenzyl)aziridine **291a** could not be isolated in completely pure (purity <80%) form by silica gel column chromatography (petroleum ether/ethyl acetate 4/1).

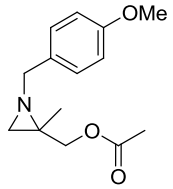
2-Acetoxymethyl-2-methyl-1-(4-methylbenzyl)aziridine 291a



Yellow oil, R_f = 0.22 (petroleum ether/ethyl acetate 4/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31 (3H, s, CH_3C), 1.35 (1H, s, (HCH)CCH_3), 1.95 (1H, s, (HCH)CCH_3), 2.07 (3H, s, CH_3CO), 2.33 (3H, s, CH_3Ar), 3.64 (2H, s, NCH_2Ar), 3.89 (H, d, J = 11.3 Hz, (HCH)O), 4.01 (H, d, J = 11.3 Hz, (HCH)O), 7.12−7.15 and 7.25−7.27 (4H, 2 × m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 12.9 (CH_3CO), 21.0 (CH_3C), 21.2 (CH_3Ar), 38.3 (CCH_3),

38.6 ($CH_2NCH_2C_{arom}$), 56.3 (CH_2C_{arom}), 71.9 (CH_2O), 127.6 and 129.1 (4 × CH_{arom}), 136.4 and 136.9 (2 x $C_{arom,quat}$), 171.1 (CO). IR (neat) ν_{CO} = 1737 cm^{-1}. MS m/z (%) 234 (M^+ + 1, 100).

2-Acetoxymethyl-1-(4-methoxybenzyl)-2-methylaziridine 291b

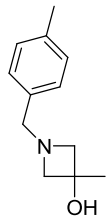


Yellow oil, R_f = 0.21 (petroleum ether/ethyl acetate 1/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31 (3H, s, CH_3C), 1.34 (1H, s, (*H*CH)CCH_3), 1.94 (1H, s, (HC*H*)CCH_3), 2.07 (3H, s, CH_3CO), 3.61 (2H, s, NCH_2Ar), 3.80 (3H, s, OCH_3), 3.88 (H, d, *J* = 11.3 Hz, (*H*CH)O), 4.00 (H, d, *J* = 11.3 Hz, (HC*H*)O), 6.85−6.88 and 7.26−7.31 (4H, 2 × m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 12.9 (CH_3CO), 21.0 (CH_3C), 38.3 (CCH_3), 38.5 ($CH_2NCH_2C_{arom}$), 55.4 (OCH_3), 56.0 (CH_2C_{arom}), 71.8 (CH_2O), 113.8 and 128.8 (4 × CH_{arom}), 132.1 ($C_{arom,quat}$), 158.6 ($C_{arom}O$), 171.1 (CO). IR (neat) ν_{CO} = 1736 cm^{-1}. MS m/z (%) 250 (M^+ + 1, 100).

5.34 Synthesis of 3-methyl-1-(4-methylbenzyl)-3-azetidinol 296

3-Bromo-3-methyl-1-(4-methylbenzyl)azetidine **261b** (1.27 g, 5 mmol) was added to a two-phase solvent system (H_2O/CH_2Cl_2 9/1, 15 mL), after which KOH (1.40 g, 5 equiv) was added, and the mixture was stirred for 10 h under reflux. The reaction mixture was poured into water (15 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were washed with H_2O (2 x 15 mL) and brine (15 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded 3-methyl-1-(4-methylbenzyl)-3-azetidinol **296** as white crystals (0.92 g, purity >95% based on NMR analysis).

3-Methyl-1-(4-methylbenzyl)-3-azetidinol 296



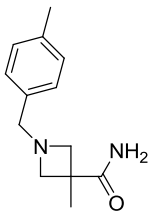
White crystals, Mp = 85.3 °C, Yield 96%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40 (3H, s, $OCCH_3$), 2.25 (3H, s, CH_3Ar), 2.99 (2H, d, *J* = 6.9 Hz, 2 x (*H*CH)C_{quat}), 3.20 (2H, d, *J* = 6.9 Hz, 2 x (HC*H*)C_{quat}), 3.53 (2H, s, NCH_2Ar), 7.02–7.10 (4H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 21.2 (CH_3Ar), 26.1 ($OCCH_3$), 63.2 (NCH_2Ar), 68.0 ($CH_2C_{quat}CH_2$), 68.9 (COH), 128.6 and 128.8 (4 x CH_{arom}), 134.9 and 136.8 (2 x $C_{arom,quat}$). IR (neat) ν_{OH} = 3359 cm^{-1}. MS (70 eV) m/z (%) 192 (M^+ + 1, 100).

5.35 Synthesis of 3-methyl-1-(4-methylbenzyl)azetidine-3-carboxamide 298 and 3-methyl-1-(4-methylbenzyl)azetidine-3-carboxylic acid 297

1-(4-Methylbenzyl)azetidine-3-carbonitrile **286a** (0.20 g, 1 mmol) was dissolved in EtOH/H_2O (5/1, 5 mL), after which KOH (0.28 g, 5 equiv) was added. The mixture was placed in a 6-mL sealed glass

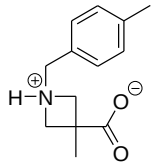
vessel, provided with an appropriate stirring bar and subjected to microwave conditions (150 °C, 10 min, 150W). The reaction mixture was neutralized with a solution of hydrochloric acid (1 M) to pH = 7 and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were washed with H_2O (2 x 15 mL) and brine (15 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded 3-methyl-1-(4-methylbenzyl)azetidine-3-carboxamide **298** as white crystals (0.09 g, 40%). The water fraction was evaporated under high vacuum to provide azetidine-3-carboxylic acid **297** as a mixture of two isomeric structures (ratio 3/2) upon NMR analysis (CD_3OD) (0.12 g, 55%).

3-Methyl-1-(4-methylbenzyl)azetidine-3-carboxamide 298



White solid, Yield 40%. ^{1}H NMR (300 MHz, CD_3OD) δ 1.36 (3H, s, CH_3CCO), 1.85 (2H, br s, NH_2), 2.33 (3H, s, CH_3Ar), 3.02 (2H, d, J = 8.0 Hz, 2 x (*H*CH)C_{quat}), 3.53 (2H, d, J = 8.0 Hz, 2 x (HC*H*)C_{quat}), 3.59 (2H, s, NCH_2Ar), 7.09–7.22 (4H, m). ^{13}C NMR (75 MHz, ref = CD_3OD) δ 21.2 (CH_3CCO), 21.4 (CH_3Ar), 40.9 (CH_3CCO), 62.9 (NCH_2Ar), 64.4 ($CH_2C_{quat}CH_2$), 128.4 and 129.2 (4 x CH_{arom}), 134.5 and 137.0 (2 x $C_{arom,quat}$), 178.9 (CO). IR (neat) ν_{CO} = 1655 cm^{-1}, ν_{max} = 2922, 1618, 1455, 1228, 798. MS (70 eV) m/z (%) 219 (M^+ + 1, 100).

3-Methyl-1-(4-methylbenzyl)azetidine-3-carboxylic acid 297 (described as a mixture of diastereomers)



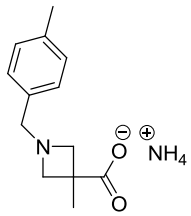
White crystals, Yield 55%. ^{1}H NMR (300 MHz, CD_3OD) δ 1.47 and 1.53 (3H, 2 x s, CH_3CCO), 2.25 (3H, s, CH_3Ar), 3.69-3.70 (1H, m, *H*CHN), 3.85-3.89 (2H, m, HCHN), 4.00-4.4.03 (3H, m, CH_2N and HC*H*N), 4.28-4.31 (3H, m, CH_2), 7.15-7.18 and 7.31-7.33 (4H, 2 x m, CH_{arom}). ^{13}C NMR (75 MHz, CD_3OD) δ 21.3 and 21.5 (CH_3CCO), 22.4 (CH_3Ar), 39.9 and 40.9 (CH_3CCO), 59.2 and 59.6 (NCH_2Ar), 61.8 and 62.5 ($CH_2C_{quat}CH_2$), 127.8 ($C_{arom,quat}$), 131.0, 131.3, 131.4 (4 x CH_{arom}), 141.3 ($C_{arom,quat}$), 175.6 and 175.8 (CO). IR (neat) ν_{CO} = 1730 cm^{-1}, ν_{OH} = 3381, ν_{max} = 2950, 2577, 1730, 1438, 1154. MS (70 eV) m/z (%) 220 (M^+ + 1, 100).

5.36 Synthesis of ammonium 3-methyl-1-(4-methylbenzyl)azetidine-3-carboxylate 299

1-(4-Methylbenzyl)azetidine-3-carbonitrile **286a** (0.20 g, 1 mmol) was dissolved in EtOH/H_2O (5/1, 5 mL), after which KOH (0.28 g, 5 equiv) was added. The mixture was placed in a 6 mL sealed glass vessel, provided with an appropriate stirring bar and subjected to microwave conditions (150 °C, 20 min, 150W). The reaction mixture was neutralized with a solution of hydrochloric acid (1 mL, 1 M) to pH = 7 and evaporated under high vacuum to provide a mixture of two isomeric structures (ratio 3/2) upon NMR analysis of azetidine-3-carboxylic acid **297**. Purification of amino acid **297** by means of ion-

exchange chromatography on Dowex H+ (50 x 8-100) afforded ammonium 3-methyl-1-(4-methylbenzyl)azetidine-3-carboxylate **299** as a single isomer in pure form (0.20 g, 85%).

Ammonium 3-methyl-1-(4-methylbenzyl)azetidine-3-carboxylate 299

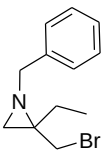


White crystals, Mp >350 °C, Yield 85%. ^{1}H NMR (300 MHz, CD_3OD) δ 1.41 (3H, s, CH_3CCO), 2.24 (3H, s, CH_3Ar), 3.73 (2H, d, J = 10.7 Hz, 2 x (HCH)C_{quat}), 4.20 (2H, d, J = 10.7 Hz, 2 x (HCH)C_{quat}), 4.20 (2H, s, NCH_2Ar), 7.16–7.27 (4H, m, CH_{arom}). ^{13}C NMR (75 MHz, CD_3OD) δ 21.3 (CH_3CCO), 23.3 (CH_3Ar), 42.3 (CH_3CCO), 59.4 (NCH_2Ar), 63.7 ($CH_2C_{quat}CH_2$), 128.6 ($C_{arom,quat}$), 131.0 and 131.1 (4 x CH_{arom}), 141.2 ($C_{arom,quat}$), 180.5 (CO). IR (neat) ν_{CO} = 1603 cm^{-1}, ν_{max} = 2965, 1439, 1379, 1146, 770. MS (70 eV) m/z (%) 218 (M^+ + 1, 100).

5.37 Synthesis of 2-bromomethyl-2-ethylaziridines 303

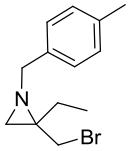
The synthesis of 2-bromomethyl-2-ethylaziridines **303** was performed according to the synthetic procedure for the preparation of 2-bromomethyl-2-methylaziridines **260** (see Section 5.13). As a representative example, the synthesis of 2-bromomethyl-2-ethyl-1-(4-methylbenzyl)aziridine **303b** is described here. *N*-(2,3-Dibromo-2-ethylpropylidene)-4-methylbenzylamine **302b** (3.47 g, 10 mmol) was dissolved in methanol (30 mL), after which $NaBH_4$ (0.76 g, 2 molar equiv) was added in small portions at 0 °C and the mixture was stirred for 36 hours at room temperature. The reaction mixture was poured into water (20 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were washed with H_2O (2 x 15 mL) and brine (20 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded 2-bromomethyl-1-(4-methylbenzyl)-2-ethylaziridine **303b** (2.33 g, 87%), as a mixture of two invertomers, which was purified by filtration through silica gel (petroleum ether/ethyl acetate 4/1) in order to obtain an analytically pure sample.

1-Benzyl-2-bromomethyl-2-ethylaziridine 303a (described as a mixture of two invertomers, ratio 63/37)



Yellow oil, R_f = 0.56 (petroleum ether /ethyl acetate 2/1), Yield 85%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (3H, t, J = 7.4 Hz, (CH_3CH_2)$_{minor}$), 0.97 (3H, t, J = 7.4 Hz, (CH_3CH_2)$_{major}$), 1.40 (1H, s, ((HCH)CCH_2Br)$_{minor}$), 1.46 (1H, s, ((HCH)CCH_2Br)$_{major}$), 1.67-1.88 (2H, m, CH_2CH_3), 1.91 (1H, s, ((HCH)CCH_2Br)$_{major}$), 1.94 (1H, s, ((HCH)CCH_2Br)$_{minor}$), 3.28 and 3.36 (2H, 2 x d, J = 10.2 Hz, CH_2Br), 3.45 and 3.78 (2H, 2 x d, J = 13.8 Hz, (N(HCH)Ar)$_{major}$), 3.41-3.48, 3.75-3.78 and 4.03-4.07 (2H, 3 x m, (NCH_2Ar)$_{minor}$), 7.16-7.32 (5H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 9.6 (CH_3CH_2)$_{minor}$, 10.9 (CH_3CH_2)$_{major}$, 20.0 (CH_2CH_3), 40.9 ($CH_2C_{quat}CH_2Br$), 41.3 (CH_2Br), 43.9 (CCH_2Br)$_{minor}$, 44.3 (CCH_2Br)$_{major}$, 56.5 (NCH_2Ar)$_{minor}$, 56.8 (NCH_2Ar)$_{major}$, 127.1, 128.0 and 128.5 (5 x CH_{arom}), 139.7 ($C_{arom,quat}$). IR (neat) ν_{max} = 3026, 2967, 2852, 1495, 1454, 1216, 731, 696 cm^{-1}. MS *m/z* (%) 254/6 (M^+ + 1, 100).

2-Bromomethyl-2-ethyl-1-(4-methylbenzyl)aziridine 303b (described as a mixture of two invertomers, ratio 66/34)

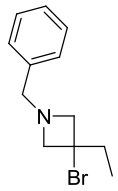


Light-yellow oil, R_f = 0.50 (petroleum ether /ethyl acetate 4/1), Yield 87%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (3H, t, J = 7.4 Hz, $(CH_3CH_2)_{minor}$), 1.04 (3H, t, J = 7.4 Hz, $(CH_3CH_2)_{major}$), 1.44(1H, s, $((H)CHCCH_2Br)_{minor}$), 1.49 (1H, s, $((H)CHCCH_2Br)_{major}$), 1.71-1.90 (2H, m, CH_2CH_3), 1.94 (1H, s, $((HCH)CCH_2Br)_{major}$), 1.97 (1H, s, $((HCH)CCH_2Br)_{minor}$), 2.33 (3H, s, CH_3Ar), 3.35 and 3.40 (2H, 2 x d, J = 10.5 Hz, CH_2Br), 3.46 and 3.81 (2H, 2 x d, J = 13.8 Hz, $(N(HCH)Ar)_{major}$), 3.51 and 4.06 (2H, 2 x d, J = 13.8 Hz, $(N(HCH)Ar)_{minor}$), 7.12-7.15 and 7.24-7.27 (4H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 9.5 $(CH_3CH_2)_{minor}$, 10.9 $(CH_3CH_2)_{major}$, 20.0 $(CH_3Ar)_{minor}$, 21.2 $(CH_3Ar)_{major}$, 28.7 $(CH_2CH_3)_{minor}$, 40.9 $(CH_2C_{quat}CH_2Br)$, 41.2 (CH_2Br), 44.0 $(CCH_2Br)_{minor}$, 44.3 $(CCH_2Br)_{major}$, 56.3 $(NCH_2Ar)_{minor}$, 56.5 $(NCH_2Ar)_{major}$, 128.0 and 129.1 (4 x CH_{arom}), 136.6 (2 x $C_{arom,quat}$). IR (neat) ν_{max} = 3026, 2967, 2877, 1515, 1458, 143, 1216, 797, 647 cm^{-1}. MS *m/z* (%) 268/70 (M^+ + 1, 100).

5.38 Synthesis of 3-bromo-3-ethylazetidines 305

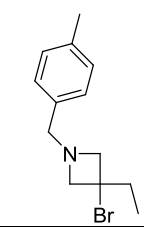
As a representative example, the synthesis of 3-bromo-3-ethyl-1-(4-methylbenzyl)azetidine **305b** is described here. 2-Bromomethyl-2-ethyl-1-(4-methylbenzyl)aziridine **303b** (2.68 g, 10 mmol) was dissolved in acetonitrile (30 mL), and the mixture was heated at reflux temperature for 15 h. The reaction mixture was cooled to room temperature, poured into water (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with H_2O (2 × 15 mL) and brine (20 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent in vacuo afforded 3-bromo-3-ethyl-1-(4-methylbenzyl)azetidine **305b** (2.57 g, 96%), which was purified by silica gel column chromatography (petroleum ether/ethyl acetate 4/1) to obtain an analytically pure sample.

1-Benzyl-3-bromo-3-ethylazetidine 305a



Yellow oil, R_f = 0.52 (hexane/ethyl acetate 4/1), Yield 94%. ^{1}H NMR (300 MHz, ref = $CDCl_3$) δ 1.03 (3H, t, J = 7.2 Hz, CH_3CH_2), 2.10 (2H, q, J = 7.2 Hz, CH_3CH_2), 3.65 (2H, d, J = 9.9 Hz, 2 x $(HCH)C_{quat}$), 3.74 (2H, d, J = 9.9 Hz, 2 x $(HCH)C_{quat}$), 3.80 (2H, s, NCH_2Ar), 7.28−7.33 (5H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 10.4 (CH_3CH_2), 36.1 (CH_2CH_3), 59.1 (CCH_2CH_3), 63.2 (NCH_2Ar), 69.2 $(CH_2C_{quat}CH_2)$, 127.3, 128.48 and 128.52 (5 x CH_{arom}), 137.7 (2 x $C_{arom,quat}$). IR (neat) ν_{max} = 2966, 2935, 1454, 1174, 732, 697 cm^{-1}. MS m/z (%) 254/6 (M^+ + 1, 100).

3-Bromo-3-ethyl-1-(4-methylbenzyl)azetidine 305b



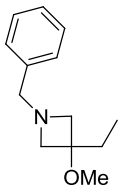
Yellow oil, R_f = 0.50 (petroleum ether/ethyl acetate 4/1), Yield 96%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03 (3H, t, J = 7.2 Hz, CH_3CH_2), 2.10 (2H, q, J = 7.2 Hz, CH_3CH_2), 2.33 (3H, s, CH_3Ar), 3.70 (2H, d, J = 8.8 Hz, 2 x $(HCH)C_{quat}$), 3.75 (2H, d, J = 8.8 Hz, 2 x $(HCH)C_{quat}$), 3.81 (2H, s, NCH_2Ar), 7.12−7.23 (4H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 10.3 (CH_3CH_2), 21.2 (CH_3Ar), 35.9 (CH_2CH_3), 58.3 (CCH_2CH_3), 62.4 (NCH_2Ar),

68.6 ($CH_2C_{quat}CH_2$), 128.8 and 129.3 (4 x CH_{arom}), 133.0 and 137.6 (2 x $C_{arom,quat}$). IR (neat) ν_{max} = 3417, 2965, 2934, 1515, 1456, 1174, 809, 731 cm^{-1}. MS m/z (%) 268/70 (M^+ + 1, 100).

5.39 Synthesis of 1-benzyl-3-ethyl-3-methoxyazetidine 306

1-Benzyl-2-bromomethyl-2-ethylaziridine **303a** (2.54 g, 10 mmol) was dissolved in methanol (30 mL), after which $NaBH_4$ (1.13 g, 3 molar equiv) was added in small portions at 0 °C and the mixture was heated for 48 hours under reflux. The reaction mixture was poured into water (20 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were washed with H_2O (2 x 15 mL) and brine (20 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded 1-benzyl-3-ethyl-3-methoxyazetidine **306** (1.83 g, 89%).

1-Benzyl-3-ethyl-3-methoxyazetidine 306

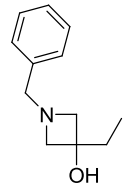


Yellow oil, R_f = 0.39 (petroleum ether/ethyl acetate 4/1), Yield 89%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84 (3H, t, *J* = 7.2 Hz, CH_3CH_2), 1.98 (2H, q, *J* = 7.2 Hz, CH_2CH_3), 3.17 (3H, s, OCH_3), 3.48 (2H, d, *J* = 10.5 Hz, 2 x (HCH)C_{quat}), 3.87 (2H, d, *J* = 10.5 Hz, 2 x (HCH)C_{quat}), 4.14 (2H, s, NCH_2Ar), 7.27-7.42 (5H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 6.8 (CH_3CH_2), 25.6 (CH_2CH_3), 50.3 (OCH_3), 60.7 (NCH_2Ar), 61.8 ($CH_2C_{quat}CH_2$), 75.2 (CO), 128.4 ($C_{arom,quat}$), 129.2, 129.3 and 129.9 (5 x CH_{arom}). IR (neat) ν_{max} = 2966, 2935, 1456, 1070, 911, 729, 699 cm^{-1}. MS *m/z* (%) 206 (M^+ + 1, 100).

5.40 Reactivity of 3-bromo-3-ethylazetidine 305 toward KOtBu in tBuOH

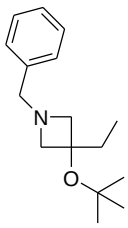
In an ice-cooled solution of 1-benzyl-3-bromo-3-ethylazetidine **305a** (1.27 g, 5 mmol) in tBuOH (30 mL), KOtBu (2.8 g, 5 equiv) was slowly added and the mixture was heated for 20 hours under reflux. The reaction mixture was cooled to room temperature, filtered, poured into water (20 mL) and extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with H_2O (2 × 15 mL) and brine (20 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent in vacuo afforded a mixture of 1-benzyl-3-ethylazetidin-3-ol **308**, 1-benzyl-3-ethylideneazetidine **307a** and 3-(*tert*-butoxy)-3-ethylazetidine **309** (**308**/**307a**/**309** = 3.4/1.5/1). Spectral data of 3-(*tert*-butoxy)-3-ethylazetidine **309** and 1-benzyl-3-ethylazetidin-3-ol **308** were deduced from the crude reaction mixture.

1-Benzyl-3-ethylazetidin-3-ol 308



Light-yellow oil, Yield 60%. ^{1}H NMR (300 MHz, ref = $CDCl_3$) δ 0.94 (3H, t, *J* = 7.4 Hz, C*H*$_3$CH$_2$), 1.77 (2H, q, *J* = 7.4 Hz, CH$_3$C*H*$_2$), 3.08 and 3.33 (4H, 2 x d, *J* = 8.5 Hz, 2 x CH$_2$C$_{quat}$CH$_2$), 3.68 (2H, s, NCH$_2$Ar), 7.22-7.34 (5H, m, CH$_{arom}$). ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 7.8 (*C*H$_3$CH$_2$), 31.7 (CH$_3$*C*H$_2$), 66.4 (NCH$_2$Ar and *C*H$_2$C$_{quat}$*C*H$_2$), 71.6 (CO), 127.3, 128.4 and 128.7 (5 x CH$_{arom}$), 137.8 (C$_{arom,quat}$). IR (neat) ν_{OH} = 3322 cm^{-1}. MS *m/z* (%) 192 (M^+ + 1, 100).

3-(*tert*-Butoxy)-3-ethylazetidine 309

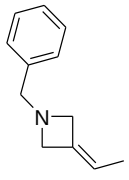


Light-yellow oil, Yield 60%. ^{1}H NMR (300 MHz, ref = $CDCl_3$) δ 0.99 (3H, t, *J* = 7.4 Hz, C*H*$_3$CH$_2$), 1.23 (9H, s, C(CH$_3$)$_3$), 1.98 (2H, q, *J* = 7.4 Hz, CH$_3$C*H*$_2$), 2.98 and 3.40 (4H, 2 x d, *J* = 8.0 Hz, 2 x CH$_2$C$_{quat}$CH$_2$), 3.68 (2H, s, NCH$_2$Ar), 7.22-7.34 (5H, m, CH$_{arom}$). ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 8.1 (*C*H$_3$CH$_2$), 30.1 (CH$_3$*C*H$_2$), 30.6 (C(*C*H$_3$)$_3$), 66.4 (*C*H$_2$C$_{quat}$*C*H$_2$), 63.5 (NCH$_2$Ar), 71.6 (COCH$_2$), 71.6 (COC(CH$_3$)$_3$), 127.3, 128.4 and 128.7 (5 x CH$_{arom}$), 137.8 (C$_{arom,quat}$). IR (neat) ν_{max} = 2962, 2934, 2828, 1453, 1362, 1184, 730, 697 cm^{-1}. MS *m/z* (%) 248 (M^+ + 1, 100).

5.41 Synthesis of 3-ethylideneazetidines 307

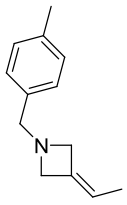
As a representative example, the synthesis of 3-ethylidene-1-(4-methylbenzyl)azetidine **307b** is described here. In an ice-cooled solution of 3-bromo-3-ethyl-1-(4-methylbenzyl)azetidine **305b** (1.34 g, 5 mmol) in dry THF (30 mL), KOtBu (0.84 g, 1.5 equiv) was slowly added and the mixture was subjected to microwave heating (150W) for 10 min at 120 °C. Afterward, the reaction mixture was cooled to room temperature, filtered and poured into water (20 mL) and extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with H_2O (2 × 15 mL) and brine (20 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent in vacuo afforded 3-ethylidene-1-(4-methyl-benzyl)azetidine **307b** (0.88 g, 94%), which was purified by silica gel column chromatography (petroleum ether/ethyl acetate 4/1) to obtain an analytically pure sample.

1-Benzyl-3-ethylideneazetidine 307a



Light-yellow oil, R_f = 0.21 (petroleum ether /ethyl acetate 4/1), Yield 92%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.47-1.51 (3H, m, C*H*$_3$CH=C), 3.72 (2H, s, NCH$_2$Ar), 3.80-3.84 (4H, m, C*H*$_2$C$_{quat}$C*H*$_2$), 5.15-5.25 (1H, m, CH=C), 7.21-7.34 (5H, m, CH$_{arom}$). ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 13.6 (*C*H$_3$CH=C), 60.9 (*C*H$_2$C=CH), 62.3 (*C*H$_2$C=CH), 63.5 (NCH$_2$Ar), 115.4 (*C*H=C), 127.2, 128.5 and 128.6 (5 x CH$_{arom}$), 131.8 and 138.1 (C$_{arom,quat}$ and C$_{quat}$). IR (neat) ν_{max} = 2918, 2808, 1453, 1274, 732, 697 cm^{-1}. MS *m/z* (%) 174 (M^+ + 1, 100). HRMS m/z (ESI) calculated for $C_{12}H_{15}N$ $[MH]^+$ 174.1277, found 174.1277.

3-Ethylidene-1-(4-methylbenzyl)azetidine 307b

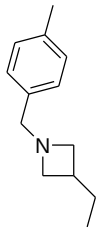


Light-yellow oil, R_f = 0.22 (petroleum ether /ethyl acetate 4/1), Yield 94%. ^{1}H NMR (300 MHz, ref = $CDCl_3$) δ 1.46-1.51 (3H, m, CH_3CH=C), 2.33 (3H, s, CH_3Ar), 3.68 (2H, s, NCH_2Ar), 3.79-3.82 (4H, m, CH_2C$_{quat}$CH_2), 5.16-5.24 (1H, m, CH=C), 7.11-7.14 and 7.18-7.21 (4H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 13.6 (*C*H_3CH=C), 21.2 (CH_3Ar), 60.8 (*C*H_2C=CH), 62.2 (*C*H_2C=CH), 63.5 (NCH_2Ar), 115.1 (*C*H=C), 128.5 and 129.1 (4 x CH_{arom}), 131.8, 135.7 and 136.7 (2 x $C_{arom,quat}$ and C_{quat}). IR (neat) ν_{max} = 2917, 2805, 1514, 1439, 1358, 1273, 1176, 1042, 1021, 806, 780, 753 cm^{-1}. MS *m/z* (%) 188 (M^+ + 1, 100). HRMS m/z (ESI) calculated for $C_{13}H_{18}N$ $[MH]^+$ 188.1434, found 188.1435.

5.42 Synthesis of 3-ethyl-1-(4-methylbenzyl)azetidine 329

3-Ethylidene-1-(4-methylbenzyl)azetidine **307b** (0.2 g, 1 mmol) was dissolved in ethyl acetate (10 mL), 10% Pd/C (0.07 g, 6 mol%) was added in small portions at 0 °C and the mixture was subjected to hydrogenation for 72 hours (5 bar, H_2) at room temperature. The reaction mixture was first then filtered through a small sintered funnel and thoroughly washed with ethyl acetate (20 mL). Subsequently, the filtrate was poured into water (20 mL) and extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with H_2O (2 x 15 mL) and brine (20 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded 3-ethyl-1-(4-methylbenzyl)azetidine **329** (0.08 g, 40%).

3-Ethyl-1-(4-methylbenzyl)azetidine 329



Light-yellow oil, Yield 40%. ^{1}H NMR (300 MHz, ref = $CDCl_3$) δ 0.73 (3H, t, *J* = 7.4 Hz, CH_3CH_2), 1.44 (2H, quin, *J* = 7.4 Hz, CHC*H*$_2$CH$_3$), 2.24 (3H, s, CH_3Ar), 2.24-2.38 (1H, m, NCH_2C*H*CH_2), 2.64-2.69 and 3.32-3.37 (4H, 2 x m, CH_2CHCH_2), 3.46 (2H, s, NCH_2Ar), 7.02-7.10 (4H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 11.6 (*C*H_3CH$_2$), 21.2 (CH_3Ar), 27.5 (*C*H_2CH$_3$), 32.8 (*C*HCH$_2$), 60.4 (*C*H_2C$_{quat}$CH_2), 63.8 (NCH_2Ar), 128.6 and 129.1 (4 x CH_{arom}), 135.3 and 136.6 (2 x $C_{arom,quat}$). IR (neat) ν_{max} = 2954, 2929, 2808, 1514, 1459, 1358, 1182, 806 cm^{-1}. MS *m/z* (%) 190 (M^+ + 1, 100). HRMS m/z (ESI) calculated for $C_{13}H_{19}N$ $[MH]^+$ 190.1590, found 190.1593.

5.43 Synthesis of *N*-benzyl-*N*-[2-(chloromethyl)but-2-enyl)]-2-alkoxyacetamides 318

To an ice-cooled mixture of methoxyacetyl chloride **315** (R = Me) (0.20 g, 1.9 mmol) in CH_2Cl_2, triethylamine (0.57 g, 3 equiv) was added and the mixture was stirred for 1 hour at room temperature. Subsequently, 3-ethylideneazetidine **307a** (0.25 g, 1.5 mmol) was added and the resulting mixture

was stirred for 15 hours at room temperature. Afterward, the reaction mixture was poured into water (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with H_2O (2 × 15 mL) and $NaHCO_3$ (20 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent in vacuo afforded a mixture of *N*-benzyl-*N*-[2-(chloromethyl)but-2-enyl)]-2-alkoxyacetamides **318a** and **318b** (R = Me) (*Z*/*E* = 1/1) (0.33 g, overall yield 78%), which was purified by silica gel column chromatography (petroleum ether/ethyl acetate 1/1) to obtain an analytically pure sample of the mixture of isomers.

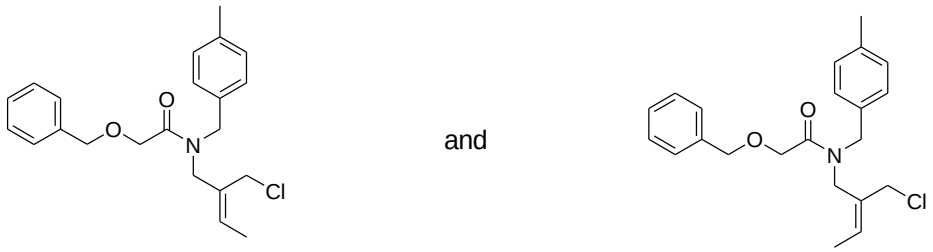
***N*-benzyl-*N*-[2-(chloromethyl)but-2-enyl)]-2-alkoxyacetamides 318a** and **318b** (R = Me) (described from the mixture of two isomers *Z*/*E* = 1/1)

Yellow oil, R_f = 0.47 (petroleum ether/ethyl acetate 1/1), Yield 78%. ^{1}H NMR (300 MHz, ref = $CDCl_3$) δ 1.56-1.63 (3H, m, C*H*$_3$CH=C), 3.44 and 3.49 (3H, 2 x s, OCH_3), 4.00-4.05 (2H, m, CH_2), 4.16-4.21 (2H, m, CH_2), 4.30-4.34 (2H, m, CH_2), 4.51-4.54 (2H, m, CH_2), 5.90-5.94 (1H, m, CH=C), 7.17-7.37 (5H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 13.6 (*C*H$_3$CH=C), 41.5 (CH_2), 41.9 (CH_2), 47.2 (CH_2), 47.4 (CH_2), 48.3 (CH_2), 49.5 (CH_2), 59.4 (OCH_3), 71.5 (CH_2O), 126.4 (*C*H=C), 127.6, 127.8, 128.2, 128.7, 129.1, 131.4, 131.6, 131.9 (5 x CH_{arom}), 136.4 and 137.0 ($C_{arom,quat}$ and *C*=CH), 170.1 (CO). IR (neat) ν_{CO} = 1649, ν_{max} = 2930, 1449, 1196, 1128, 1108, 699 cm^{-1}. MS *m/z* (%) 282/4 (M^+ + 1, 100). HRMS m/z (ESI) calculated for $C_{15}H_{20}ClNO_2$ $[MH]^+$ 282.1255, found 282.1252.

5.44 Synthesis of 2-benzyloxy-*N*-[(2-chloromethyl)but-2-enyl)]-*N*-(4-methylbenzyl)acetamides 318

To an ice-cooled mixture of benzoxyacetyl chloride **315** (R = Bn) (0.1 g, 0.5 mmol) in CH_2Cl_2, triethylamine (0.16 g, 3 equiv) was added and the mixture was stirred for 1 hour at room temperature. Subsequently, 3-ethylideneazetidine **307a** (0.07 g, 0.38 mmol) was added and the resulting mixture was stirred for 15 hours at room temperature. Afterward, the reaction mixture was poured into water (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with H_2O (2 × 15 mL) and $NaHCO_3$ (20 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent in vacuo afforded a mixture of 2-benzyloxy-*N*-[(2-chloromethyl)but-2-enyl)]-*N*-(4-methylbenzyl)acetamides **318a** and **318b** (R = Bn) (*Z*/*E* = 1/1) (0.11 g, overall yield 75%).

2-Benzyloxy-*N*-[(2-chloromethyl)but-2-enyl)]-*N*-(4-methylbenzyl)acetamides 318a and **318b** (R = Me) (described from the mixture of two isomers *Z*/*E* = 1/1)

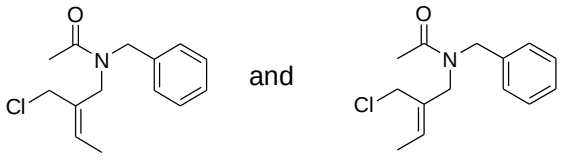


Dark-yellow oil, R_f = 0.30 (petroleum ether/ethyl acetate 4/1), Yield 75%. ^{1}H NMR (300 MHz, ref = $CDCl_3$) δ 1.49-1.61 (3H, m, C*H*$_3$CH=C), 2.33 (3H, s, CH_3Ar), 3.96-4.04 (2H, m, CH_2), 4.09-4.10 (2H, m, CH_2), 4.15-4.29 (2H, m, CH_2), 4.35-4.67 (2H, m, CH_2), 5.29 (2H, s, ArCH_2O), 5.85-5.92 (1H, m, CH=C), 7.07-7.15 and 7.29-7.36 (9H, 2 x m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 13.6 (*C*H_3CH=C), 41.6 (CH_2), 41.8 (CH_2), 53.5 (CH_3Ar), 67.0 (CH_2), 68.9 (CH_2), 73.4 (CH_2O), 126.4 (*C*H=C), 128.0, 128.2, 128.5, 128.6 (9 x CH_{arom}), 129.4, 129.7, 131.7 and 137.4 (3 x $C_{arom,quat}$ and *C*=CH), 170.2 (CO), 172.4 (CO). IR (neat) ν_{CO} = 1753, 1649 cm^{-1}, ν_{max} = 2925, 1454, 1205, 1118, 738, 698 cm^{-1}. MS *m/z* (%) 372/4 (M^+ + 1, 100).

5.45 Synthesis of *N*-benzyl-*N*-[(2-chloromethyl)but-2-enyl)]acetamides 323

3-Ethylideneazetidine **307a** (0.08 g, 0.5 mmol) was dissolved in CH_2Cl_2 (10 mL), acetyl chloride (0.06 g, 1.5 equiv) was added and the mixture was stirred for 15 hours under reflux. The reaction mixture was then poured into water (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with H_2O (2 × 15 mL) and $NaHCO_3$ (20 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent in vacuo afforded a mixture of *N*-benzyl-*N*-[(2-chloromethyl)but-2-enyl)]acetamides **323a** and **323b** (*Z*/*E* = 1/1) (0.12 g, overall yield 100%).

***N*-benzyl-*N*-[(2-chloromethyl)but-2-enyl)]acetamides 323a** and **323b**



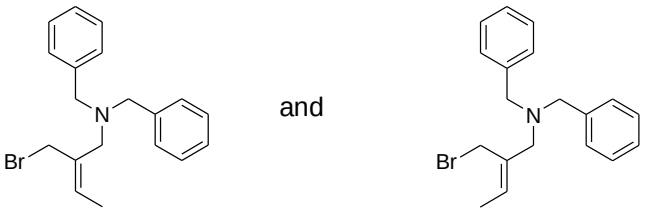
Yellow oil, R_f = 0.18 (petroleum ether/ethyl acetate 4/1), Yield 100%. ^{1}H NMR (300 MHz, ref = $CDCl_3$) δ 1.49-1.53 (3H, m, C*H*$_3$CH=C), 2.09 (3H, m, CH_3CO), 2.24 (3H, m, CH_3CO), 3.94 (2H, s, CH_2), 3.97 (2H, s, CH_2), 4.14 (2H, s, CH_2), 4.44-4.46 (2H, m CH_2), 5.79-5.88 (1H, m, CH=C), 7.09-7.33 (5H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 13.6 (*C*H_3CH=C), 21.8 (CH_3CO), 21.9 (CH_3CO), 41.8

(CH_2), 43.2 (CH_2), 47.1 (CH_2), 47.5 (CH_2), 48.4 (CH_2), 51.3 (CH_2), 126.2 (*C*H=C), 127.5, 127.7, 128.1, 128.6, 129.1, 131.0, 131.4 (5 x CH_{arom}), 131.9, 132.4, 136.7, 137.3 ($C_{arom,quat}$ and *C*=CH), 171.5 (CO), 171.7 (CO). IR (neat) ν_{CO} = 1645 cm^{-1}, ν_{max} = 2950, 1739, 1420, 1242, 733, 699 cm^{-1}. MS *m/z* (%) 252/4 (M^+ + 1, 40). HRMS m/z (ESI) calculated for $C_{14}H_{18}ClNO$ $[MH]^+$ 252.1150, found 252.1148.

5.46 Synthesis of *N*,*N*-dibenzyl-*N*-[(2-bromomethyl)but-2-enyl)]amines 324

3-Ethylideneazetidine **307a** (0.09 g, 0.5 mmol) was dissolved in MeCN (10 mL), benzyl bromide (0.09 g, 1 equiv) was added and the mixture was stirred for 15 hours under reflux. The reaction mixture was then poured into water (20 mL) and extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with H_2O (2 × 15 mL) and brine (20 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent in vacuo afforded a mixture of *N*,*N*-dibenzyl-*N*-[(2-bromomethyl)but-2-enyl)]amines **324a** and **324b** (*Z*/*E* = 36/64 or vice versa) (0.17 g, overall yield 100%).

***N*,*N*-Dibenzyl-*N*-[(2-bromomethyl)but-2-enyl)]amines 324a** and **324b** (described as a mixture of 2 isomers, *Z*/*E* = 36/64 or vice versa)



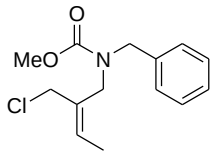
Yellow oil. R_f = 0.75 (petroleum ether/ethyl acetate 4/1), overall yield 100%. ^{1}H NMR (300 MHz, ref = $CDCl_3$) δ 1.60-1.62 (3H, m, (CH_3CH=C)$_{major}$), 1.676-1.681 and 1.700-1.703 (3H, m, (CH_3CH=C)$_{minor}$), 3.00 (1H, s, (NCH_2C=CH)$_{major}$), 3.10 (1H, s, (NCH_2C=CH)$_{minor}$), 3.43 (4H, s, 2 x NCH_2Ar), 4.04 (2H, s, (CH_2Br)$_{major}$), 4.09 (2H, s, (CH_2Br)$_{minor}$), 5.59-5.66 (1H, m, (CH=C)$_{major}$), 5.77-5.84 (1H, m, (CH=C)$_{minor}$), 7.13-7.33 (10H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 13.6 (CH_3CH=C)$_{major}$, 13.8 (CH_3CH=C)$_{minor,}$ 28.8 (CH_2Br)$_{major}$, 37.9 (CH_2Br)$_{minor}$, 58.3 (NCH_2C=CH)$_{major}$, 50.2 (NCH_2C=CH)$_{minor}$, 58.0 (2 x NCH_2Ar), 114.6 (*C*H=C), 126.99, 127.04, 128.4, 128.5, 128.9 and 129.1 (10 x CH_{arom}), 137.9, 139.5 and 139.4 (2 x $C_{arom,quat}$ and *C*=CH). IR (neat) ν_{max} = 3058, 2919, 2795, 1494, 1453, 735, 697 cm^{-1}. MS *m/z* (%) 344/6 (M^+ + 1, 70). HRMS m/z (ESI) calculated for $C_{19}H_{22}BrN$ $[MH]^+$ 344.1014, found 344.1013.

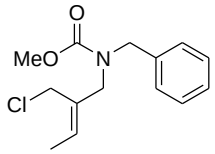
5.47 Synthesis of methyl *N*-[(2-(chloromethyl)but-2-enyl)]carbamates 326

As a representative example, the synthesis of *N*-benzyl-*N*-[(2-(chloromethyl)but-2-enyl)]carbamates **326a** and **326b** (R = H) is described here. *N*-Benzyl-3-ethylideneazetidine **307a** (0.07 g, 0.4 mmol) was dissolved in MeCN (10 mL), methyl chloroformate (0.06 g, 1.5 equiv) was added and the mixture was stirred for 15 hours under reflux. The reaction mixture was then poured into water (20 mL) and

extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with H_2O (2 × 15 mL) and $NaHCO_3$ (20 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent in vacuo afforded a mixture of methyl *N*-benzyl-*N*-[(2-(chloromethyl)but-2-enyl)]carbamates **326a** and **326b** (*Z*/*E* = 50/50) (0.11 g, overall yield 100%).

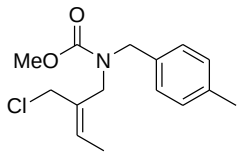
Methyl *N*-benzyl-*N*-[(2-(chloromethyl)but-2-enyl)]carbamates 326a and **326b** (R = H) (described as a mixture of isomers *Z*/*E* = 50/50)

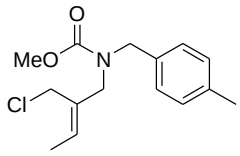


and


Yellow oil, Yield 100%. ^{1}H NMR (300 MHz, ref = $CDCl_3$) δ 1.52-1.54 (3H, m, C*H*$_3$CH=C), 3.70 (OCH_3), 3.96 (4H, brs, CH_2Cl and NC*H*$_2$C=CH), 4.38 (NCH_2Ar), 5.77-5.80 (1H, m, CH=C), 7.17-7.28 (5H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 14.2 (*C*H$_3$CH=C), 48.1 (CH_2) and 49.7 (CH_2), 52.2 (OCH_3), 53.9 (NCH_2Ar), 127.5, 127.8 and 128.6 (5 x CH_{arom}), 130.5 (*C*H=C), 132.4 and 137.5 (2 x $C_{arom,quat}$), 157.5 (CO). IR (neat) ν_{CO} = 1698 cm^{-1}, ν_{max} = 2956, 1467, 1452, 1405, 1242, 1117, 699 cm^{-1}. MS *m/z* (%) 268/70 (M^+ + 1, 100).

Methyl *N*-(4-methylbenzyl)-*N*-[(2-(chloromethyl)but-2-enyl)]carbamates 326a and **326b** (R = Me) (described as a mixture of isomers *Z*/*E* = 50/50)



and


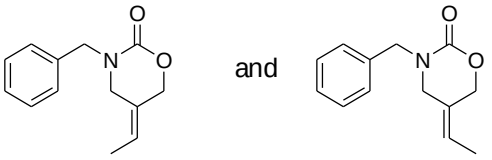
Yellow oil, Yield 100%. ^{1}H NMR (300 MHz, ref = $CDCl_3$) δ 1.61-1.63 (3H, m, C*H*$_3$CH=C), 2.34 (CH_3Ar), 3.77 (OCH_3), 4.03 (4H, brs, CH_2Cl and NC*H*$_2$C=CH), 4.41 (NCH_2Ar), 5.83-5.89 (1H, m, CH=C), 7.06-7.21 (4H, m, CH_{arom}). MS *m/z* (%) 282 (M^+ + 1, 100). HRMS m/z (ESI) calculated for $C_{15}H_{20}ClNO_2$ $[MH]^+$ 282.1255, found 282.1256.

5.48 Synthesis of 5-ethylidene-1,3-oxazinan-2-ones 327

As a representative example, the synthesis of 3-benzyl-5-ethylidene-1,3-oxazinan-2-ones **327a** and **327b** (R = H) is described here. A mixture of methyl *N*-benzyl-*N*-[(2-(chloromethyl)but-2-

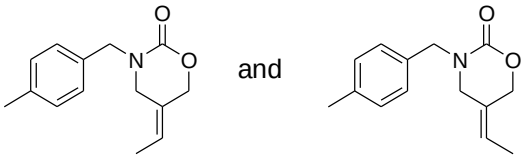
enyl)]carbamates **326a** and **326b** (0.08 g, 0.3 mmol) was dissolved in DMF (5 mL) and placed in 80 mL sealed vessel, provided with an appropriate stirrer bar and subjected to microwave conditions (140 °C, 150 W_{max}) for 30 min. The resulting reaction mixture was subsequently poured into water (15 mL) and extracted with Et_2O (3 x 15 mL). The combined organic extracts were thoroughly washed with H_2O (2 × 15 mL) and brine (15 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded a mixture of 3-benzyl-5-ethylidene-1,3-oxazinan-2-ones **327a** and **327b** (*Z*/*E* = 50/50) (0.06 g, overall yield 96%), which was purified by filtration through silica gel (petroleum ether/ethyl acetate 1/1).

3-Benzyl-5-ethylidene-1,3-oxazinan-2-ones 327a and **327b** (R = H) (described as a mixture of isomers *Z*/*E* = 50/50)



Yellow oil, R_f = 0.33 (petroleum ether/ethyl acetate 1/1), Yield 96%. ^{1}H NMR (300 MHz, ref = $CDCl_3$) δ 1.48-1.50 (3H, m, C*H*$_3$CH=C), 1.56-1.58 (3H, m, C*H*$_3$CH=C), 3.79-3.81 (2H, m, NC*H*$_2$C=CH), 4.56 (2H, s, CH_2), 4.59 (2H, s, CH_2), 5.05-5.115 (1H, m, CH=C), 5.57-5.63 (1H, m, CH=C), 7.27-7.39 (5H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 13.3 (CH_3), 18.1 (CH_3), 45.9 (CH_2N), 49.4 (CH_2N), 52.3 (CH_2N), 52.7 (CH_2N), 70.7 (CH_2O), 74.8 (CH_2O), 111.0 (*C*H=C), 123.2 (*C*H=C), 127.8, 126.2, 128.2 and 128.8 (5 x CH_{arom}), 136.5 and 138.3 ($C_{arom,quat}$ and *C*=CH), 155.5 (CO). IR (neat) ν_{CO} = 1689 cm^{-1}, ν_{max} = 2983, 1480, 1441, 1239, 1122, 704 cm^{-1}. MS *m/z* (%) 218 (M^+ + 1, 100). HRMS m/z (ESI) calculated for $C_{13}H_{15}NO_2$ $[MH]^+$ 218.1176, found 218.1170.

5-Ethylidene-3-(4-methylbenzyl)-1,3-oxazinan-2-ones 327a and **327b** (R = Me) (described as a mixture of isomers *Z*/*E* = 50/50)

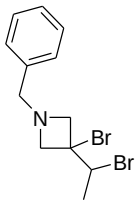


Yellow oil, R_f = 0.42 (petroleum ether/ethyl acetate 1/1), Yield 85%. ^{1}H NMR (300 MHz, ref = $CDCl_3$) δ 1.46-1.49 (3H, m, C*H*$_3$CH=C), 1.55-1.58 (3H, m, C*H*$_3$CH=C), 2.34 (3H, s, CH_3Ar), 3.75-3.79 (2H, m, NC*H*$_2$C=CH), 4.54 (4H, s, 2 x CH_2), 5.04-5.10 (1H, m, CH=C), 5.55-5.62 (1H, m, CH=C), 7.13-7.23 (4H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 13.3 (*C*H$_3$CH=C), 18.0 (*C*H$_3$CH=C), 21.2 (CH_3Ar), 29.8 (CH_3Ar), 45.8 (CH_2N), 49.2 (CH_2N), 52.0 (CH_2N), 52.4 (CH_2N), 70.7 (CH_2O), 74.8 (CH_2O), 111.0 (*C*H=C), 123.1 (*C*H=C), 126.2, 128.3, 129.5 and 133.4 ((4 x CH_{arom})$_{isomer1}$, (4 x CH_{arom})$_{isomer2}$), 133.3, 137.5, 137.6, 138.3 ((2 x $C_{arom,quat}$)$_{isomer1}$, (2 x $C_{arom,quat}$)$_{isomer2}$, and (*C*=CH)$_{isomer1}$, (*C*=CH)$_{isomer2}$), 154.4 (CO), 155.5 (CO). IR (neat) ν_{CO} = 1688 cm^{-1}, ν_{max} = 2920, 1478, 1440, 1238, 1121, 762. MS *m/z* (%) 218 (M^+ + 1, 100).

5.49 Synthesis of 1-benzyl-3-bromo-3-(1-bromoethyl)azetidine 332

3-Ethylideneazetidine **307a** (0.13 g, 0.7 mmol) was dissolved in $CHCl_3$ (10 mL), NBS (0.26 g, 2 equiv) was added and the mixture was stirred for 20 hours under reflux. The reaction mixture was poured into water (15 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were washed with H_2O (2 × 15 mL) and brine (15 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent in vacuo afforded 1-benzyl-3-bromo-3-(1-bromoethyl)azetidine **332** (0.17 g, 70%), which was purified by filtration through silica gel (petroleum ether/ethyl acetate 4/1) in order to obtain an analytically pure sample.

1-Benzyl-3-bromo-3-(1-bromoethyl)azetidine 332

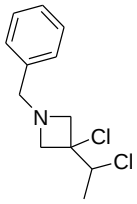


Yellow oil, R_f = 0.55 (petroleum ether/ethyl acetate 4/1), Yield 70%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.66 (3H, d, *J* = 6.6 Hz, CH_3), 3.53 (2H, d, *J* = 7.7 Hz, 2 x (*H*CH)C_{quat}), 3.66 (2H, d, *J* = 7.7 Hz, 2 x (HC*H*)C_{quat}), 3.67 (2H, s, NCH_2Ar), 4.42 (1H, q, *J* = 7.7 Hz, C*H*CH_3), 7.18-7.26 (5H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 22.7 (CH_3), 56.0 (*C*HCH_3), 61.4 (CBr), 62.7 (CH_2N), 66.8 (CH_2N), 69.2 (CH_2N), 127.5 and 128.6 (5 × CH_{arom}), 137.2 ($C_{arom,quat}$). IR (neat) ν_{max} = 2925, 1495, 1452, 1378, 1364, 1206, 1177, 1112, 1072, 755, 714, 697 cm^{-1}. MS m/z (%) 332/4/6 (M^+ + 1, 100). HRMS m/z (ESI) calculated for $C_{12}H_{15}Br_2N$ $[MH]^+$ 331.9644, found 331.9644

5.50 Synthesis of 1-benzyl-3-chloro-3-(1-chloroethyl)azetidine 333

3-Ethylideneazetidine **307a** (0.11 g, 0.6 mmol) was dissolved in CH_2Cl_2 (10 mL) and gaseous HCl was introduced for 10 min. Subsequently, *m*CPBA (0.11 g, 1 equiv) was slowly added and the mixture was stirred for 24 hours under reflux. The reaction mixture was poured into water (15 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were washed with $NaHCO_3$ (3 x 15 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent in vacuo afforded 1-benzyl-3-chloro-3-(1-chloroethyl)azetidine **333** (0.14 g, 92%), which was purified by filtration through silica gel (petroleum ether/ethyl acetate 4/1) in order to obtain an analytically pure sample.

1-Benzyl-3-chloro-3-(1-chloroethyl)azetidine 333

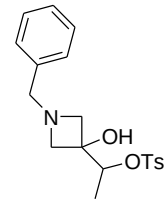


Yellow oil, R_f = 0.52 (petroleum ether/ethyl acetate 4/1), Yield 92%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.55 (3H, d, J = 6.6 Hz, CH_3), 3.47 and 3.54 (2H, 2 x d, J = 8.8 Hz, CH_2N), 3.50 and 3.73 (2H, 2 x d, J = 11.6 Hz, CH_2N), 3.71 (2H, s, CH_2N), 4.54 (1H, q, J = 6.6 Hz, C*H*CH_3), 7.24-7.34 (5H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 19.9 (CH_3), 62.4 (*C*HCH_3), 62.9 (CH_2N), 65.8 (CH_2N), 66.8 (CCl), 66.9 (CH_2N), 127.5 and 128.6 (5 x CH_{arom}), 137.3 ($C_{arom,quat}$). IR (neat) ν_{max} = 2953, 2940, 2850, 1495, 1453, 1364, 1182, 1074, 721, 697, 674 cm^{-1}. MS m/z (%) 244/6 (M^+ + 1, 100). HRMS m/z (ESI) calculated for $C_{12}H_{15}Cl_2N$ $[MH]^+$ 244.0654, found 244.0655.

5.51 Synthesis of 3-hydroxy-3-(1-tosyloxyethyl)azetidines 334

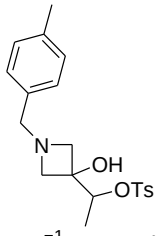
As a representative example the synthesis of 3-hydroxy-1-(4-methylbenzyl)-3-(1-tosyloxyethyl)azetidine **334b** was described here. 3-Ethylidene-(4-methylbenzyl)azetidine **307b** (0.9 g, 0.5 mmol) was dissolved in dry CH_2Cl_2 (15 mL), *p*TsOH (0.91 g, 1 equiv) was added and the mixture was stirred for 10 min at room temperature. Subsequently, *m*CPBA (1.25 g, 1.5 equiv) was slowly added and the mixture was stirred for 15 hours under reflux. The reaction mixture was poured into water (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with aqueous $NaHCO_3$ (3 x 20 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent in vacuo afforded 3-hydroxy-1-(4-methylbenzyl)-3-(1-tosyloxyethyl)azetidine **334b** (1.67 g, 93%).

1-Benzyl-3-hydroxy-3-(1-tosyloxyethyl)azetidine 334a



Yellow oil, Yield 92%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19 (3H, d, J = 6.0 Hz, CH_3CH), 2.44 (3H, s, CH_3Ar), 3.33-3.38 and 3.43-3.53 (4H, 2 x m, 2 x CH_2N), 3.77-3.79 (2H, m, CH_2N), 4.77 (1H, q, J = 6.3 Hz, C*H*CH_3), 7.25-7.36 and 7.80-7.83 (9H, 2 x m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 14.5 (*C*H_3CH), 21.4 (CH_3Ar), 60.9, 62.4 and 62.7 (3 x CH_2N), 71.8 (COH), 81.2 (*C*HO), 127.8, 128.0, 128.9, 129.1 and 130.1 (9 x CH_{arom}), 133.8, 134.9 and 145.3 (3 x $C_{arom,quat}$). MS m/z (%) 362 (M^+ + 1, 100).

3-Hydroxy-1-(4-methylbenzyl)-3-(1-tosyloxyethyl)azetidine 334b

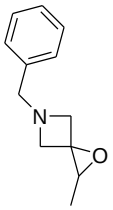


Yellow oil, Yield 93%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19 (3H, d, J = 6.6 Hz, CH_3CH), 2.33 and 2.44 (6H, 2 x s, 2 x CH_3Ar), 3.25-3.31 and 3.38-3.47 (4H, 2 x m, 2 x CH_2N), 3.65-3.74 (2H, m, CH_2N), 4.75 (1H, q, J = 6.6 Hz, C*H*CH_3), 7.11-7.36 and 7.80-7.83 (8H, 2 x m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 14.6 (*C*H_3CH), 21.2 (CH_3Ar), 61.6 (CH_2N), 62.3 (CH_2N), 63.1 (CH_2N), 71.9 (COH), 81.9 (*C*HO), 127.9, 128.8, 129.3 and 130.1 (8 x CH_{arom}), 132.9, 133.9, 137.5 and 145.2 (4 x $C_{arom,quat}$). IR (neat) ν_{OH} = 3295 cm^{-1}, ν_{max} = 2970, 2924, 1361, 1221, 1175, 1121, 1032, 1009, 909, 814, 730, 681 cm^{-1}. MS m/z (%) 376 (M^+ + 1, 100).

5.52 Synthesis of 2-methyl-1-oxa-5-aza-spiro[2.3]hexanes 335

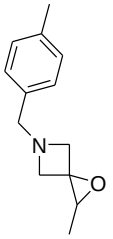
As a representative example the synthesis of 5-benzyl-2-methyl-5-aza-1-oxaspiro[2.3]hexane **335a** is described here. In an ice-cooled solution of 1-benzyl-3-hydroxy-3-(1-tosyloxyethyl)azetidine **307a** (0.19 g, 0.5 mmol) in dry THF (15 mL), NaH (60% suspension) (0.02 g, 1 equiv) was slowly added and the mixture was stirred for 15 hours at room temperature. The reaction mixture was poured into water (20 mL) and extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with H_2O (2 × 15 mL) and brine (20 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent in vacuo afforded 5-benzyl-2-methyl-5-aza-1-oxaspiro[2.3]hexane **335a** (0.10 g, 95%), which was purified by means of column chromatography on basic aluminium oxide (petroleum ether/ethyl acetate 4/1) in order to obtain an analytically pure sample.

5-Benzyl-2-methyl-5-aza-1-oxaspiro[2.3]hexane 335a



Light-yellow oil, R_f = 0.22 (petroleum ether/ethyl acetate 4/1), Yield 95%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23 (3H, d, J = 5.5 Hz, CH_3CH), 3.07 (1H, q, J = 5.5 Hz, CHCH$_3$), 3.35-3.38 and 3.43-3.46 (2H, 2 x m, 2 x (*H*CH)N), 3.60-3.66 (2H, m, 2 x (HC*H*)N), 3.76 (2H, s, CH_2N), 7.23-7.36 (5H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 15.5 (CH_3), 56.2 (*C*HCH$_3$), 59.5 (*C*H$_2$CO), 60.4 (CO), 61.6 (*C*H$_2$CO), 64.1 (NCH$_2$Ar), 127.3 and 128.6 (5 x CH_{arom}), 138.2 ($C_{arom,quat}$). IR (neat) ν_{max} = 2925, 2831, 1495, 1453, 1363, 1161, 826, 725, 697 cm^{-1}. MS m/z (%) 190 (M^+ + 1, 100). HRMS m/z (ESI) calculated for $C_{12}H_{15}NO$ [MH]$^+$ 190.1232, found 190.1232.

2-Methyl-5-(4-methylbenzyl)-5-aza-1-oxaspiro[2.3]hexane 335b



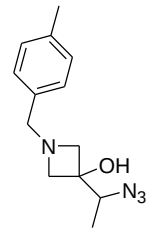
Light-yellow oil, R_f = 0.22 (petroleum ether/ethyl acetate 4/1), Yield 96%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.14 (3H, d, J = 5.0 Hz, CH_3CH), 2.25 (3H, s, CH_3Ar), 2.98 (1H, q, J = 5.0 Hz, CHCH$_3$), 3.25-3.28 and 3.34-3.37 (2H, 2 x m, 2 x (*H*CH)N), 3.50-3.57 (2H, m, 2 x (HC*H*)N), 3.64 (2H, s, CH_2N), 7.03-7.13 (4H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 15.5 (*C*H$_3$CH), 21.2 (CH_3Ar), 56.2 (*C*HCH$_3$), 59.4 (*C*H$_2$CO), 60.3 (CO), 61.5 (*C*H$_2$CO), 63.8 (NCH$_2$Ar), 128.6 and 129.2 (4 x CH_{arom}), 135.0 and 137.20 (2 x $C_{arom,quat}$). IR (neat) ν_{max} = 2925, 2852, 1515, 1449, 1377, 828, 809, 733 cm^{-1}. MS m/z (%) 204 (M^+ + 1, 100). HRMS m/z (ESI) calculated for $C_{13}H_{17}NO$ [MH]$^+$ 204.1383, found 204.1382.

5.53 Synthesis of 3-(1-azidoethyl)-1-(4-methylbenzyl)azetidin-3-ol 339

In an ice-cooled mixture of 2-methyl-5-(4-methylbenzyl)-5-aza-1-oxaspiro[2.3]hexane **335b** (0.06 g, 0.03 mmol) in Me_2CO/H_2O (8/1, 9 mL), NaN_3 (0.06 g, 3 equiv) and NH_4Cl (0.03 g, 2 equiv) were added and the mixture was stirred for 15 hours under reflux. The reaction mixture was poured into water (15

mL) and extracted with Et_2O (3 × 15 mL). The combined organic extracts were washed with H_2O (2 × 15 mL) and brine (15 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent in vacuo afforded 3-(1-azidoethyl)-1-(4-methylbenzyl)azetidin-3-ol **339** (0.06 g, 80%).

3-(1-Azidoethyl)-1-(4-methylbenzyl)azetidin-3-ol 339

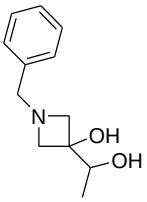


Yellow oil, Yield 80%. ^{1}H NMR (300 MHz, $CDCl_3$) δ ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31 (3H, d, *J* = 6.6 Hz, C*H*$_3$CH), 2.32 (3H, s, CH_3Ar), 2.32-2.35 (1H, m, C*H*CH_3), 3.02-3.06 (2H, m, 2 x (*H*CH)N), 3.27-3.30 and 3.39-3.41 (2H, 2 x m, 2 x (HC*H*)N), 3.59 (2H, s, CH_2N), 7.09-7.17 (4H, m, CH_{arom}). MS m/z (%) 247 (M^+ + 1, 100).

5.54 Synthesis of 3-(1-hydroxyethyl)azetidin-3-ols 340

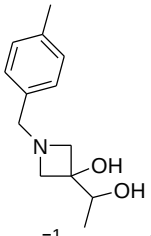
As a representative example the synthesis of 1-benzyl-3-(1-hydroxyethyl)azetidin-3-ol **340a** is described here. In an ice-cooled solution of 3-ethylidene-1-(4-methylbenzyl)azetidine **307a** (0.16 g, 0.9 mmol) in Me_2CO/H_2O (4/1, 10 mL), *N*-methylmorpholine-*N*-oxide (0.12 g, 1.1 equiv) and OsO_4 (4% in water) (5 mol%, 0.58 g) were added and the mixture was stirred for 4 hours at room temperature. Subsequently, an aqueous saturated solution of Na_2SO_3 (7 mL) was added and the mixture was stirred for 10 min. The reaction mixture was filtered and the filtrate was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were washed with H_2O (2 × 15 mL) and brine (15 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent in vacuo afforded 1-benzyl-3-(1-hydroxyethyl)azetidin-3-ol **340a** (0.15 g, 82%), which was purified by filtration through silica gel (dichloromethane/methanol = 9/1) to obtain an analytically pure sample.

1-Benzyl-3-(1-hydroxyethyl)azetidin-3-ol 340a



Dark yellow oil, R_f = 0.18 (dichloromethane/methanol 9/1), Yield 82%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13 (3H, d, *J* = 5.0 Hz, C*H*$_3$CH), 2.99-3.01 (2H, m, 2 x (*H*CH)N), 3.28-3.31 and 3.38-3.40 (2H, 2 x m, 2 x (HC*H*)N), 3.58 (2H, s, NCH_2Ar), 3.88 (1H, q, *J* = 5.0 Hz, C*H*CH_3), 7.18-7.24 (5H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 16.8 (CH_3CH), 63.1 ($CH_2C_{quat}CH_2$), 64.2 (NCH_2Ar), 71.2 (CHOH), 72.7 (COH), 127.4, 128.5 and 128.7 (5 x CH_{arom}), 137.6 ($C_{arom,quat}$). IR (neat) ν_{OH} = 3355 cm^{-1}, ν_{max} = 2963, 2930, 2849, 1453, 1364, 1189, 1082, 1027, 733, 698 cm^{-1}. MS m/z (%) 208 (M^+ + 1, 100).

3-(1-Hydroxyethyl)-1-(4-methylbenzyl)azetidin-3-ol 340b

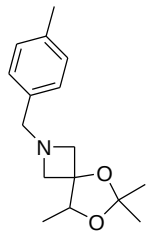


Dark yellow oil, R_f = 0.19 (dichloromethane/methanol 9/1), Yield 84%. ^{1}H NMR (300 MHz, CDCl3) δ 1.20 (3H, d, *J* = 6.0 Hz, C*H*$_3$CH), 2.33 (3H, s, CH$_3$Ar), 3.07-3.11 (2H, m, 2 x (*H*CH)N), 3.37-3.40 and 3.47-3.49 (2H, 2 x m, 2 x (HC*H*)N), 3.64 (2H, s, NCH$_2$Ar), 3.96 (1H, q, *J* = 6.0 Hz, C*H*CH$_3$), 7.10-7.18 (4H, m, CH$_{arom}$). ^{13}C NMR (75 MHz, ref = CDCl$_3$) δ 16.8 (*C*H$_3$CH), 21.2 (CH$_3$Ar), 62.7 (*C*H$_2$C$_{quat}$) and 63.0 (*C*H$_2$C$_{quat}$), 64.0 (NCH$_2$Ar), 71.1 (CHOH), 72.8 (COH), 128.7 and 129.2 (4 x CH$_{arom}$), 134.2 and 137.1 (2 x C$_{arom,quat}$). IR (neat) ν_{OH} = 3352 cm^{-1}, ν_{max} = 2933, 2852, 1449, 1362, 1186, 1104, 731 cm^{-1}. MS m/z (%) 222 (M$^+$ + 1, 100). HRMS m/z (ESI) calculated for $C_{13}H_{19}NO_2$ [MH]$^+$ 222.1489, found 222.1492.

5.55 Synthesis of 6,6,8-trimethyl-2-aza-5,7-dioxaspiro[3.4]octane 342

3-(1-Hydroxyethyl)-1-(4-methylbenzyl)azetidin-3-ol **340b** (0.22 g, 1 mmol) was dissolved in acetone (15 mL), *p*TsOH (0.19 g, 1.1 equiv) and $CuSO_4$ (0.80 g, 5 equiv) were added and the mixture was heated for 24 hours under reflux. Afterward, the reaction mixture was poured into water (15 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were washed with H_2O (2 × 15 mL) and brine (15 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent in vacuo afforded 6,6,8-trimethyl-2-(4-methylbenzyl)-2-aza-5,7-dioxaspiro[3.4]octane **342b** (0.25 g, 96%) which was purified by filtration through silica gel (dichloromethane/methanol = 9/1) to obtain an analytically pure sample.

1-(4-Methylbenzyl)-6,6,8-Trimethyl-2-aza-5,7-dioxaspiro[3.4]octane 342b

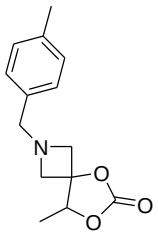


Yellow oil, R_f = 0.22 (dichloromethane/methanol 9/1), Yield 96%. ^{1}H NMR (300 MHz, CDCl$_3$) δ ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.24 and 1.28 (6H, 2 x s, C(CH$_3$)$_2$), 1.35 (3H, d, *J* = 6.6 Hz, C*H*$_3$CH), 2.25 (3H, s, CH$_3$Ar), 2.92 (1H, d, *J* = 8.0 Hz, (*H*CH)N), 3.20 and 3.30 (2H, 2 x d, *J* = 7.7 Hz, (HCH)N), 3.47 (1H, d, J = 8.0 Hz, (HC*H*)N), 3.52 (2H, s, NCH$_2$Ar), 4.08 (1H, q, *J* = 6.6 Hz, C*H*CH$_3$), 7.02-7.10 (4H, m, CH$_{arom}$). ^{13}C NMR (75 MHz, ref = CDCl$_3$) δ 16.2 (*C*H$_3$CH), 21.2 (CH$_3$Ar), 26.4 and 28.2 (C(*C*H$_3$)$_2$), 61.8 (*C*H$_2$C$_{quat}$), 63.4 (*C*H$_2$C$_{quat}$), 64.2 (NCH$_2$Ar), 77.4 (*C*HCH$_3$), 78.3 (CH$_2$*C*O), 107.9 (*C*(CH$_3$)$_2$), 128.4 and 129.1 (4 x CH$_{arom}$), 135.2 and 136.7 (2 x C$_{arom,quat}$). IR (neat) ν_{max} = 2983, 2931, 2830, 1378, 1370, 1224, 1171, 1099, 998, 810 cm^{-1}. MS m/z (%) 262 (M$^+$ + 1, 100).

5.56 Synthesis of 8-methyl-2-(4-methylbenzyl)-2-aza-5,7-dioxaspiro[3.4]octan-6-one 345

In an ice-cooled solution of 3-(1-Hydroxyethyl)-1-(4-methylbenzyl)azetidin-3-ol **340b** (0.22 g, 1 mmol) in dry CH_2Cl_2 (15 mL), NaH (60% suspension) (0.04 g, 1 equiv) and triethylamine (0.30 g, 3 equiv) were added and the mixture was stirred for 5 min at 0 °C. Subsequently, oxalyl chloride (0.14 g, 1 equiv) was added at 0 °C, and the mixture was stirred for 15 hours at room temperature. The reaction mixture was then poured into water and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were washed with H_2O (2 × 15 mL) and brine (15 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent in vacuo afforded 8-methyl-2-(4-methylbenzyl)-2-aza-5,7-dioxaspiro[3.4]octan-6-one **345b** (0.15 g, 60%).

8-Methyl-2-(4-methylbenzyl)-2-aza-5,7-dioxaspiro[3.4]octan-6-one 345



Yellow oil, Yield 60%, ^{1}H NMR (300 MHz, $CDCl_3$) δ ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.47 (3H, d, *J* = 6.6 Hz, C*H*$_3$CH), 2.27 (3H, s, CH_3Ar), 3.35 (2H, d, *J* = 9.4 Hz, 2 x (*H*CH)C_{quat}), 3.52 (2H, d, *J* = 9.4 Hz, 2 x (HC*H*)C_{quat}), 3.70 (2H, s, NCH_2Ar), 4.78 (1H, q, *J* = 6.6 Hz, C*H*CH_3), 7.06-7.12 (4H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 16.6 (*C*H_3CH), 21.2 (CH_3Ar), 58.9 (*C*H_2C_{quat}), 62.0 (*C*H_2C_{quat}), 63.7 (NCH_2Ar), 77.3 (*C*HCH_3), 79.7 (CH*C*O), 128.9 and 129.5 (4 x CH_{arom}), 130.1 and 137.8 (2 x $C_{arom,quat}$), CO (not detected). IR (neat) ν_{CO} = 1807 cm^{-1}, ν_{max} = 2923, 2853, 1643, 1182, 1081 cm^{-1}. MS m/z (%) 248 (M^+ + 1, 100).

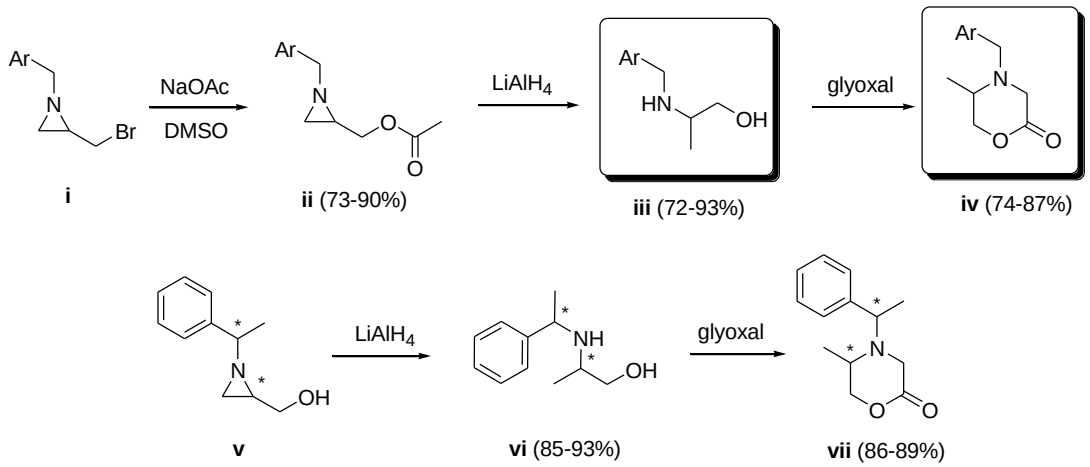
6 Summary

Aziridines display an uncommon combination of reactivity, atom economy and synthetic utility related to the ring strain of this class of nitrogen-containing heterocycles. As a consequence, aziridines are frequently deployed as versatile synthetic intermediates for the preparation of a variety of ring-opened and ring-expanded amines via regio- and stereoselective transformations. Azetidines, the higher homologues of aziridines, have acquired a prominent position in organic chemistry as well. Next to their synthetic relevance, compounds containing an azetidine moiety have been shown to possess a wide range of biological activities. For example, 3-alkoxy- and 3-aryloxyazetidines have been described as G-protein coupled receptor agonists, inhibitors of stearoyl-coenzyme d-9 desaturase and antibacterial agents.

Within the class of 2-substituted, non-activated aziridines, 2-(bromomethyl)aziridines are known to be good substrates for ring-opening reactions and nucleophilic substitutions, and these intriguing compounds have found many applications in synthetic chemistry. In particular, these compounds have been used as suitable synthons for the preparation of cyclopropanes, morpholines, pyrrolizidines, pyrrolidines, 2-imino-1,3-thiazoli(di)nes and piperidine derivatives.

Bearing in mind the high synthetic potential of these strained species, 2-(bromomethyl)aziridines were used as valuable synthons towards biologically and synthetically relevant species. In particular, the unexplored behavior of aziridines with regard to complex metal hydrides was addressed in this work.

Thus, in the first part of this PhD thesis, aziridines **i** were first transformed to the corresponding 2-(acetoxymethyl)aziridines **ii**, which were then subjected to regioselective ring opening with $LiAlH_4$ under microwave irradiation to provide useful β-amino alcohols **iii** (Scheme 1). β-Amino alcohols are applied extensively in organic chemistry as building blocks in designing natural and biologically active substances, and their chiral versions are also used in catalytic asymmetric synthesis. Subsequently, these compounds **iii** were used as suitable substrates for the preparation of six-membered oxazaheterocycles **iv** through the reaction with glyoxal. In light of the importance of chirality in medicinal chemistry, the synthesis of enantiopure amino alcohols **vi** and morpholin-2-ones **vii** was also explored starting from the commercially available 2-(hydroxymethyl)aziridines **v** using the same synthetic approach (i.e., reductive ring opening by $LiAlH_4$).

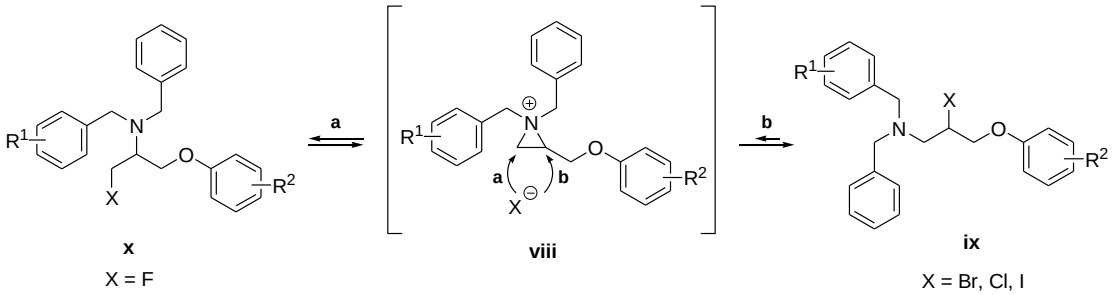


Scheme 1

In comparison with the reactivity of activated aziridines, i.e., aziridines bearing an electron-withdrawing substituent at the nitrogen atom, the reactivity profile of non-activated aziridines has been examined to a far lesser extent in the chemical literature. Non-activated aziridines require activation toward intermediate aziridinium salts for nucleophilic ring-opening reactions, whereas activated aziridines do not. In that respect, the ring opening of aziridinium salts by halides constitutes a convenient approach towards β-halo amines, which are generally recognized as useful building blocks in organic chemistry and valuable targets in medicinal chemistry (nitrogen mustards – chemotherapy agents). Although the issue of regioselectivity in the ring opening of 2-substituted non-activated aziridines had been addressed in a number of literature reports, no systematic study has been performed in which aziridinium substrates deriving from non-activated aziridines are subjected to ring opening by fluoride, chloride, bromide and iodide.

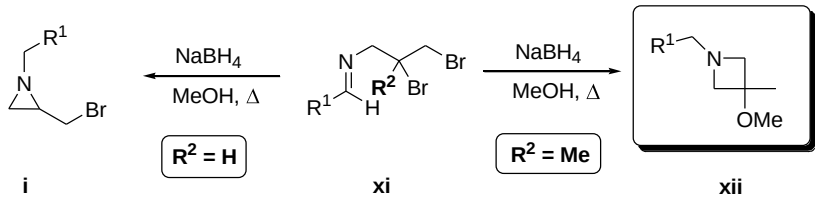
Therefore, in the second part of this work, the systematic study of the ring opening of *in situ* generated aziridinium salts **viii** by halides was investigated. As depicted in Scheme 2, the ring opening of aziridinium salts **viii** can occur at either the unsubstituted (path a) or substituted aziridine carbon atom (path b), leading either to primary halides **x** (path a) or secondary halides **ix** (path b). The different regioselectivity controlled by the type of nucleophile (halide) used in the ring opening of 2-(aryloxymethyl)aziridinium ion **viii** was discussed and the results were elucidated by means of molecular modelling calculations performed at the Center for Molecular Modeling of Ghent University (Prof. V. Van Speybroeck and Prof. M. Waroquier).

Both experimental and computational evidence was provided for the fact that product stabilities dictate the reaction outcome through thermodynamic control in the chloride, bromide and iodide case, involving rearrangement of the initially formed primary halides **x** to the more stable secondary halides **ix** via a thermodynamic equilibrium (Scheme 2). The ring opening of the same aziridinium salts by fluoride, however, was shown to be mediated by steric interactions (kinetic control), and primary fluorides **x** were formed as major products. In this way, the synthesis of a wide range of novel secondary β-bromo amines, β-chloro amines, β-iodo amines **ix** (X = Br, Cl, I) and primary β-fluoro amines **x** (as major products) was performed.



Scheme 2

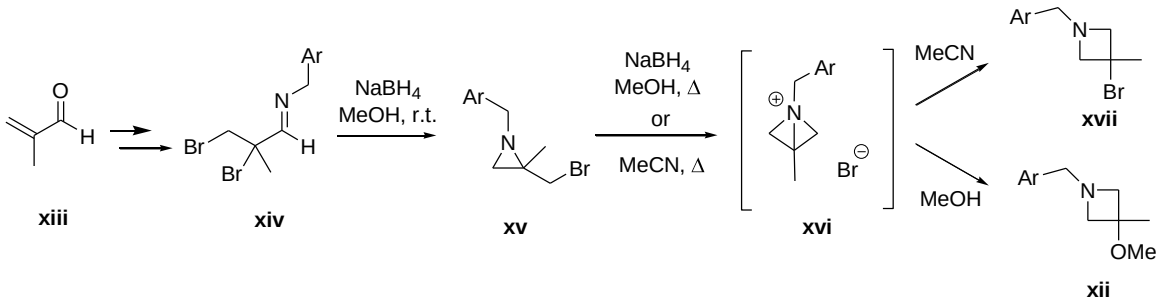
The reactivity of 2-(bromomethyl)aziridines **i** and their synthesis through the $NaBH_4$-reduction of *N*-alkylidene-(2,3-dibromopropyl)amines **xi** (R^2 = H) in methanol under reflux has been the subject of many literature reports. On the other hand, in a preliminary study at the Department of Sustainable Organic Chemistry and Technology, it has been shown that structurally similar *N*-alkylidene-(2,3-dibromo-2-methylpropyl)amines **xi** (R^1 = iPr, $CHEt_2$, R^2 = Me) afforded 3-methoxyazetidines **xii** under the same reaction conditions (Scheme 3), although the factors governing this peculiar reactivity remained unclear.



Scheme 3

In order to elucidate this unexpected reactivity of imines **xi** (R^2 = Me) and the influence of an additional methyl substituent in these substrates **xi** on the reaction outcome, the kinetically controlled synthesis of 2-bromomethyl-2-methylaziridines **xv**, as potential intermediates in this reaction was investigated in the third part of this PhD thesis. For this purpose, 2-bromomethyl-2-methylaziridines **xv** were prepared in an efficient way, comprising bromination of 2-methylacrolein **viii**, imination and subsequent $NaBH_4$-mediated ring closure of the corresponding imines **xiv** at room temperature (Scheme 4). This result clearly showed the intermediacy of aziridines **xv** in the formation of 3-methoxyazetidines **xii**. Furthermore, upon treatment of 2-bromomethyl-2-methylaziridines **xv** with $NaBH_4$ in methanol under reflux, 3-methoxy-3-methylazetidines **xii** were obtained, showing these species to be the thermodynamic products of the $NaBH_4$-mediated reduction of imines **xiv**. The theoretical elucidation of the reaction mechanism at the Center for Molecular Modeling (UGent) supported the intermediacy of bicyclic aziridinium ions **xvi** in this aziridine to azetidine ring rearrangement.

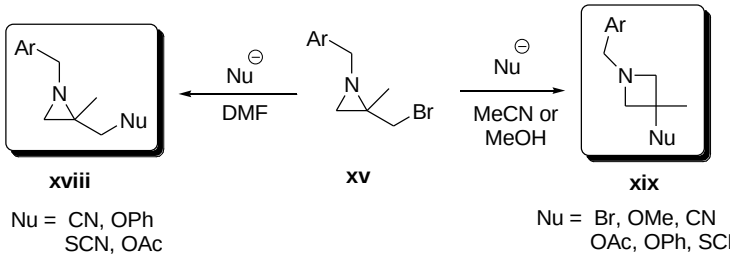
In addition, the propensity of aziridines **xv** to undergo ring expansion thorough the formation of intermediates **xvi** was also shown in the formation of 3-bromo-3-methylazetidines **xvii** obtained upon heating of these aziridines in acetonitrile under reflux (Scheme 4).



Scheme 4

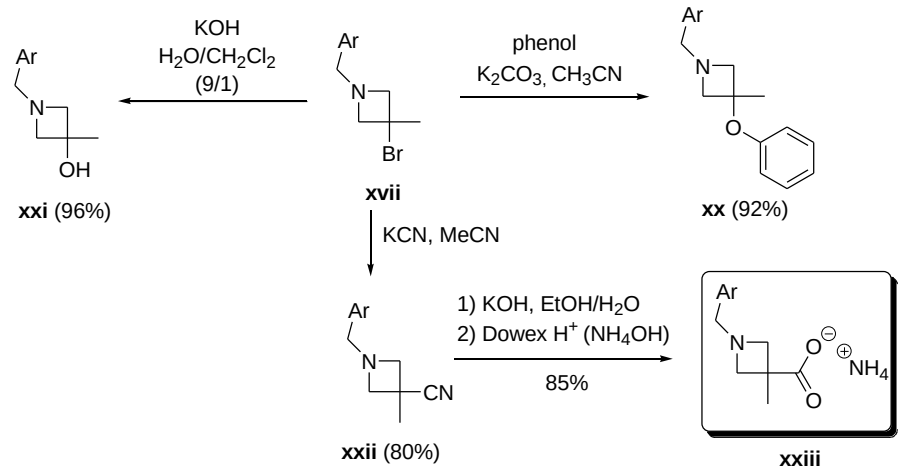
The high synthetic potential of 2-bromomethyl-2-methylaziridines with respect to the ring expansion to 3-substituted azetidines made these substrates valuable for further elaboration in terms of azetidine synthesis. The limited number of reports regarding aziridine to azetidine ring expansions and the mainly unexplored synthetic potential of 2-bromomethyl-2-methylaziridines opened a new possibility to access a novel class of 3-functionalized azetidines in an efficient way.

Therefore, in the fourth part of this work, the reactivity of 2-bromomethyl-2-methylaziridines **xv** toward different oxygen, sulfur and carbon nucleophiles in different solvent systems was envisaged. Surprisingly, it was shown that the choice of the solvent has a profound influence on the reaction outcome. In this way, the selective formation of functionalized aziridines **xviii** in dimethylformamide (DMF) and 3-substituted azetidines **xix** in acetonitrile (MeCN) was enabled (Scheme 5). The formation of aziridines **xviii** and azetidines **xix** in different solvents was studied by the high-level molecular modeling calculations at the Center for Molecular Modeling (UGent).



Scheme 5

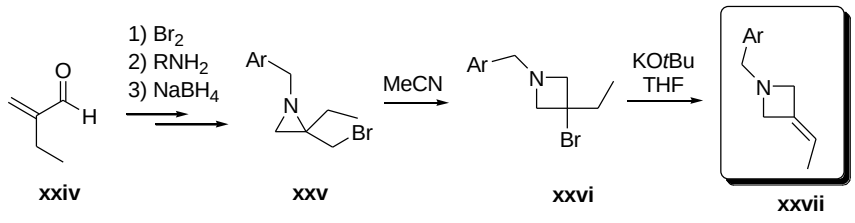
Bearing in mind the broad synthetic potential of 3-haloazetidines, 3-bromo-3-methylazetidine **xvii** was used as a suitable synthon to access a window of novel 3-functionalized azetidines. Treatment of azetidine **xvii** with phenoxide or hydroxide nucleophiles afforded 3-phenoxy- and 3-hydroxyazetidines **xx** and **xxi**, respectively (Scheme 6). 3-Bromo-3-methylazetidine **xvii** was also shown to be a good substrate for the synthesis of azetidine-3-carbonitriles **xxii** upon treatment with KCN in acetonitrile. The hydrolysis of the cyano group in latter azetidines **xxii** provided a convenient approach toward cyclic amino acids **xxiii**, which can be considered as analogue of azetidine-2-carboxylic acid, a natural molecule isolated from *Convallaria majalis* (lily of the valley) with impressive biological properties (Scheme 6).



Scheme 6

In addition, 3-alkyl-3-bromoazetidines can be considered as useful starting synthons for the preparation of the corresponding 3-alkylideneazetidines as versatile synthetic intermediates. 3-Alkylideneazetidines are strained cyclic allylamines and only limited information on the reactivity of this class of compounds is present in the literature. In most cases, the 3-alkylideneazetidine moiety was incorporated in the structure of more complex molecules, and no special attention has been devoted to the chemical nature of this strained system. In addition, the incorporation of conformational constraint at the 3-position of azetidine rings is known to increase the potency of human and rat FAAH inhibitors and showed to be an important structural feature of some drugs.

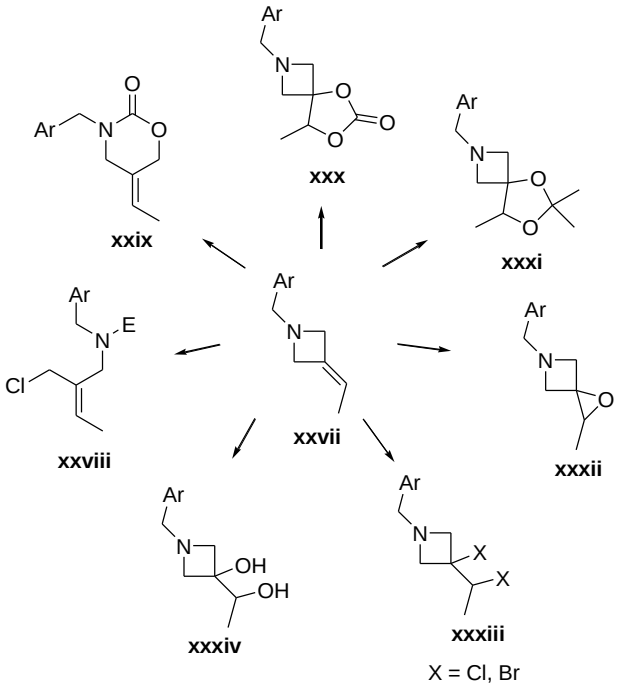
In the last part of this PhD work, a facile and efficient synthesis of 3-ethylideneazetidines **xxvii** was reported starting from the corresponding 3-bromo-3-ethylazetidines **xxvi**, obtained via ring expansion of aziridines **xxv** prepared by a synthetic methodology previously established in this PhD thesis (Scheme 7). Although the combination of two functionalities, i.e., an azetidine moiety and an exocyclic double bond, might result in unstable structures, this type of substrates was considered to be valuable for further study.



Scheme 7

Therefore, two aspects of the reactivity of 3-ethylideneazetidines were separately studied, i.e., the activation and subsequent ring opening of the azetidine moiety on the one hand, and functionalization of the exocyclic double bond on the other. In this way, azetidines **xxvii** were used as eligible substrates for the synthesis of a range of novel ring-opened amines **xxviii**, cyclic carbamates **xxix**,

cyclic carbonates **xxx**, 5,7-dioxa-2-azaspiro[3.4]octanes **xxxi**, 1-oxa-5-azaspiro[2,3]hexanes **xxxii**, 3-halo-3-(1-haloethyl)azetidines **xxxiii** and 3-(1-hydroxyethyl)-azetidin-3-ols **xxxiv** (Scheme 8).



Scheme 8

In this PhD thesis, the high synthetic potential of non-activated 2-(bromomethyl)aziridines and 2-bromomethyl-2-methylaziridines as fruitful synthons in organic chemistry has been illustrated by means of their elaboration toward a vast number of novel synthetically and biologically interesting nitrogen-containing compounds, which provide an entry to novel chemical space and diversity. In that respect, these non-activated aziridines, and especially the less known 2-bromomethyl-2-methylaziridines, should be recognized as important building blocks for further elaboration in the future.

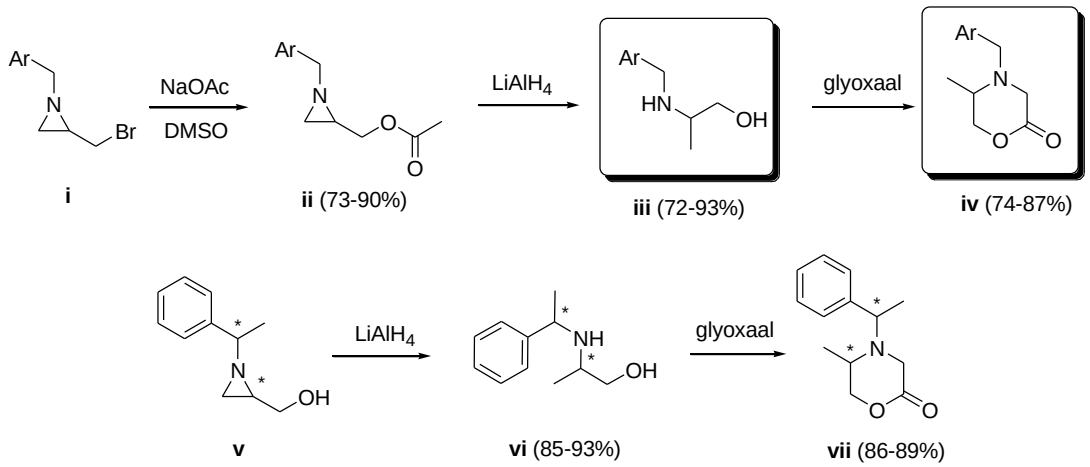
7 Samenvatting

Aziridinen verenigen een aantal interessante eigenschappen, zoals reactiviteit, atoomeconomie en synthetische toepasbaarheid te danken aan de ringspanning in deze stikstofbevattende heterocyclische verbindingen. Bijgevolg worden aziridinen vaak aangewend als veelzijdige precursoren in de synthese van ringgeopende en ringgeëxpandeerde structuren, via regio- en stereoselectieve transformaties. Azetidinen, de hogere homologen van aziridinen, hebben ook een prominente plaats in de organische chemie verworven. Naast hun synthetische toepasbaarheid bezitten vele verbindingen met een azetidinering in hun structuur een interessante biologische activiteit. Zo zijn 3-alkoxy- en 3-aryloxyazetidinen gekend als agonisten van G-proteïne-gekoppelde receptoren, inhibitoren van stearoylcoenzyme d-9 desaturase en antibacteriële middelen.

Binnen de klasse van 2-gesubstitueerde, niet-geactiveerde aziridinen staan 2-(broommethyl)aziridinen bekend als goede substraten voor ringopeningsreacties en nucleofiele substituties. Deze interessante verbindingen vonden reeds een groot aantal toepassingen in de synthetische chemie. In het bijzonder werden deze verbindingen in het verleden reeds gebruikt als synthon voor de bereiding van cyclopropanen, morfolinen, pyrrolizidinen, pyrrolidinen, 2-imino-1,3-thiazoli(di)nen en piperidinederivaten.

Omwille van hun groot potentieel werden 2-(broommethyl)aziridinen in dit werk aangewend als waardevolle bouwstenen voor de synthese van biologisch en synthetisch relevante verbindingen. In het bijzonder werd de tot hier toe onbekende reactiviteit van aziridinen ten aanzien van complexe metaalhydriden bestudeerd.

In het eerste deel van het onderzoek werden aziridinen **i** omgezet tot de overeenkomstige 2-(acetoxymethyl)aziridinen **ii**, die vervolgens regioselectief werden ringgeopend met $LiAlH_4$ bij verhoogde temperatuur onder microgolfbestraling. Deze transformatie gaf aanleiding tot de vorming van interessante β-aminoalcoholen **iii** (Schema 1); deze klasse van verbindingen kent een breide toepasbaarheid in de organische chemie als synthon in de bereiding van natuurproducten en biologisch actieve stoffen en chirale β-aminoalcoholen worden ook gebruikt in katalytische asymmetrische synthese. Vervolgens werden deze verbindingen **iii** gebruikt als substraat in de bereiding van zesatooms oxazaheterocyclische verbindingen **iv**, via reactie met glyoxaal. Gezien het belang van chiraliteit in de medicinale chemie werd de synthese van enantiomeer zuivere aminoalcoholen **vi** en oxazolinonen **vii** eveneens onderzocht, uitgaande van commercieel beschikbare 2-(hydroxymethyl)aziridinen **v**, via dezelfde syntheseweg ($LiAlH_4$-gemedieerde reductieve ringopening).



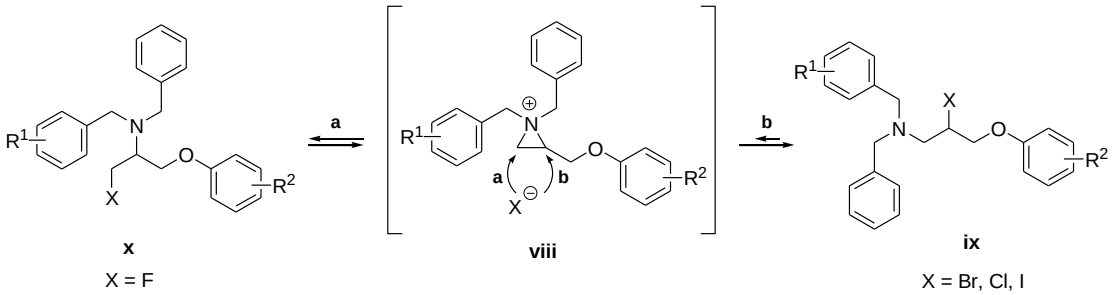
Schema 1

In vergelijking met de geactiveerde aziridinen, met een elektronenzuigende substituent op het stikstofatoom, genoot het reactiviteitsprofiel van niet-geactiveerde aziridinen tot op heden veel minder aandacht in de chemische literatuur. Niet-geactiveerde aziridinen moeten worden geactiveerd tot de overeenkomstige aziridiniumzouten alvorens ze nucleofiele ringopening kunnen ondergaan, terwijl bij geactiveerde aziridinen geen activatie tot een aziridiniumzout nodig is. In dat opzicht is de ringopening van aziridiniumzouten door middel van halogeniden een handige methode voor de synthese van β-halogeenaminen. Deze laatste verbindingen worden algemeen erkend als bruikbare bouwstenen in de organische chemie en vormen een waardevolle doelstructuur in de medicinale chemie (chemotherapeutica). Hoewel de regioselectiviteit bij ringopening van 2-gesubstitueerde niet-geactiveerde aziridinen reeds in het verleden behandeld werd, is tot nu toe nog geen systematisch onderzoek uitgevoerd waarbij aziridiniumsubstraten, bereid uit niet-geactiveerde aziridinen, ringopening ondergaan door middel van fluoride, chloride, bromide en jodide.

Daarom werd in het tweede deel van dit werk een systematische studie van de ringopening van *in situ* bereide aziridiniumzouten **xviii** door middel van halogeniden uitgewerkt. Zoals weergegeven in Schema 2 kan de ringopening van aziridiniumzouten **xviii** zowel op het ongesubstitueerd (pad a) of op het gesubstitueerd aziridinekoolstofatoom (pad b) gebeuren, hetgeen respectievelijk in primaire **x** en secundaire halogeniden **ix** resulteert. Het verschil in regioselectiviteit bij de ringopening van 2-(aryloxymethyl)aziridiniumionen **xviii**, afhankelijk van het type nucleofiel (halide), werd besproken. Deze resultaten zijn onderbouwd met theoretische berekeningen uitgevoerd aan het centrum voor Moleculaire Modellering van de Universiteit Gent (Prof V. Van Speybroeck en Prof. M. Waroquier).

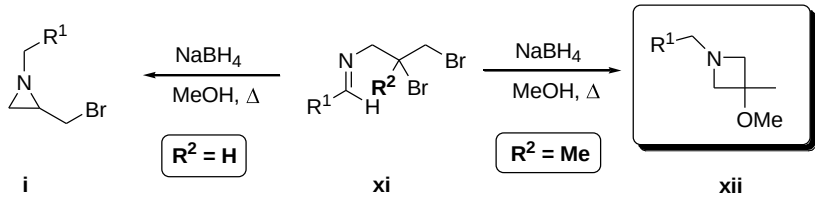
De experimentele en computationele gegevens bevestigden dat de reactie-uitkomst bepaald werd door thermodynamische controle indien chloride, bromide of jodide gebruikt werden als nucleofiel. Daarbij vindt een omzetting van de initieel gevormde primaire halogeniden **x** tot de meer stabiele secundaire halogeniden **ix** plaats (Schema 2). De ringopening van dezelfde aziridiniumzouten door middel van fluoride werd echter gecontroleerd door sterische interacties (kinetische controle), met vorming van primaire fluoriden **x** als hoofdproducten. Uit deze studie werden een groot aantal nieuwe

secundaire β-broomaminen, β-chlooraminen, β-joodaminen **ix** (X = Br, Cl, I) en primaire β-fluoraminen **x** (als belangrijkste producten) bekomen.



Schema 2

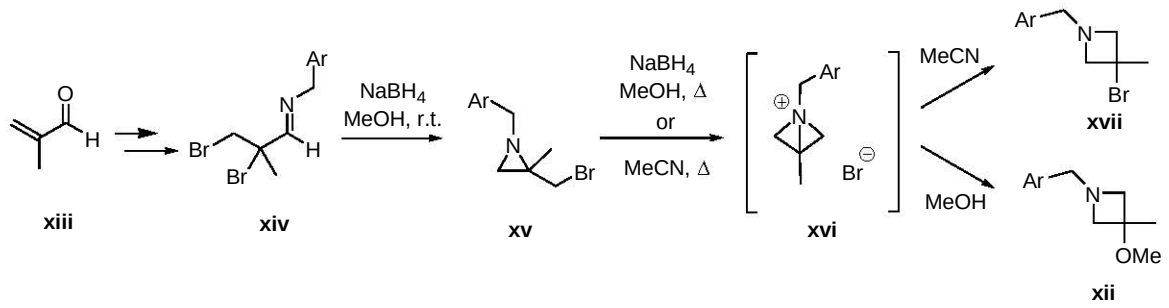
De reactiviteit van 2-(broommethyl)aziridinen **i**, alsook hun synthese via $NaBH_4$-gemedieerde reductie van *N*-alkylideen-(2,3-dibroompropyl)aminen **xi** (R^2 = H) in methanol onder reflux is reeds beschreven in de literatuur. In een preliminaire studie aan de vakgroep Duurzame Organische Chemie en Technologie, bleek echt dat structureel vergelijkbare *N*-alkylideen-(2,3-dibroom-2-methylpropyl)aminen **xi** (R^2 = Me) onder dezelfde reactieomstandigheden 3-methoxyazetidinen **xii** leveren (Schema 3). De reden voor deze onverwachte reactiviteit bleef tot op heden onduidelijk.



Schema 3

Om deze onverwachte reactiviteit van iminen **xi** (R^2 = Me), en de invloed van een extra methylsubstituent in substraten **xi** op de reactie-uitkomst te onderzoeken, werd in het derde deel van dit doctoraatsproefschrift de kinetisch gecontroleerde synthese van 2-broommethyl-2-methylaziridinen **xv** als potentiële tussenproducten van deze reactie bestudeerd. Hiertoe werden 2-broommethyl-2-methylaziridinen **xv** op een efficiënte manier bereid, via bromering van 2-methylacroleine **xviii**, iminering en daaropvolgende $NaBH_4$-gemedieerde ringsluiting van iminen **xiv** (Schema 4). Dit resultaat toonde het bestaan van aziridinen **xv** als intermediairen in de vorming van 3-methoxyazetidinen **xii** aan. Bovendien werden, na behandeling van 2-broommethyl-2-methylaziridinen **xv** met $NaBH_4$ in methanol onder reflux, 3-methoxy-3-methylazetidinen **xii** verkregen. Deze waarneming bevestigt dat producten **xii** worden gevormd als gevolg van de thermodynamisch gecontroleerde, $NaBH_4$-gemedieerde reductie van iminen **xiv**. Een theoretische studie van het reactiemechanisme, uitgevoerd aan het centrum voor Moleculaire Modellering (UGent), bevestigde de aanwezigheid van bicyclische aziridiniumionen **xvi** in de ringexpansie van aziridinen **xv** tot azetidinen **xii** en **xvii**.

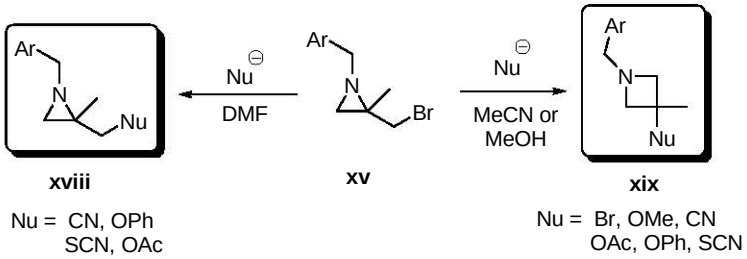
Bovendien is het ook aangetoond dat aziridinen **xv** ringexpansie kunnen ondergaan met vorming van 3-broom-3-methylazetidinen **xvii** via intermediairen **xvi**. Deze reactie gaat door bij verhitting van aziridinen **xv** onder reflux in acetonitril (Schema 4).



Schema 4

Het aldus aangetoonde potentieel van 2-broommethyl-2-methylaziridinen om ringexpansie tot 3-gesubstitueerde azetidinen te ondergaan opent nieuwe wegen op het gebied van de azetidinesynthese. Het beperkt aantal publicaties, die de ringexpansie van aziridinen tot azetidinen beschrijven en het (grotendeels) niet-onderzocht synthetische potentieel van 2-broommethyl-2-methylaziridinen, zorgde voor een efficiënte toetreding tot een nieuwe klasse van 3-gefunctionaliseerde azetidinen.

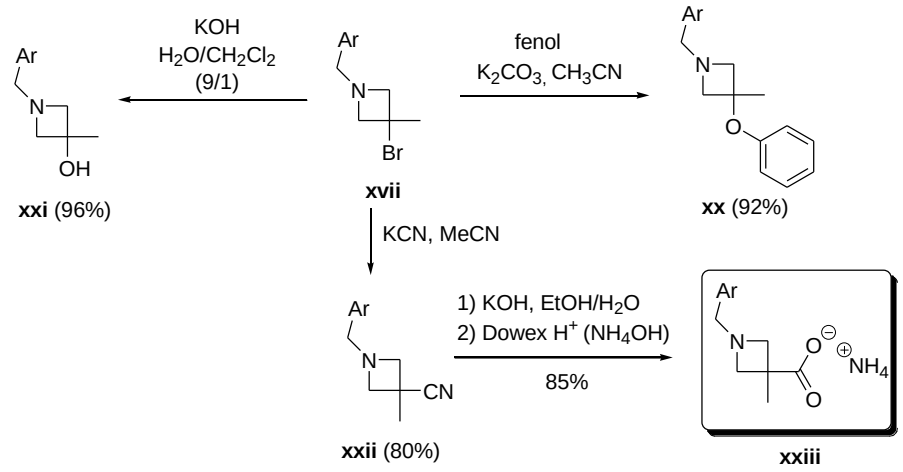
Bijgevolg werd in het vierde deel van dit werk de reactiviteit van 2-broommethyl-2-methylaziridinen **xv** ten opzichte van andere zuurstof-, zwavel- en koolstofnucleofielen in verschillende solventen geëvalueerd. Verrassend genoeg is gebleken dat de keuze van het solvent een grote invloed heeft op de reactie-uitkomst. Zo werd de selectieve vorming van gefunctionaliseerde aziridinen **xviii** in dimethylformamide (DMF) en 3-gesubstitueerde azetidinen **xix** in acetonitril (MeCN) gediscussieerd (Schema 5). Een verklaring voor de vorming van aziridinen **xviii** en azetidinen **xix** in verschillende solventen werd gezocht met behulp van de theoretische berekeningen, uitgevoerd aan het centrum voor Moleculaire Modellering (UGent).



Schema 5

Gezien het grote synthetische belang van 3-haloazetidinen werd 3-broom-3-methylazetidine **xvii** bestudeerd als een geschikt synthon voor de bereiding van nieuwe 3-gefunctionaliseerde azetidinen. De behandeling van azetidine **xvii** met fenoxide of hydroxide als nucleofielen leverde respectievelijk

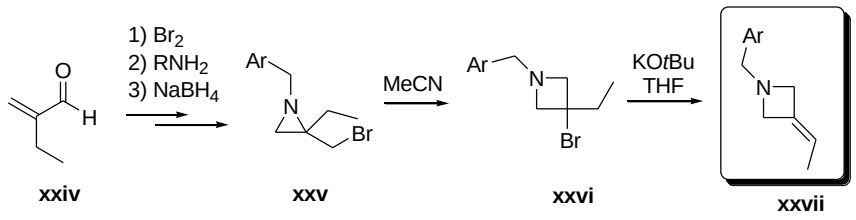
3-fenoxy- en 3-hydroxyazetidinen **xx** en **xxi** (Schema 6). 3-Broom-3-methylazetidine **xvii** bleek ook een goed substraat te zijn voor de synthese van azetidine-3-carbonitrillen **xxii** na behandeling met KCN in acetonitril. De hydrolyse van de cyaangroep in deze azetidinen **xxii** bleek een geschikte manier voor de synthese van cyclische aminozuren **xxiii**, die beschouwd kunnen worden als analogen van azetidine-2-carbonzuur, een natuurproduct met bijzondere biologische eigenschappen geïsoleerd uit *Convallaria majalis* (lelietje-van-dalen) (Schema 6).



Schema 6

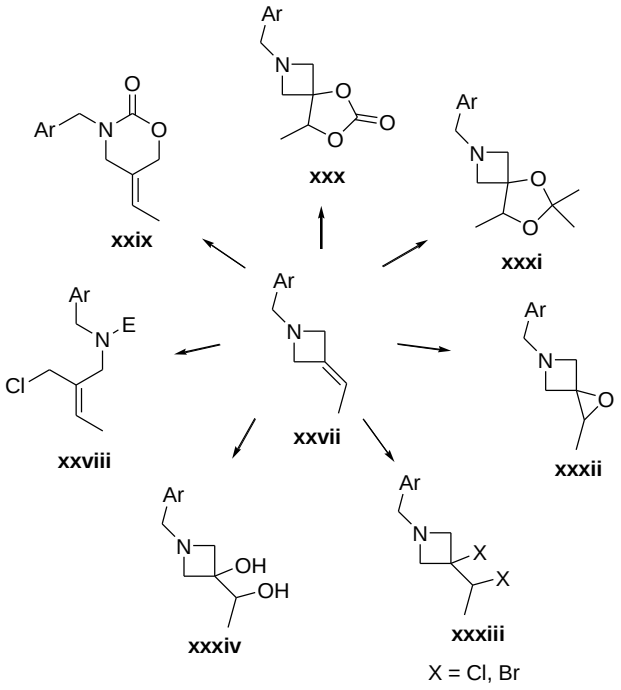
Daarnaast kunnen 3-alkyl-3-bromoazetidinen beschouwd worden als nuttige synthons voor de bereiding van de overeenkomstige 3-alkylideenazetidinen. 3-Alkylideenazetidinen zijn gespannen cyclische allylaminen met potentieel als veelzijdige synthetische bouwstenen die tot op heden echter weinig bestudeerd zijn in de literatuur. In de meeste gevallen werd de 3-alkylideenazetidine-eenheid opgenomen in meer complexe moleculen, en werd geen speciale aandacht besteed aan de chemische aard van dit gespannen systeem. Bovendien is gebleken dat de introductie van een conformationele beperking op de 3-plaats van azetidineringen FAAH-inhibitie in mens en rat versterkt; dit motief bleek reeds vak ook een belangrijke structurele eigenschap van sommige geneesmiddelen te zijn.

In het laatste deel van dit onderzoek werd een gemakkelijke en efficiënte synthese van 3-ethylideenazetidinen **xxvii** ontwikkeld uitgaande van de overeenkomstige 3-broom-3-ethylazetidinen **xxvi**. Deze bereiding verloopt via ringexpansie van aziridinen **xxv**, die eerder in dit doctoraatsonderzoek werden gesynthetiseerd (Schema 7). Hoewel de combinatie van een azetidinegroep en een exocyclische dubbele binding kan resulteren in instabiele structuren, werd de studie van dit type substraten toch als waardevol beschouwd.



Schema 7

Omwille van voornoemde instabiliteit werden twee aspecten van de reactiviteit van 3-ethylideenazetidinen afzonderlijk onderzocht: de activering en daaropvolgende ringopening van de azetidinegroep enerzijds, en de functionalisering van de exocyclische dubbele binding anderzijds. Uit deze studie blijkt dat azetidinen **xxvii** geschikte substraten zijn voor de synthese van een reeks van nieuwe aminen **xxviii**, cyclische carbamaten **xxix**, cyclische carbonaten **xxx**, 5,7-dioxa-2-azaspiro[3.4]octanen **xxxi**, 1-oxa-5-azaspiro[2,3]hexanen **xxxii**, 3-halogeen-3-(1-halogeenethyl)azetidinen **xxxiii** en 3-(1-hydroxyethyl)-azetidin-3-olen **xxxiv** (Schema 8).



Schema 8

In dit doctoraatsproefschrift werd het rijke potentieel van niet-geactiveerde 2-(broommethyl)aziridinen en 2-broommethyl-2-methylaziridinen als synthons in de organische chemie geïllustreerd, door hun derivatisatie naar een groot aantal nieuwe synthetisch en biologisch interessante stikstofverbindingen te bewerkstelligen. Deze verbindingen dragen bij tot de verdere expansie van de chemische ruimte. Aldus verdienen de niet-geactiveerde aziridinen, en vooral de minder bekende 2-broommethyl-2-methylaziridinen, verdere uitwerking in de toekomst.

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- 12th Belgian Organic Synthesis Symposium (BOSS XII), July 11-16, 2010, Namen, Belgium. Poster: S. Stanković, M. D'hooghe, N. De Kimpe, Microwave-assisted regioselective ring opening of nonactivated aziridines by lithium aluminium hydride.

- 14th Sigma Aldrich Organic Synthesis Meeting, December 2-3, 2010, Sol Cress, Spa, Belgium. Poster: S. Stanković, M. D'hooghe, K. Abbaspour Tehrani, N. De Kimpe, Ring expansion of 2-bromomethyl-2-methylaziridines to 3-methoxy-3-methylazetidines.

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