ir. MATTHIAS D'HOOGHE

2-(BROMOMETHYL)AZIRIDINES AS VERSATILE BUILDING BLOCKS IN ORGANIC CHEMISTRY

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

Opgedragen aan Kamiel

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The promoter:

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Woord vooraf

Op 1 september 2001 brak, na vijf jaren van intense studie, een nieuwe periode aan in mijn professioneel leven toen ik werd aangesteld als voltijds assistent bij de Vakgroep Organische Chemie. Gezien mijn interesse in onderzoek in het vakgebied van de organische chemie enerzijds en mijn motivatie om te kunnen bijdragen aan het onderwijs anderzijds, was de keuze voor een assistentenmandaat snel gemaakt, daar beide aspecten vervat zitten in het takenpakket. Mijn verwachtingen voor de komende jaren waren dan ook zeer hoog gespannen.

Nu, ruim vijf jaar later, is het gevoel van voldoening zeer groot, en blik ik met tevredenheid terug op mijn keuze van toen. De grootste uitdaging tijdens de eerste jaren van mijn mandaat was wellicht de zoektocht naar een goed evenwicht tussen onderzoek, onderwijs en dienstverlening. Door het streven naar kwalitatief onderwijs onder de vorm van werkcolleges en practica en de noodzakelijke administratieve verplichtingen was een degelijke planning van het wetenschappelijk onderzoek onontbeerlijk. Ik wens bij deze dan ook mijn promotor, Prof. dr. ir. N. De Kimpe, van harte te bedanken voor de voortdurende stimulans en professionele omkadering tijdens de voorbije jaren, waardoor ik de beschikbare tijd voor onderzoek optimaal kon benutten en laten renderen. Na verloop van tijd werd de invulling van mijn divers takenpakket dan ook geen opgave meer, en de verschillende opdrachten vloeiden samen tot een uiterst boeiend en uitdagend geheel. Ook hier wens ik Prof. De Kimpe te bedanken voor de vrijheid bij de tijdsindeling van elke dag, zonder de efficiëntie van uitvoeren en het resultaat hierbij uit het oog te verliezen.
Bij het finaliseren van mij doctoraal proefschrift wens ik ook alle leden van de examencommissie te danken voor hun deskundige beoordeling van mijn thesis, *in casu* Prof. M. Álvarez, Prof. D. Tourwé, Prof. A. Madder, Prof. B. De Meulenaer, Prof. C. Stevens en Prof. N. De Pauw. Ook een woordje van dank aan de professoren van de Vakgroep die niet in de examencommissie zetelden voor hun ondersteuning en bereidwilligheid. Verder wil ik alle collega’s van nu en toen danken voor de aangename samenwerking: Guido, Ellen, Kristof, Vera, Dominick, Sven C., Nicolai, Davy, Jan, Eva, Diederica, Kurt, Lorand, Pascal, Viviane, Sandra, Pieter, Theo, Frank, Tamer en in het bijzonder Sven, An, Willem en Bram, alsook alle andere (ex-)collega’s die hier niet bij naam vermeld werden.

Niet enkel de omringing tijdens de werkuren, maar ook en vooral de ondersteuning vóór en ná de dagtaak zijn bepalend voor het uiteindelijke resultaat. De trots waarmee ik dit proefschrift kan voorleggen is in zeer grote mate de verdienste van het thuisfront, en mijn dankbaarheid is dan ook meer dan evenredig. In de eerste plaats wil ik mijn ouders van harte bedanken voor hun visie, inzet en ondersteuning, waardoor alles al zoveel jaren de goede richting is uitgegaan. Daarnaast heeft ook de steun en aanwezigheid van vele andere familieleden zo dikwijls kleur gegeven aan ons leven: mijn grootouders bomma, bompa en oma, mijn zus Isabelle, mijn schoonouders Dany en Jeannine en mijn schoonbroers Peter en Sammy.

Maar boven dit alles gaat de zekerheid en geborgenheid van een warme thuis, en die is er voor mij steeds geweest dankzij jou, Ann. De weg die we samen al hebben afgelegd was prachtig, en kreeg een wonderlijke wending met de geboorte van ons zoontje Kamiel, toen liefde leven werd. Op deze weg wil ik verder gaan, bedankt voor alles.

Liefste Kamiel, sinds jij er bent, schijnt de zon elke dag. Ik draag deze thesis dan ook in het bijzonder aan jou op.

Matthias D'hooghe

Evergem, september 2006

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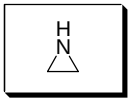
Introduction and Goals

The enhanced prevalence of infectious diseases and the rapid emergence of multi-drug resistant strains has become a major concern in medicine worldwide and, therefore, the development of new potential drugs is one of the key issues and challenges for medicinal chemistry and related disciplines nowadays. Furthermore, the search for alternative drugs and pesticides with improved properties – such as higher selectivity and lower toxicity – has always been an important incentive for the synthesis of new organic compounds with potential biological activity.

At present, the vast majority of the novel biologically active compounds contains a heterocyclic moiety and, consequently, heterocyclic chemistry has acquired a prominent place in organic synthesis. Besides their applicability in medicine and agriculture, (small-ring) heterocycles have been used intensively as synthons for the preparation of other interesting (a)cyclic targets with various applications. Furthermore, organic compounds with a nitrogen atom in their structure, especially amines, include some of the most important natural compounds with diverse functions, such as bioregulation, neurotransmission and defense mechanisms.

Consequently, it is not to be wondered at that azaheterocyclic compounds, i.e. compounds with a nitrogen atom incorporated in a ring system, comprise an important group of biologically active amines (e.g. alkaloids). Among these azaheterocycles, aziridines constitute a peculiar class of constrained cyclic amines with an uncommon combination of reactivity, synthetic flexibility and atom economy. The parent aziridine **1** (Chart 1), synthesized for the first time in 1888 by Gabriel,[1] is a water-soluble, colorless, distillable liquid (bp. 57°C) which is sensitive to polymerization, explosively when treated with acids.



1

Chart 1

As powerful alkylating agents, aziridines have an inherent *in vivo* potency, often based primarily on toxicity rather than specific activity. There are, however, several classes of aziridine containing natural products with important biological activities. Mitosanes **2**, first

isolated from *Streptomyces verticillatus*, are known for their anti-tumor and antibiotic activity (Chart 2).[2] Structure-activity relationships have identified the aziridine ring as being essential for this anti-tumor activity through DNA alkylation. Also the azinomycin family **3** (Chart 2), isolated from *Streptomyces griseofuscus*, possesses a wide range of activity against cancers by acting as DNA cross-linking agents.[3] Furthermore, *N*-mustard-based ADEPT (antibody-directed enzyme pro-drug therapy) strategies using compounds such as amines **4** have attracted great interest in recent years for potential cancer chemotherapies through double DNA alkylation via intermediate aziridinium salts **5** towards cross-linked DNA **6** (Scheme 1).[4]

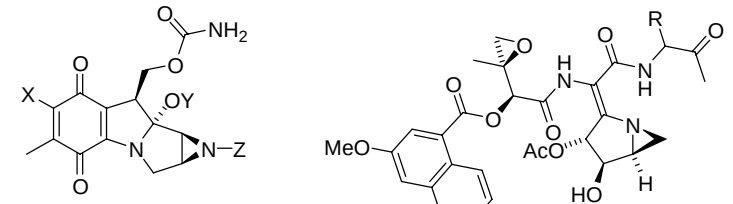
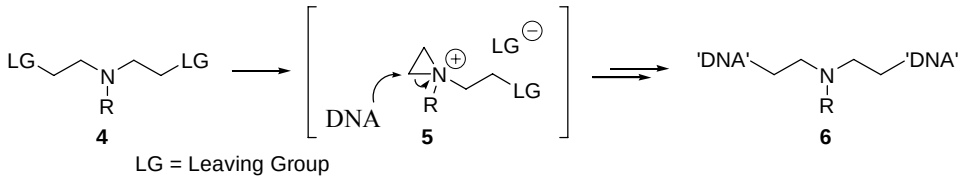


Chart 2



Scheme 1

Although the presence of an aziridine ring in natural compounds is limited to a few examples, aziridines have been used intensively for the synthesis of a whole variety of natural and synthetic products with different applications.[5] For example, the Amaryllidaceae alkaloid crinine **7**[6] and the naturally occurring 2-benzylisoquinoline alkaloids sendaverine and corgoine **8**[7] have been synthesized using aziridine derivatives as intermediates (Chart 3).

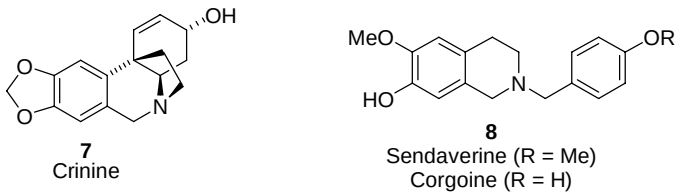


Chart 3

Indeed, ring strain renders aziridines susceptible to ring opening reactions that dominate their chemistry and which makes them useful synthetic intermediates in the arsenal of the organic chemist.

2-(Halomethyl)aziridines **9** comprise a peculiar and scarcely evaluated class of β-halo amines with high synthetic potential due to the presence of three different electrophilic carbon atoms and the nucleophilicity of the nitrogen atom (Chart 4). Furthermore, these synthons can be prepared in high yield and high purity using simple and straightforward methodologies, and their relative stability allows a long shelf life. These features, combined with the inherent reactivity of the aziridine ring and of the halogenated carbon atom, make 2-(halomethyl)aziridines **9** excellent substrates for various transformations in organic synthesis.

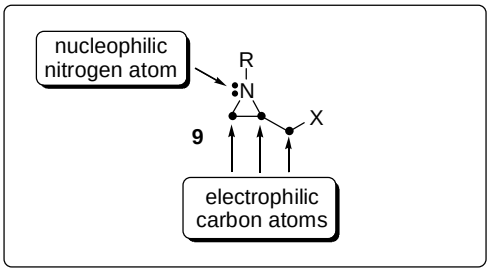


Chart 4

In this PhD thesis, the reactivity and synthetic potential of 1-sulfonyl- (i.e. activated) and 1-alkyl- (i.e. non-activated) 2-(bromomethyl)aziridines **10** and **11** will be evaluated thoroughly (Chart 5). Aziridines can be classified as 'activated' or 'non-activated' according to whether or not quaternization towards an aziridinium intermediate is required for nucleophilic ring opening reactions, and this classification is intimately related to the nature of the *N*-substituent.[8]

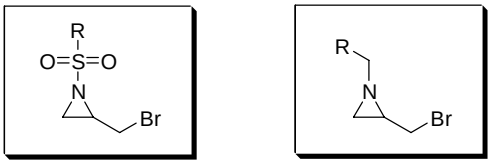
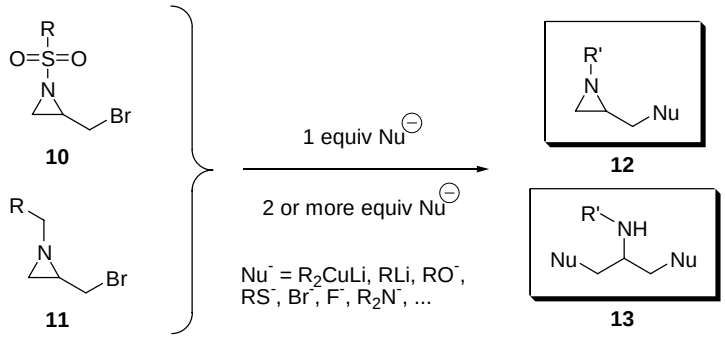


Chart 5

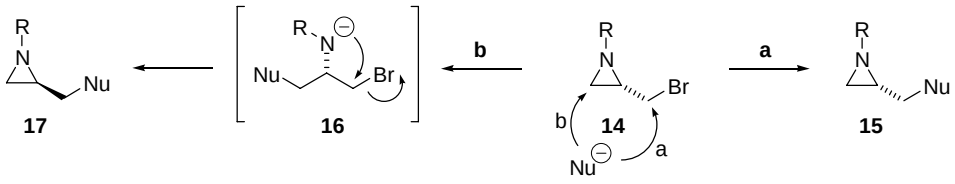
The study of these 2-(bromomethyl)aziridines **10** and **11** will be divided into two different topics. In the first part, the reactivity of 2-(bromomethyl)aziridines towards a variety of

nucleophiles will be evaluated. Comparison will be made between the behavior of activated versus non-activated 2-(bromomethyl)aziridines **10** and **11** upon treatment with either one or with two or more equivalents of different types of nucleophiles. Both carbon-centered nucleophiles and heteroatom-centered nucleophiles will be used in these experiments (Scheme 2). In this way, the degree of electrophilicity of the three electrophilic carbon atoms will be evaluated, as well as the stability of the aziridine ring upon treatment with these nucleophiles. The aim of this part is to afford a general reactivity profile of activated versus non-activated 2-(bromomethyl)aziridines **10** and **11** upon treatment with different types of nucleophiles, and to offer synthetic tools for the preparation of substituted aziridines **12** on the one hand and ring opened derivatives **13** on the other hand (Scheme 2).



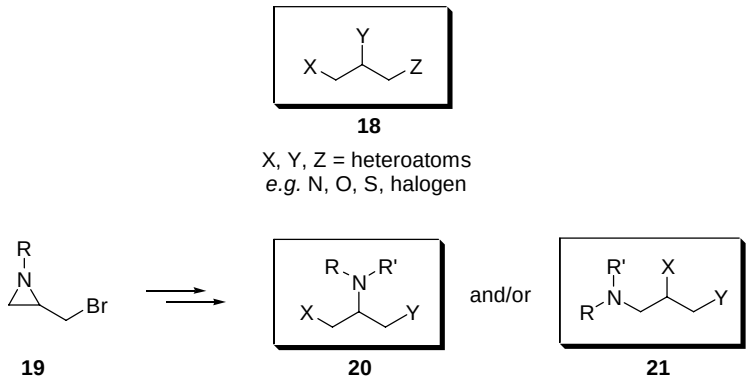
Scheme 2

Special attention will be devoted to the underlying reaction mechanisms in these substitution reactions, which will be studied using chiral 2-substituted aziridines as a model for aziridines **11**. Although it is known that activated aziridines **14** (R = sulfonyl) suffer from ring opening – ring closure towards the corresponding substitution products **17** with inversion of chirality (pathway b, Scheme 3), instead of direct substitution at the halogenated carbon atom (pathway a), no information is available on the reaction profile of unactivated 1-alkyl-(2-bromomethyl)aziridines **14** (R = alkyl) upon treatment with nucleophiles up to now.



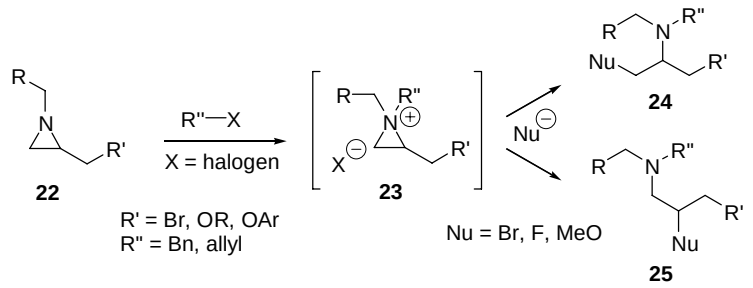
Scheme 3

The interest in substituted aziridine derivatives **12** (Scheme 2) can be explained considering their well-known applicability in organic synthesis for the preparation of a variety of nitrogen containing target compounds. Furthermore, also ring opened amines **13** are frequently used as building blocks or target compounds in organic chemistry. Especially the class of 1,2,3-triheteroatom substituted propane derivatives **18** (Scheme 4) has received a great deal of interest in recent years due to their broad applicability in medicinal chemistry, for example as β-blockers (propranolol, atenolol, metoprolol) and as antibiotics (chloramphenicol, thiamphenicol and florfenicol). Consequently, the conversion of 2-(bromomethyl)aziridines **19** into aminopropanes **20** and/or **21** as potential biologically relevant targets will be investigated thoroughly by means of substitution and ring opening reactions (Scheme 4).



Scheme 4

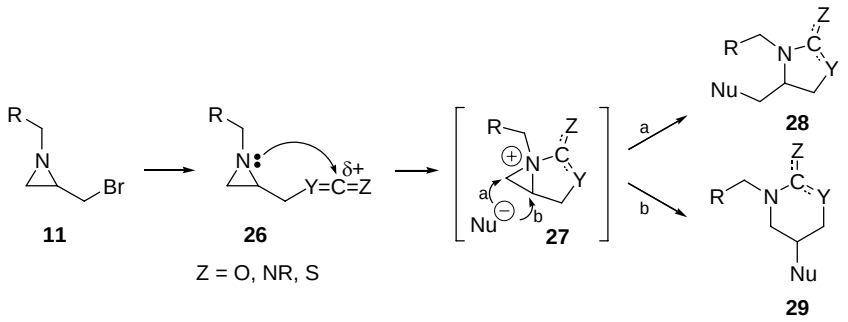
Throughout this work, the reactivity of intermediate aziridinium salts **23**, obtained by alkylation of 2-substituted 1-alkylaziridines **22**, will be investigated. Although it is generally known that alkylation of non-activated aziridines and subsequent ring opening constitutes a powerful tool for the synthesis of acyclic amines, only limited information on the regio- and stereoselectivity of the ring opening of aziridinium salts is available in the literature. In this PhD thesis, the reactivity of different 2-substituted aziridinium salts **23** will be studied in detail utilising a set of nucleophiles in different solvents in order to obtain a good insight in the synthetic potential of these intermediates **23** towards amines **24** and/or **25** (Scheme 5).



Scheme 5

Special attention will be given to the mechanistic profile of the reaction of 2-substituted 1-alkylaziridines **22** with an arylmethyl bromide, which can result in β-bromo amines **24** and/or **25** (R'' = Bn, X = Br, Scheme 5). The fate of the asymmetric aziridine carbon atom throughout this transformation will be studied using a chiral aziridine as a model compound. The elucidation of the underlying reaction mechanism is of primordial importance when the design of asymmetric syntheses towards chiral amines is contemplated starting from enantiopure aziridine derivatives **22**.

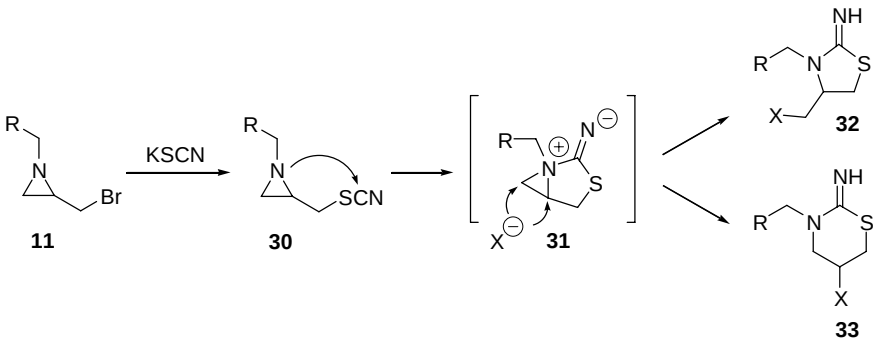
In the second part of this work, the usefulness of 2-(bromomethyl)aziridines **11** in ring transformations towards other azaheterocyclic compounds such as **28** and **29** via the ring opening of intermediates **27** will be investigated by means of the introduction of an electrophilic centre in the aziridine side-chain and subsequent intramolecular ring closure by the nucleophilic aziridine nitrogen lone pair (Scheme 6). The goal of this part is to offer (novel) approaches towards (new) azaheterocyclic compounds which feature structural resemblance to other compounds with known biological activity.



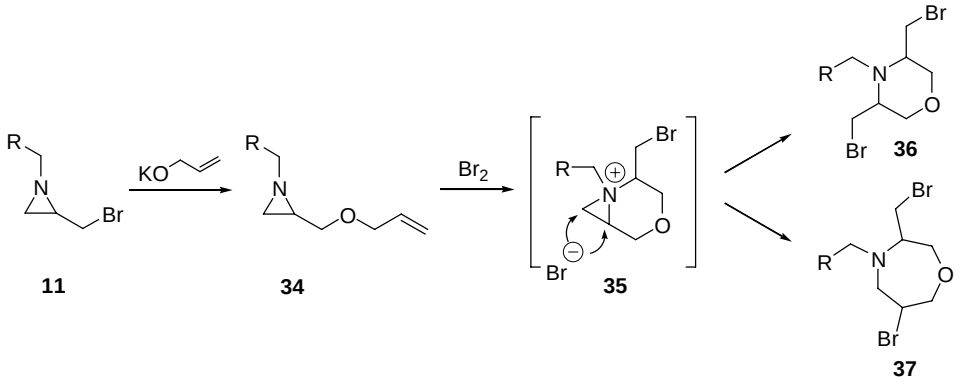
Scheme 6

For example, substitution of the bromo atom in 2-(bromomethyl)aziridines **11** by thiocyanate can give rise to the corresponding 2-(thiocyanomethyl)aziridines **30**, and subsequent

intramolecular ring closure would then result in the bicyclic aziridinium intermediate **31**. Ring opening of this intermediate **31** can afford five- and/or six-membered azaheterocycles **32** and **33** (Scheme 7). Analogously, 2-(allyloxymethyl)aziridines **34**, prepared from the corresponding 2-(bromomethyl)aziridines **11**, will be activated by means of bromine in order to create an electrophilic centre in the side chain. Intramolecular ring closure and subsequent ring opening of the intermediate aziridinium salt **35** can result in six- and/or seven membered ring systems **36** and **37** (Scheme 8).



Scheme 7



Scheme 8

All the methods presented in this work involve the use of a new and promising class of starting materials, i.e. 2-(bromomethyl)aziridines, as synthons for various applications. The aim of this PhD thesis is to acquire a profound insight in the reactivity of these substrates and to offer a new and versatile set of synthetic tools for the preparation of different classes of (novel) nitrogen containing compounds, which are structurally related to other compounds with significant biological activity.

Chapter 1. Literature review of aziridines in general and 2-(halomethyl)aziridines in particular

1.1. Aziridines: general aspects[9]

1.1.1. Introduction

The interest in aziridines as synthons in organic chemistry, complementary to the yet well-established epoxide chemistry, is due to the general influence of ring strain on chemical reactivity. The stability and the overall profile of chemical reactivity of these constrained azaheterocycles is attributable not only to the combined effects of bond shortening and angle compression, but also to the presence of the electronegative nitrogen atom.

1.1.2. Bond lengths, bond angles and ring strain

The dimensions of monocyclic aziridine have been determined by different methods, demonstrating a pronounced C-C bond shortening (1.46 Å) and a considerable C-N bond lengthening (1.48 Å) when compared to normal open chain C-C (1.54 Å) and C-N (1.46 Å) bond lengths. Endocyclic angles are all close to 60° and the geometry at nitrogen is pyramidal. The strain energy associated with three-membered rings is due principally to deformation of normal bond angles between the atoms of the ring and, to a lesser extent, resulting from interactions of substituents with the ring and with other substituents. Values of 112-113 kJ/mol have been reported for the conventional ring strain energy (CRSE) of aziridines, which is almost equal to the CRSE of cyclopropanes (115-116 kJ/mol). The presence of ring strain in small compounds results in the formation of bent bonds which are high in p-character. For an aziridine carbon atom, the two orbitals directed to the outside bonds have more s-character ($sp^{2.3}$) than a normal sp^3 orbital, while the two orbitals involved in ring bonding have less (sp^4). Lone pair hybridization has been estimated to be $sp^{2.2}$.

1.1.3. Infrared Spectroscopy

Absorptions specifically attributable to the various modes of ring deformations in aziridines have been assigned in the 1230-1250 cm^{-1} and 850 cm^{-1} regions (fingerprint).

1.1.4. Nuclear Magnetic Resonance Spectroscopy

NMR spectroscopy has found wide application to the study of structure and stereochemistry of aziridines. Vicinal proton-proton coupling constants of 5-9 Hz for *cis* related protons and of 2-6 Hz for *trans* related protons generally enable the stereochemistry at C2 and C3 to be determined. Extensive tables of vicinal and geminal J-values show that the average magnitudes follow the order: J_{cis} = 6.4 Hz, J_{trans} = 3.3 Hz and J_{gem} = 1.4 Hz. Protons attached to the parent aziridine ring carbons resonate at ca. 1.5 ppm in ^{1}H NMR and substituents almost invariably have a deshielding influence upon them.

1.1.5. Mass spectrometry

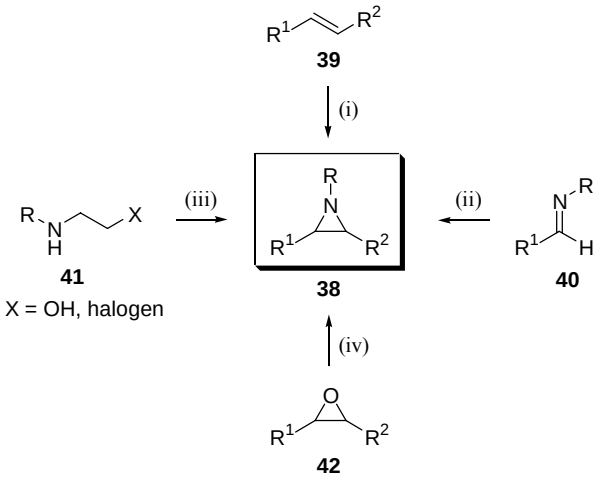
Mass spectra of C-alkyl substituted aziridines show a prominent β-cleavage process which can be rationalized as resulting from concerted fragmentation and ring collapse. α-Cleavage appears to be a significant but less important pathway. *N*-Alkyl substituted aziridines show ions resulting principally from α-cleavage, but sequential β-, γ-, etc. cleavages within the side chain are also observed.

1.1.6. Nitrogen inversion

In contrast to most cyclic and acyclic amines, the bonding constraints of the aziridine ring have the effect of retarding nitrogen inversion rates to extents where they are measurable by NMR spectroscopy. It is qualitatively evident that substituents bound to nitrogen have pronounced effects upon the barriers to nitrogen inversion. Those substituents able to delocalize the lone pair electrons, which occupy a p-orbital in the transition state, lower the barrier to (or increase the rate of) inversion. An increase in substituent bulk has the same effect since the destabilizing non-bonded interactions in the ground state configuration are partially relieved in the transition state. Halogens or other substituents bearing unshared electron pairs (e.g. alkoxides) have the effect of dramatically raising the barriers to inversion to an extent which often enables the physical separation and isolation of invertomers at ambient temperature.

1.1.7. Synthesis

The chemistry of aziridines has been hindered by the lack of suitable methods for their preparation or, as Atkinson has observed, "aziridiniation is epoxidation's poor relation".[10] Principally, the synthetic methods available for the preparation of aziridines **38** can be divided into 4 categories: (i) by addition of nitrene-like species to alkenes **39**, (ii) by addition of carbenes and ylids to imines **40**, (iii) from 1,2-aminoalcohols and 1,2-aminohalides **41**, and (iv) from epoxides **42** (Scheme 9). These methods have been discussed in detail in several review articles, and more information can be found therein.[9,10,11] Asymmetric syntheses of aziridines often rely on the presence of pre-existing chiral centres, and it is fair to say that no truly general method for direct asymmetric aziridination has been developed up to now.



Scheme 9

1.1.8. Reactivity

When compared to epoxides, the chemistry of aziridines is further complicated by the presence of an additional valency on the heteroatom, and since the mid-1960s aziridines have been classified as 'activated' or 'non-activated' according to whether or not quaternization towards an aziridinium intermediate is required for nucleophilic ring opening reactions. A major and characteristic reaction of the aziridine ring is its reactivity towards a wide variety of reagents, an effect undoubtedly resulting from the necessary compression of bond angles in the three-membered ring. Thus, this ring system is susceptible towards ring cleavage because of the favourable release of strain energy involved. For this reason, aziridines may be converted into a wide variety of functionalized nitrogen containing compounds by ring opening reactions and ring transformations.

1.2. Synthesis and reactivity of 2-(halomethyl)aziridines

1.2.1. Introduction

In this paragraph, the chemistry of 2-(halomethyl)aziridines **43** with a general structure as depicted in Chart 6 will be discussed, including the synthesis and reactivity of representatives with different substituents at nitrogen (R) and at the aziridine carbon atoms (R'). Analogous compounds substituted at the exocyclic methylene carbon atom will not be dealt with.

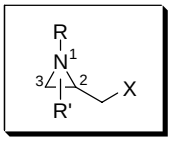


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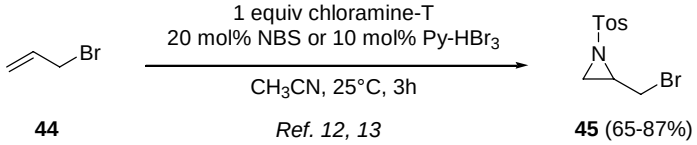
Chart 6

1.2.2. Synthesis of 2-(halomethyl)aziridines

1.2.2.1. Direct aziridination of olefins

A simple and convenient method for the synthesis of 2-(bromomethyl)-1-tosylaziridine **45** comprises aziridination of allyl bromide **44** in acetonitrile using *N*-chloro-*N*-sodio-p-toluenesulfonamide (chloramine-T) as a nitrogen source and *N*-bromosuccinimide (NBS) as an efficient catalyst (Scheme 10).[12] The same transformation has also been performed using pyridinium hydrobromide perbromide as a catalyst, although the yield was slightly lower (Scheme 10).[13]

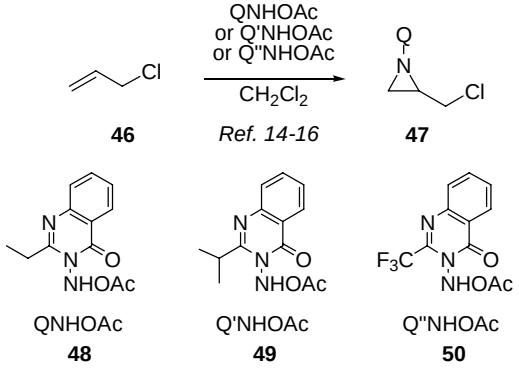


44 *Ref. 12, 13* **45** (65-87%)

Scheme 10

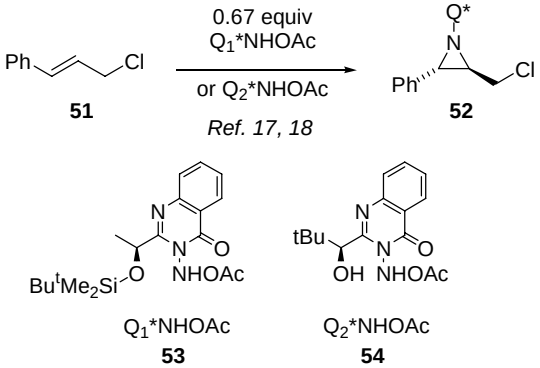
The use of different 3-acetoxyaminoquinazolinones for the aziridination of allyl chlorides has been studied intensively by Atkinson *et al*. 2-(Chloromethyl)aziridine **47** has been prepared from allyl chloride **46** upon treatment with 3-acetoxyamino-2-ethylquinazolinone **48** (QNHOAc) in the presence of trifluoroacetic acid (Scheme 11).[14] Also other 3-acetoxyaminoquinazolinones have been evaluated for the synthesis of aziridines. For

example, treatment of allyl chloride **46** with 3-acetoxyamino-2-isopropylquinazolinone **49** (Q'NHOAc) in the presence of hexamethyldisilazane (HMDS) afforded the corresponding 2-(chloromethyl)aziridine **47**, although the yield was very low (18%).[15] Finally, also 3-acetoxyamino-2-trifluoromethylquinazolinone **50** (Q''NHOAc) has been used towards the corresponding 2-(chloromethyl)aziridine **47** in 46% yield.[16]



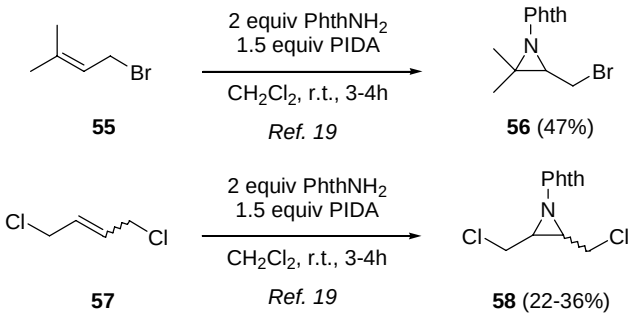
Scheme 11

Furthermore, a diastereoselective approach for the aziridination of allyl chloride **51** involves the use of enantiopure 3-acetoxyaminoquinazolinone **53** Q_1*NHOAc towards *trans*-2-phenyl-3-(chloromethyl)aziridine **52** (dr 10:1).[17] Alternatively, 3-acetoxyaminoquinazolinone **54** Q_2*NHOAc has been used towards the analogous aziridine **52** with excellent diastereoselectivity (dr > 50:1, Scheme 12).[18]



Scheme 12

A recently developed method for direct aziridination of olefins comprises the reaction with *N*-aminophthalimide ($PhthNH_2$). Starting from allyl halides **55** and **57**, the corresponding 2-(halomethyl)aziridines **56** and **58** were prepared in moderate yields using phenyliodine(III) diacetate (PIDA) as a mild oxidant (Scheme 13).[19]



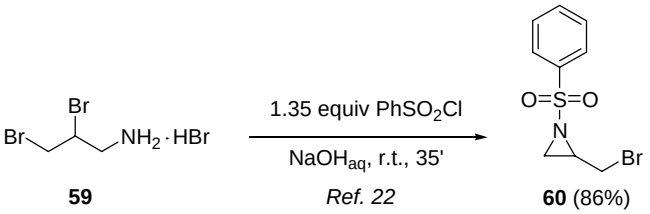
Scheme 13

By means of the electrochemical variant of the latter procedure (+1.80 V), which involves the generation and trapping of highly reactive nitrene-transfer reagents under mild conditions on platinum electrodes, similar results were obtained in slightly higher yields. Only allyl bromide appeared to be inert in electrochemical aziridination, and the corresponding 2-(bromomethyl)aziridine could not be synthesized.[20,21]

1.2.2.2. Synthesis of 2-(halomethyl)aziridines from β-halo amines and β-amino alcohols

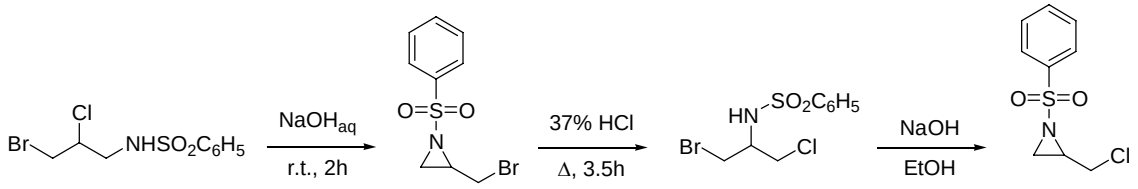
Intramolecular ring closure of amines with a suitable leaving group in β-position of the nitrogen atom comprises a very powerful and frequently used method for the construction of three-membered azaheterocycles. In most cases, the substrates are β-halo amines or β-amino alcohols, in which the hydroxyl group is first transformed into a better leaving group.

One of the first reports on the synthesis of 2-(halomethyl)aziridines has been published by Gensler *et al*. This procedure involves treatment of 1-amino-2,3-dibromopropane hydrobromide **59** with benzenesulfonyl chloride in water in the presence of sodium hydroxide, resulting in 1-benzenesulfonyl-2-(bromomethyl)aziridine **60** (Scheme 14).[22]



Scheme 14

Aziridine **60** has also been synthesized from *N*-(3-bromo-2-chloropropyl)benzenesulfonamide **61**, which was prepared from *N*-allylbenzenesulfonamide by addition of bromine in the presence of hydrogen chloride. This sulfonamide **61** was converted into 2-(bromomethyl)aziridine **60** in aqueous sodium hydroxide solution. The latter 2-(bromomethyl)aziridine **60** was ring opened at the unsubstituted aziridine carbon atom to form 1-bromo-2-benzenesulfonamido-3-chloropropane **62** upon treatment with HCl, and the amine **62** was subsequently ring closed towards 2-(chloromethyl)aziridine **63** by intramolecular nucleophilic displacement of the bromo atom (Scheme 15).[23]

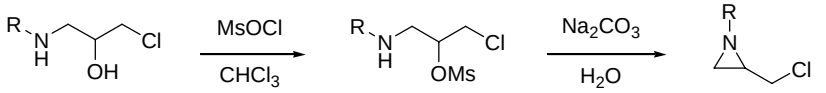


61 **60** **62** (68%) **63** (85%)

Ref. 23

Scheme 15

1-Alkyl-2-(chloromethyl)aziridines **66** have been prepared selectively starting from β-amino alcohols **64**, which were mesylated to **65** using mesyl chloride and subsequently ring closed towards aziridines **66** in an aqueous sodium carbonate solution in good overall yields (54-55%, Scheme 16).[24]

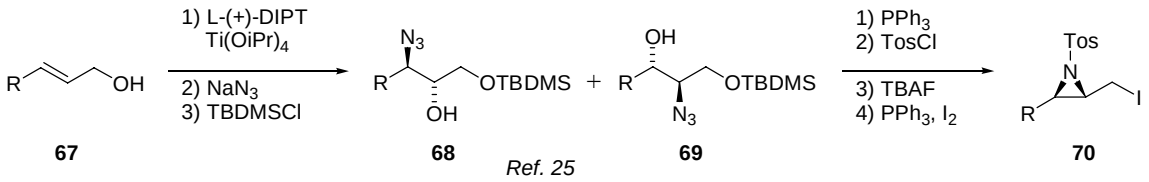


64 R = *tert*-Bu, cHex **65** **66** (54-55%)

Ref. 24

Scheme 16

β-Amino alcohols have also been used for the enantioselective synthesis of 2-(iodomethyl)- and 2-(chloromethyl)aziridines. For example, chiral 2-(iodomethyl)aziridines **70** have been synthesized starting from allylic alcohols **67** in a seven-step procedure, involving a Sharpless asymmetric epoxidation and subsequent ring opening of the epoxides affording azido alcohols **68** and **69**, which were in their turn cyclized towards aziridines **70** (Scheme 17). Treatment of 2-(iodomethyl)aziridines **70** with indium metal in refluxing methanol resulted in the corresponding chiral allyl amines in excellent yields.[25]

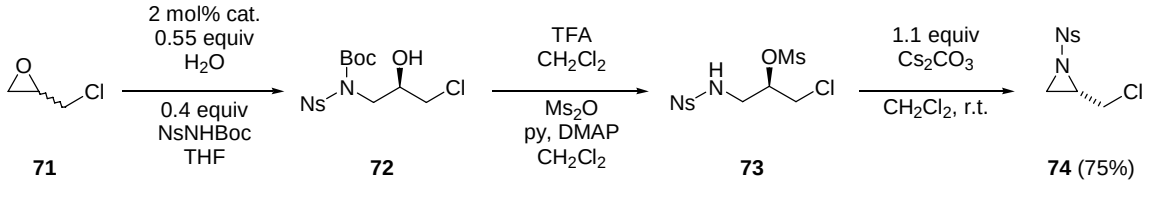


67 **68** **69** **70**

Ref. 25

Scheme 17

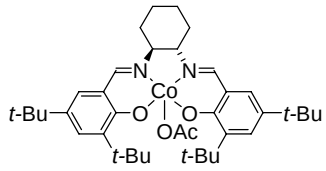
The catalytic synthesis of highly enantiomerically enriched 2-(chloromethyl)aziridines **74** from racemic epoxides comprised sequential addition of water and *N*-boc-2-nitrobenzenesulfonamide to a solution of epoxide **71** and catalyst (*S*,*S*)-**75** in THF, affording the chiral aminoalcohol **72**. Removal of the Boc group and mesylation furnished amine **73**, which was subsequently cyclized towards 2-(chloromethyl)aziridine **74** using Cs_2CO_3 in CH_2Cl_2 (ee > 99%, Scheme 18).[26]



71 **72** **73** **74** (75%)

Ns = nosyl (4-nitrobenzenesulfonyl)

Ref. 26

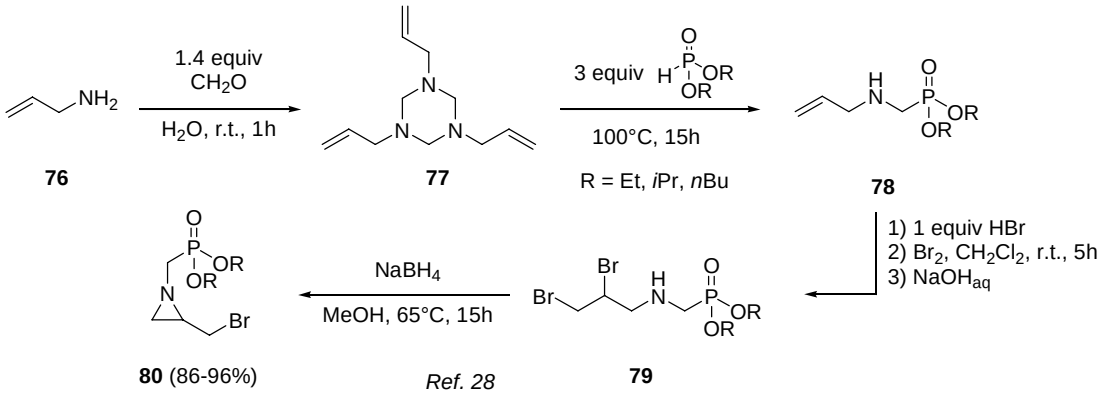


(*S*,*S*)-**75**

Scheme 18

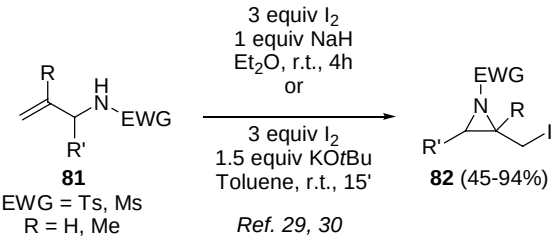
Other methods for the activation of alcohols have been reported, such as the transformation of a hydroxyl group into a chloro atom by means of thionyl chloride towards the synthesis of 2,2-di(chloromethyl)aziridines.[27]

The first synthesis of dialkyl ((2-(bromomethyl)aziridin-1-yl)methyl)phosphonates **80** comprised condensation of allyl amine **76** with formaldehyde towards triazine **77**, followed by treatment with different dialkyl phosphites resulting in phosphonates **78** after heating at 100°C for 15 hours. Bromination of the double bond in allyl amines **78** and subsequent reductive ring closure of β,γ-dibromo amines **79** by means of sodium borohydride afforded β-azaphosphonates **80** in high yields (Scheme 19).[28]



Scheme 19

2-(Iodomethyl)aziridines **82** have been prepared by NaH-mediated iodoaziridination of *N*-allylsulfonamides **81** in order to promote the nucleophilicity of nitrogen by deprotonation, followed by iodination of the double bond with I_2 and subsequent intramolecular ring closure (Scheme 20).[29] The same procedure was successfully applied using 1.5 equiv of KO*t*Bu in toluene, resulting in sulfonylaziridines **82** (Scheme 20).[30]

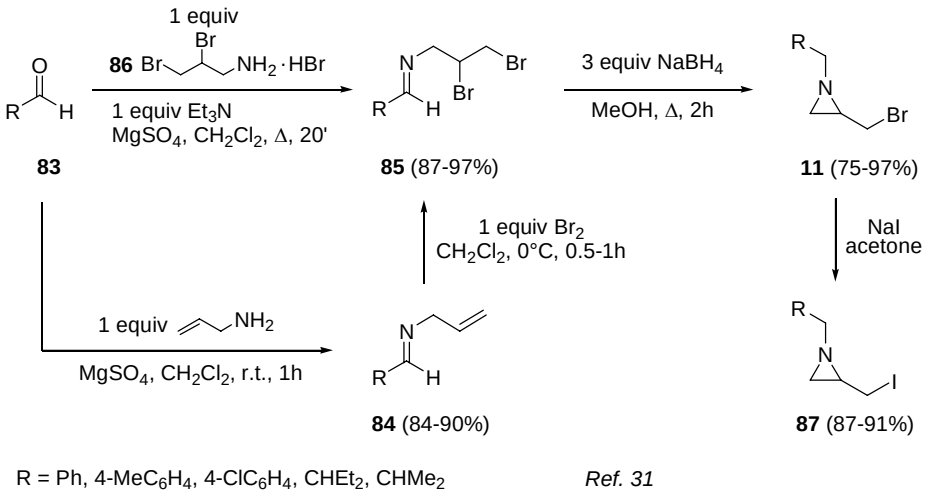


Scheme 20

1.2.2.3. Synthesis of 2-(halomethyl)aziridines from imines

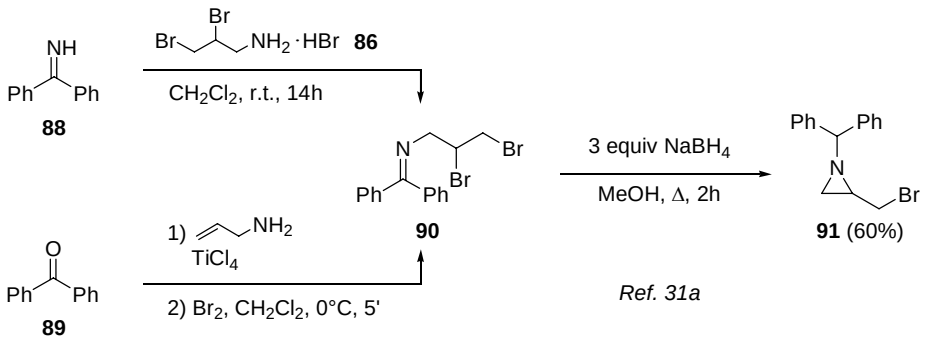
1-Alkyl-2-(bromomethyl)aziridines **11** can be easily prepared in a three-step procedure starting from the appropriate aldehydes via reduction of intermediate imines.[31] Condensation of aldehydes **83** with allyl amine in the presence of magnesium sulfate afforded the corresponding *N*-allylimines **84**, which were subsequently brominated by bromine to give 2,3-dibromopropylamines **85** in a quantitative yield. The latter dibromoimines were used as such because of their instability and hence treated with sodium borohydride, furnishing 1-alkyl-2-(bromomethyl)aziridines **11** in high yields (Scheme 21). Alternatively, aldehydes **83** are condensed with 2,3-dibromo-1-propylammonium bromide **86** in the presence of triethylamine and magnesium sulfate. Reduction of the dibromoimines **85**, thus obtained, with sodium

borohydride afforded 2-(bromomethyl)aziridines **11** in high yields. Treatment of 2-(bromomethyl)aziridines **11** with sodium iodide in acetone afforded the corresponding 2-(iodomethyl)aziridines **87**.



Scheme 21

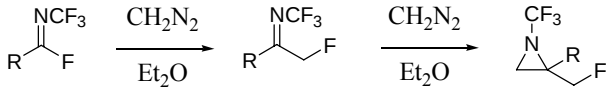
Analogously, 2-(bromomethyl)-1-(diphenylmethyl)aziridine **91** has been synthesized in 60% yield by reduction of ketimine **90** with sodium borohydride in methanol. The latter imine **90** was prepared both from diphenylketimine **88** and benzophenone **89** via *trans*-imination with 2,3-dibromopropylamine **86** or via imination with allyl amine and bromination, respectively (Scheme 22).[31a]



Scheme 22

The synthesis of 2-(fluoromethyl)aziridines **94** is one of the only reports on the chemistry of this interesting class of compounds. Addition of diazomethane across imidoyl fluorides **92** resulted in α-fluoro imines **93** after a fluoride shift and expulsion of nitrogen gas. A second

addition of diazomethane and liberation of N_2 afforded 2-(fluoromethyl)aziridines **94** (Scheme 23).[32]



92 **93** **94**

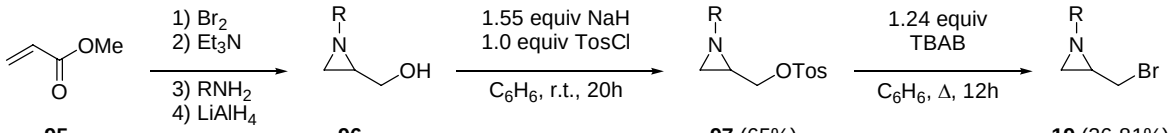
R = CF=CHCF$_3$, C$_3$F$_7$ *Ref. 32*

Scheme 23

Also imidoyl chlorides have been treated with diazomethane in ether, affording a mixture of 2-(chloromethyl)aziridines as the major compounds (76%) and 2-chloroaziridines as the minor constituents (20%), which were separated by distillation.[33]

1.2.2.4. Synthesis of 2-(halomethyl)aziridines from other aziridines

Several examples are known in which 2-(oxymethyl)aziridines are transformed into the corresponding 2-(halomethyl)aziridines. For example, 2-(hydroxymethyl)aziridines **96** have been converted into the corresponding 2-(tosyloxymethyl)aziridines **97** using tosyl chloride and sodium hydride in benzene. The latter aziridines **97** underwent nucleophilic displacement towards 2-(bromomethyl)aziridines **19** in moderate to good yields upon treatment with tetrabutylammonium bromide (TBAB) in refluxing benzene (Scheme 24).[34] The starting 2-(hydroxymethyl)aziridines **96** have been prepared from methyl acrylate **95** by subsequent bromination, treatment with an amine and reduction with $LiAlH_4$.[35]



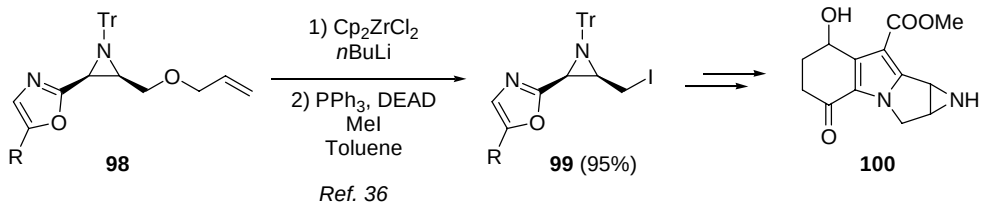
95 **96** **97** (65%) **19** (36-81%)

Ref. 34, 35

Scheme 24

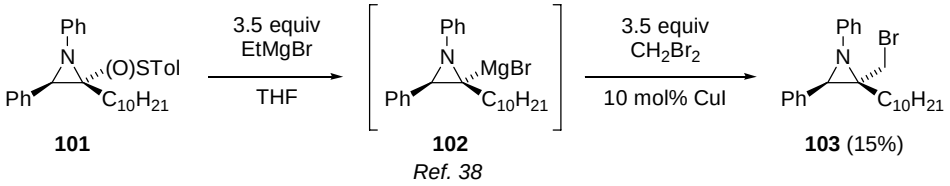
2-(Iodomethyl)aziridine **99** has been prepared as an intermediate in a total synthesis of aziridinomitosenes (such as **100**) due to the fascinating chemistry of these targets and their clinical antitumor activity. 2-(Allyloxymethyl)aziridine **98** was converted into the corresponding alcohol using an in situ generated zirconium(II) reagent, followed by Mitsunobu reaction utilising triphenylphosphine (PPh_3), diethyl azodicarboxylate (DEAD)

and methyl iodide in toluene towards 2-(iodomethyl)aziridine **99** in excellent yield (Scheme 25).[36] The deprotection of *N*-tritylaziridine **99** by means of trifluoroacetic acid (4 equiv) and triethylsilane (4 equiv) in CH_2Cl_2 has been reported elsewhere.[37]



Scheme 25

In a different approach, 2-sulfinylaziridine **101** was treated with ethylmagnesium bromide resulting in the nonstabilized aziridinylmagnesium **102** by a sulfoxide-magnesium exchange reaction, followed by a cross-coupling with dibromomethane using CuI as a catalyst towards 2-(bromomethyl)aziridine **103**, although the yield was low (Scheme 26). When diiodomethane was used instead of dibromomethane, a complex reaction mixture was obtained.[38]

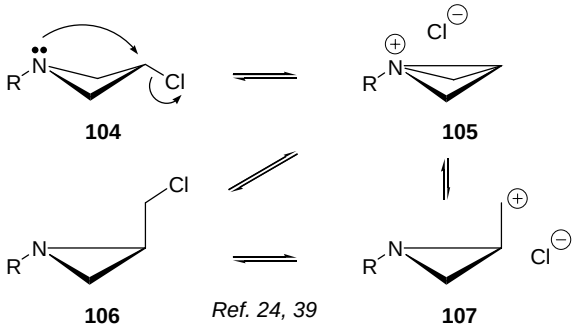


Scheme 26

1.2.2.5. Other reactions leading to 2-(halomethyl)aziridines

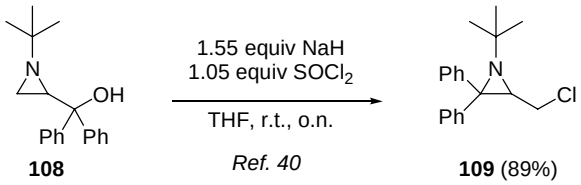
Aziridines have been reported as rearrangement products from other heterocyclic compounds. The formation of 2-(chloromethyl)aziridine **106** from 3-chloroazetidine **104** has been observed and explained by the fact that the aziridine **106** is more thermally stable and ionizes more slowly, resulting in measurable amounts of **106** (up to 59%). On the contrary, the isomerization of aziridines **106** into azetidines **104** only occurred in some cases (for < 5%), probable due to a long N-CH_2 distance in aziridines **106** and the less basic nitrogen as compared to the azetidine nitrogen. The formation of these small amounts of azetidines **104** can be explained considering ionisation of aziridine **106** to cation **107**, followed by rapid isomerization of **107** into **105** and recombination with chloride (Scheme 27). More recently,

the relative stability of bicyclic cations such as **105** and their isomeric 3-azetidinyl and aziridinylmethyl cations has been assessed by means of *ab initio* calculations, pointing to the conclusion that the bicyclic ions are much more stable than the corresponding 3-azetidinyl cations and that transition states for conversion of the bicyclic ions to azetidinyl carbocations and to aziridinylmethyl cations are not achievable from the bicyclic ions.[39]



Scheme 27

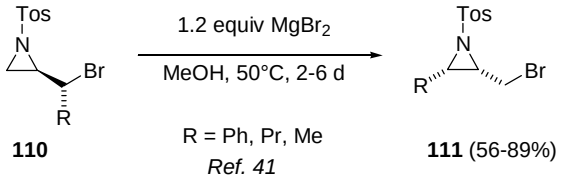
Furthermore, the isomerization of some aziridine derivatives substituted at the exocyclic methylene carbon atom towards 2-(halomethyl)aziridines has been reported. The reaction of aziridinemethanol **108** with thionyl chloride in the presence of sodium hydride afforded 2-(chloromethyl)aziridine **109** as the sole reaction product through a rearrangement process (Scheme 28). The presence of the phenyl substituents in aziridine **108** was found to be essential for the rearrangement into 2-(chloromethyl)aziridines, since reaction of 1-*t*ert-butyl-2-(hydroxymethyl)aziridine with thionyl chloride and sodium hydride afforded only 2% of the corresponding 2-(chloromethyl)aziridine besides oxathiazolidines as the major compounds (50%).[40]



108 **109** (89%)

Scheme 28

Finally, the stereospecific isomerization of 2-(1-bromoalkyl)-1-sulfonylaziridines **110** into 2-(bromomethyl)-3-alkyl-1-sulfonylaziridines **111** using magnesium bromide in methanol has been reported as an efficient approach towards *cis*-2,3-disubstituted aziridines (Scheme 29).[41]



110 **111** (56-89%)

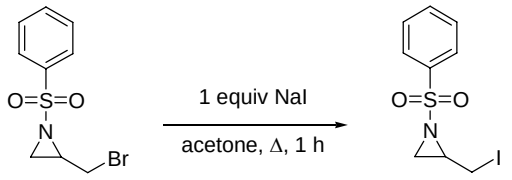
Scheme 29

1.2.3. Reactivity of 2-(halomethyl)aziridines

1.2.3.1. Substitution reactions

The presence of a halogenated carbon atom in 2-(halomethyl)aziridines allows the nucleophilic displacement of this halogen by a variety of nucleophiles. Consequently, a range of 2-substituted aziridines becomes accessible as substrates for further elaboration.

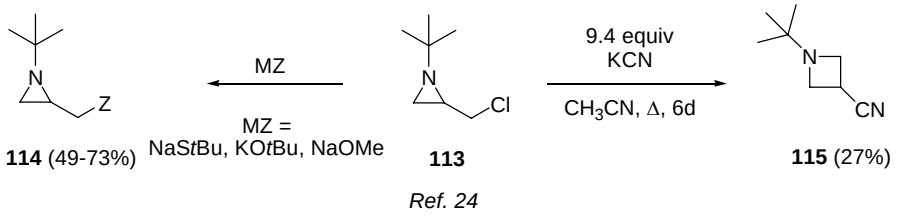
A first example involves the substitution of the halide by another halide. Treatment of 2-(bromomethyl)aziridine **60** with sodium iodide in refluxing acetone afforded 2-(iodomethyl)aziridine **112** in good yield (Scheme 30).[42] The same reactivity has also been reported for 1-arylmethyl- and 1-alkylmethyl-2-(bromomethyl)aziridines towards the corresponding 2-(iodomethyl)aziridines (vide supra, Scheme 21).



60 **112** (85%)

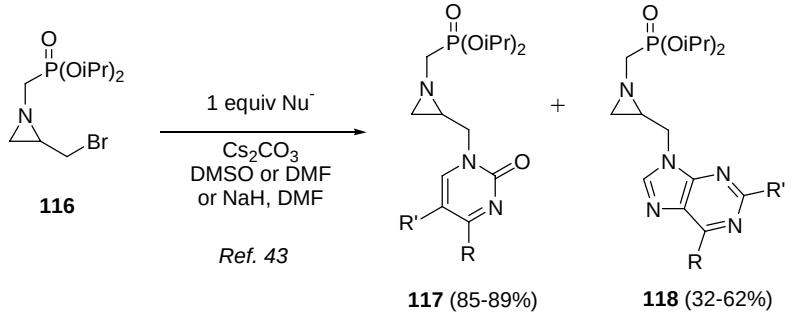
Scheme 30

Also heteroatom nucleophiles and carbon nucleophiles have been evaluated in substitution reactions with 2-(halomethyl)aziridines. Treatment of 2-(chloromethyl)aziridine **113** with for example NaS*t*Bu, KO*t*Bu and NaOMe (MZ) afforded the corresponding substitution products **114**, whereas reaction with a large excess of potassium cyanide in CH_3CN gave 3-cyanoazetidine **115** after 6 days at 100°C, and no aziridine derivatives were detected in the reaction mixture (Scheme 31).



Scheme 31

Treatment of 2-(bromomethyl)aziridine **116** with cytosine, thymine, acetylguanine and adenine afforded 2-substituted aziridines **117** and **118** as precursors for the corresponding nucleoside phosphonates as potential biologically active compounds (Scheme 32).[43] In the case of acetylguanine and adenine, the alkylation reaction resulted in a mixture of N^7- and N^9-isomers, hence the lower yields.

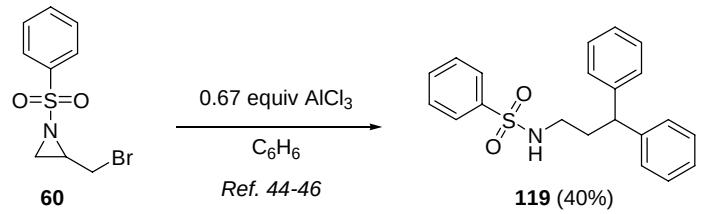


Scheme 32

1.2.3.2. Ring opening reactions

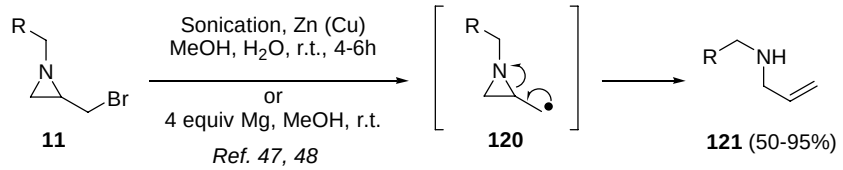
Aziridines are extremely susceptible towards ring cleavage because of the favorable release of strain energy involved and, consequently, their chemistry is dominated by ring opening reactions.

More then fifty years ago, the Friedel-Crafts reaction of 1-benzenesulfonyl-2-(bromomethyl)aziridine **60** and benzene has been described, resulting in the formation of *N*-(3,3-diphenylpropane)benzenesulfonamide **119** in 40% yield (Scheme 33).[44] Two different ^{14}C labeling experiments revealed the underlying reaction mechanism and pointed to the conclusion that the order of atoms in the starting aziridine **60** persists unchanged in the end-product **119**.[45,46]



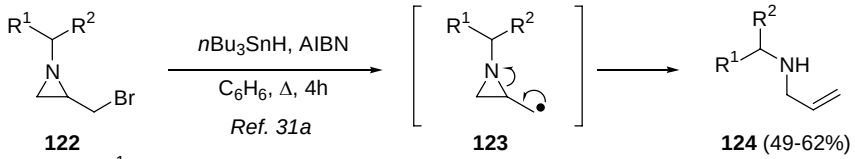
Scheme 33

A frequently reported ring opening of non-activated 2-(halomethyl)aziridines involves their transformation into allyl amines. For example, 2-(bromomethyl)aziridines **11** are readily cleaved by the sonochemical zinc-copper couple in aqueous methanol at room temperature towards allyl amines **121**.[31b] Also the reductive cleavage of the C_2-N bond of aziridines **11** mediated by magnesium in methanol afforded allyl amines **121** in excellent yields (Scheme 34).[47] This transformation proceeds through the generation of an aziridinylmethyl radical **120** by single electron transfer, which suffers from ring opening towards allyl amines **121** via radical cleavage or anionic cleavage by accepting another electron.

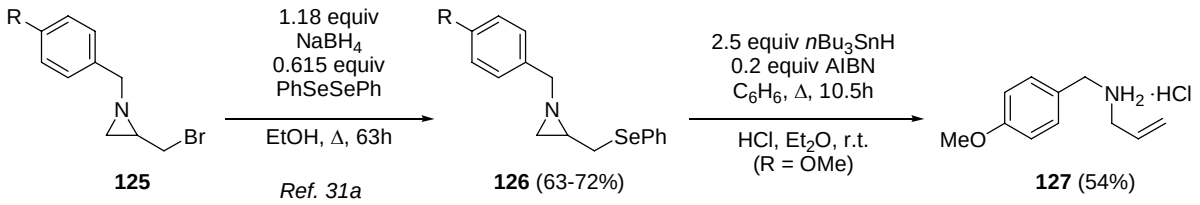


Scheme 34

Accordingly, 2-(bromomethyl)aziridines **122** can be easily transformed into aziridinylmethyl radicals **123** upon treatment with tributyltin hydride in benzene under reflux in the presence of AIBN. These radicals **123** spontaneously undergo ring cleavage towards allyl amines **124** in good yields (Scheme 35).[31a] Furthermore, 2-(phenylselenomethyl)aziridines **126** were prepared from 2-(bromomethyl)aziridines **125** upon treatment with diphenyldiselenide in refluxing ethanol in the presence of $NaBH_4$, and converted into allyl amine **127** by reaction with *n*Bu_3SnH in refluxing benzene in the presence of AIBN (Scheme 36).[31a]

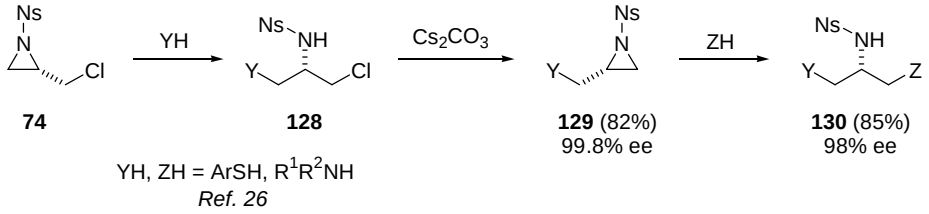


Scheme 35



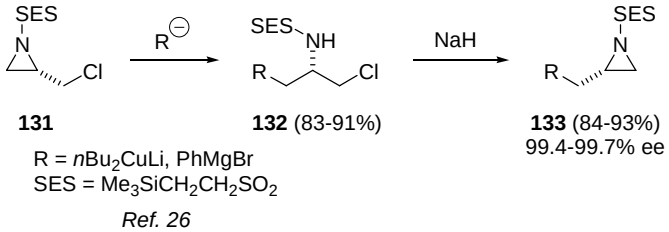
Scheme 36

2-(Chloromethyl)aziridine **74** has been elaborated to other enantio-enriched *N*-nosyl aziridines **129** through a simple two-step nucleophilic ring opening/base-induced ring closure sequence, and addition of a second equivalent of nucleophile results in α-branched *N*-nosylamides **130**. The net reaction after addition of one equivalent is a nucleophilic substitution of the chloro atom by the nucleophile (Scheme 37).



Scheme 37

Analogously, the chiral *N*-SES-protected 2-(chloromethyl)aziridine **131** (SES = 2-(trimethylsilyl)ethanesulfonyl) underwent clean reaction with carbon-centered nucleophiles towards 2-alkylaziridines **133** via intermediate β-chloro amines **132** (Scheme 38).



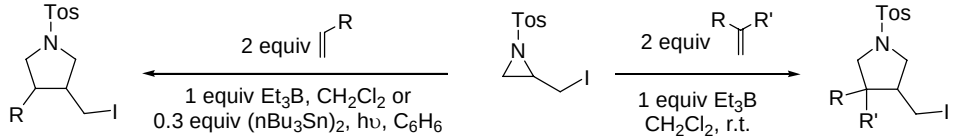
Scheme 38

1.2.3.3. Ring transformations

The various nucleophilic interactions with the constrained heterocyclic ring and with the halogenated carbon atom of 2-(halomethyl)aziridines, combined with the nucleophilicity of

the nitrogen lone pair, allow useful (intramolecular) reactions for the construction of a variety of heterocyclic compounds.

Treatment of 2-(iodomethyl)aziridine **134** with Et_3B efficiently produced the corresponding azahomoallyl radical species, which reacted with electron-rich alkenes such as enol ethers and ketene acetals through iodine atom transfer [3+2] cycloaddition towards pyrrolidine derivatives **135** and **136** (Scheme 39).[48,49]



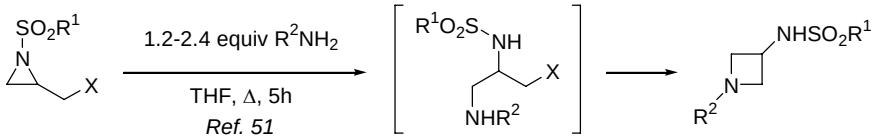
135 (48-80%) **134** **136** (34-71%)

R, R' = alkyl, alkoxy

Ref. 49, 50

Scheme 39

A one-step approach towards biologically relevant 3-aminoazetidines **139** has been described based on a ring transformation of 2-(halomethyl)-1-sulfonylaziridines **137** upon treatment with primary amines in refluxing THF via intermediate 1,2-diamines **138** (Scheme 40). The yields were rather low (13 – 38%) due to the formation of some undesired by-products such as the corresponding 1,2,3-triaminepropane derivatives.[50]



137 **138** **139** (13-38%)

Ref. 51

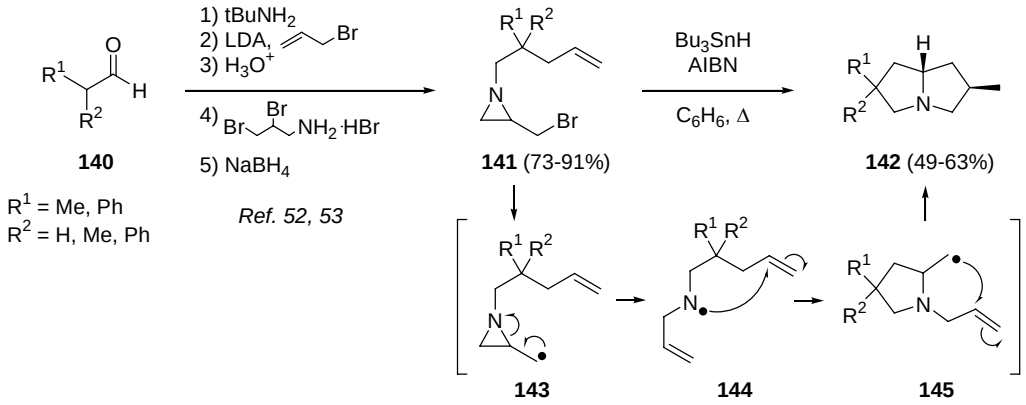
R^1 = p-Tol, Me, Ph, 4-$CF_3C_6H_4$

R^2 = Bn, tBu, cHex

Scheme 40

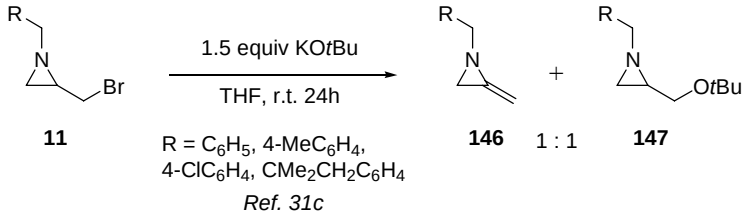
Pyrrolizidines **142** have been synthesized diastereoselectively from 2-(bromomethyl)aziridines **141** in a one-step procedure via a cascade of radical reactions. This transformation proceeds through the intermediacy of aziridinylmethyl radicals **143**, *N*-allylaminyl radicals **144** and (2-pyrrolidinyl)methyl radicals **145** (Scheme 41).[51] The aziridines **141** are easily accessible from aldehydes **140** via a sequence of reactions involving imination with *tert*-butylamine, α-alkylation with allyl bromide, hydrolysis to the corresponding aldehyde, imination with 2,3-dibromopropylamine and reductive cyclization

with sodium borohydride. Based on molecular modeling, a large preference for cyclisation towards pyrrolidines as compared to indolizidines was found.[52]



Scheme 41

2-Methyleneaziridines belong to a rare class of highly strained heteromethylenecyclopropanes as valuable substrates in organic chemistry. Several base-solvent pairs have been evaluated for the dehydrobromination of 2-(bromomethyl)aziridines **11**, but only KO*t*Bu in THF resulted in the formation of methyleneaziridines **146** besides equimolar amounts of the corresponding substitution products **147** (Scheme 42).[31c]



Scheme 42

Based on this literature overview, it is clear that the chemistry of 2-(halomethyl)aziridines is still an underdeveloped area in organic synthesis, despite of their synthetic potential. Especially for the non-activated 1-alkyl-2-(halomethyl)aziridines, little or no information can be found regarding their reactivity profile and their utility as building blocks. Consequently, an in-depth investigation of the reactivity and synthetic potential of both activated and non-activated 2-(halomethyl)aziridines would be of significant importance in order to provide a general view on the differences and similarities between both classes of compounds as well as on their scope and limitations in organic synthesis.

Chapter 2. Results, Discussion and Perspectives

2.1. Introduction

The results presented in this thesis are based on several papers, published in peer-reviewed international SCI-journals or ready to be submitted, referred to in the text by the Roman numerals I-XV. In this chapter, a comprehensive overview of the chemistry described in these papers will be discussed and the main conclusions will be highlighted. More details regarding the experimental set-up, reaction conditions and mechanistic considerations can be found in these papers and will not be dealth with in this chapter.

I. **Matthias D'hooghe** and Norbert De Kimpe. "The mechanism of nucleophilic substitution of 1-alkyl-2-(tosyloxymethyl)aziridines" ***Synlett*** **2004**, 271-274. (I.F. 2.693)[53]

II. **Matthias D'hooghe**, Inge Kerkaert, Mario Rottiers and Norbert De Kimpe. "Ring opening reactions of 1-arenesulfonyl-2-(bromomethyl)aziridines" ***Tetrahedron*** **2004**, *60*, 3637-3641. (I.F. 2.610)[54]

III. **Matthias D'hooghe**, Mario Rottiers, Robrecht Jolie and Norbert De Kimpe. "Coupling of 1-alkyl-2-(bromomethyl)aziridines with lithium dialkylcuprates towards 1,2-dialkylaziridines" ***Synlett*** **2005**, 931-934. (I.F. 2.693)[55]

IV. **Matthias D'hooghe**, Mario Rottiers, Inge Kerkaert and Norbert De Kimpe. "Ring opening of 2-(bromomethyl)-1-sulfonylaziridines towards 1,3-heteroatom substituted 2-aminopropane derivatives" ***Tetrahedron*** **2005**, *61*, 8746-8751. (I.F. 2.610)[56]

V. **Matthias D'hooghe** and Norbert De Kimpe. "Highly unusual conversion of 1-alkyl-2-(bromomethyl)aziridines into 1-alkyl-2-(*N*-alkyl-*N*-ethylaminomethyl)aziridines using methyllithium" *To be submitted*.

VI. **Matthias D'hooghe** and Norbert De Kimpe. "Reactivity of 1-alkyl-2-(bromomethyl)aziridines towards butyllithium" *To be submitted*.

VII. **Matthias D'hooghe**, Willem Van Brabandt and Norbert De Kimpe. "New synthesis of propargylic amines from 2-(bromomethyl)aziridines. Intermediacy of 3-bromoazetidinium salts" ***J. Org. Chem.*** **2004**, *69*, 2703-2710. (I.F. 3.675)[57]

VIII. **Matthias D'hooghe**, Alex Waterinckx, Tim Vanlangendonck and Norbert De Kimpe. "A new approach towards 2-amino-1-aryloxy-3-methoxypropanes from 1-arylmethyl-2-(bromomethyl)aziridines" ***Tetrahedron*** **2006**, *62*, 2295-2303. (I.F. 2.610)[58]

IX. **Matthias D'hooghe** and Norbert De Kimpe. "Opposite regioselectivity in the sequential ring opening of 2-(alkanoyloxymethyl)aziridinium salts by bromide and fluoride in the synthesis of functionalized β-fluoro amines" ***Synlett*** **2006**, 2089-2093. (I.F. 2.693)[59]

X. **Matthias D'hooghe**, Willem Van Brabandt and Norbert De Kimpe. "Synthesis of quaternary allylammonium salts via ring opening of 1-benzyl-2-(bromomethyl)aziridines" ***Tetrahedron*** **2003**, *59*, 5383-5386. (I.F. 2.610)[60]

XI. **Matthias D'hooghe**, Veronique Van Speybroeck, Michel Waroquier and Norbert De Kimpe. "Regio- and stereospecific ring opening of 1-alkyl-2-(aryloxymethyl)aziridinium salts by bromide" ***Chem. Commun.*** **2006**, 1554-1556. (I.F. 4.426)[61]

XII. **Matthias D'hooghe**, Alex Waterinckx and Norbert De Kimpe. "A novel entry toward 2-imino-1,3-thiazolidines and 2-imino-1,3-thiazolines by ring transformation of 2-(thiocyanomethyl)aziridines" ***J. Org. Chem.*** **2005**, *70*, 227-232. (I.F. 3.675)[62]

XIII. **Matthias D'hooghe**, Tim Vanlangendonck, Karl W. Törnroos and Norbert De Kimpe. "Novel synthesis of cis-3,5-disubstituted morpholine derivatives" ***J. Org. Chem.*** **2006**, *71*, 4678-4681. (I.F. 3.675)[63]

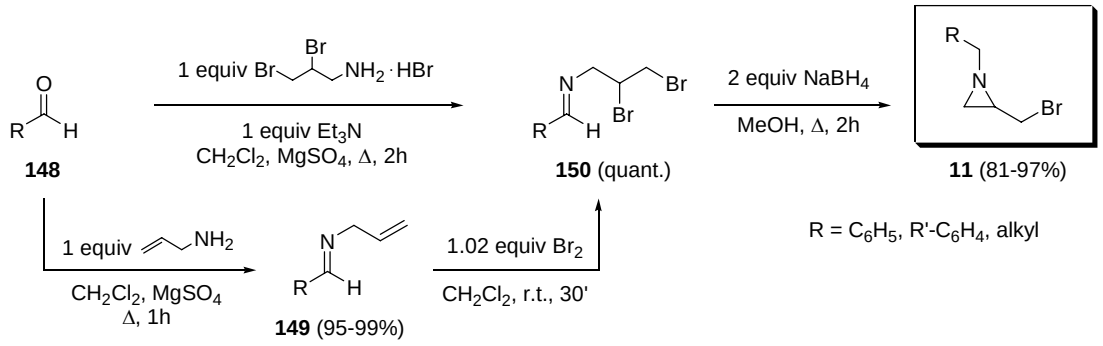
XIV. **Matthias D'hooghe**, Sven Mangelinckx, Evelien Persyn, Willem Van Brabandt and Norbert De Kimpe. "Synthesis of 1-arylmethyl-2-(cyanomethyl)aziridines and their ring transformation into methyl *N*-(2-cyanocyclopropyl)benzimidates" ***J. Org. Chem.*** **2006**, *71*, 4232-4236. (I.F. 3.675)[64]

XV. **Matthias D'hooghe** and Norbert De Kimpe. "Synthetic approaches towards 2-iminothiazolidines: an overview" ***Tetrahedron*** **2006**, *62*, 513-535. (I. F. 2.610)[65]

2.2. Synthesis of 1-alkyl-2-(bromomethyl)aziridines

In the literature, only one simple and efficient procedure of 1-arylmethyl- and 1-alkylmethyl-2-(bromomethyl)aziridines **11** is available (vide supra, Scheme 21), which was developed at the Department of Organic Chemistry (Faculty of Bioscience Engineering, Ghent University). Besides this procedure, one other approach towards 1-alkyl-2-(bromomethyl)aziridines has been reported involving bromination of methyl acrylate, substitution with a primary amine, reduction of the ester moiety and substitution of the resulting alcohol by bromide (vide supra, Scheme 24), although this method is cumbrous and has a limited applicability.

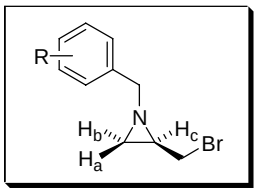
Condensation of aldehydes **148** with 1.05 equivalents of allyl amine in dichloromethane in the presence of magnesium sulfate afforded the corresponding *N*-allylimines **149** in excellent yields (95-99%), which were distilled and subsequently brominated by bromine in dichloromethane to give *N*-(arylmethylidene)- and *N*-(alkylidene)-2,3-dibromopropylamines **150** in a quantitative yield. The latter dibromoimines **150** were used as such because of their instability and hence treated with 2 equivalents of sodium borohydride in methanol under reflux for two hours, furnishing 1-arylmethyl- and 1-alkylmethyl-2-(bromomethyl)aziridines **11** in high yields via reduction of the imino bond and intramolecular nucleophilic substitution (Scheme 43). Alternatively, dibromoimines **150** were prepared by condensation of aldehydes **148** with 1 equivalent of 2,3-dibromo-1-propylammonium bromide in dichloromethane in the presence of 1 equivalent of triethylamine and magnesium sulfate as drying agent. The latter approach is required when α-protons are present in imines **149** with respect to the imino bond, since side-reactions occur upon bromination of this type of imines.



Scheme 43

This methodology has been used for the synthesis of a large variety of novel 1-arylmethyl-2-(bromomethyl)aziridines **151** with different substituents on the aromatic ring (e.g. Me, MeO, Cl, Br, F). The applicability of this class of aziridines has hardly been investigated in the literature, although the reactivity of the constrained heterocyclic ring combined with the electrophilic exocyclic methylene group offers a tremendous synthetic potential. Furthermore, the high yields and purity of the above described synthesis, as well as the long shelf-life of 2-(bromomethyl)aziridines **11** make these compounds very attractive substrates in organic chemistry.

Since 1-arylmethyl-2-(bromomethyl)aziridines **151** (Chart 7) are fairly unknown in the literature, some general characteristics of these compounds in NMR spectroscopy and mass spectrometry have been summarized based on the spectroscopical data of a whole set of 1-arylmethyl-2-(bromomethyl)aziridines **151**.



151

Chart 7

2.2.1. Nuclear Magnetic Resonance Spectroscopy

1-Arylmethyl-2-(bromomethyl)aziridines **151** can be easily identified in ^{1}H NMR based on their characteristic pattern (Table 1). Both protons H_a and H_b are observed as doublets in the region 1.61-1.90 ppm and proton H_c can be identified as a multiplet somewhere between 1.84 and 2.17 ppm ($CDCl_3$). In all derivatives **151**, no geminal coupling between protons H_a and H_b has been observed (J_{gem} = 0 Hz) and, as a consequence, these protons always appear as doublets due to a vicinal (*cis* or *trans*) coupling with proton H_c (Table 1). Furthermore, the protons of the CH_2Br moiety mostly appear as a multiplet in the region 3.22-3.37 ppm, whereas the benzylic protons are always observed as doublets (3.33-3.70 ppm) with a geminal coupling constant of 13.2-15.0 Hz (Table 1).

Table 1: ^{1}H NMR characteristics of 1-arylmethyl-2-(bromomethyl)aziridines **151** in $CDCl_3$

Protons	Chemical shift (δ)	Multiplicity	Coupling constant (J)
H_a	1.76 – 1.90 ppm	D	3.3 – 3.5 Hz
H_b	1.61 – 1.68 ppm	D	5.3 – 6.3 Hz
H_c	1.84 – 2.17 ppm	M	-
CH_2Br	3.22 – 3.37 ppm	m*	-
CH_2Ar	3.33 – 3.70 ppm	2×d	13.2 – 15.0 Hz

* occasionally 2×d×d (5.5 – 6.3, 6.9 – 7.3, 10.2 – 10.5 Hz)

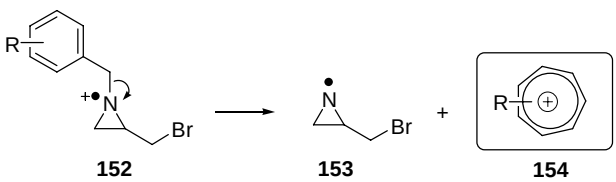
Also in ^{13}C NMR spectroscopy ($CDCl_3$), the geometrical constraint of the three-membered ring has a significant influence on the resonance values, resulting in a considerable shielding effect (Table 2). Thus, $H_a\underline{C}H_b$ can be observed upfield (32.1-35.2 ppm) when compared to triethylamine (CH_2 at 46.5 ppm), as well as $\underline{C}H_c$ (39.6-40.3 ppm) when compared to *N*,*N*-dimethyl-*N*-isopropylamine (CH at 54.9 ppm). The methylene carbon atoms from $\underline{C}H_2Br$ and $\underline{C}H_2Ar$ resonate at δ-values which can be compared to other systems without geometrical constraint.

Table 2: ^{13}C NMR characteristics of 1-arylmethyl-2-(bromomethyl)aziridines **151** in $CDCl_3$

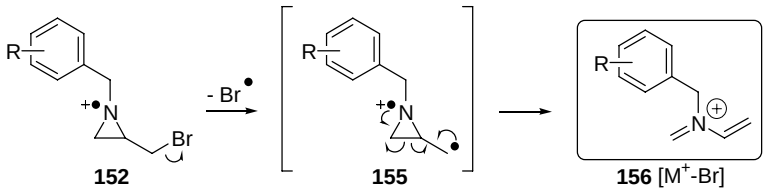
	$H_a\underline{C}H_b$	$\underline{C}H_c$	$\underline{C}H_2Br$	$\underline{C}H_2Ar$
δ	32.1 – 35.2 ppm	39.6 – 40.3 ppm	35.4 – 39.4 ppm	60.6 – 64.0 ppm

2.2.2. Mass spectrometry

Upon mass spectroscopic analysis, 1-arylmethyl-2-(bromomethyl)aziridines are characterized by a benzylic cleavage with expulsion of a tropylium ion **154** as the most abundant ion (Scheme 44). Furthermore, loss of a bromo radical through β-cleavage and subsequent ring opening appears to be a significant pathway since an ion **156** with m/z [M^+-Br] has been observed in all cases (Scheme 45).



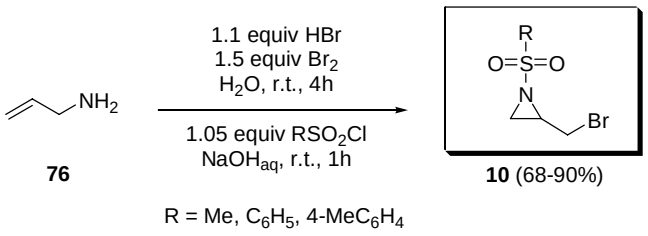
Scheme 44



Scheme 45

2.3. Synthesis of 2-(bromomethyl)-1-sulfonylaziridines 10

Besides the non-activated 1-alkyl-2-(bromomethyl)aziridines **11**, also 2-(bromomethyl)-1-sulfonylaziridines **10** have been prepared and evaluated as starting materials in organic synthesis.[12,13,45,46,47b,50,66] Treatment of allyl amine **76** with 1.1 equivalents of hydrobromic acid and 1.5 equivalents of bromine in water resulted in 1-amino-2,3-dibromopropane hydrobromide after stirring for 4 hours at room temperature. Subsequently, treatment of this ammonium salt with 1.05 equivalents of a sulfonylchloride in aqueous sodium hydroxide (2.5 M) afforded the desired 2-(bromomethyl)aziridines **10** after one hour stirring at room temperature, based on a known literature procedure (Scheme 46). Due to the presence of an electron withdrawing group at nitrogen, the aziridine protons resonate at higher δ-values in ^{1}H NMR (2.21-3.18 ppm, $CDCl_3$) when compared to their non-activated counterparts.[66b]



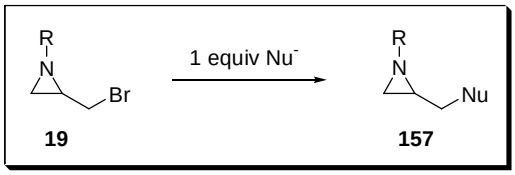
Scheme 46

2.4. Reactivity of 2-(bromomethyl)aziridines

In this paragraph, the focus will be on the study of the chemical reactivity of 2-(bromomethyl)aziridines, and special attention will be devoted to the regio- and stereochemistry of these transformations. The applicability of 2-(bromomethyl)aziridines for the synthesis of biologically relevant intermediates and target compounds will be discussed in the next section.

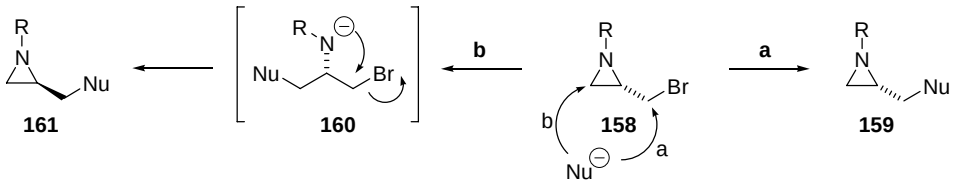
2.4.1. Treatment of 2-(bromomethyl)aziridines with one equivalent of a nucleophile

One of the most striking features of 2-(bromomethyl)aziridines concerns their general reactivity towards nucleophiles. Independent of the nature of the *N*-substituent, the corresponding 2-substituted aziridines **157** are isolated upon treatment of 2-(bromomethyl)aziridines **19** with one equivalent of a nucleophile (Scheme 47). Heteroatom-centered as well as carbon-centered nucleophiles can be applied successfully in this reaction, enabling the synthesis of a large variety of 2-substituted aziridines **157** as valuable synthons for further elaboration.



Scheme 47

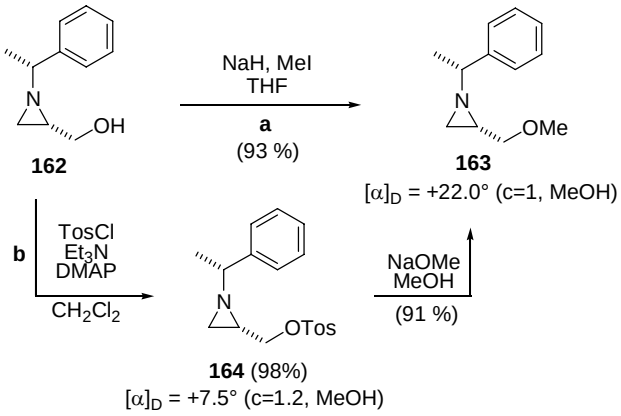
Although the net reaction comprises replacement of the bromo atom by a nucleophile, the underlying mechanism of this transformation requires a more detailed explanation. As depicted in Scheme 48, 2-(bromomethyl)aziridine **158** can undergo a direct S_N2 nucleophilic substitution at the halogenated carbon atom towards aziridine **159** (pathway a) or, alternatively, the nucleophile can attack the unsubstituted aziridine carbon atom resulting in a ring opened intermediate **160**, which is prone to intramolecular ring closure towards the substituted aziridine **161** (pathway b). When a chiral substrate **158** is used, direct substitution results in retention of configuration (pathway a), whereas ring opening – ring closure furnishes the other enantiomer (pathway b). If both pathways are competitive, a mixture of both enantiomers will be obtained. It is clear that a deeper understanding of this mechanism is of high importance whenever the synthesis of chiral targets starting from chiral 2-(bromomethyl)aziridines **158** is contemplated.



Scheme 48

In the literature, it has already been demonstrated that the activated 1-tosyl-2-(tosyloxymethyl)aziridines suffer from ring opening upon treatment with organocuprate reagents by attack at the least hindered carbon atom of the aziridine moiety, immediately followed by ring closure by displacement of the tosylate in a straightforward manner.[67] Also for *N*,*O*-bis(diphenylphosphinyl)-2-(hydroxymethyl)aziridine, an aziridine with a different electron withdrawing substituent at nitrogen, comparable results were published.[68] These results point to a pronounced preference for pathway b (i.e. ring opening – ring closure, Scheme 48) if activated 2-(bromomethyl)aziridines **158** are used, e.g. 1-sulfonylaziridines **10**.

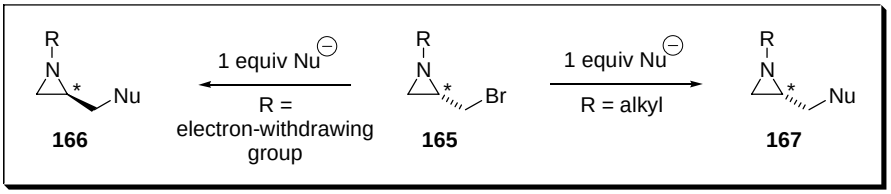
To unravel the unknown mechanism of nucleophilic substitution of non-activated 1-alkyl-2-(bromomethyl)aziridines **11**, the enantiomerically pure and commercially available (1*R*,2*S*)-1-(α-methylbenzyl)-2-(hydroxymethyl)aziridine **162** was alkylated at oxygen towards (1*R*,2*S*)-2-(methoxymethyl)aziridine **163** via a Williamson ether synthesis (Scheme 49). The same substrate **162** was also tosylated towards (1*R*,2*S*)-2-(tosyloxymethyl)aziridine **164** as a model for non-activated 2-(bromomethyl)aziridines **11** in general. Treatment of this aziridine **164** with sodium methoxide in methanol afforded the corresponding 2-(methoxymethyl)aziridine **163**, which appeared to be exactly the same as the aziridine **163** obtained via Williamson ether synthesis instead of the other diastereomer (Scheme 49). These observations clearly pointed to the conclusion that the substitution of non-activated 2-(bromomethyl)aziridines with nucleophiles proceeds via direct S_N2 substitution with retention of configuration (***Paper I***).



Scheme 49

In conclusion, the choice of the appropriate *N*-substituent is determining for the stereochemical outcome if a chiral 2-(bromomethyl)aziridine **165** is used in a substitution reaction (Scheme 50).

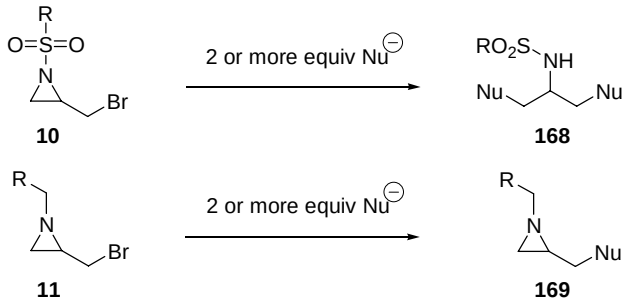
Both carbon-centered nucleophiles and heteroatom-centered nucleophiles have been used in these studies, all pointing to the conclusion that non-activated 1-alkyl-2-(bromomethyl)aziridines **11** undergo direct S_N2 substitution at the halogenated carbon atom with retention of configuration, whereas activated 1-sulfonyl-2-(bromomethyl)aziridines **10** suffer from ring opening – ring closure resulting in inversion of configuration (Scheme 50).



Scheme 50

2.4.2. Treatment of 2-(bromomethyl)aziridines with two or more equivalents of a nucleophile (Paper I, II, III and IV)

Whereas treatment of activated and non-activated 2-(bromomethyl)aziridines with one equivalent of a nucleophile results in the same type of substitution product, i.e. the corresponding 2-substituted aziridine, their behaviour becomes different if two or more equivalents of a nucleophile are used. Obviously, due to the presence of an electron withdrawing group at nitrogen in activated aziridines **10**, the aziridine ring is much more susceptible to ring opening reactions, and treatment with an excess of nucleophile will always lead to acyclic amines **168** by means of ring opening of the intermediate 2-substituted aziridines. On the other hand, treatment of non-activated 2-(bromomethyl)aziridines **11** with an excess of nucleophile will only result in the corresponding 2-substituted aziridines **169**, without affecting the aziridine moiety (Scheme 51).



Scheme 51

Both carbon-centered nucleophiles (lithium dialkylcuprates, ***Paper II and III***) and heteroatom-centered nucleophiles (alkoxides, carboxylates, thiolates, azides, phenoxides, fluoride, isothiocyanate, ***Paper I, IV, VIII, IX, XI, XII and XIII***) have been evaluated in reaction with 2-(bromomethyl)-1-sulfonylaziridines **10** and 1-alkylmethyl-2-(bromomethyl)aziridines **11**, all pointing to the conclusion that 2-(bromomethyl)-1-sulfonylaziridines **10** can be applied successfully as synthetic equivalents for the 2-aminopropane dication synthon **170** towards α-branched *N*-tosylamides, whereas 1-alkyl-2-(bromomethyl)aziridines **11** can be considered as synthetic equivalents for the aziridinylmethyl cation synthon **171** towards the preparation of a large variety of 2-substituted aziridines (Chart 8). In only one case, i.e. treatment of 1-arylmethyl-2-(bromomethyl)aziridines with 2 equiv of potassium cyanate, no substitution took place and the starting material was recovered.

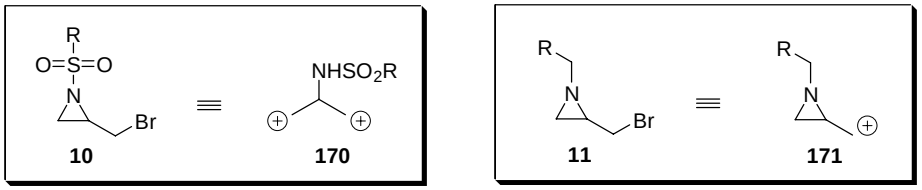


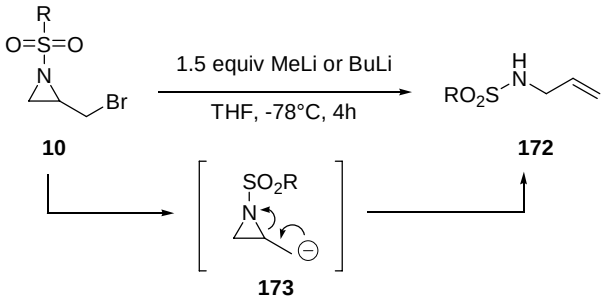
Chart 8

2.4.3. Reactivity towards alkyllithium reagents

In the light of the above described general conclusions regarding the behaviour of 2-(bromomethyl)aziridines towards nucleophiles, their reactivity with respect to alkyllithium reagents has to be discussed separately.

2.4.3.1. 2-(Bromomethyl)-1-sulfonylaziridines

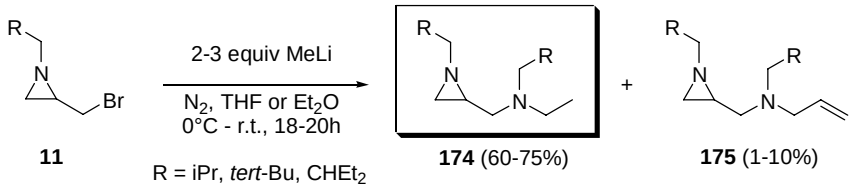
Treatment of 2-(bromomethyl)-1-sulfonylaziridines **10** with alkyllithium reagents, such as methyllithium and butyllithium, resulted in *N*-(allyl)sulfonylamides **172** due to metal-halogen exchange and subsequent ring opening of the intermediate aziridinylmethyl anion **173** (Scheme 52, ***Paper II***).



Scheme 52

2.4.3.2. 1-Alkyl-2-(bromomethyl)aziridines (Unpublished results)

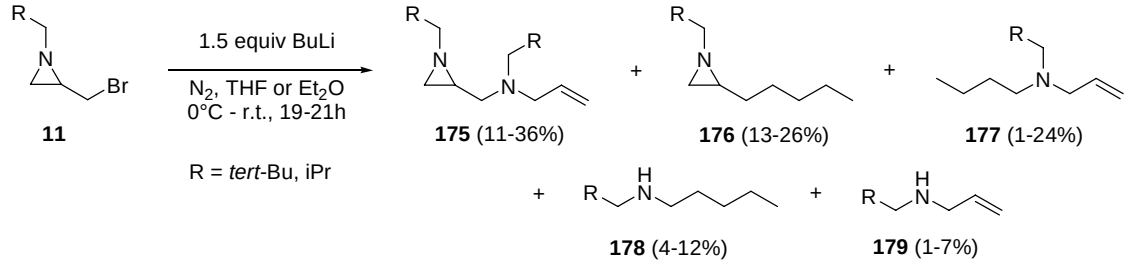
When non-activated 1-alkyl-2-(bromomethyl)aziridines **11** were treated with 2 or more equiv of methyllithium in diethyl ether or THF, the reaction mixtures thus obtained contained 2-(*N*-ethylaminomethyl)aziridines **174** as the major constituents (60-75%) and aziridines **175** as the minor constituents (1-10%) (Scheme 53, ***Paper V***). The formation of these compounds **174** was totally unexpected, and the presence of an *N*-ethyl group, which is quite surprising based on the structure of the starting material, as well as the total number of carbon atoms indicated a highly unusual reaction course. It should be remarked that the aziridines **174** contain one carbon atom less then double the number of carbon atoms in the starting material, which rules out a simple dimerisation process. A provisory explanation for this unusual transformation can be suggested, in which the substrate undergoes an S_N2'-type substitution, followed by conversion of the resulting enamine into a lithium amide and loss of a carbon unit, furnishing 2-(aminomethyl)aziridines **174** upon nucleophilic substitution at the halogenated carbon atom of an unreacted aziridine.



Scheme 53

Treatment of *N*-neopentyl- and *N*-isobutyl-2-(bromomethyl)aziridines **11** with 1.5 equiv of butyllithium in dry diethyl ether or THF under nitrogen atmosphere resulted in complex reaction mixtures, in which at least 10 different compounds were present based on GC analysis (***Paper VI***). The main components in these reaction mixtures are 1-alkyl-2-(*N*-allyl-

N-alkylaminomethyl)aziridines **175** (11-36%) and 1-alkyl-2-pentylaziridines **176** (13-26%). Furthermore, also *N*-allyl-*N*-alkyl-*N*-butylamines **177** (1-24%), *N*-alkyl-*N*-pentylamines **178** (4-12%) and *N*-allyl-*N*-alkylamines **179** (1-7%) were identified in these mixtures (Scheme 54). Obviously, competitive reaction pathways give rise to different reaction products upon treatment with butyllithium, in contrast with the previously observed reactivity of these 1-alkyl-2-(bromomethyl)aziridines **11** towards other reagents such as lithium dialkylcuprates and O-centered nucleophiles, in which nucleophilic displacement of the bromo atom results in the corresponding 2-substituted aziridine as the sole reaction product.

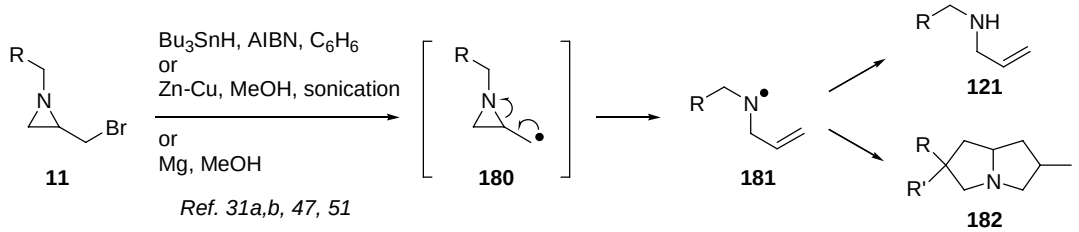


Scheme 54

2.4.4. Ring opening reactions

2.4.4.1. Radical chemistry

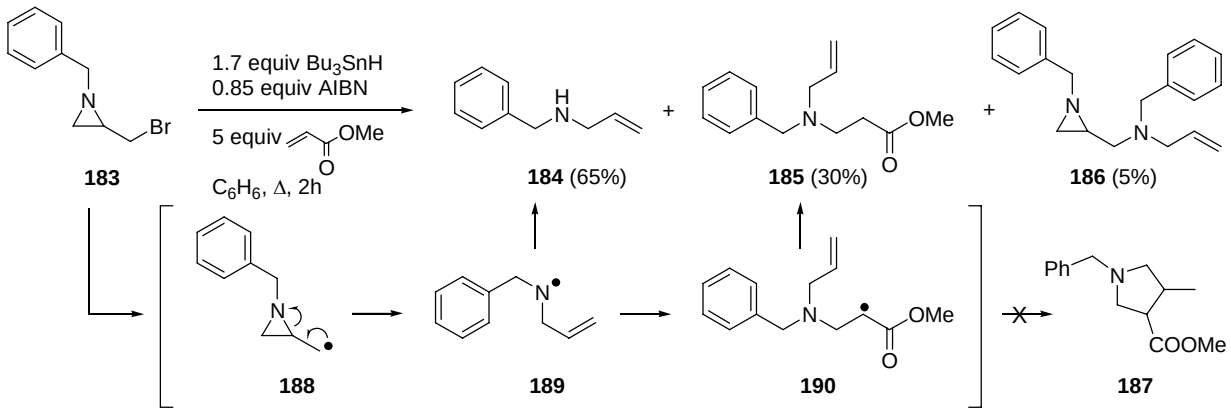
The generation of aminyl radicals **181** from 2-(bromomethyl)aziridines **11** through radical induced ring opening of intermediate aziridinylmethyl radicals **180** has been studied in the past and applied for the synthesis of allyl amines **121** and pyrrolizidines **182** (Scheme 55).[31a,b,47,51]



Scheme 55

In order to evaluate a cascade radical cyclization reaction towards pyrrolidines **187** involving aminyl radicals **189**, 1-benzyl-2-(bromomethyl)aziridine **183** was treated with 1.7 equiv of Bu_3SnH and 0.85 equiv of AIBN (azoisobutyronitrile) in refluxing benzene in the presence of

5 equiv of methyl acrylate. The major compound in the reaction mixture was allyl amine **184** (65%), besides β-amino ester **185** (30%) and 2-(aminomethyl)aziridine **186** (5%), which were all separated by means of column chromatography (Scheme 56). Obviously, only a minor fraction of the *in situ* formed aminyl radical **189** furnished the desired radical Michael addition towards the Michael adduct **190**, and further intramolecular cyclization towards pyrrolidine **187** did not occur under these circumstances. The formation of aziridines **186** can be the result of a coupling between the aminyl radical **189** and an aziridinylmethyl radical **188**. In the literature, β-amino ester **185** has been used for the cyclization towards pyrrolidine **187** upon treatment with LDA and $ZnBr_2$ in ether.[69]



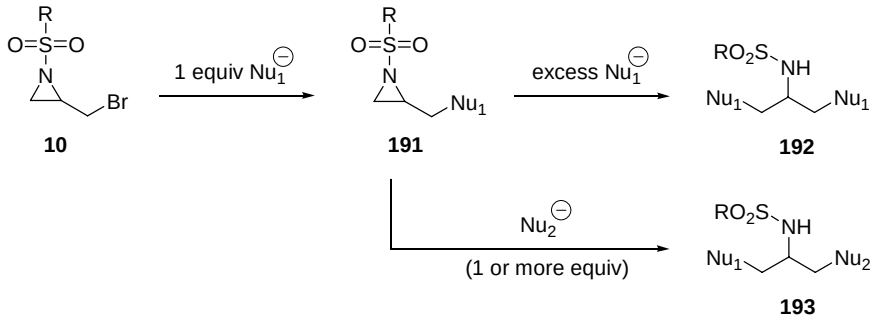
Scheme 56

Several factors can influence the outcome of this reaction and, most probably, the ratio of the reaction products can be shifted in favor of β-amino ester **185** and perhaps even towards pyrrolidine **187** by changing the equivalents, the reaction time and the concentration of the reagents. These aspects need to be evaluated in due course.

2.4.4.2. Ring opening of activated 2-(bromomethyl)-1-sulfonylaziridines

As described before, 2-(bromomethyl)-1-sulfonylaziridines **10** are highly susceptible towards ring opening reactions and, when treated with nucleophiles, the aziridine moiety suffers from ring opening instead of direct nucleophilic attack at the halogenated carbon atom. When exactly one equivalent of a nucleophile is used, the corresponding 2-substituted aziridine **191** is isolated due to intramolecular displacement of the bromide, whereas if an excess of nucleophile is employed, the newly formed 2-substituted aziridines **191** immediately undergo ring opening towards the corresponding α-branched *N*-sulfonylamides **192** (Scheme 57).

Consequently, this approach enables the synthesis of unsymmetrical α-branched *N*-sulfonylamides **193** by treating the starting aziridines **10** with exactly one equivalent of a nucleophile, followed by the addition of at least one equivalent of a different nucleophile (Scheme 57). In this way, a large variety of amines becomes accessible using a variety of both carbon-centered (organocuprates, ***Paper II***) as well as heteroatom-centered nucleophiles (O-, N- and S-nucleophiles, ***Paper IV***).



Scheme 57

The sensitivity of 1-sulfonylaziridines **194** towards ring opening is the result of an augmentation of the polarization of the C-N bonds by the inductive effect of the electron withdrawing group at nitrogen (kinetic activation, Chart 9). Furthermore, the amide anion **195** produced after ring opening is stabilized by resonance and induction (thermodynamic effect, Chart 9).[9b]

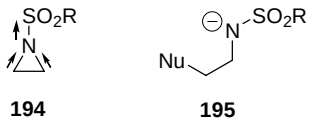
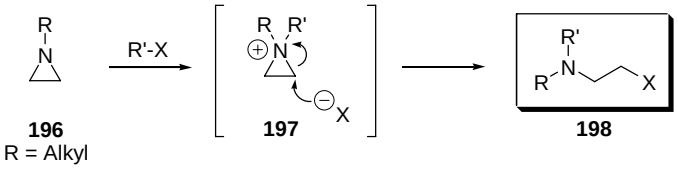


Chart 9

2.4.4.3. Ring opening of non-activated 1-alkyl-2-(bromomethyl)aziridines

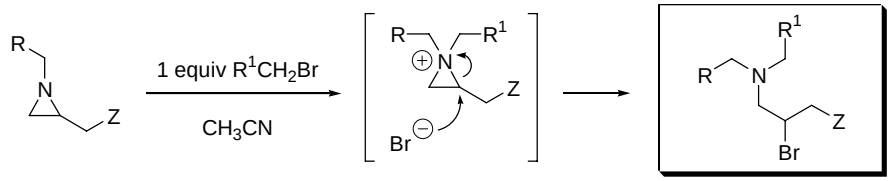
As mentioned before, aziridines can be classified as 'activated' or 'non-activated' according to whether or not quaternization towards an aziridinium intermediate is required for nucleophilic ring opening reactions. Whereas the ring opening of activated aziridines has been studied very intensively,[70] the ring opening of simple *N*-alkylated (and thus non-activated) aziridines has been investigated to a lesser extent. The easiest way to induce ring opening of 1-alkylaziridines **196** comprises *N*-alkylation with a suitable electrophile in order to obtain the

corresponding aziridinium salt **197**, and these highly electrophilic species **197** readily undergo ring opening upon treatment with nucleophiles (in most cases the counter ion) towards amines **198** (Scheme 58).



Scheme 58

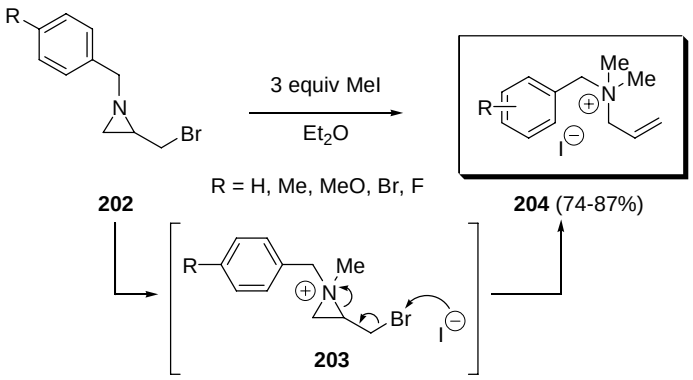
A powerful method for the regioselective ring opening of 2-substituted 1-alkylaziridines **199** involves treatment with an arylmethyl bromide in acetonitrile. In all cases, the *in situ* formed intermediate aziridinium ion **200** undergoes attack by the counterion bromide at the more hindered aziridine carbon atom, affording the corresponding *N*-(2-bromopropyl)amines **201** in a quantitative yield (Scheme 59). This methodology has been applied succesfully using 2-(bromomethyl)-, 2-(aryloxymethyl)-, 2-(alkanoyloxymethyl)- and 2-(cyanomethyl)aziridines towards the corresponding *N*-(2-bromopropyl)amines **201** in a regiospecific way (***Paper VII and VIII***). Instead of an arylmethyl bromide, also allyl bromide has been applied successfully in this reaction (***Paper IX***). Remarkably, no reaction occurred upon treatment of 2-(bromomethyl)-1-[(2-chlorophenyl)methyl]aziridine with methyl 2-bromoacetate in refluxing acetonitrile for 3-30 hours, and the starting material was recovered.



Scheme 59

When 2-(bromomethyl)aziridines **202** were treated with an excess of iodomethane, ring opening of the thus formed aziridinium intermediates **203** proceeded in a totally different way, resulting in *N*-allyl-*N*-arylmethyl-*N*,*N*-dimethylammonium salts **204** (Scheme 60). Apparently, the iodide anion attacked the bromo atom in a halophilic reaction, resulting in the

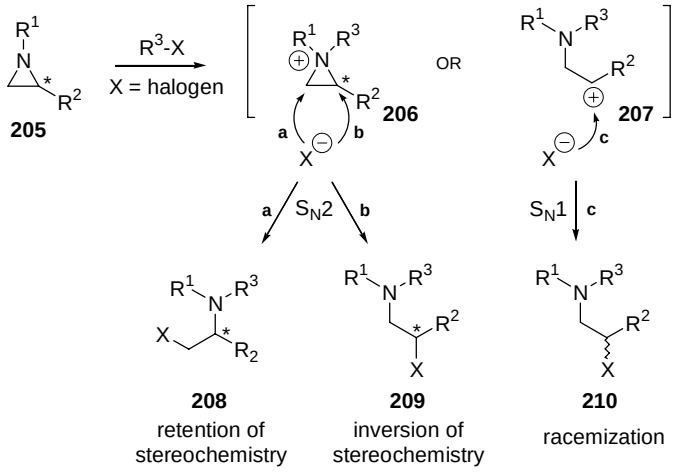
corresponding allylic amine. This tertiairy allylic amine reacted then further with the excess of iodomethane, yielding the quaternary allylammonium salts **204** (***Paper X***).



Scheme 60

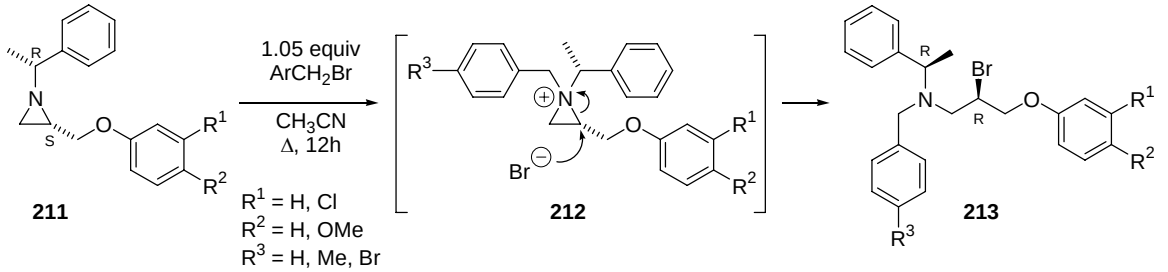
2.4.4.4. Ring opening of aziridinium salts: regioselectivity issues

Due to the high regioselectivity observed in the ring opening of aziridinium salts by bromide in acetonitrile (Scheme 59), a detailed investigation of the underlying reaction mechanism urged itself. As depicted in Scheme 61, the reaction of a chiral aziridine **205** with an alkyl halide may lead to three different amines **208**-**210** depending on the reaction mechanism. In this way, the initial chiral center at the substituted aziridine carbon atom can be retained (pathway **a**, amine **208**), inverted (pathway **b**, amine **209**) or racemized (pathway **c**, amine **210**). Consequently, the elucidation of the underlying reaction mechanism is of primordial importance when the design of asymmetric syntheses towards chiral amines is contemplated starting from chiral 2-substituted aziridines such as **205**.



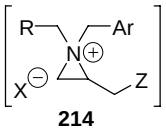
Scheme 61

Therefore, enantiomerically pure 2(*S*)-(aryloxymethyl)-1-(1(*R*)-phenylethyl)aziridines **211** have been transformed efficiently into chiral *N*-(2-bromo-3-aryloxypropyl)amines **213** as one single (*R*,*R*)-isomer via a regio- and stereospecific ring opening of the intermediate aziridinium salts **212** (Scheme 62), which is in accordance with an S_N2 type reaction mechanism (***Paper XI***). The experimental results have been rationalized on the basis of some high level *ab initio* calculations, pointing to an important influence of taking into account solvent effects.



Scheme 62

It is known that the regioselectivity in ring opening reactions of aziridinium salts is dependent on the nature of the substrate, the nucleophile and the solvent. In order to obtain a more detailed view on the reactivity of 2-substitituted aziridinium salts with a general structure **214** (Chart 10), several experiments have been conducted using different nucleophiles for the ring opening of these salts. Aziridinium salts have been used frequently as intermediates in the synthesis of natural products and their analogues.[5a]

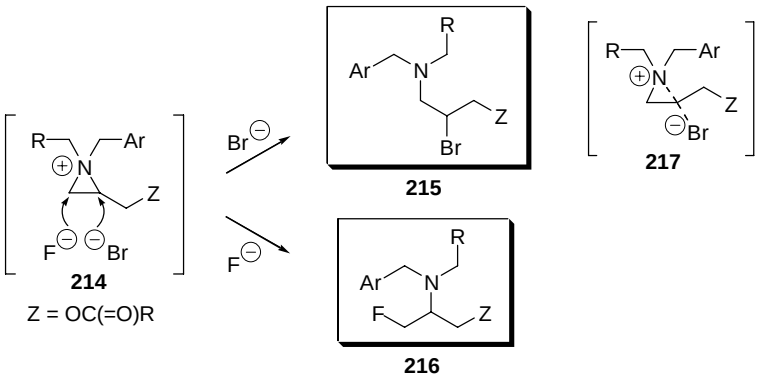


214

Chart 10

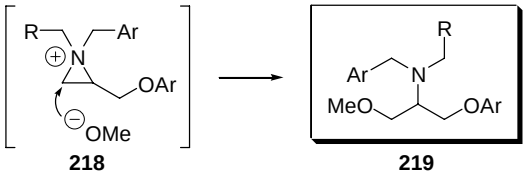
In this study, a different reactivity of the same substrates **214** in the same solvent (CH_3CN) has been observed upon ring opening by bromide and fluoride. The ring opening of these salts **214** by bromide occurs only at the more hindered carbon atom towards *N*-(2-bromopropyl)amines **215**, whereas fluoride has a preference for attack at the less hindered carbon atom towards 1-fluoro-2-aminopropane derivatives **216** (Scheme 63). The difference in polarizability between bromide and fluoride can account for this behavior, since the high

polarizability of bromide enables the formation of a favorable transition state **217** – stabilized by acetonitrile – upon attack at the substituted aziridine carbon atom,[9c] whereas the low polarizability of fluoride impede such a stablizing interaction, hence the preferential attack of fluoride at the unsubstituted carbon atom (***Paper IX***).



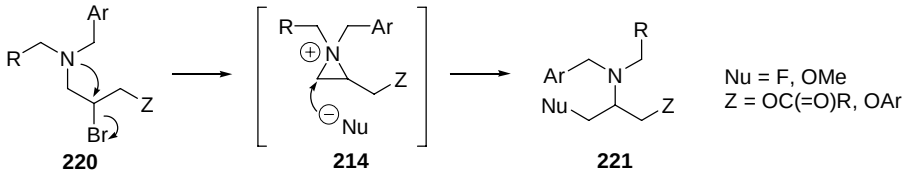
Scheme 63

The same reactivity as described for fluoride has been observed in the ring opening of aziridinium salts **218** by methoxide in methanol towards amine **219** (Scheme 64), which can be explained considering the high nucleophilicity of the methoxide anion as compared to bromide (***Paper VIII***).



Scheme 64

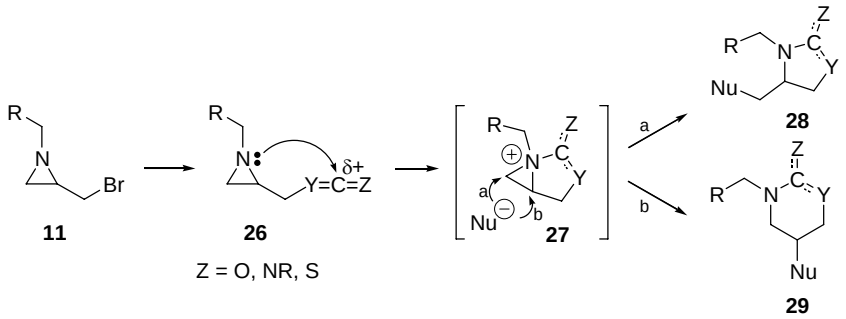
In the ring opening reactions with fluoride and methoxide, the intermediate aziridinium salts **214** were formed *in situ* by intramolecular displacement of the bromo atom upon heating of β-bromo amines **220**. Since the amino moiety has moved from the terminus of the propane skeleton in compounds **220** towards the central carbon atom in the isolated compounds **221**, this transformation can only be rationalized considering the formation of an intermediate aziridinium ion **214** (Scheme 65).



Scheme 65

2.4.5. Ring transformations of 2-(bromomethyl)aziridines

The various nucleophilic interactions with the constrained heterocyclic ring and with the halogenated carbon atom of aziridines **11**, combined with the nucleophilicity of the nitrogen lone pair, allow useful (intramolecular) reactions for the construction of a variety of heterocyclic compounds. Nucleophilic displacement of the bromo atom in aziridines **11** by a suitable nucleophile in which an electrophilic centre is present enables intramolecular attack of the nitrogen lone pair of the aziridine moiety onto this electrophile, resulting in a bicyclic aziridinium intermediate **27**. This intermediate can suffer from ring opening upon nucleophilic attack at the less (a) or the more (b) hindered aziridinium carbon atom, affording the corresponding azaheterocyclic systems **28** and **29** with a different ring size (Scheme 66).

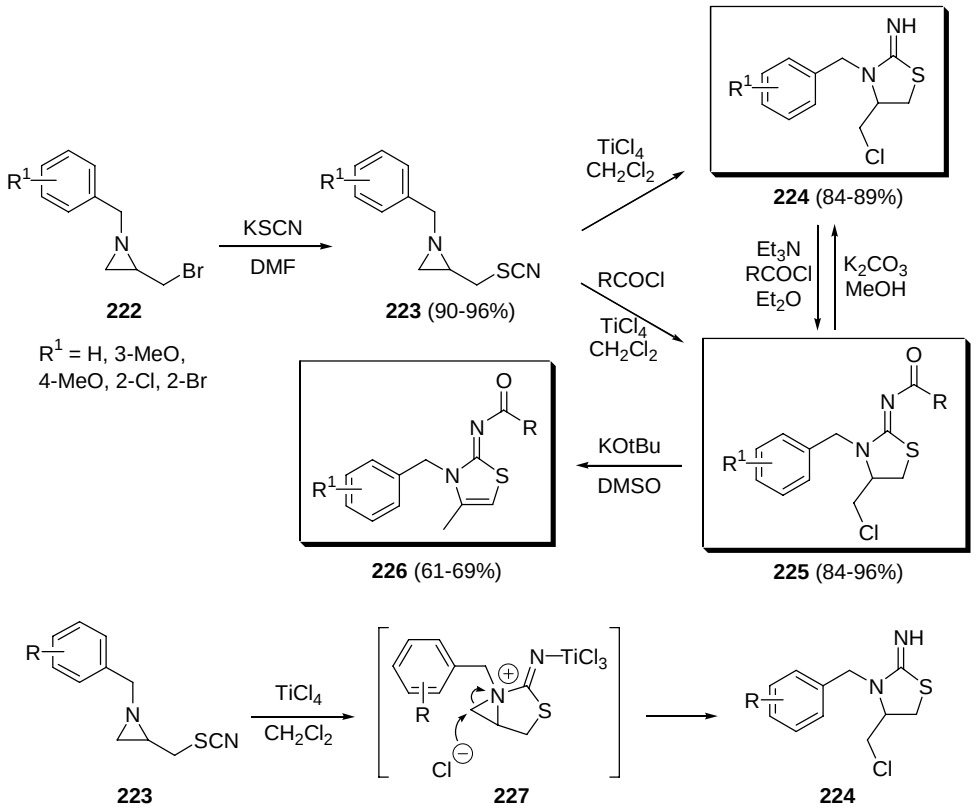


Scheme 66

This methodology, based on electrophile-induced ring closure, has been applied succesfully in this research work towards the synthesis of five-membered azaheterocycles (2-iminothiazolidines) and six-membered azaheterocycles (morpholines).

The synthesis of 2-iminothiazolidines **224** was accomplished by introduction of the ambident nucleophile potassium thiocyanate into 2-(bromomethyl)aziridines **222**, resulting in 1-arylmethyl-2-(thiocyanomethyl)aziridines **223**. The presence of an electrophilic centre in δ-position of the nucleophilic nitrogen atom in the latter substrates **223** allowed the preparation

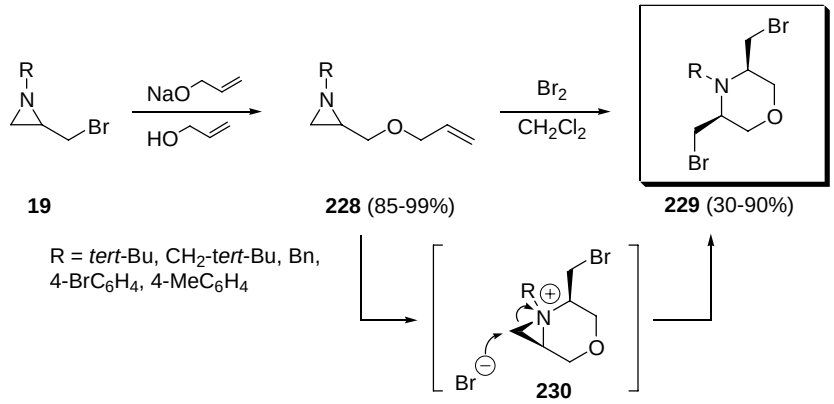
of 3-arylmethyl-4-chloromethyl-2-iminothiazolidines **224** via intermediate aziridinium salts **227** by addition of a catalytic amount of the Lewis acid titanium(IV) chloride (Scheme 67, ***Paper XII***). 2-Iminothiazolidines **224** and 2-(*N*-acylimino)thiazolidines **225** can be easily interconverted, either by treatment with an acid chloride and a base in ether towards 2-(*N*-acylimino)thiazolidines **225** or by treatment with potassium carbonate in methanol towards *N*-deprotected 2-iminothiazolidines **224**. Dehydrohalogenation of 2-(*N*-acylimino)-3-arylmethyl-4-(chloromethyl)thiazolidines **225** by means of potassium *t*-butoxide in DMSO afforded 2-(*N*-acylimino)-4-methylthiazolines **226** in good yields (Scheme 67). It is noteworthy that the very sticky reaction mixture, obtained after treatment of aziridines **223** with $TiCl_4$ and stirring for two hours at room temperature, had to be neutralized using a saturated sodium bicarbonate solution until pH 7 upon stirring for 15 minutes, after which the sticky paste became clear. Without this neutralization step no thiazolidines **224** or other products could be isolated from the reaction mixtures.



Scheme 67

Also 3,5-di(bromomethyl)morpholines **229** have been prepared diastereoselectively by ring expansion of aziridine derivatives. Addition of bromine to 2-(allyloxymethyl)aziridines **228** and subsequent electrophile-induced cyclisation afforded morpholines **229** via ring opening of

the intermediate bicyclic aziridinium salts **230** (Scheme 68, ***Paper XIII***). The yields of morpholines **229** were strongly dependent on the nature of the *N*-substituent, and the best results were obtained for the *N*-*tert*-butyl derivative **231**, prepared starting from 1-*tert*-butyl-2-(hydroxymethyl)aziridine. Nothworthy is the excellent diastereoselectivity involved in this reaction, since only *cis*-3,5-di(bromomethyl)morpholines were isolated. This was acknowledged by an X-ray analysis of 3,5-di(bromomethyl)-1-*tert*-butylmorpholine **231** (Chart 11).



Scheme 68

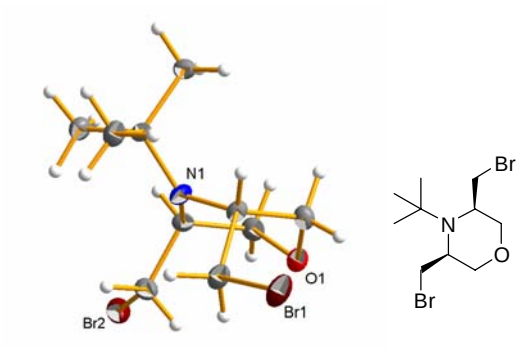


Chart 11 (morpholine **231**)

2.5. 2-(Bromomethyl)aziridines as substrates for the synthesis of biologically relevant compounds

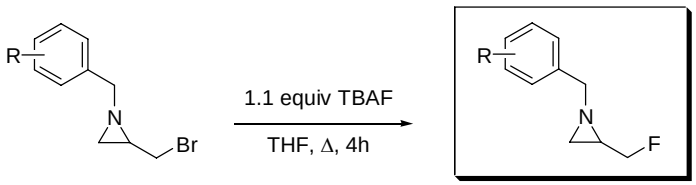
In this paragraph, the focus will be on the use of 2-(bromomethyl)aziridines as substrates for the synthesis of compounds with potential biological activity because of their resemblance to

other compounds with known activity, as well as the preparation of precursors useful for the synthesis of interesting target compounds. The synthesis of all these compounds is based on the methodologies described in the previous section, therefore the emphasis will be put on the relevance of the target compounds.

2.5.1. Synthesis of 1-arylmethyl-2-(fluoromethyl)aziridines (Unpublished results)

In recent years, the introduction of a fluoro atom in an organic compound is emerging as a powerful and versatile tool for the development of effective drugs and agrochemicals, since fluorine can dramatically alter both the chemical and the biological properties of these compounds.[71] Therefore, the synthesis of aziridines bearing a fluoro atom in one of the substituents might be of interest for further elaboration towards for example β-fluoro amines, the latter being known for their pronounced biological activities (e.g. as powerful antimicrobial agents and their activity on the central nervous system).[72,73]

1-Arylmethyl-2-(bromomethyl)aziridines **232** were efficiently transformed into the corresponding novel 2-(fluoromethyl)aziridines **233** upon treatment with 1.1 equiv of tetrabutylammonium fluoride (TBAF) as a fluoride source in refluxing THF (Scheme 69).[74] 2-(Fluoromethyl)aziridines **233** comprise useful new substrates for further elaboration towards a variety of fluorinated amines due to the reactivity of the aziridine moiety. Only two references could be found in which analogous di- or trisubstituted 2-(fluoromethyl)aziridines have been described,[32,75] i.e. 2-aryl-3-ethoxycarbonyl-2-(fluoromethyl)aziridines and 2-(fluoromethyl)-2-(polyfluoroalkyl)aziridines, although no general and convenient synthesis of 2-(fluoromethyl)aziridines is available in the literature up to now.



232 **233** (92-99%)

R = 2-Cl, 3-Me, 4-MeO, 4-Me, 4-Br

Scheme 69

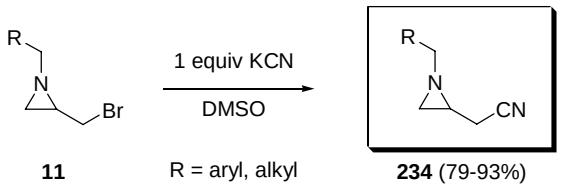
2.5.2. Synthesis of amino nitriles

The search for new pathways towards amino nitriles as precursors of the corresponding amino acids is an important challenge in organic synthesis.[76] In recent years, enzymatic methods

have been established using nitrilases, nitrile hydratases and amidases as an alternative to the usually harsh reaction conditions of chemical hydrolysis of nitriles,[77] hence the actual interest in the synthesis of novel amino nitriles. Furthermore, the interesting pharmacological properties of e.g. β- and γ-amino acids and their use in the synthesis of the corresponding β- and γ-peptides have, especially in the last decade, renewed the interest of organic chemists.[78] For example, β-amino acids are key structural components of a variety of natural products and drugs,[79] and alicyclic β-amino acids have been used for the synthesis of β-oligopeptides with unnatural backbones.[80]

*2.5.2.1. Synthesis of 2-(cyanomethyl)aziridines (**Paper XIV**)*

The introduction of a cyano group into 2-(bromomethyl)aziridines **11** can easily be accomplished by a nucleophilic displacement of the bromo atom by cyanide towards the corresponding 2-(cyanomethyl)aziridines **234** upon treatment with 1 equiv of potassium cyanide in DMSO (Scheme 70). Upon prolonged reaction times however, i.e. more then 6 hours, complex reaction mixtures were obtained. The combination of an aziridine moiety and a nitrile group in the same molecule results in a versatile substrate **234**, allowing the synthesis of a whole variety of functionalized amino nitriles due to the reactivity of the constrained aziridine ring.

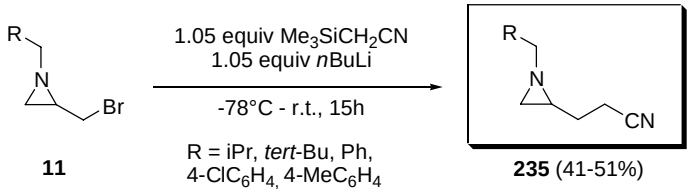


Scheme 70

2.5.2.2. Synthesis of 2-(2-cyanoethyl)aziridines (Unpublished results)

The higher homologues of 2-(cyanomethyl)aziridines **234**, i.e. 2-(2-cyanoethyl)aziridines **235**, comprise a novel class of compounds in organic chemistry. Only one analogous compound is known in the literature, i.e. 2-cyano-2-(2-cyanoethyl)-1-butylaziridine, which has been synthesized by a cycloaddition reaction of an azide with an electron-poor olefin.[81] Trimethylsilylacetonitrile was treated with 1 equivalent of *n*-BuLi in THF at 0°C,[82] followed by the addition of 1 equivalent of 2-(bromomethyl)aziridines **11** at -78°C under nitrogen

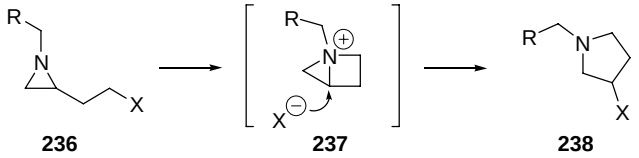
atmosphere. The resulting mixture was stirred for 15 hours at room temperature, yielding the corresponding 1-alkyl-2-(2-cyanoethyl)aziridines **235** in good yields after aqueous work up and column chromatography (Scheme 71).[83] 2-(2-Cyanoethyl)aziridines **235** comprise interesting new substrates for a variety of ring opening reactions and ring transformations towards acyclic and cyclic amino nitriles, the study of which is currently in progress.



Scheme 71

Upon addition of a catalytic amount of the Lewis acid titanium(IV) chloride to nitriles **235** (in analogy with the reaction of 2-(thiocyanomethyl)aziridines **223**, Scheme 67), no reaction occurred and the starting material was recovered.

The above described approach towards 2-(2-cyanoethyl)aziridines **235** comprises an elegant alternative for the nucleophilic displacement of the halogen by cyanide in 2-(2-haloethyl)aziridines **236**, since the latter compounds are prone to intramolecular ring closure towards the bicyclic aziridinium ion **237** and subsequent ring opening towards 3-halopyrrolidines **238**.[84]



Scheme 72

*2.5.2.3. Synthesis of methyl N-(2-cyanocyclopropyl)benzimidates (**Paper XIV**)*

Besides their interest as constituents of peptides, β-ACC **239** derivatives (2-aminocyclopropanecarboxylates) can also be considered as conformationally restricted γ-aminobutyric acid **240** (GABA) analogues (Chart 12), which are known for their effect on the central nervous system.[85] Very recently, significant new contributions concerning the

chemistry of β-ACC derivatives have been acomplished at the Department of Organic Chemistry (Faculty of Bioscience Engineering, Ghent University).[86]

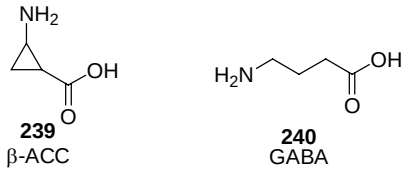
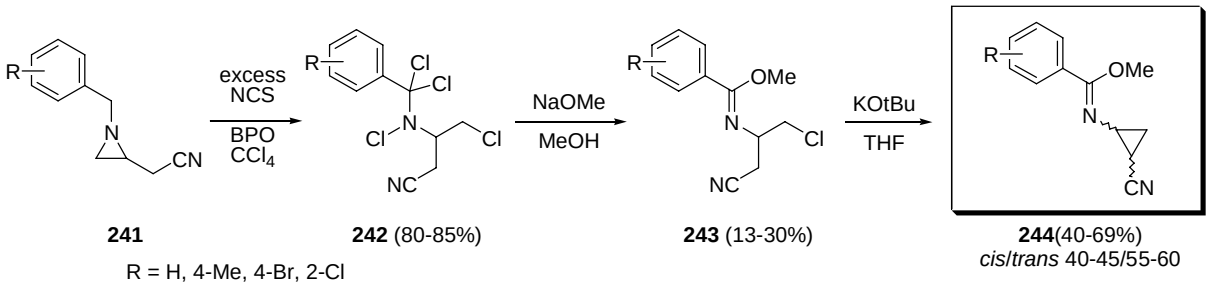


Chart 12

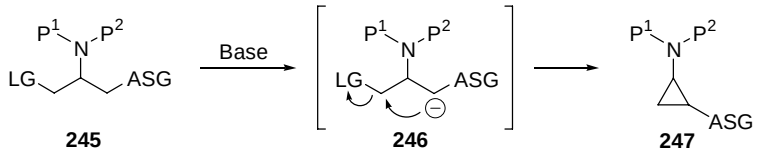
Ring opening of the aziridine moiety of 2-(cyanomethyl)aziridines **241** with an excess of *N*-chlorosuccinimide in CCl_4 in the presence of BPO (benzoyl peroxide) and subsequent treatment of the thus formed 4-chloro-3-(*N*-chloro-*N*-(α,α-dichlorobenzyl)amino)-butanenitriles **242** with sodium methoxide in methanol resulted in novel methyl *N*-(2-chloro-1-(cyanomethyl)ethyl)benzimidates **243**, although in low yields (13-30%). Treatment of 2-(cyanomethyl)aziridines **241** with 2 equiv of NCS in refluxing CCl_4 did not always gave reproducible results, as sometimes a partial conversion towards 4-chloro-3-(*N*-chlorobenzylamino)butanenitriles was observed, whereas in other cases using exactly the same reaction conditions all the starting material was consumed. γ-Chloro nitriles **243** were smoothly converted into *cis*/*trans* mixtures of methyl *N*-(2-cyanocyclopropyl)benzimidates **244** as precursors of biologically relevant β-ACC derivatives through a 1,3-cyclisation protocol by reaction with potassium *t*-butoxide in THF (Scheme 73).



Scheme 73

The net conversion of this methodology concerns the ring transformation of an aziridine into a cyclopropylamine derivative, involving the stepwise synthesis of a three-carbon unit **245** with an anion-stabilizing group at C1 (*in casu* a nitrile), a suitable protected amino function at C2 (*in casu* an imidate) and a leaving group at C3 (in casu a chloro atom). α-Deprotonation to

anion **246** and subsequent intramolecular displacement of the leaving group via a 3-*exo*-*tet* ring closure affords β-aminocyclopropane nitriles **247** (Scheme 74). Remarkably, this convenient and straightforward approach towards cyclopropane derivatives has not been developed until now, probably due to the necessity of a suitable substrate **245** in order to avoid side-reactions such as aziridine formation and retro-Michael reactions.

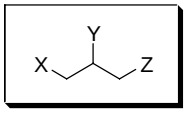


ASG = Anion Stabilising Group
LG = Leaving Group
P^1, P^2 = Protecting Group

Scheme 74

2.5.3. Synthesis of 1,2,3-triheteroatom substituted propane derivatives (Paper IV, VIII and IX)

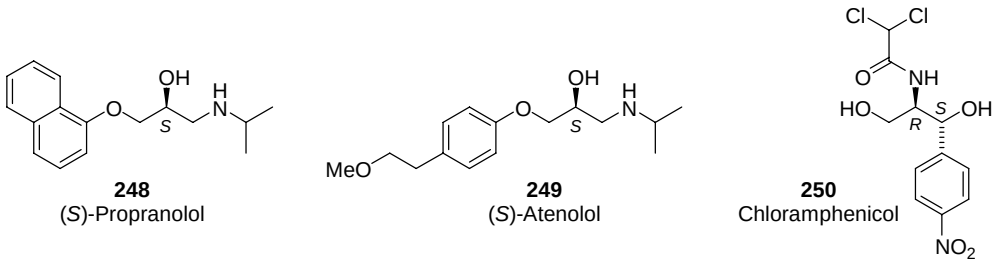
A key element present in a whole range of physiologically active natural products and their synthetic analogues comprises a 1,2,3-triheteroatom substituted three-carbon unit **18** (Chart 13). Many drugs accommodate such a moiety in their structure,[87] for example aryloxypropanolamines (β-blockers propranolol **248** and atenolol **249**, Chart 14), 2-[(arylmethyl)amino]propanediols (antitumor DNA intercalators), and broad-spectrum antibiotics (chloramphenicol **250**, Chart 14), hence the significant interest in the development of new entries towards compounds bearing a 1,2,3-trisubstituted propane skeleton.



18

X, Y, Z = heteroatoms
e.g. N, O, S, halogen

Chart 13



248 (*S*)-Propranolol

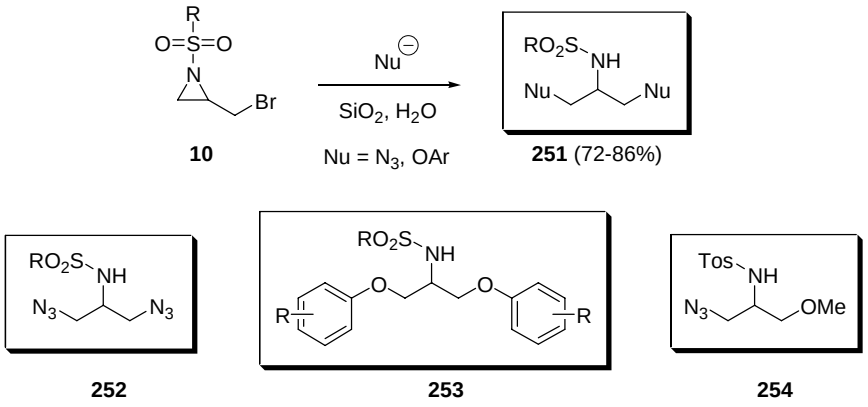
249 (*S*)-Atenolol

250 Chloramphenicol

Chart 14

2-(Bromomethyl)aziridines are excellent substrates for the synthesis of 1,2,3-trisubstituted propane derivatives since their structure comprises a three-carbon unit in which the three electrophilic carbon atoms are structurally differentiated from each other, allowing the selective preparation of different substituted propylamines.

The activated 2-(bromomethyl)-1-sulfonylaziridines **10** have been converted into 1,3-disubstitituted 2-aminopropane derivatives **251** by means of an environmentally benign process using water as a solvent in the presence of silica gel (Scheme 75, ***Paper IV***). The nucleophiles used for this ring opening reaction were sodium azide and different potassium phenoxides, affording sulfonamides **252** and **253** respectively. Accordingly, also the non-activated 2-(bromomethyl)-1-neopentylaziridine could be transformded into the corresponding 2-amino-1,3-diazidopropane derivative upon treatment with 3 equiv of NaN_3 in H_2O and heating at 80°C for 30h in the presence of silica gel. A stepwise approach using two different nucleophiles enabled the synthesis of the unsymmetrical α-branched *N*-sulfonylamide **254**.

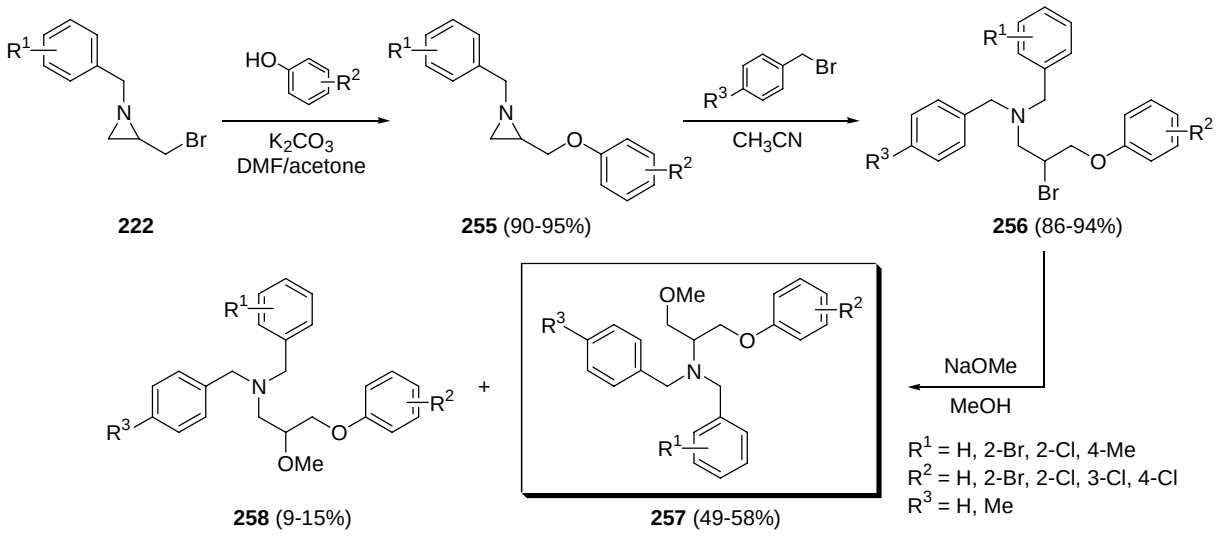


10 Nu = N_3, OAr **251** (72-86%)

252 **253** **254**

Scheme 75

Also the non-activated 1-arylmethyl-2-(bromomethyl)aziridines **222** can be applied successfully for the synthesis of 1,2,3-trisubstituted propane derivatives (***Paper VIII***). In a first step, the bromo atom has been replaced by an aryloxy group using a phenolate anion as a nucleophile in DMF/acetone, affording the corresponding 2-(aryloxymethyl)aziridines **255** in good yield. The introduction of an aryloxy moiety is of importance since structure-activity relationship studies on propranolol analogues (and β-blockers in general) have pointed to the relevance of such a group for biological activity. Subsequently, these aziridines **255** were treated with an arylmethyl bromide in acetonitrile towards the ring opened *N*-(3-aryloxy-2-bromopropyl)amines **256** via a regioselective ring opening of intermediate aziridinium salts (vide supra). In the last step, β-bromoamines **256** were converted into 2-amino-1-aryloxy-3-methoxypropanes **257** as the major reaction products (49-58%) upon treatment with sodium methoxide in methanol, besides minor quantities of 3-amino-1-aryloxy-2-methoxypropanes **258** (9-15%, Scheme 76). The formation of the major constituents can only be explained considering the formation of intermediate aziridinium salts and subsequent ring opening at the less hindered carbon atom (vide supra, Scheme 65). Attempts to introduce a hydroxyl group instead of a methoxy group using sodium hydroxide (3N in H_2O) in CH_2Cl_2/H_2O (1/1) or in DMF/H_2O (3/1) (r.t. or 80°C, 30 min. - 5h), or using KOH in Et_2O (r.t., 6h) were unsuccessful and the starting material was recovered.



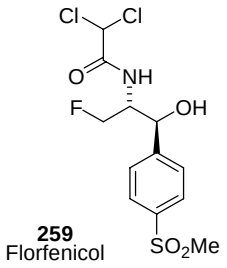
222 **255** (90-95%) **256** (86-94%)

258 (9-15%) **257** (49-58%)

Scheme 76

A similar approach has been applied for the synthesis of functionalized β-fluoro amines due to the well-known biological importance of the introduction of a fluoro atom into organic compounds.[88] Furthermore, the incorporation of a β-fluoro amine moiety into a 1,2,3-

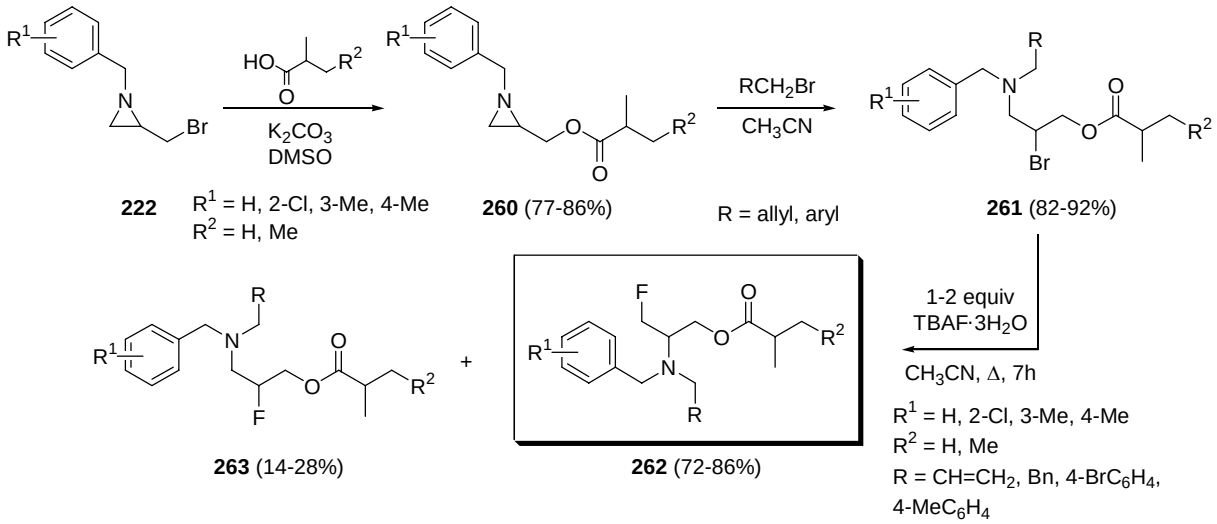
triheteroatom substituted propane skeleton has led to the discovery of a new class of powerful antimicrobial agents, such as florfenicol **259** (Chart 15).[73a,b]



259
Florfenicol

Chart 15

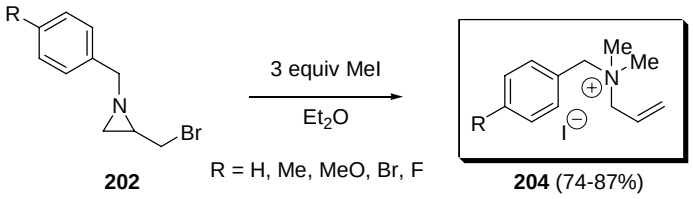
1-Arylmethyl-2-(bromomethyl)aziridines **222** were converted into the corresponding novel 2-(alkanoyloxymethyl)aziridines **260** as valuable substrates in organic synthesis upon treatment with potassium 2-methylpropanoate or potassium 2-methylbutyrate in DMSO. Subsequently, these aziridines **260** were treated with allyl bromide or an arylmethyl bromide in CH_3CN and thus converted into the corresponding *N*-(2-bromo-3-alkanoyloxypropyl)amines **261** via a regioselective ring opening of intermediate aziridinium salts (vide supra). Finally, the latter β-bromo amines **261** were treated with tetrabutylammonium fluoride ($TBAF{\cdot}3H_2O$) in acetonitrile, affording a mixture of β-fluoro amines **262** as the major constituents (72-90%) and β-fluoro amines **263** as the minor compounds (14-28%, Scheme 77, ***Paper IX***). The formation of the major constituents can only be explained considering the formation of intermediate aziridinium salts and subsequent ring opening at the less hindered carbon atom (vide supra, Scheme 65). Attempts to induce ring opening of aziridines **260** towards β-fluoro amines by means of $Et_3N{\cdot}3HF$ in CH_3CN failed. No reaction was observed upon treatment of **260** with 1 equiv of $Et_3N{\cdot}3HF$ after reflux for 5 hours, and complex reaction mixtures were obtained upon prolonged reaction times (0.67-3 equiv of $Et_3N{\cdot}3HF$ and reflux for 20-30 hours).



Scheme 77

2.5.4. Synthesis of quaternary allylammonium salts (Paper X)

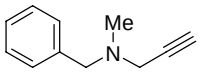
Treatment of 2-(bromomethyl)aziridines **202** with an excess of iodomethane in diethyl ether resulted in *N*-allyl-*N*-arylmethyl-*N*,*N*-dimethylammonium salts **204** (Scheme 78) via halophilic ring opening of the intermediate aziridinium salts (vide supra, Scheme 60). The interest in convenient syntheses of allylammonium salts is a direct result of their broad applicability in various fields. For example, ammonium salts in general and *N*-allyl-*N*-benzyl-*N*,*N*-dimethylammonium salts in particular are of significant importance in agriculture because of their plant growth regulating activity,[89] and related ammonium salts also exhibit anti-microbial activity which makes them attractive as potential antibiotics.[90] Furthermore, quaternary ammonium salts are useful in organic synthesis for phase transfer catalysis, as starting material or reagent, for dyeing and printing cellulose textiles and as emulsion stabilizers.[91]



Scheme 78

2.5.5. Synthesis of propargylic amines (Paper VII)

Propargyl amines are very much in demand in medicinal chemistry due to the pronounced physiological activities of these compounds and their derivatives. A very generally occurring mode of action of propargyl amines concerns the inhibition of the enzyme monoamine oxidase (MAO), which makes them potential drugs for treatment of neurotic, psychiatric and other disorders, such as depression, panic disorder, social phobia, Parkinson's disease and Alzheimer's disease.[92] A well-known example is the drug pargyline,[93] a monoamine oxidase inhibitor with antihypertensive properties, sold as the hydrochloride salt **264** (Chart 16).

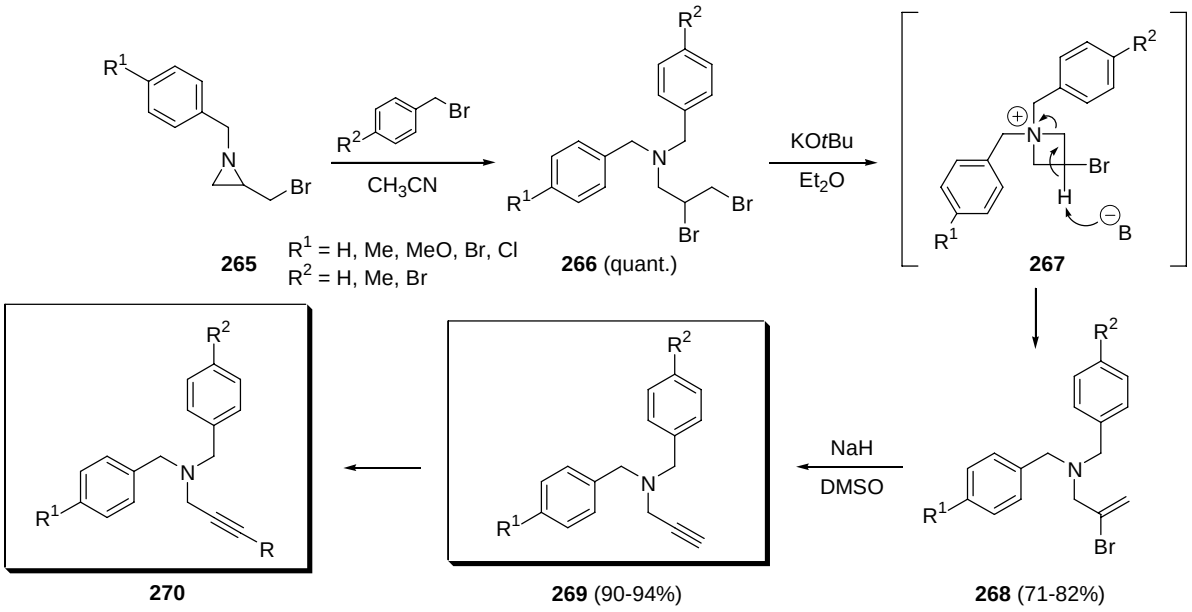


264
Pargyline

Chart 16

A new, efficient and straightforward synthesis of *N*,*N*-di(arylmethyl)-*N*-(2-propynyl)amines **269** was developed starting from 1-arylmethyl-2-(bromomethyl)aziridines **265** *via* *N*-(2,3-dibromopropyl)amines **266** and *N*-(2-bromo-2-propenyl)amines **268**, respectively (Scheme 79). The conversion of *N*-(2,3-dibromopropyl)amines **266** into *N*-(2-bromo-2-propenyl)amines **268** is based on a novel analogue of the Hofmann elimination via intermediate 3-bromoazetidinium salts **267**. In order to verify the intermediacy of the latter azetidinium salts **267**, a chloro analogue of these presumptive intermediates has been prepared by methylation of 3-chloroazetidine **271** with methyl iodide and subsequent treatment with a base, affording vinyl chloride **272** (Scheme 80). However, alkylation of the 3-trimethylsilyloxy derivative of azetidine **271** with iodomethane, followed by treatment of the corresponding azetidinium salt with base (KO*t*Bu in ether or sodium hydride in DMSO) resulted in complex reaction mixtures without any trace of the desired allylamine.

A Yamaguchi-Hirao alkylation, a Sonogashira coupling or a hydroarylation reaction further functionalized these propargyl amines **269** towards potentially interesting compounds **270** and other derivatives for medicinal and agrochemical use (compounds **273**-**281**, Chart 17).



Scheme 79

Scheme 80

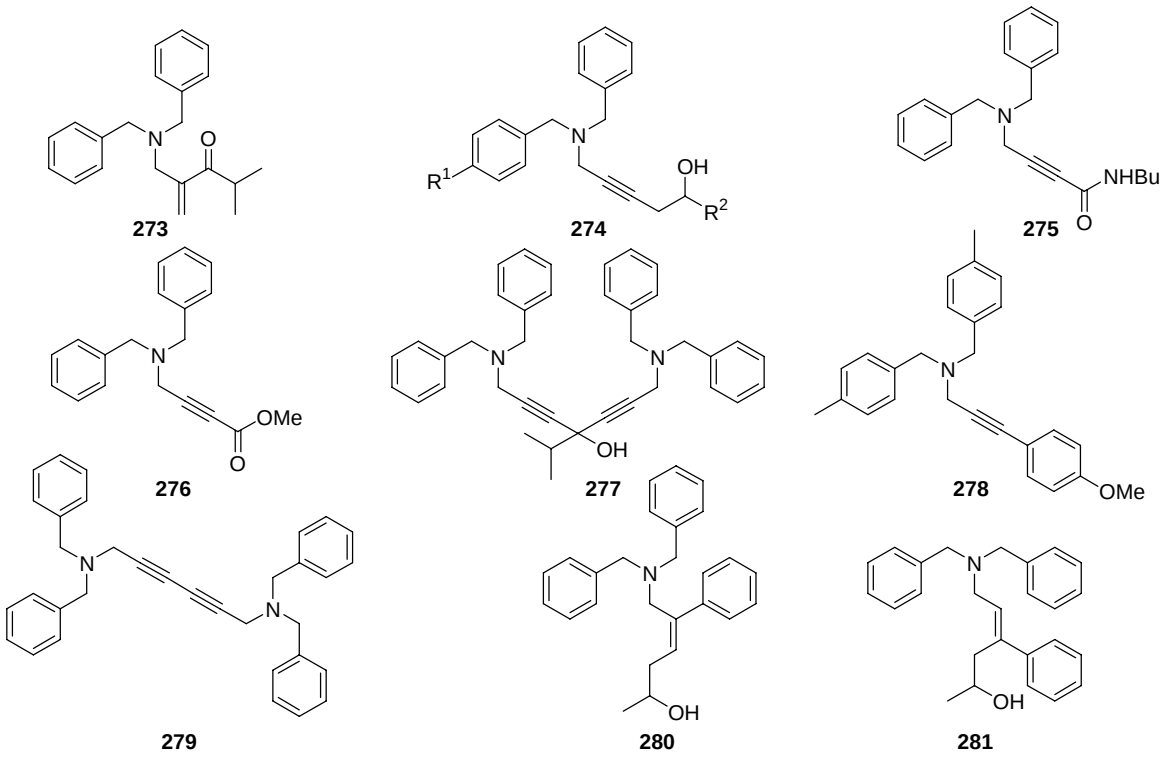
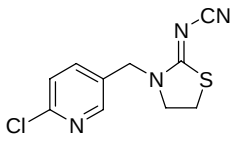


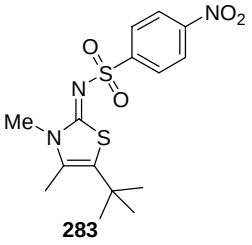
Chart 17

2.5.6. Synthesis of 2-iminothiazolidines and 2-iminothiazolines (Paper XII)

An impressive list of physiological activities illustrates the relevance of 2-iminothiazolidines and 2-iminothiazolines as target compounds in organic synthesis. 2-Iminothiazolidines are known and appreciated for their anti-inflammatory, anodyne and anti-Alzheimer activity,[94] their use in agriculture (such as the insecticide thiacloprid **282**, Chart 18),[95] and their applicability against γ-radiation due to their protective properties.[96] The chemistry of 2-iminothiazolidines has recently been covered in a review article (***Paper XV***). The unsaturated 2-iminothiazolines in their turn have also drawn the attention of the pharmaceutical chemistry, featuring important biological activities such as anti-HIV, antimicrobial, anti-inflammatory, antihistaminic, antihypertensive, hypnotic and anticonvulsant activity, and very recently for their applicability for the identification of human cells with positive myeloperoxidase reactivity.[97] For example, 2-iminothiazoline **283** has been reported as a novel HIV-1 reverse transcriptase inhibitor (Chart 18).[98] Furthermore, thiazolines have interesting applications in agriculture as acaricides, insecticides and plant growth regulators.[99]



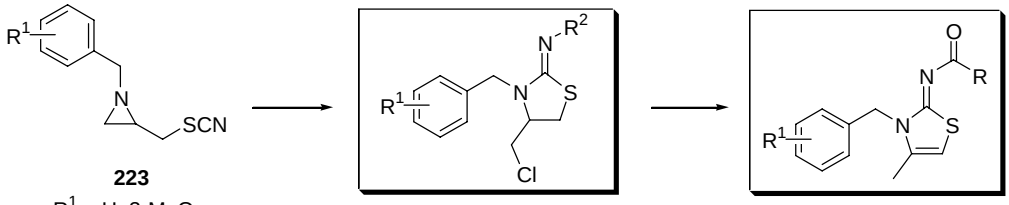
282
Thiacloprid



283

Chart 18

As described before, 3-arylmethyl-4-chloromethyl-2-iminothiazolidines **284** (R^2 = H) and 2-(*N*-acylimino)-4-methylthiazolines **284** (R^2 = (C=O)R) were synthesized starting from 1-arylmethyl-2-(thiocyanomethyl)aziridines **223** in a straightforward way (vide infra, Scheme 67). This novel methodology enables the preparation of 2-iminothiazolidines **284** and their unsaturated analogues 2-iminothiazolines **226** as relevant targets due to the general interest in these azaheterocyclic moieties.



Scheme 81

2.5.7. Synthesis of cis-3,5-disubstituted morpholine derivatives (Paper XIII)

Although morpholines are frequently used in organic synthesis as bases or as *N*-alkylating agents, less attention has been devoted to the development of novel carbon-substituted morpholine derivatives. However, the latter class of compounds has gained much interest in recent years due to the pronounced biological activities ascribed to many representatives and their use as chiral reagents in asymmetric synthesis. The applications of biologically relevant carbon-substituted morpholines vary from medicinal use as e.g. antidepressants, appetite suppressants, antitumor agents, antioxidants, antibiotics, anti-HIV, to agricultural use as fungicides. For example, reboxetine **285** is an antidepressant drug used in the treatment of clinical depression, panic disorder and attention deficit disorder,[100] and fenpropimorph **286** is a widely-used leaf fungicide whose major use is to control fungal diseases in cereals (Chart 19).[101] Furthermore, the growing importance of asymmetric synthesis has led to the development of several *trans*-disubstituted morpholine derivatives as a novel class of C_2-symmetric auxiliaries.

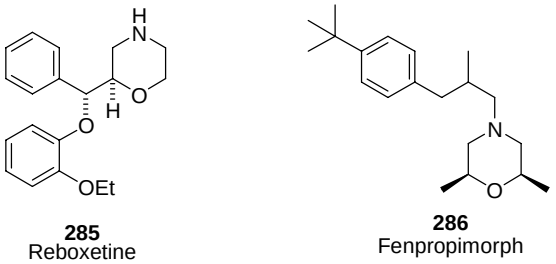
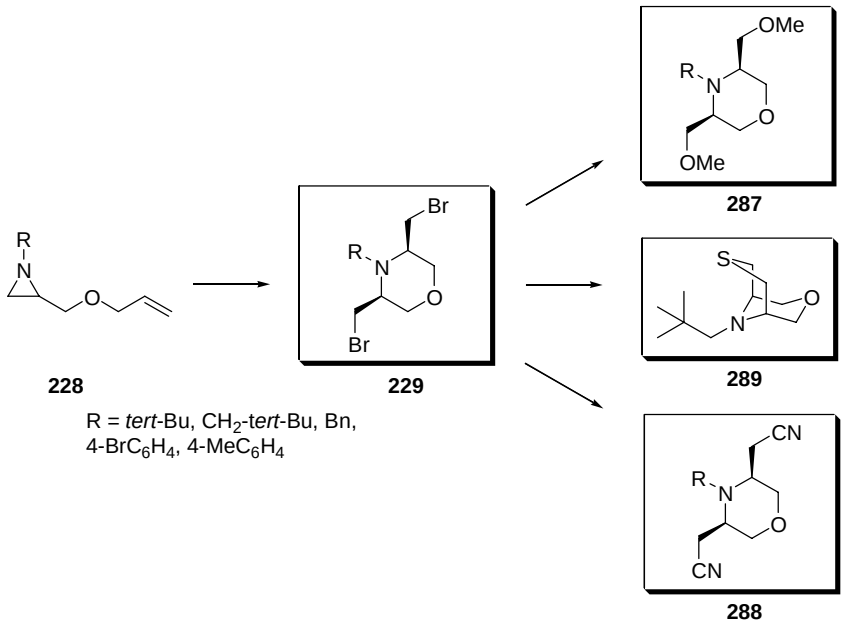


Chart 19

As mentioned before, *cis*-3,5-di(bromomethyl)morpholines **229** were prepared from 2-(allyloxymethyl)aziridines **228** by addition of bromine (vide infra, Scheme 68). The latter morpholines **229** were used as a substrate for the synthesis of the corresponding 3,5-di(methoxymethyl)morpholines **287** and 3,5-di(cyanomethyl)morpholines **288** and as novel

morpholine derivatives upon nucleophilic displacement of both bromo atoms by methoxide and cyanide (Scheme 82). Furthermore, the *N*-neopentylmorpholine derivative was transformed into a 3-oxa-7-thia-9-azabicyclo[3.3.1]nonane scaffold **289** upon treatment with Li_2S in EtOH (Scheme 82).

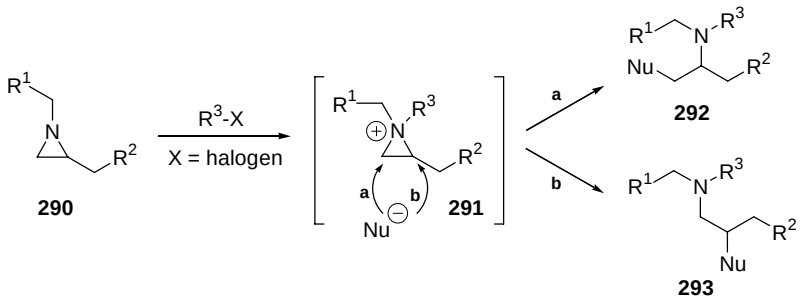


Scheme 82

2.6. Perspectives

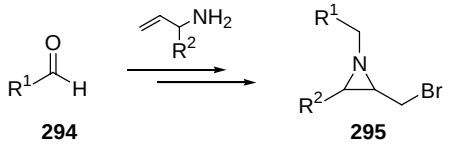
Whereas the ring opening of activated aziridines has been studied intensively in the past, little is known about the reactivity of their non-activated counterparts. The chemistry of aziridinium salts, obtained from non-activated 1-alkylaziridines upon quaternization of the aziridine nitrogen, has been evaluated only sporadically, and no general reactivity profile of these synthetic intermediates is available in the literature. The results obtained in this thesis pave the way for a more profound understanding of the chemistry of 2-substituted aziridinium salts in terms of regio- and stereoselectivity of their ring opening, especially concerning the ring opening of 2-substituted 1,1-dialkylaziridinium salts by halides and other nucleophiles in solvents of different polarity. The change in regioselectivity upon ring opening of aziridinium salts by fluoride and methoxide when compared to bromide illustrated the complexity of this matter. Prospective research in this area using different substrates **290**, different nucleophiles (e.g. halogens, alcohols, amines,…) and different solvents, in combination with molecular

modelling, is of high importance in order to obtain a comprehensive overview of the reactivity of 2-substituted aziridinium salts **291** and their applicability in organic synthesis towards amines **292** and **293** as substrates for further elaboration (Scheme 83).



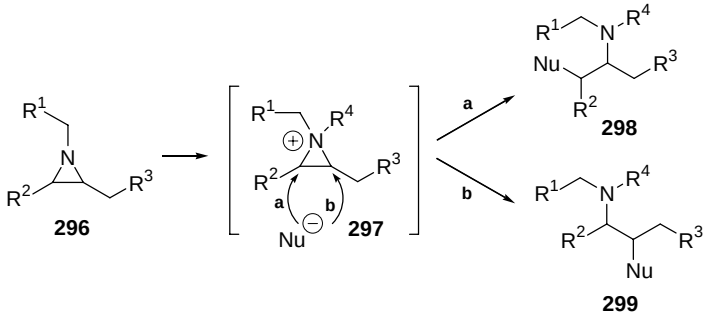
Scheme 83

Secondly, the synthetic protocols developed in this thesis for the transformation of 2-(bromomethyl)aziridines towards a variety of compounds can be applied for the synthesis of more complex target compounds, for example starting from 3-substituted 2-(bromomethyl)aziridines **295**. The latter aziridines **295**, obtained from aldehydes **294** according to the presented procedure (Scheme 84), can then be used for substitution reactions, ring opening reactions and ring transformations.



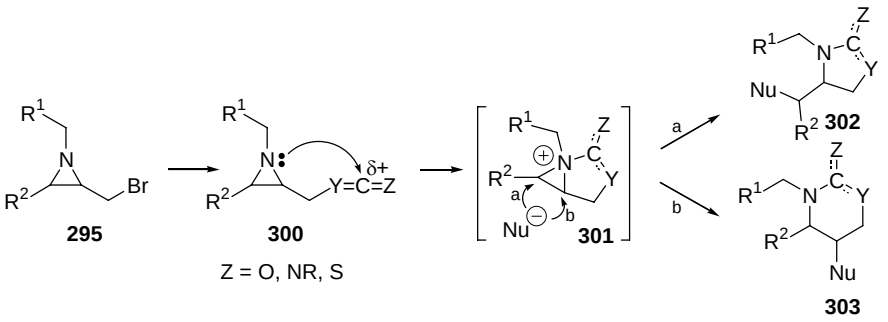
Scheme 84

Most probably, the presence of an additional substituent (R^2) will have a significant impact on the regioselectivity of the ring opening of aziridinium salts **297** as well as on the relative stereochemistry, and this will definitely lead to new insights in the chemistry of aziridinium salts and their use for the synthesis of functionalized amines **298** and **299** (Scheme 85).



Scheme 85

When the methods towards the synthesis of azaheterocyclic compounds such as 2-iminothiazolidines and morpholines described in this PhD thesis are applied to 2,3-disubstituted aziridines **295**, the regioselectivity of the ring opening of the intermediate bicyclic aziridinium salts **301** can be influenced due to the presence of the additional substituent (R^2) and, consequently, the reaction outcome might be different.



Scheme 67

Furthermore, the reactivity and usefulness of two novel classes of aziridine substrates **233** and **235**, prepared in this thesis, has to be evaluated thoroughly in the future (Chart 20). 2-(Fluoromethyl)aziridines **233** are of importance as substrates in organic synthesis, especially since recently the interest in fluorine containing compounds in medicinal chemistry has increased drastically. Also 2-(2-cyanoethyl)aziridines **235** have to be elaborated towards potentially valuable amino nitriles due to their significance as amino acid precursors.

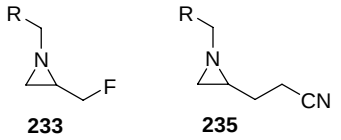
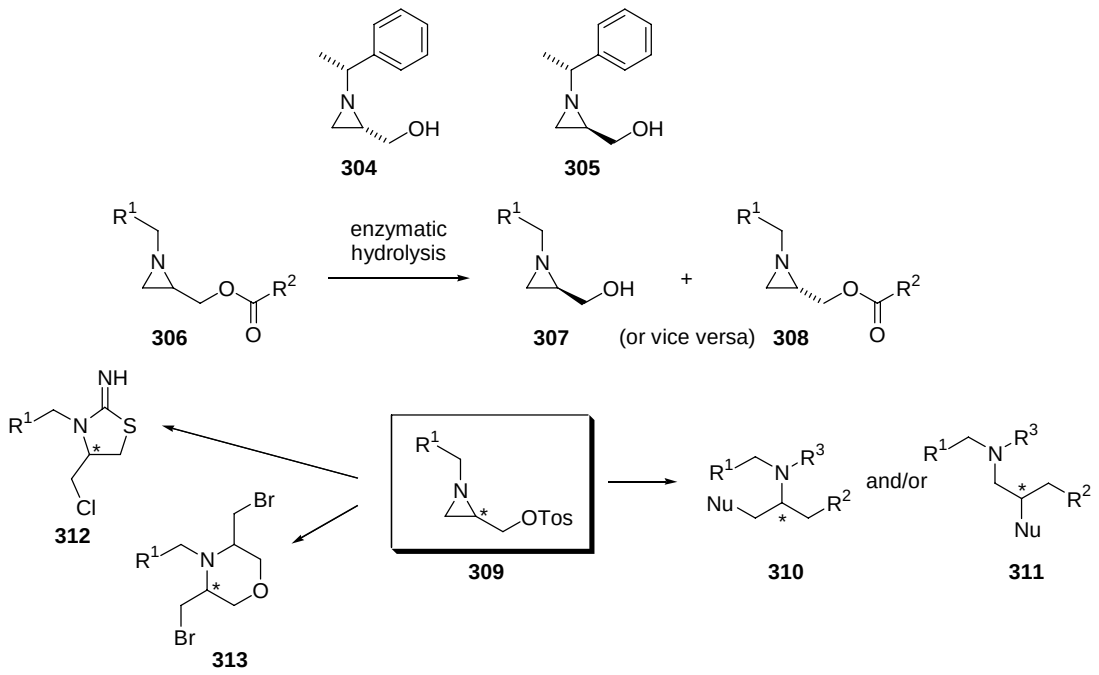


Chart 20

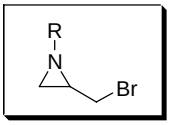
Finally, the synthesis of a whole variety of cyclic and acyclic nitrogen containing compounds starting from racemic substrates in this PhD thesis justifies the development of asymmetric routes towards the chiral analogues of these target compounds (for example compounds **310-313**), especially when the latter analogues have shown to exhibit interesting biological activities. The enantiomerically pure and commercially available 2-(hydroxymethyl)aziridines **304** and **305** or, alternatively, a set of chiral 2-(hydroxymethyl)aziridines **307**, prepared by enzymatic hydrolysis of the esters **306** (for which an elegant approach has been developed in this work) can, after tosylation towards chiral aziridines **309**, be used for the asymmetric versions of the methods presented in this work (Scheme 68).



Scheme 68

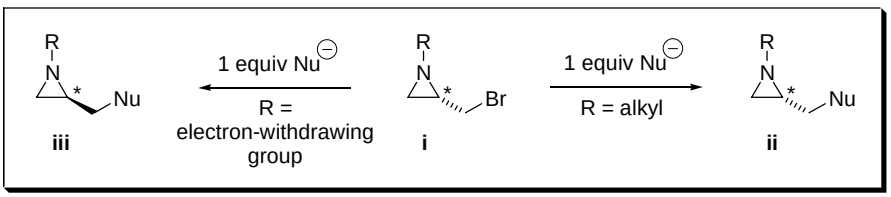
Summary

The results presented in this PhD thesis clearly demonstrate the versatility of 2-(bromomethyl)aziridines **i** as synthons in organic chemistry. The inherent reactivity of the constrained azaheterocyclic ring, combined with the electrophilicity of the halogenated carbon atom, results in a plethora of potential organic transformations towards a large variety of different target compounds, many of which feature structural resemblance to other compounds with known biological activity.



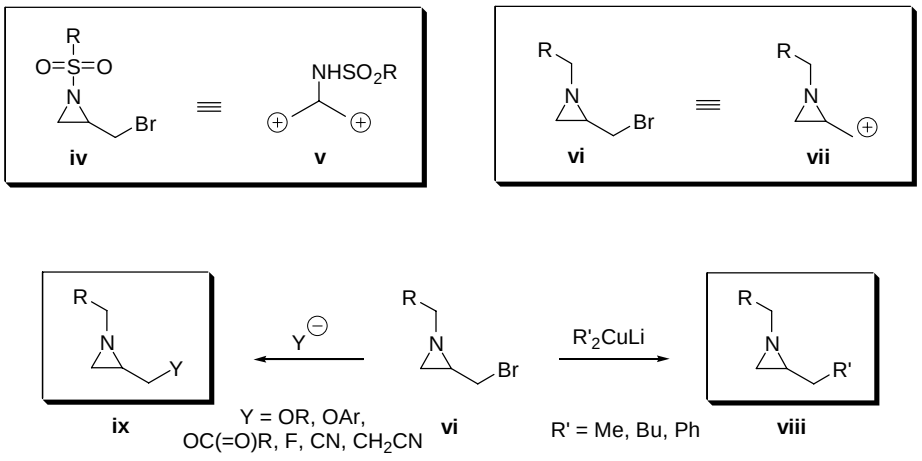
i

The first part of this work comprised an extensive evaluation of the reactivity of 1-alkyl- and 1-sulfonyl-2-(bromomethyl)aziridines in order to obtain a comprehensive overview of their applicability in organic synthesis. A comparative study between the behavior of activated versus non-activated 2-(bromomethyl)aziridines upon treatment with one equivalent of a nucleophile revealed a totally different yet complementary reactivity profile of these substrates. This study showed that non-activated 1-alkyl-2-(bromomethyl)aziridines **i** (R = alkyl) undergo direct S_N2 substitution at the halogenated carbon atom with retention of configuration towards aziridines **ii**, whereas activated 1-sulfonyl-2-(bromomethyl)aziridines **i** (R = EWG) suffer from ring opening – ring closure with inversion of configuration towards aziridines **iii**. These conclusions are of significance whenever asymmetric synthesis towards chiral targets compounds is contemplated utilizing chiral substrates **i**.



Furthermore, treatment of 1-alkyl- and 1-sulfonyl-2-(bromomethyl)aziridines with more then one equivalent of different types of carbon-centered and heteroatom-centered nucleophiles has resulted in a different applicability of both these substrates, pointing to the conclusion that

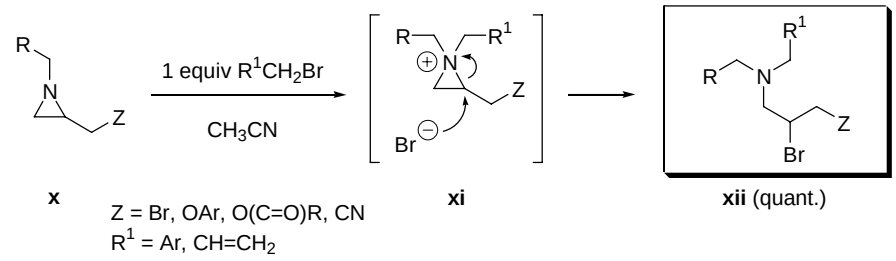
2-(bromomethyl)-1-sulfonylaziridines **iv** can be used successfully as synthetic equivalents for the 2-aminopropane dication synthon **v** towards α-branched *N*-tosylamides, whereas 1-alkyl-2-(bromomethyl)aziridines **vi** can be considered as synthetic equivalents for the aziridinylmethyl cation synthon **vii** towards the preparation of a large variety of 2-substituted aziridines. The latter equivalency has been exploited for the coupling between 1-alkyl-2-(broommethyl)aziridines and organocuprates as a novel protocol towards the synthesis of 1,2-dialkylaziridines **viii**, as well as the substitution by a variety of heteroatom centered nucleophiles towards the corresponding 2-substituted azirdines **ix**. For example, this has lead to the synthesis of novel 2-(fluoromethyl)aziridines and 2-(2-cyanoethyl)aziridines as versatile substrates for further elaboration.



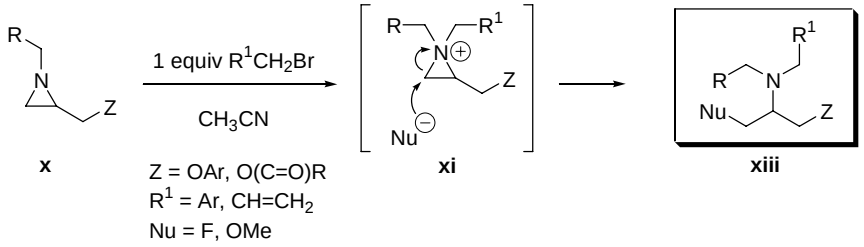
It is clear that the central element in the comparison between activated and non-activated 2-(bromomethyl)aziridines comprises the stability of the aziridine ring as compared to the reactivity of the halogenated carbon atom. The reactive centre in 1-alkyl-2-(bromomethyl)aziridines **vi** is the brominated carbon atom, whereas in 1-sulfonyl-2-(bromomethyl)aziridines **iv** the aziridine moiety is the most electrophilic part.

The relative inertness of the aziridine ring in 1-alkylaziridines towards nucleophiles has hampered the study and use of these substrates for ring opening reactions as compared to the ring opening of their activated counterparts. Since 1-alkylaziridines have to be 'activated' prior to ring opening, *N*-alkylation towards aziridinium salts constitutes a powerful method for the transformation of 1-alkylaziridines into acyclic target compounds. A central theme in this research work involved the study of 2-substituted aziridinium salts as reactive intermediates in organic synthesis. Special attention was devoted to the regio- and

stereoselectivity of the ring opening of these aziridinium salts **xi**, derived from the corresponding 2-substituted 1-alkylaziridines **x**, by bromide in acetonitrile. The applicability of this transformation has been demonstrated by the synthesis of a large variety of β-bromo amines **xii** in a regiospecific way via ring opening of the intermediate aziridinium salts **xi** at the more hindered aziridine carbon atom. The use of an enantiomerically pure substrate acknowledged the stereospecificity of this transformation, in accordance with an S_N2 type reaction mechanism. Furthermore, the regio- and stereospecificity of this transformation was rationalized on the basis of some high level *ab initio* calculations.

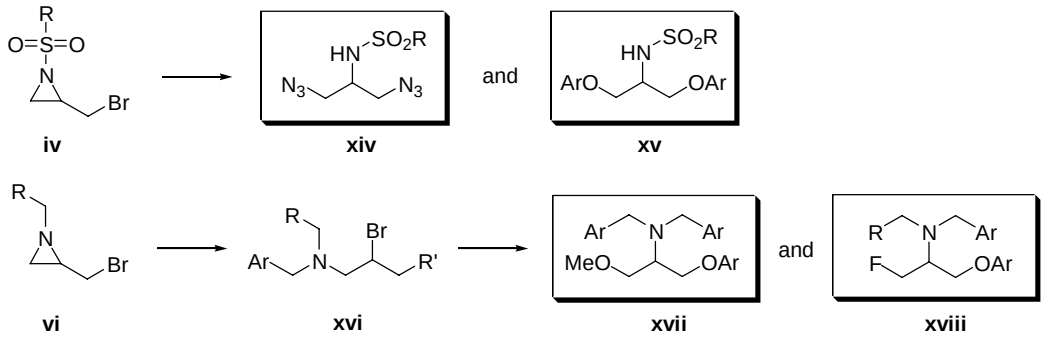


In contrast with the ring opening by bromide, an opposite regioselectivity was observed in the ring opening of the same aziridinium salts **xi** by fluoride and methoxide, resulting in the formation of 2-aminopropane derivatives **xiii** as the main reaction products via ring opening of the intermediate aziridinium salts **xi** at the less hindered aziridine carbon atom.

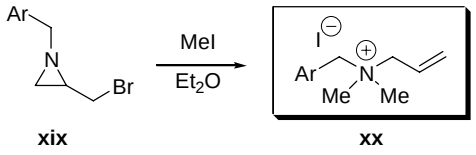


Due to the broad applicability of 1,2,3-triheteroatom substituted propane derivatives in medicinal chemistry, for example as β-blockers (propranolol, atenolol, metoprolol) and as antibiotics (chloramphenicol, thiamphenicol and florfenicol), the conversion of both 1-sulfonyl- and 1-alkyl-2-(bromomethyl)aziridines **iv** and **vi** into aminopropane derivatives has been evaluated thoroughly using the methodologies described above. In this way, 1-sulfonylaziridines **iv** have been converted into 2-aminopropane derivatives **xiv** and **xv** by means of a novel protocol in water, and 1-alkyl-2-(bromomethyl)aziridines **vi** have been

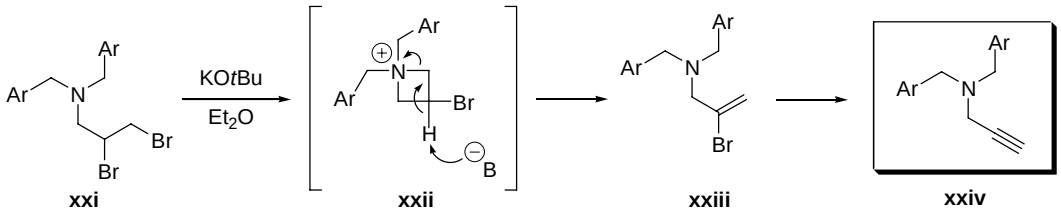
transformed in β-bromo amines **xvi** and subsequently into aminopropanes **xvii** and **xviii** via intermediate aziridinium salts and substitution reactions.



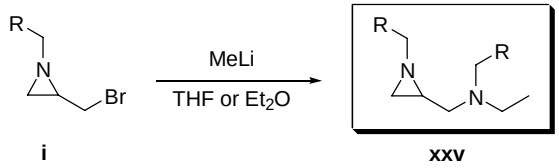
Furthermore, three special transformations have been observed in the study of the reactivity of 1-alkyl-2-(bromomethyl)aziridines. The first reaction involved ring opening of 2-(bromomethyl)aziridinium salts by means of iodide via a halophilic reaction, resulting in allylammonium salts **xx**, which are important in agriculture as for example plant growth regulators.



Secondly, a remarkable transformation of dibromopropylamines **xxi** into vinyl bromides **xxiii** has been observed, and the intermediacy of 3-bromoazetidinium salts **xxii** in this novel analogue of the Hofmann elimination was irrefutably proven by means of an independent synthesis. The applicability of vinyl bromides **xxiii** has been demonstrated by their conversion into propargyl amines **xxiv**, the latter being known as inhibitors of the enzyme monoamine oxidase (MAO), which makes them potential drugs for treatment of neurotic, psychiatric and other disorders such as depression, Parkinson's disease and Alzheimer's disease.

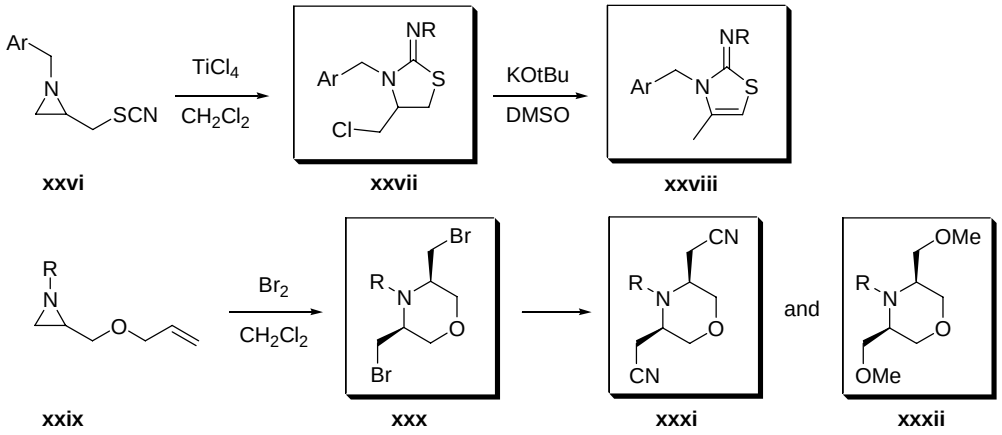


The third remarkable reaction involved treatment of 1-alkyl-2-(bromomethyl)aziridines with methyllithium, resulting in a totally unexpected 2-(aminomethyl)aziridine **xxv** via a peculiar reaction mechanism.



i **xxv**

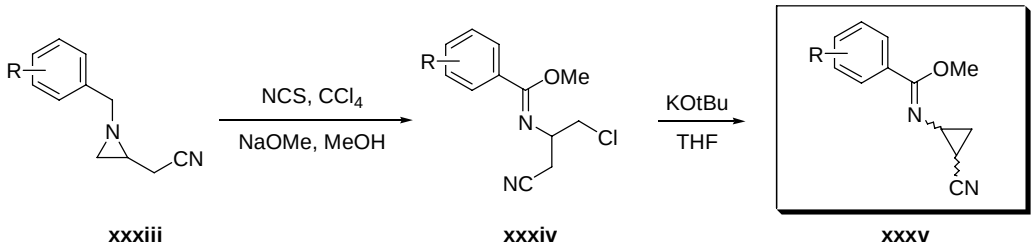
The final part of this PhD thesis comprised elaboration of 1-alkyl-2-(bromomethyl)aziridines towards other (azahetero)cyclic compounds. This has resulted in the development of a novel protocol for the synthesis of 2-iminothiazolidines **xxvii** and 2-iminothiazolines **xxviii**, compounds known for their anti-inflammatory, antimicrobial, antihistaminic, antihypertensive, anticonvulsant and anti-Alzheimer activity and their use as pesticides, by ring expansion of 2-(thiocyanomethyl)aziridines **xxvi**. Furthermore, 2-(allyloxymethyl)aziridines **xxix** have been transformed into *cis*-3,5-disubstituted morpholine derivatives **xxx** and the corresponding substitution products **xxxi** and **xxxii** for the first time. The interest in the synthesis of carbon-substituted morpholine derivatives results from their applicability in medicine (antidepressants, appetite suppressants, antitumor agents, antioxidants, antibiotics, anti-HIV) and agriculture (fungicides).



xxvi **xxvii** **xxviii**

xxix **xxx** **xxxi** **xxxii**

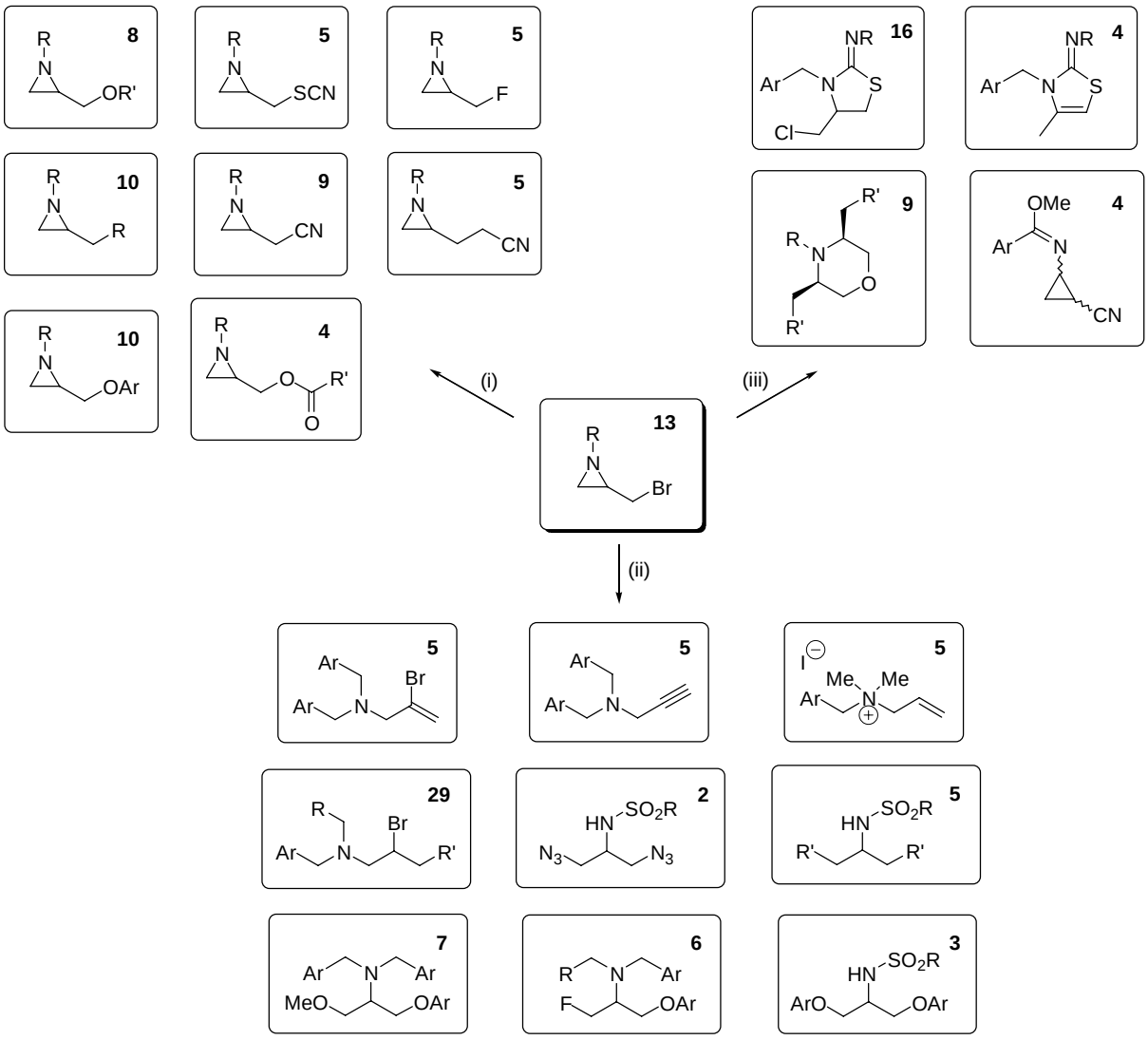
In a totally different approach, 2-(cyanomethyl)aziridines **xxxiii** were transformed into suitable substrates **xxxiv** for a novel type of 3-*exo-tet* ring closure towards methyl *N*-(2-cyanocyclopropyl)benzimidates **xxxv**, the later being of interest as precursors of biologically relevant 2-aminocyclopropanecarboxylates or β-ACC derivatives.



xxxiii **xxxiv** **xxxv**

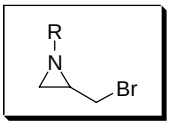
In this thesis, a selected number of reactions and transformations of 2-(bromomethyl)aziridines has been elaborated in order to demonstrate the synthetic potential of these substrates in organic synthesis. It is clear that the chemistry of 2-(halomethyl)aziridines is still an emerging area of research and, undoubtedly, many other interesting transformations will be described in the future. The present knowledge of the reactivity of 2-(halomethyl)aziridines and the available synthetic tools for their transformation allow further elaboration towards the synthesis of more complex compounds, for example starting from 3-substituted 2-(halomethyl)aziridines.

Overview of the number of novel compounds prepared from 2-(bromomethyl)aziridines:



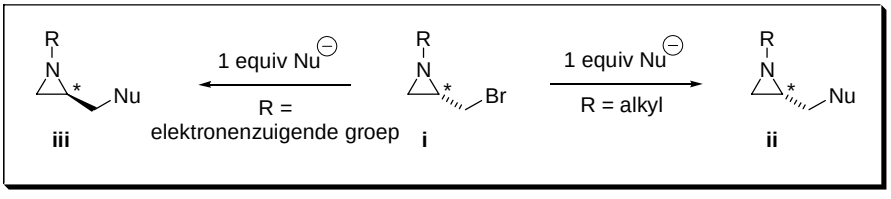
Samenvatting

In dit doctoraal proefschrift werd de inzetbaarheid van *N*-alkyl- en *N*-sulfonyl-2-(broommethyl)aziridinen als bouwstenen in de organische chemie bestudeerd. De eenvoudige en efficiënte synthese van dergelijke verbindingen, gecombineerd met de inherente reactiviteit van de gespannen driering en van het gehalogeneerd koolstofatoom maken van deze bouwstenen aantrekkelijke synthons voor diverse toepassingen. De brede inzetbaarheid van 2-(broommethyl)aziridinen werd aangetoond aan de hand van de synthese van een uitgebreide waaier aan stikstofhoudende verbindingen, waarvan de chemische structuur gelijkenis vertoont met andere verbindingen met gekende biologische activiteiten.



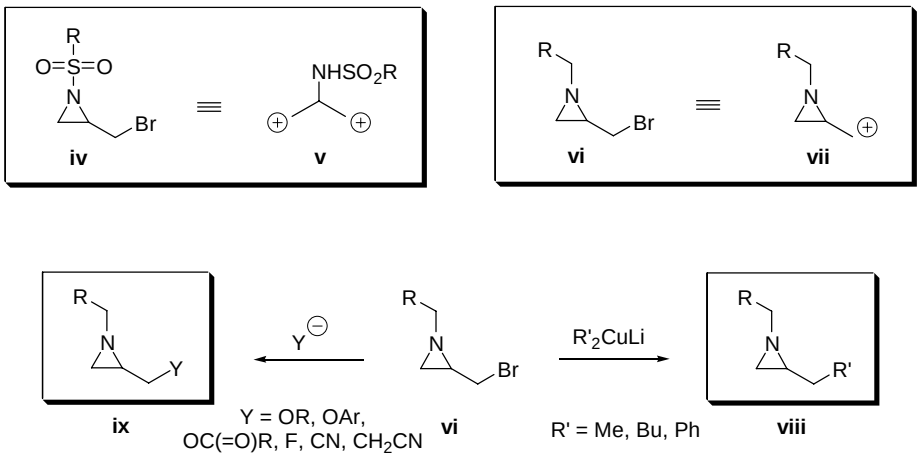
i

In het eerste deel werd de reactiviteit van 1-alkyl- en 1-sulfonyl-2-(broommethyl)aziridinen zeer uitgebreid onderzocht met de bedoeling een overzichtelijk beeld te krijgen van de toepasbaarheid van deze verbindingen in de organische chemie. Een vergelijkende studie tussen het chemisch gedrag van enerzijds geactiveerde en anderzijds niet-geactiveerde 2-(broommethyl)aziridinen bij de behandeling met één equivalent van een nucleofiel onthulde een totaal verschillend doch wel complementair reactiviteitsprofiel van deze substraten. Deze studie toonde immers aan dat de niet-geactiveerde 1-alkyl-2-(broommethyl)aziridinen **i** (R = alkyl) een directe S_N2 substitutie-reactie ondergaan op het gehalogeneerde koolstofatoom tot aziridinen **ii** met retentie van configuratie, daar waar de geactiveerde 1-sulfonyl-2-(broommethyl)aziridinen **i** (R = elektronenzuigende groep) onderhevig zijn aan een ringopening-ringsluiting-protocol resulterend in aziridinen **iii** met inversie van configuratie. Deze conclusies zijn van groot belang wanneer asymmetrische synthese van chirale doelverbindingen beoogd wordt gebruik makend van chirale substraten zoals **i**.



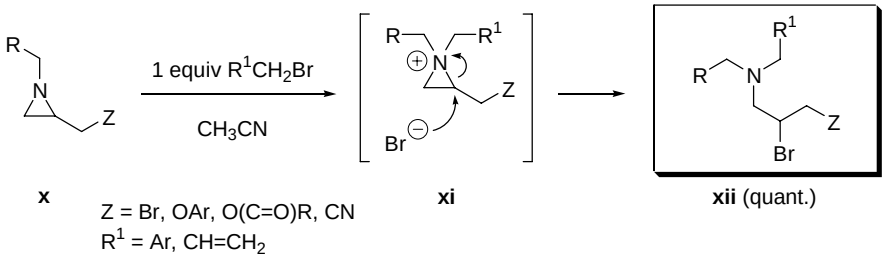
iii **i** **ii**

De behandeling van 1-alkyl- en 1-sulfonyl-2-(broommethyl)aziridinen met meer dan één equivalent van verschillende types van koolstof- en heteroatoomgecentreerde nucleofielen resulteerde in een verschillende toepasbaarheid van beide substraten. Immers, 2-(broommethyl)-1-sulfonylaziridinen **iv** kunnen ingezet worden als synthetische equivalenten van het 2-aminopropaandikation-synthon **v** voor de bereiding van α-vertakte-*N*-tosylamiden, daar waar 1-alkyl-2-(broommethyl)aziridinen **vi** beschouwd kunnen worden als synthetische equivalenten van het aziridinylmethylkation-synthon **vii** voor de synthese van een verscheidenheid aan 2-gesubstitueerde aziridinen. Deze chemische equivalentie werd onder meer aangewend voor de koppeling tussen 1-alkyl-2-(broommethyl)aziridinen en organocupraten als een nieuw protocol voor de bereiding van 1,2-dialkylaziridinen **viii**, alsook de substitutie door een waaier aan heteroatoom-gecentreerde nucleofielen tot de overeenkomstige 2-gesubstitueerde aziridinen **ix**. Zo werd bijvoorbeeld de veelbelovende klasse der 2-(fluormethyl)aziridinen en 2-(2-cyaanethyl)aziridinen aangemaakt als substraten voor verdere synthese.



Het weze duidelijk dat het onderscheid in reactiviteit tussen geactiveerde en niet-geactiveerde 2-(broommethyl)aziridinen gerelateerd is aan de stabiliteit van de aziridinering ten opzichte van het gehalogeneerde koolstofatoom. Het reactieve element van 1-alkyl-2-(broommethyl)aziridinen **vi** betreft het gebromeerde koolstofatoom, daar waar bij 1-sulfonyl-2-(broomomethyl)aziridines **iv** de aziridinering het meest electrofiele deel van de verbinding uitmaakt.

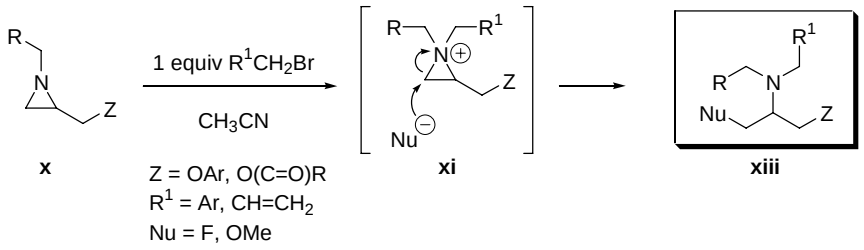
De relatieve ongevoeligheid van de aziridinering in 1-alkylaziridinen ten opzichte van nucleofielen heeft de studie en het gebruik van deze verbindingen in ringopeningsreacties belemmerd in vergelijking met de ringopening van hun geactiveerde tegenpolen. Aangezien 1-alkylaziridinen 'geactiveerd' moeten worden voor ringopening vormt alkylering tot aziridiniumzouten een krachtige methode voor de omzetting van 1-alkylaziridinen tot acyclische targets. De studie van 2-gesubstitueerde aziridiniumzouten als reactieve intermediairen in de organische chemie liep dan ook als een rode draad doorheen dit onderzoek. Bijzondere aandacht werd hierbij geschonken aan de regio- en stereoselectiviteit van de ringopeningsreacties van dergelijke aziridiniumzouten **xi**, afgeleid van de overeenkomstige 2-gesubstitueerde aziridinen **x**, door middel van bromide in acetonitril. De toepasbaarheid van deze methodologie werd uitgebreid aangetoond aan de hand van de synthese van een grote verscheidenheid aan β-broomaminen **xii** op regiospecifieke wijze via ringopening van de intermediaire aziridiniumzouten **xi** op het meest gesubstitueerde aziridine-koolstofatoom. Het gebruik van een enantiomeer zuiver substraat bevestigde de stereospecificiteit van deze omzetting in overeenstemming met een S_N2-type reactiemechanisme. Bovendien werd de experimenteel geobserveerde regio- en stereospecificiteit van deze transformatie bevestigd aan de hand van *ab initio* berekeningen op hoog niveau.



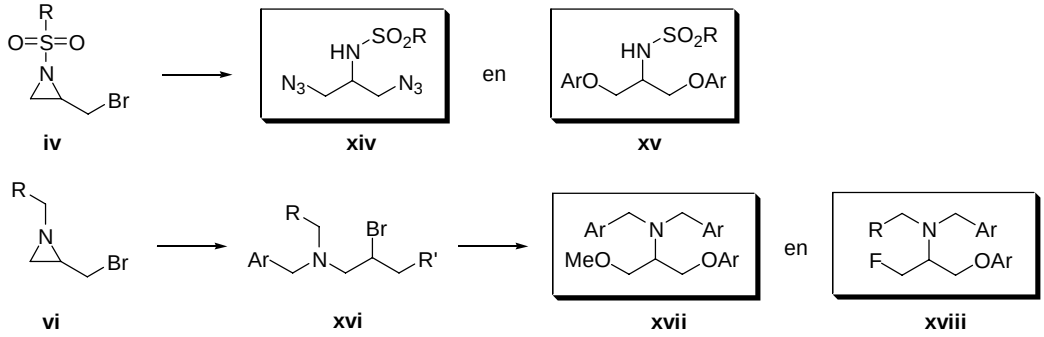
x **xi** **xii** (quant.)

Z = Br, OAr, O(C=O)R, CN
R^1 = Ar, $CH=CH_2$

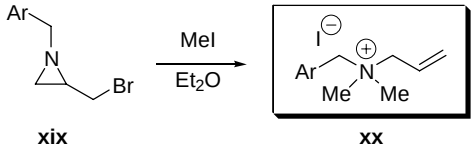
In vergelijking met bromide werd in het geval van de ringopening van dezelfde aziridiniumzouten **xi** door fluoride en methoxide een tegenovergestelde regioselectiviteit waargenomen, resulterend in de vorming van 2-aminopropaanderivaten **xiii** via ringopening van de intermediaire aziridiniumzouten **xi** op het minst gehinderde aziridine-koolstofatoom.



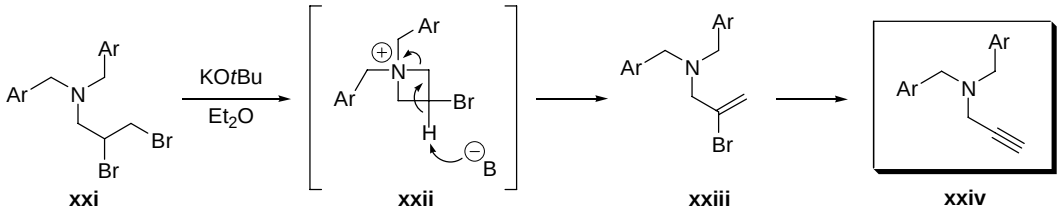
Gezien het brede toepassingsgebied van 1,2,3-triheteroatoomgesubstitueerde propaanderivaten in de geneeskunde, bv. als β-blockers (propranolol, atenolol, metoprolol) en als antibiotica (chloramfenicol, thiamfenicol and florfenicol) werd in dit proefschrift uitgebreid onderzoek verricht naar de omzetting van zowel 1-sulfonyl- als 1-alkyl-2-(broommethyl)aziridinen tot aminopropanen gebruik makend van de hierboven beschreven methodologieën. Op deze wijze werden 1-sulfonylaziridinen **iv** omgezet tot 2-aminopropaanderivaten **xiv** en **xv** door middel van een nieuw protocol in water. 1-Alkyl-2-(broommethyl)aziridinen **vi** werden omgezet tot β-broomaminen **xvi** en aminopropanen **xvii** en **xviii** via intermediaire aziridiniumzouten en substitutiereacties.



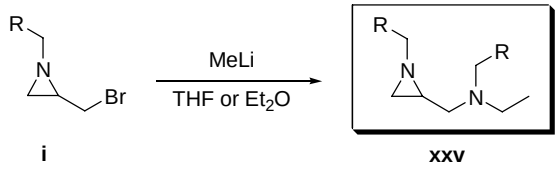
De reactiviteitstudie van 1-alkyl-2-(broommethyl)aziridinen bracht bovendien drie bijzondere omzettingen aan het licht. De eerste omzetting betrof de ringopening van 2-(broommethyl)aziridiniumzouten door jodide via een halofiele reactie, resulterend in allylammoniumzouten **xx**. Dergelijke allylammoniumzouten zijn onder meer belangrijk in de landbouw als plantengroeiregulatoren.



Ten tweede werd een opmerkelijke omzetting van dibroompropylaminen **xxi** tot vinylbromiden **xxiii** beschreven, waarbij de aanwezigheid van intermediaire 3-broomazetidiniumzouten **xxii** in deze nieuwe variant op de Hofmann-eliminatie onweerlegbaar werd aangetoond aan de hand van een onafhankelijke synthese. De toepasbaarheid van de vinylbromiden **xxiii** werd bovendien aangetoond door de verdere omzetting tot propargylaminen **xxiv**. Deze groep van verbindingen staan gekend als inhibitoren van het enzym monoamine-oxidase (MAO), met als mogelijke toepassingen de behandeling van neurotische, psychiatrische en andere aandoeningen zoals depressie, de ziekte van Parkinson en Alzheimer.

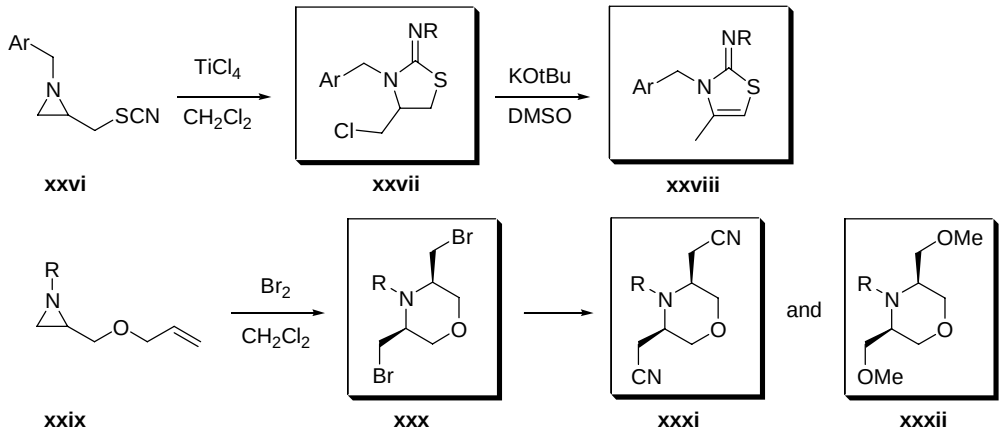


De derde opmerkelijke reactie betrof de geheel onverwachte omzetting van 1-alkyl-2-(broommethyl)aziridinen tot 2-(aminomethyl)aziridinen **xxv** via een ongewoon reactiemechanisme.

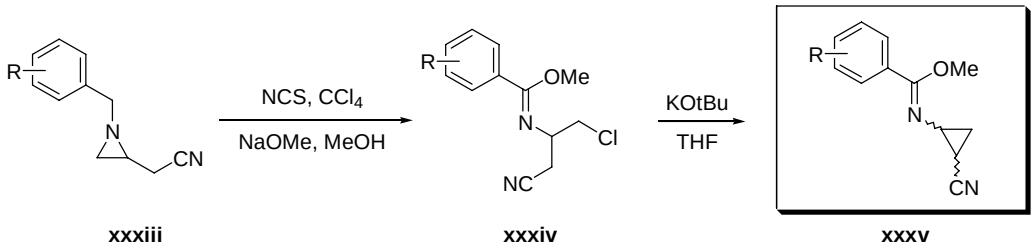


In het laatste deel van deze doctoraatsthesis werden mogelijke ringexpansies van 1-alkyl-2-(broommethyl)aziridinen tot andere (azahetero)cyclische systemen bestudeerd. Dit onderzoek resulteerde in de ontwikkeling van een nieuwe route tot 2-iminothiazolidinen **xxvii** en 2-iminothiazolinen **xxviii** via een ringexpansie van 2-(thiocyaanmethyl)aziridinen **xxvi**. 2-Iminothiazolidinen en 2-iminothiazolinen zijn populaire verbindingen met toepassingen in de geneeskunde (ontstekingswerend, antimicrobieel, anti-Alzheimer,…) en in de agrochemie (insecticiden). Verder werden ook 2-(allyloxymethyl)aziridinen **xxix** voor de eerste maal omgezet tot *cis*-3,5-digesubstitueerde morfolinederivaten **xxx** en de overeenkomstige substitutieproducten **xxxi** en **xxxii**. Het belang van koolstof-gesubstitueerde

morfolinederivaten volgt eveneens uit de brede toepasbaarheid in de medische wereld en de fytofarmacie (antidepressiva, antitumor, antibiotica, anti-HIV, fungiciden).

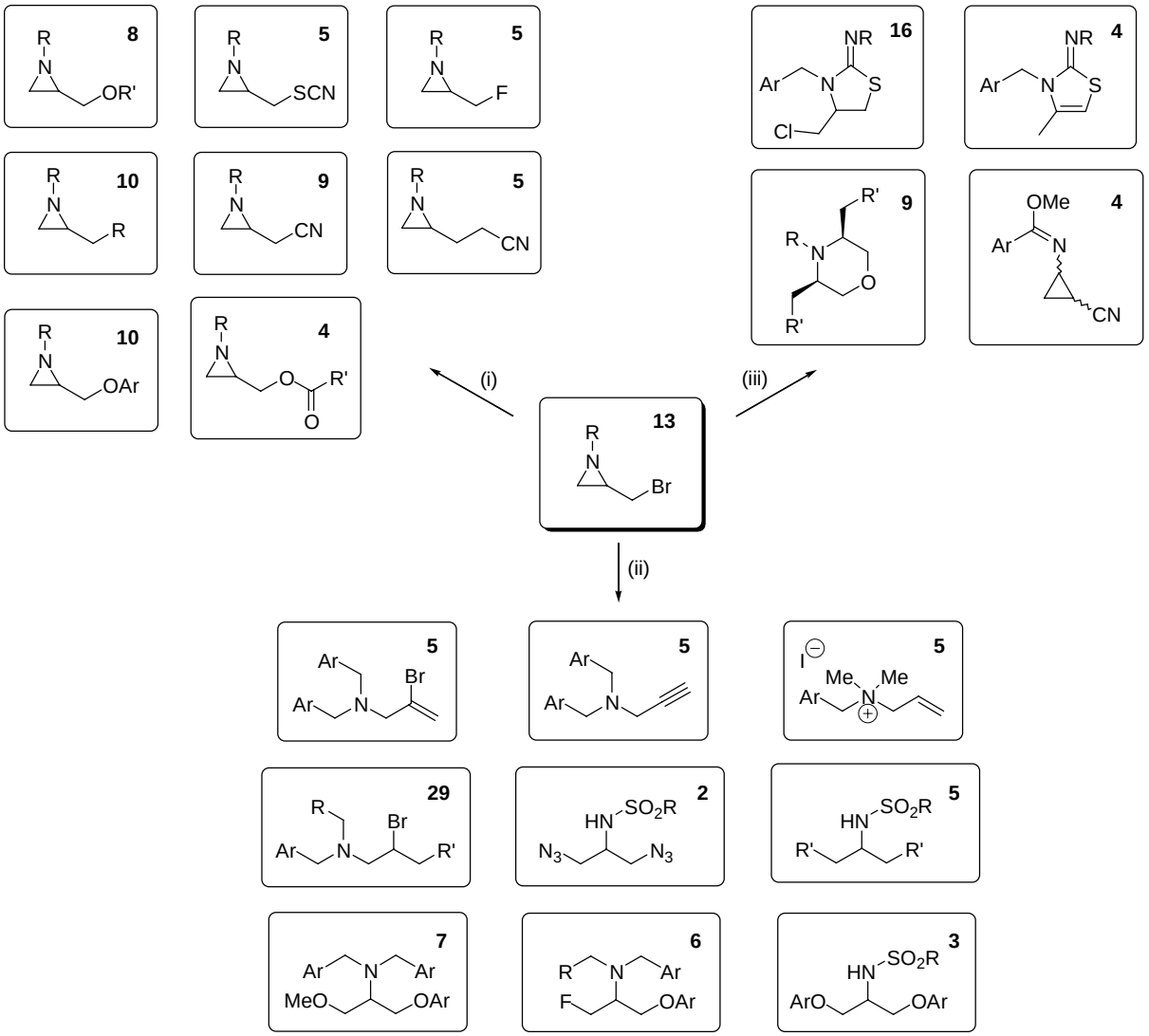


In een totaal andere benadering werden 2-(broommethyl)aziridinen **xxxiii** omgezet tot geschikte substraten **xxxiv** voor een nieuw type van 3-*exo*-*tet*-ringsluiting tot methyl-*N*-(2-cyaancyclopropyl)benzimidaten **xxxv**. Deze verbindingen kunnen beschouwd worden als precursoren voor de farmacologisch interessante 2-aminocyclopropaancarbonzuren.



In dit proefschrift werden verschillende typen van reacties en omzettingen van 2-(broommethyl)aziridinen uitgewerkt met de bedoeling het synthetisch potentieel van deze verbindingen in de organische chemie aan te tonen. Het weze duidelijk dat de chemie van deze verbindingen nog vele onontgonnen domeinen kent, en zonder twijfel zullen in de toekomst nog verschillende waardevolle omzettingen van 2-(broommethyl)aziridinen beschreven worden. De resultaten van deze thesis bieden alvast een veelzijdige set aan reactiemogelijkheden die toelaten om heel wat verschillende structurele eenheden te bereiden uitgaande van 2-(broommethyl)aziridinen, waarbij in de toekomst de synthese van meer complexe doelverbindingen vooropgesteld kan worden startend van bv. 3-gesubstituteerde 2-(halogeenmethyl)aziridinen.

Overzicht van het aantal nieuwe verbindingen bereid uitgaande van 2-(broommethyl)aziridinen:



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[74] The synthesis of 1-(2-chlorophenylmethyl)-2-(fluoromethyl)aziridine is described as a representative example for the synthesis of 2-(fluoromethyl)aziridines **233**. To 2-(bromomethyl)-1-(2-chlorophenylmethyl)aziridine (0.13 g, 0.5 mmol) was added tetrabutylammonium fluoride (TBAF, 0.55 mL, 1.1 equiv, 1N in THF), and the resulting solution was heated under reflux for 4 hours. Extraction with Et_2O (3×5 mL), drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded 1-(2-chlorophenylmethyl)-2-(fluoromethyl)aziridine. Yield 95%, colorless liquid. Flash chromatography on silica gel: Hexane/EtOAc 7/1, R_f=0.32. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.61 (1H, d×d, J = 6.6, 2.8 Hz, (H_{cis}CH)N); 1.87 (1H, d×d, J = 3.6, 1.7 Hz, (HCH_{trans})N); 1.93-2.03 (1H, m, CHN); 3.58 and 3.63 (2H, 2×d, J = 15.1 Hz, N(HCH)Ar); 4.34 and 4.47 (2H, 2×d×d×d, J = 47.3, 9.6, 6.7, 4.0 Hz, (HCH)F); 7.18-7.36 and 7.67-7.69 (4H, 2×m, C_6H_4). ^{13}C NMR (75 MHz, $CDCl_3$): δ 31.03 (d, J = 8.1 Hz, CH*C*H_2N); 38.00 (d, J = 25.4 Hz, CHN); 60.80 (N*C*H_2Ar); 85.43 (d, J = 169.6 Hz, CH_2F); 126.92, 128.16 and 129.06 (CH_{arom}); 132.83 (CCl); 136.54 (NCH_2*C*$_{quat}$). IR (NaCl, cm^{-1}): ν_{max} = 3061, 2989, 2953, 1573, 1472, 1444,

1348, 1004, 752. MS (70 eV) m/z (%): 199/201 (M^+, 2); 164 (38); 127 (17); 125 (49); 99 (5); 89 (15); 74 (100); 63 (6).

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[83] The synthesis of 2-(2-cyanoethyl)-1-isobutylaziridine is described as a representative example for the synthesis of 2-(2-cyanoethyl)aziridines **235**. To an ice-cooled solution of trimethylsilyl acetonitrile (0.12 g, 1.05 equiv) in dry THF (2 mL) was added nBuLi (0.4 mL, 1.05 equiv, 2.5M) via a syringe under nitrogen atmosphere, and the resulting solution was stirred for 1 h at 0°C. Subsequently, the solution was cooled to -78°C, followed by the addition of a solution of 2-(bromomethyl)-1-isobutylaziridine (0.19 g, 1 mmol) in THF (1 mL) via a syringe. This solution was then stirred for 1.5 h at -78°C and 15 h at room temperature. The reaction mixture was poured into a 1N $NaOH_{aq}$ solution (20 mL) and extracted with Et_2O (3×10 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded 2-(2-cyanoethyl)-1-isobutylaziridine. Yie1d 51%, colorless liquid. Flash chromatography on silica gel: Hexane/EtOAc 1/1, R_f=0.50. ^{1}H NMR

(300 MHz, $CDCl_3$): δ 0.89 and 0.95 (6H, 2×d, J = 6.7 Hz, (CH_3)$_2$CH); 1.31 (1H, d, J = 6.3 Hz, (H_{cis}CH)N); 1.36-1.85 (4H, m, CH_2CH_2CN, CHN, (CH_3)$_2$C*H*); 1.62 (1H, d, J = 3.3 Hz, (HCH_{trans})N); 2.01-2.13 (2H, m, NCH_2CH(CH_3)$_2$); 2.36-2.46 (2H, m, CH_2CN). ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.21 (*C*H_2CN); 20.86 and 20.96 ((*C*H_3)$_2$CH); 28.69 and 29.15 (*C*H_2CH_2CN and ((CH_3)$_2$*C*H); 34.08 (CH*C*H_2N); 37.50 (*C*HCH$_2$N); 69.38 (N*C*H$_2$CH(CH_3)$_2$); 119.44 (CN). IR (NaCl, cm^{-1}): ν_{CN} = 2247. MS (70 eV) m/z (%): 152 (M^+, 2); 151 (17); 137 (6); 112 (33); 109 (100); 98 (63); 97 (20); 82 (24); 70 (30); 57 (25); 56 (54); 55 (22); 54 (17).

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Curriculum Vitae

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Scientific publications in international SCI-journals with peer review (a1)

1. **Matthias D'hooghe**, Arn Hofkens and Norbert De Kimpe. "A new route towards *N*-(α-methoxybenzyl)aziridines." *Tetrahedron Lett.* **2003**, *44*, 1137-1139. (I.F. 2.477)
2. Kourosch Abbaspour Tehrani, **Matthias D'hooghe** and Norbert De Kimpe. "Novel synthesis of indolizidines and quinolizidines." *Tetrahedron* **2003**, *59*, 3099-3108. (I.F. 2.610)
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3) **Matthias D'hooghe**, Sven Mangelinckx, Evelien Persyn, Willem Van Brabandt and Norbert De Kimpe. "Synthesis of 1-arylmethyl-2-(cyanomethyl)aziridines and their ring transformation into methyl *n*-(2-cyanocyclopropyl)benzimidates" *Workshop organized in the framework of the Bilateral Scientific Cooperation Hungary – Flanders, Ghent, Book of Abstracts p.6, 10 July 2006.*