Bicyclic Aziridinium Ions in Azaheterocyclic Chemistry – Preparation and Synthetic Application of 1-Azoniabicyclo[n.1.0]alkanes

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Abstract: Recent advances in the field of ring-expansion chemistry, involving 1-azoniabicyclo[n.1.0]alkane scaffolds (bicyclic aziridinium ions) as key transient intermediates, have made it possible to efficiently construct a broad variety of medium- and large-sized functionalized nitrogen-containing heterocycles. In this tutorial review, a comprehensive survey of all pathways leading to the generation of 1-azoniabicyclo[n.1.0]alkanes is provided, as well as a discussion on their subsequent ring expansions to relevant azaheterocycles governed by ring size, substitution pattern, and/or nature of applied nucleophiles.

1 Introduction

Efficient and selective syntheses of nitrogen-containing heterocycles (azaheterocycles) have attracted considerable attention from many synthetic and medicinal chemists due to their particular interest within the realm of organic and medicinal chemistry.[1] Among many possible routes for their preparation, the strategy involving ring expansion of a small-ring system comprises an attractive way with many advantages.[2] Smaller ring systems have less conformational freedom, culminating in an enhanced reaction selectivity profile. Furthermore, due to their high ring strain, these small rings display a high reactivity to nucleophilic attack, often triggering a subsequent ring-expansion reaction. Moreover, judicious selection of nucleophiles enables the introduction of additional functional groups at specific sites with proper stereochemistry.[3]

The aziridine unit, being the smallest nitrogen-containing ring system, represents a prominent candidate susceptible to undergo reactions towards (a)cyclic target compounds because of its large ring strain energy.[4] However, its ring opening is strictly dependent on the characteristics of the N-substituent present on the aziridine core.[5] Activated aziridines, bearing an electron-withdrawing group at nitrogen, are very prone to undergo ring-opening reactions. Moreover, nucleophilic attack across these activated aziridines occurs mainly at the less-hindered carbon atom (steric effects), apart from some special cases with regard to 2-vinyl- and 2-benzyl-substituted aziridines (electronic reasons). Aziridines with an electron-donating substituent at nitrogen, so-called non-activated aziridines (like N-alkyl derivatives), are far more stable and activation of the ring system is essential to effect ring opening. As depicted in Scheme 1, the addition of an appropriate electrophile to aziridines

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leads to the formation of an aziridinium intermediate 2, which is very compliant to undergo nucleophilic attack. More specifically, the external addition of Lewis acids, acyl or alkoxy carbonyl electrophiles, acids, alkyl halides or alkyl triflates, and silylation reagents has been proven to be successful in a broad range of ring-opening reactions. Depending on the incoming nucleophile (Nu), the used electrophile (E) and the nature of the substituent (R²) on the aziridine moiety, the envisioned ring-opening reaction can be controlled in a regio- and stereoselective manner.\[6\]

Besides activation of the aziridine moiety via intermolecular N-alkylation/acylation/protonation [Scheme 2, Eq. (1)], implying the addition of external

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electrophiles, analogous aziridinium intermediates can be obtained in an intramolecular manner, leading to transient bicyclic aziridinium salts \(6\) [Scheme 2, Eq. (2)] which can act as a source for ring-expanded products. Depending on the distance between the nucleophilic aziridine nitrogen atom and the carbon atom attached to the leaving group, bicyclic aziridinium ions of different ring size can be generated. Due to their high ring strain energy, these bicyclic aziridinium salts, i.e., 1-azoniabicyclo[1.1.0]alkanes \(6\), are consequently very prone to experience nucleophilic attack (often in a regioselective way), resulting in azaheterocycles of larger ring size.

This review covers the preparation and synthetic utilization of various bicyclic aziridinium ions as polyvalent intermediates. Herein, a classification will be adopted according to the size of the bicyclic intermediates, i.e., distinction will be made between 1-azoniabicyclo[1.1.0]butanes, 1-azoniabicyclo[2.1.0]pentanes, 1-azoniabicyclo[3.1.0]hexanes and 1-azoniabicyclo[4.1.0]heptanes as intermediates in the formation of functionalized azetidines, pyrrolidines, piperidines and azepanes. Emphasis will be put on the relationship between the observed regioselectivity and inherent structural features, such as the nature of the substituents of the bicyclic aziridinium ion and the incoming nucleophile.

2 Preparation and Synthetic Utilization of Bicyclic Aziridinium ions

The most evident method for the production of 1-azoniabicyclo[1.1.0]alkanes involves the intermolecular reaction between bicyclic azaheterocycles \(7\) (in casu 1-azoniabicyclo[1.1.0]alkanes) and suitable electrophiles (Scheme 3, route a), although these 1-azoniabicycloc...
benium ion intermediates) cannot be completely excluded in some cases. Anyhow, recent advances in the field of ring-expansion chemistry, involving bicyclic aziridinium ions 10 as key transient intermediates, made it possible to construct a variety of medium- and large-size functionalized nitrogen-containing heterocycles in a regio- and stereoselective way.

Due to the high ring strain comprised in bicyclic intermediates 10, attention has to be devoted to three possible monocyclic isomeric cations, including azacyclocarbenium ions 13, primary methylium ions 14 and aziridinyl alkan-1-ylium ions 15, as depicted in Scheme 4,[8] which may be equilibrated or contribute electronically, depending on the substitution pattern of the aziridinium intermediates. As a consequence, the outcome of the reactions stemming from bicyclic intermediates 10 is determined by the kinetics of the nucleophilic attack across 10 and/or its isomeric cations 13, 14 and 15. In most cases, formation of aziridinyl cations 15 from 1-azoniabicyclo[n.1.0]alkanes is very rare due to the strain of the three-membered ring and the highly unstable primary carbenium ion. Moreover, theoretical calculations showed that bicyclic intermediates 10 are generally the most stable cations. Although the intermediacy of 1-azoniabicyclo[n.1.0]alkanes 10 was not experimentally observable in most cases, their ring-expansion products are produced in high yields and with high stereoselectivity, rendering this ring-enlargement methodology to be unique and providing access to a broad library of elegant azaheterocycles with many substituents along the ring. Judging from the reaction kinetics and the high stereoselectivity, it is not always possible to exclude the intervention of a concerted reaction mechanism for the preparation of these azaheterocycles instead of a mechanism via cationic intermediates, although the formation and interception of transient 1-azoniabicyclo[n.1.0]alkanes is generally believed to represent the correct mechanistic interpretation in the majority of literature examples. Nonetheless, in the following sections, careful notice will be taken of the possible appearance of different ionic intermediates to gain a better understanding of the underlying processes for the formation of regio- and stereocontrolled end products.

2.1 Preparation and Synthetic Utility of 1-Azoniabicyclo[1.1.0]butanes

The most basic strategy to prepare 1-azoniabicyclo[1.1.0]butanes involves the intermolecular reaction between 1-azoniabicyclo[1.1.0]butane and an appropriate electrophile. This intermolecular activation method has, for example, been used in the smooth reaction of 1-azoniabicyclo[1.1.0]butane 16 with aromatic thiols (Scheme 5).[9] Furthermore, ring opening of the in situ created aziridinium intermediate was also attained with a variety of aromatic nitrogen nucleophiles and dibenzylamine, however, in the presence of Mg(ClO₄)₂ which acts as a Lewis acid. Direct reaction of azabicycle 16 with cyclic amines did not proceed, but this drawback was circumvented via nucleophilic substitution of N-benzyl-3-bromoazetidine 21, acquired by treatment of 1-azoniabicyclo[1.1.0]butane 16 with benzyl bromide (Scheme 6). From a mechanistic
point of view, direct substitution of the bromo atom in azetidine 21 could result in the desired azetidines 23. However, an intramolecular expulsion of bromide followed by reaction with cyclic amines is more plausible. Due to the absence of stabilizing substituents at the C-3 position, formation of the corresponding azetidine carbenium ion 13 (n = 0) can be excluded.

Starting from alkyl- and phenyl-substituted 1-azabicyclo[1.1.0]butanes 24, a variety of 3-azidoazetidines 27 has been prepared using the same methodology (Scheme 7). According to the regioselective formation of 3-azidoazetidines 27, the formation of bicyclic aziridinium intermediates 25 is most acceptable. However, in the case of 3-phenyl-substituted substrates 24 (R2 = Ph), the in situ occurrence of carbenium intermediate 26 is more likely due to a higher stabilization of the carbenium ion in the α-position with respect to the phenyl substituent. This benzylic stabilization has to be considered when the reactivity of 3-phenyl-1-azabicyclo[1.1.0]butanes towards halides is investigated, resulting in the regioselective synthesis of 3-halo-3-phenylazetidines.[11]

Finally, in addition to the above-mentioned examples on the regioselective attack of nucleophiles across 1-azoniabicyclo[1.1.0]butanes, the stereocontrolled ring opening of 1-azoniabicyclo[1.1.0]butanes has also been reported by Hortmann et al.[12] Herein, reaction of bicyclic aziridine 28 with hydrogen chloride resulted in the stereoselective formation of azetidinium salt 29. Analogously, treatment of bicyclic aziridine 30 using the same reaction conditions delivered the diastereomeric counterpart 31 (Scheme 8).

Formation of 1-azoniabicyclo[1.1.0]butane 32 and its subsequent ring expansion in the reaction of 1-azabicyclo[1.1.0]butane with hydrochloric acid was found to yield the corresponding azetidine in a stereoselective manner, with cleavage of the C–N bond from concave attack by the chloride anion as a representative example of acid-assisted ring expansion.

Another strategy for the preparation of 1-azoniabicyclo[1.1.0]butanes is related to the intramolecular expulsion of a good leaving group attached to the α-carbon in the tether of non-activated aziridines. Depending on the R substituent present on the bridgehead carbon of the in situ created 1-azoniabicyclo[1.1.0]butanes, nucleophilic attack across these bicyclic intermediates resulted either in aziridines (pathway i, Scheme 3) or their higher homologues, azetidines (pathway ii, Scheme 3). This substituent-dependency has been observed during the reductive ring closure of N-arylmethylidene-2,3-dibromopropylamines 33. When N-arylmethylidene-2,3-dibromopropylamines 33 (R2 = H) were subjected to 3 molar equiv. of NaBH₄ in methanol at reflux, 2-(bromomethyl)aziridines 34 were formed as the sole reaction products (Scheme 9). However, an additional methyl group (R2 = Me in 33) changed the reactivity completely, i.e., treatment of N-alkylmethylidene-2,3-dibromo-2-methylpropylamines 33 (R = Me) applying the same reaction conditions afforded 3-methoxy-3-methylazetidines 38 in a clean and selective way.[14] Treatment of this starting material 33 with a smaller amount of NaBH₄ (2 molar equiv.) at room temperature, however, yielded 2-methyl-2-(bromomethyl)aziridines 35 as the major products, which were then converted to 3-methoxy-3-methylazetidines 38 using 3
molar equiv. of NaBH₄ under reflux. 3-Methoxyazetidines 38 were also obtained by reaction of N-(2,3-dibromo-2-methylpropylidene)arylmethylamines 39 \( (R' = \text{Ar}) \) with 3 molar equiv. of NaBH₄ under reflux. This result supported the presumption that 2-methyl-2-(bromomethyl)aziridines 35 are the kinetically controlled products, which are transformed into the thermodynamically more stable 3-methoxy-3-methylazetidines 38 via transient 1-azoniabicyclo[1.1.0]butane intermediates 36 in methanol.

From a mechanistic point of view, the formation of 3-methoxy-3-methylazetidines 38 is reasonable considering the different isomeric cations involved during this ring transformation. Despite the presence of an extra methyl group at C-3, enabling a higher stabilization of the carbenium ion in isomer 37, the equilibri-

um is shifted towards the bicyclic cation 36 based on computational analysis. Subsequent solvolysis in methanol finally resulted in 3-methoxy-3-methylazetidines 38. As a consequence of these observations, nucleophilic substitution reactions of 2-alkyl-2-(bromomethyl)aziridines are temperature sensitive to yield either 2-substituted 2-alkylaziridines or 3-substituted 3-alkylazetidines. Furthermore, it was found that these transformations were remarkably influenced by the choice of the solvent. Whereas the use of dimethylformamide (DMF) resulted in direct displacement of bromide in 2-bromomethyl-2-methylaziridines 35, the employment of acetonitrile \( (\text{CH}_3\text{CN}) \) as a solvent favored the selective preparation of 3-methylazetidines 41 (Scheme 10). These experimental observations have been supported by means of DFT calcula-

![Scheme 9. Reduction of amines 33 and 39 to aziridines 34 and azetidines 38.](image)

![Scheme 10. Solvent-dependent transformation of 2-(bromomethyl)aziridines 35.](image)
tions, which revealed a better coordination and stabilization of the nucleophiles in CH₂CN, hence allowing the formation of 1-azoniabicyclo[1.1.0]butanes 36 in CH₂CN to afford the corresponding azetidines. It is worth mentioning that the formation of substituted 2-methylaziridines 40 in DMF is more complicated due to two possible routes, including a simple direct displacement of bromide by an appropriate nucleophile with retention of the aziridine core, or nucleophilic attack at the less hindered site of the in situ created 1-azoniabicyclo[1.1.0]butanes 36.

Additional support for the occurrence of different isomeric cations has been provided by the ring expansion of 2-(bromomethyl)aziridines 42 to the corresponding 3-substituted azetidines 46.[16] In that study, the isomerization reaction of alkyl aziridine-2-carboxylates 42 to alkyl azetidine-3-carboxylates 45 has been investigated (Scheme 11). Heating of 2-(bromomethyl)aziridines 42 in DMSO during 5 to 48 hours resulted in the ring-expanded target compounds 45. The addition of external nucleophiles could not effect the desired ring expansion [apart from a small amount (4–5%) in the case of phenoxide as the nucleophile], but afforded the corresponding 2,2-disubstituted azetidines 43 instead. However, treatment of the obtained alkyl 3-bromoazetidine-3-carboxylates 45 with the same nucleophiles seemed successful, furnishing a variety of 3-substituted azetidine-3-carboxylates 46 in good yields.

The intervention of an 1-azoniabicyclo[1.1.0]butane intermediate is also highlighted in the synthesis of 3-substituted azetidines 48 starting from 3-bromo-3-methylazetidines 47 (Scheme 12),[17] in which treatment of azetidines 47 with a variety of nucleophiles afforded 3-substituted azetidines 48 in high yields (63–96%) via bicyclic aziridinium intermediates 36.

Formation of a 1-azoniabicyclo[1.1.0]butane intermediate has also been suggested in the substitution reaction of 3-chloroazetidines 49 by a variety of nucleophiles in the preparation of 3-substituted azetidines 51 (Scheme 13).[18] Because of the retention of configuration, a double S₂2 reaction can be assumed. The initial displacement of the chloride atom by nitrogen results in the corresponding bicyclic intermediate 50, followed by regio- and stereoselective attack by a suitable nucleophile.

The synthesis of 3-substituted azetidines from properly decorated 3-halo- or 3-sulfonyloxyazetidines has been covered in 2009, although without a systematic analysis to elucidate the influencing parameters on these transformations and the intervention of transient 1-azoniabicyclo[1.1.0]butane cations.[19]

In some cases, analogous reactions have also provided ring-contraction products, as exemplified by Okutani and Masuda.[20] When trans-azetidine 52 was
treated with various nucleophiles including KCN and NaSPh, substituted azetidines 53a, b were obtained as the sole products (Scheme 14). On the other hand, the reaction with NaOH in 50% aqueous dioxane furnished a major amount of 2-substituted aziridine 54c (62%), in contrast to the expected azetidine scaffold according to thermodynamic principles. Depending on the selection of the nucleophile, the reaction outcome could thus be regiocontrolled. Whereas carbon and sulfur nucleophiles afforded the thermodynamically stable products 53a and 53b, the employment of the oxygen nucleophile (hydroxide) delivered the kinetically stable aziridine 54c as the major isomer.

Analogous to the depicted azetidine-to-aziridine ring contraction in Scheme 14, ring contractions have also been observed for 2-aryl-3,3-dichloroazetidines 55.[21] When these 3,3-dichloroazetidines 55 were treated with a large excess of NaOMe in MeOH at reflux, 2-(dimethoxymethyl)aziridines 60 were obtained in high yields via elusive 2-azetine intermediates 56 (Scheme 15). From a mechanistic point of view, the formation of the kinetic products 54c and 60 is reasonable considering the in situ created aziridin-2-ylmethylcarbenium ions 14 (n = 0) or 15 (n = 0). As depicted in Scheme 15 for the formation of aziridines 60, the expulsion of the second chloride atom results in bicyclic aziridinium intermediates 58, which are in equilibrium with aziridin-2-ylmethylcarbenium ions 59 due to stabilization of the positive charge by means of the phenyl and methoxy substituent in the α-position. Finally, trapping of these intermediates 59 by a second methoxide afforded aziridines 60.

The above-mentioned results clearly demonstrated the formation of 1-azoniabicyclo[1.1.0]butane intermediates from either 2-(bromomethyl)aziridines or 3-(halo/sulfonyloxy)azetidines upon intramolecular leaving group displacement by the nitrogen atom of the aziridine or azetidine ring. Once the 1-azoniabicyclo[1.1.0]butane intermediate 10 (n = 0) is generated, it can be transformed into either a 3-azetidinecarbenium ion 13 (n = 0) or an aziridin-2-ylmethylcarbenium ion 14 (n = 0) or 15 (n = 0) (Scheme 4). Among three isomeric cations, the 3-azetidinecarbenium ion 13 (n = 0) dominates when the reaction is governed by thermodynamic control due to the lowest ring-strain

Scheme 14. Nucleophile-dependent conversion of mesyloxyazetidine 52.

Scheme 15. Ring contraction of 3,3-dichloroazetidines 55 to aziridines 60.
energy. However, when there are substituents along the ring system which influence the stability of and the equilibrium between the different possible isomeric cations, the aziridin-2-ylmethylcarbenium ion \( n = 0 \) or \( n = 0 \) can occur as well in particular cases, resulting in a kinetically-controlled product outcome. As a consequence, the ring expansion pattern is adjustable taking into account the design of the substrate and the selection of the nucleophile.

### 2.2 Preparation and Synthetic Utility of 1-Azoniabicyclo[2.1.0]pentanes

In the literature, only one report has been published so far dealing with the synthesis of 1-azoniabicyclo[2.1.0]pentanes via intermolecular reaction between 1-azabicyclo[2.1.0]pentanes and an activating agent.\[22\] Therein, treatment of 1-azabicyclo[2.1.0]pentanes \( 61 \) with hydrogen bromide led to the \textit{in situ} formation of bicyclic intermediates \( 62 \), which were regioselectively opened to afford 4-bromopyrrolidines \( 63 \) in excellent yields (Scheme 16).

Among two other methods for the preparation of 1-azoniabicyclo[2.1.0]pentanes from properly substituted azetidines or aziridines, mainly the employment of decorated azetidine substrates with a leaving group attached to the \( \alpha \)-carbon of the C-2 side chain has been reported. Furthermore, the subsequent ring-opening reactions always proceed following pathway \( \text{ii} \) (Scheme 3), resulting in pyrrolidines regardless of the substituents. Reactions according to pathway \( \text{i} \) (Scheme 3) would afford a more constrained azetidine structure, which explains the selectivity. Furthermore, pathway \( \text{ii} \) is both kinetically and thermodynamically favorable due to the large difference of ring strain energy (about 20 kcalmol\(^{-1}\)).\[23\]

One of the few reactions related to the generation of 1-azoniabicyclo[2.1.0]pentane intermediates from aziridines has been employed in a route from a \( \beta \)-lactam over an aziridine to a pyrrolidine.\[24\] Reduction of \( \beta \)-lactams \( 64 \) with LiAlH\(_4\) afforded 2-(2-hydroxyethyl)aziridines \( 65 \), which were consecutively subjected to Mitsunobu conditions in the presence of NBS (Scheme 17). After 18 hours stirring at room temperature, cis-3-bromopyrrolidines \( 67 \) were finally produced in a stereoselective way via bromide interception of bicyclic aziridinium intermediates \( 66 \).

This aziridine-to-pyrrolidine ring transformation has also been employed by the same group for the synthesis of 3-bromo-2-methylpyrrolidines \( 70 \) and \( 71 \) starting from 2-(2-hydroxyethyl)-3-methylaziridines \( 68 \) (Scheme 18).\[25\] Thus, 2-(2-hydroxyethyl)aziridines \( 68 \) were analogously treated with PPh\(_3\) and NBS, resulting in bicyclic aziridinium intermediates \( 69 \). Consecutive ring opening by the bromide anion afforded the thermodynamically favored \textit{cis}- and \textit{trans}-pyrrolidines \( 70 \) and \( 71 \), which could be separated by means of column chromatography.

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**Scheme 16.** Conversion of 1-azabicyclo[2.1.0]pentanes \( 61 \) to pyrrolidines \( 63 \).

**Scheme 17.** Conversion of \( \beta \)-lactams \( 64 \) to pyrrolidines \( 67 \).

**Scheme 18.** Conversion of 2-(2-hydroxyethyl)aziridines \( 68 \) to \textit{cis}- and \textit{trans}-pyrrolidines \( 70 \) and \( 71 \).
Generation and utilization of 1-azoniabicyclo[1.1.0]pentane intermediates has also been shown to be synthetically valuable for the preparation of ring-expanded and multi-substituted pyrrolidines 73 and 74, as exemplified in Scheme 19, Table 1 and Table 2. The reactions of 2-chloromethyl- and 2-(methanesulfonyloxymethyl)azetidines 72 with a variety of nucleophiles afforded 3-substituted pyrrolidines 73 and 74 through regioselective ring opening of the in situ created 1-azoniabicyclo[2.1.0]pentanes 75 at the bridgehead carbon atom, which is fully consistent with the mechanism of the production of azetidines from 1-azoniabicyclo[1.1.0]butanes (vide supra).

The same group has also investigated the fluoride-induced ring expansion of 2-(hydroxymethyl)azetidines 76 upon treatment with DAST (diethylamino-sulfur trifluoride), resulting in the synthesis of the corresponding 3-fluoropyrrolidines 77 (Scheme 20). However, for one example (R1, R2 = Me, R3 = Ph, R4 = n-Bu), an overall hydroxy-by-fluoride substitution occurred. Furthermore, retention of configuration indicated that the mechanism was based on the intermediacy of a bicyclic aziridinium intermediate, which was not attacked at the bridgehead carbon atom but at C-4. When an additional substituent was present in the α-position of the hydroxy group in azetidines 76 (resulting in the development of a quaternary center, for example, a gem-dimethyl unit), no rearrangement product was observed, which might be explainable by the fact that bicyclic azetidinium ion (75) formation could not be realized as a result of steric hindrance. Thus, depending on the selected nucleophile, the ring opening of bicyclic aziridinium intermediates 75 can be regiocontrolled to a certain extent, although these transformations predominantly proceeded at the bridgehead carbon atom in a regioselective manner to produce pyrrolidines 77.

A DAST-promoted azetidine-to-pyrrolidine transformation has also been described by the group of Cossy. In that regard, treatment of chiral azetidine 79 with 1.4 equiv. of DAST in dichloromethane resulted in the regioselective formation of pyrrolidine 80 with excellent enantioselectivity (Scheme 21).

In analogy, ring-expansion reactions have been elaborated starting from enantiopure 2-(chloromethyl)-a-
Table 1. Scope of the ring expansion of 2-chloromethyl- and 2-(methanesulfonyloxymethyl)azetidines 72 in the absence of an external nucleophile.

![Scheme 21. Ring expansion of chiral azetidine 79 to pyrrolidine 80.](image)


The high stereoselective ring rearrangement of analogous 2-(chloromethyl)azetidines 84 into the corresponding 3-chloropyrrolidines 85 without intervention of an external nucleophile has been described (Scheme 23). Furthermore, the introduction of different nucleophiles (hydroxide, cyanide, azide and hydride) was established, furnishing 3-substituted pyrrolidines 86 (Scheme 23) and 90 (Scheme 24). In the case of β-lactams 87, an initial reduction to azetidines 88 with monochloroalane in diethyl ether under reflux took place, followed by a rearrangement to pyrrolidines 90 via bicyclic aziridinium ions 89.
Ring-expansion reactions of 2-(halomethyl)azetidines to 3-substituted pyrrolidines have also been reported by Feula et al.\cite{30} In that respect, iodocyclization of allylamines \(91\) yielded 2-(iodomethyl)azetidines \(92\) through a 4\texttext{-}\textit{exo}\texttext{-}trig cyclization, the appearance of which was confirmed by NMR analysis (Scheme 25). Heating of azetidines \(92\) in CH\(_3\)CN at 60°C resulted in the formation of cis-4-iodopyrrolidines \(94\). In the same way, azetidine-to-pyrrolidine transformations have been performed upon treatment of azetidines \(92\) with \(O\)- and \(N\)-nucleophiles, affording cis-4-hydroxy- and cis-4-aminopyrrolidines \(93\) and \(96\), respectively. The retention of configuration is attributed to the formation of bicyclic aziridinium intermediates \(98\) (via intramolecular expulsion of iodide), which underwent ring opening upon nucleophilic attack in a regio- and stereoselective manner. Reaction of cis-4-iodopyrrolidines \(94\) with \(N\)-nucleophiles (azide and amines) furnished trans-pyrrolidines \(95\) and \(97\). In contrast to the substitution reactions of 3-halozetidines, involving the \texttext{in situ} creation of 1-azoniabicyclo[1.1.0]butanes (\textit{vide supra}), 1-azoniabicyclo[2.1.0]pentanes are not formed in these substitution reactions (\(94\) to \(95/97\)), resulting in the inversion of configuration by direct displacement of the iodide atom by the nucleophile.

Although 1-azoniabicyclo[2.1.0]pentane intermediates have never been isolated and characterized, theoretical calculations have indicated that the strained 1-azoniabicyclo[2.1.0]pentane structure is a viable inter-

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**Table 2.** Scope of the ring expansion of 2-chloromethyl- and 2-(methanesulfonyloxymethyl)azetidines \(72\) in the presence of an external nucleophile.

<table>
<thead>
<tr>
<th>R(^1)</th>
<th>R(^2)</th>
<th>R(^3)</th>
<th>R(^4)</th>
<th>X</th>
<th>MZ</th>
<th>DMSO</th>
<th>Δ, (18) h</th>
<th>CH(_3)CN</th>
<th>R(^2)O</th>
<th>N</th>
<th>Nu</th>
<th>DMSO, Δ, (18) h</th>
<th>MNU = NaOH, KCN, NaN(_3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl</td>
<td>Ph</td>
<td>Z = OH, CN</td>
<td>Ph</td>
<td>10 equiv MZ, DMSO</td>
<td>40–50 °C, 12–72 h</td>
<td>74 (19–85%)</td>
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<td></td>
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<td></td>
<td></td>
<td>KOH, KCN, NaN(_3), NaOAc</td>
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<tr>
<td>Cl</td>
<td>Ph</td>
<td>Z = OH, CN</td>
<td>Ph</td>
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<tr>
<td>R(^1)</td>
<td>R(^2)</td>
<td>R(^3)</td>
<td>R(^4)</td>
<td>X</td>
<td>MZ</td>
<td>DMSO</td>
<td>Δ, (18) h</td>
<td>CH(_3)CN</td>
<td>R(^2)O</td>
<td>N</td>
<td>Nu</td>
<td>DMSO, Δ, (18) h</td>
<td>MNU = NaOH, KCN, NaN(_3)</td>
</tr>
<tr>
<td>c-Hex</td>
<td>i-Pr</td>
<td>allyl</td>
<td>n-Bu</td>
<td>Cl</td>
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<tr>
<td>Me</td>
<td>Ph</td>
<td>Bu</td>
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**Scheme 22.** Ring expansion of 2-(chloromethyl)azetidines \(81\) to 3-chloropyrrolidines \(83\).

**Scheme 23.** Ring expansion of 2-(chloromethyl)azetidines \(84\) to 3-substituted pyrrolidines \(85\) and \(86\).

**Scheme 24.** Monochloroalane-induced ring expansion of \(\beta\)-lactams \(87\) to pyrrolidines \(90\).
mediate in the ring expansion of 2-chloromethyl-1-isopropylazetidine to 3-chloro-1-isopropylpyrrolidine.[31] As is clear from previously mentioned examples involving nucleophilic attack at the bridgehead carbon atom of in situ generated 1-azoniabicyclo[2.1.0]pentanes 10 (n = 1), pyrrolidin-3-ylum cations 13 (n = 1) should also be taken into consideration as possible intermediates in azetidine-to-pyrrolidine ring transformations, in contrast to the two other possible isomers 14 (n = 1) and 15 (n = 1) (Scheme 4). Because of the large difference in ring strain energies between the azetidine and pyrrolidine ring system, release of ring strain in 1-azoniabicyclo[2.1.0]pentanes preferentially gives rise to isomers 13 (n = 1) among the four possible isomeric cations.

2.3 Preparation and Synthetic Utility of 1-Azoniabicyclo[3.1.0]hexanes

In contrast to their lower homologues, the synthesis of 1-azoniabicyclo[3.1.0]hexanes via intermolecular reaction between polysubstituted 1-azabicyclo[3.1.0]hexanes and electrophiles has been well documented. Furthermore, isolation and characterization of 1-ethyl-1-azoniabicyclo[3.1.0]hexane perchlorate 100 has been realized, pointing to the higher stability of these larger ring intermediates (Scheme 26).[32] In that study, the feasibility of all possible routes for the formation of the 1-azoniabicyclo[3.1.0]hexane skeleton 100 was demonstrated as well. 1-Azabicyclo[3.1.0]hexane 101 has also been employed as a starting material in the synthesis of a variety of compounds.
ety of 2-(chloromethyl)pyrrolidines 103/105 and 3-halo-
opiperidines 104/106 (Scheme 27).[33] Reaction of aza-
bicycle 101 with acyl halides resulted mainly in the
formation of the corresponding pyrrolidines 103, where-
treatment of the same starting material with a range of alkyl halides afforded piperidines 106 as the major compounds, apart from the reaction with bromoacetanilide (R₂ = CN) yielding the corresponding pyrrolidine 105 as the main constituent. Activation of bicyclic azaheterocycle 101 with an electrophile resulted in bicyclic aziridinium intermediates 108, which were then attacked at the least hindered side, affording 2-(halomethyl)pyrrolidines 107 as the kinetic products. Depending on the nature of the N-
substituent, recyclization to intermediates 108 can
occur, followed by nucleophilic attack across the
bridgehead carbon atom to give the thermodynamically
stable 3-halopiperidines 109 (thermodynamic control). Because of the fact that N-acylation reduces the nucleophilicity of the nitrogen atom, these equilibrium reactions are considerably less favored as compared to N-alkyl-induced ring transformations. As a result, 2-(halomethyl)piperidines 107 are considered to be the kinetically controlled products, whereas the isomeric 3-halopiperidines 109 are the thermody-
namic products.

Besides the production of 1-azoniabicyclo[3.1.0]-
hexanes via intermolecular activation procedures, the preparation of these bicyclic intermediates via intra-
molecular reactions are ubiquitous as well, starting either from 2-propylaziridines with a terminal leaving group in the side chain, or from 2-(halomethyl/sulfonyloxy)methyl)piperidines.

The employment of 2-(3-hydroxypropyl)aziridine 110 for the synthesis of a variety of 3-substituted pi-
peridines and their regioisomorphic pyrrolidines has ex-
tensively been investigated by Ha et al. (Scheme 28).[34] Furthermore, the structure of the decisive 1-azoniabicyclo[3.1.0]hexane tosylate 111 in this study was identified by means of NMR analysis. This product unexpectedly proved to remain stable in CH₃CN upon storage for 5 days at room temperature. Dissolving this bicyclic intermediate in CH₂Cl₂, how-
ever, resulted in 3-tosyloxypiperidine 112 formation, indicating a major solvent issue with respect to the stability and reactivity of bicyclic aziridinium salt 111.

This stable 1-azoniabicyclo[3.1.0]hexane tosylate 111 was also treated with various nucleophiles in CH₃CN. As shown in Scheme 29, the proposed ring-
opening reactions can proceed through two different pathways to yield either pyrrolidines (pathway i, Scheme 3) or piperidines (pathway ii, Scheme 3), de-
pending on the nature of the selected nucleophile.

Addition of CsF, NaN₃, NaOAc and (n-Bu)₄NOAc af-
forded a mixture of those two regioisomers within the
ratio 1:1–1:2 in 42–93% yields. Reaction of the bicy-
clic intermediate 111 with chloride as nucleophile
[TsCl, (n-Bu)₄NCl] and iodine (I₂), however, selec-
tively furnished piperidines 114, whereas (n-Bu)₄NCN only afforded the five-membered ring product 113.

Furthermore, these regioselective nucleophile-depen-
dent ring transformations were also supported by DFT calculations to rationalize the observed reactivi-
ties.

In another study, an equilibration between the pyr-
rolidine ring and the corresponding piperidine has not
been observed, affording the five-membered ring 117 as the sole regioisomer (Scheme 30). Treatment of enantiopure aziridine 115 with mesyl chloride, triethylamine and DMAP resulted in an in situ produced 1-azoniabicyclo[3.1.0]hexane intermediate 116, followed by regioselective ring opening by chloride to furnish the kinetically favored end product 117. Additional factors (such as steric interactions) might come in play in this particular transformation, accounting for the opposite reactivity as observed for the formation of 3-chloropiperidine 114 (Nu=Cl). This type of ring expansion with 1-azoniabicyclo[1.1.0]hexane as an intermediate was further utilized for the synthesis of the hydroxylated alkaloid hyacinthin.\[35\]

Another powerful method to provide access to 1-azoniabicyclo[3.1.0]hexanes starts from 2-(halomethyl/hydroxymethyl)pyrrolidines. Due to the fact that a more stable piperidine scaffold can be obtained from these pyrrolidines, expulsion of the $\beta$-carbon-attached leaving group within these pyrrolidines occurs, resulting in a bicyclic intermediate. Subsequent nucleophile-induced ring opening across the bridgehead carbon atom finally affords the thermodynamically controlled piperidine. A first example of this ring transformation involved (2S)-1-alkyl-2-(chloromethyl)pyrrolidines 118, which were converted to (3R)-1-alkyl-3-chloropiperidines 120 as the sole products at a high reaction temperature (Scheme 31).\[36\] These conversions implied that the reaction proceeded via

**Scheme 29.** Nucleophile-dependent ring transformation of 2-(3-hydroxypropyl)aziridine 110.

**Scheme 30.** Conversion of 3-(hydroxypropyl)aziridine 115 to 2-(chloromethyl)pyrrolidine 117.

**Scheme 31.** Thermodynamic controlled ring expansion of 2-(chloromethyl)pyrrolidines 120.
1-azoniabicyclo[1.1.0]hexane intermediates 119, followed by chloride attack at the bridgehead carbon atom rather than at the less-substituted site. This regiochemical outcome to yield \((3R)-1\)-alkyl-3-chloropiperidines 120 stems from the kinetic and thermodynamic behavior of chloride attack, i.e., \((3R)-1\)-alkyl-3-chloropiperidines 120 are the thermodynamic products, while their kinetic products, \((2S)-1\)-alkyl-2-(chloromethyl)pyrrolidines 118 are in equilibrium with the corresponding 1-azoniabicyclo[1.1.0]hexanes 119.

Although a similar pyrrolidine-to-piperidine transformation has been observed by Brain et al., treatment of substrate 118 \((R = Et)\) with various nucleophiles resulted in a mixture of pyrrolidines, obtained via an apparent direct chloride-by-nucleophile displacement, and the desired piperidines.\(^{[32]}\) Extensive studies have also been carried out on the ring expansion of prolinols and their derivatives for the synthesis of optically active 3-substituted piperidines, which has been well documented by Cossy and co-workers.\(^{[37]}\)

Besides the nucleophile dependency of these ring transformations, related to a thermodynamically or kinetically controlled reaction pathway, the nature of the substituents on the nitrogen atom and along the ring comprises a determining factor as well. As a representative example, the influence of the substitution pattern on the fluoride-induced ring transformation of prolinols 121 will be illustrated here (Scheme 32).\(^{[38]}\)

Upon altering the \(R^2\) and \(R^3\) substituents, only the replacement of \(R^2\) with larger groups culminated in a higher ratio of the two regioisomers in favor of the piperidine structure. The presence of a more bulky \(N\)-protecting group \((R^1)\) was also shown to improve the selectivity of the reaction to piperidine formation (in the order: \(CH_2-t-Bu < CHPh_2 < CPh_3\)). Finally, when an extra alkyl group was introduced at C-2 \((R^4 = Et, allyl, Bn)\), resulting in a quaternary carbon center, the rearrangement proceeded selectively to give piperidines 125. As a consequence, these bicyclic aziridinium ion-interceded ring transformations could be controlled in a regiospecific manner depending on the substitution pattern on the ring of prolinols 121. Because of a more steric \(N\)-substituent, the length of the C-5–N bond in aziridinium intermediates 123 increased and the equilibrium was shifted more towards piperidin-3-ylium cations 124, improving the selectivity in favor of a ring expansion. Also, the development of a quaternary center due to an extra alkyl group at C-2 in prolinols 121 \((R^4)\) led to a higher stability of the produced cations 123 and, as a result, prolinols 121 were completely converted into their higher homologues 125.

In another study, the influence of a quaternary center in the \(a\)-position with respect to the nitrogen atom has also been evaluated by employing cyclic amino alcohols 127 and 129 as substrates, resulting in complete regioselective ring-transformation reactions in favor of piperidine formation (Scheme 33).\(^{[28]}\) Moreover, DAST-induced ring expansion of \(\beta\)-amino alcohols 129 proceeded with excellent enantioselectivity (\(ee = 98–99\%\)). Depending on the type of nucleo-

\[\text{Scheme 32. DAST-promoted ring transformation of prolinols 121 to piperidines 125 and pyrrolidines 126.}\]
phile, the reaction proceeds under thermodynamic or kinetic control. The regioselective attack of the nucleophiles across the aziridinium intermediate is affected by the nature of the substituents on the nitrogen atom and the C-2 position of the starting prolinol.

All these observations can be interpreted and rationalized by comparing the possible contribution of four isomeric cations including 10, 13, 14 and 15 (n = 2, Scheme 4), which each could be generated from a 1-azoniabicyclo[3.1.0]hexane intermediate. The relative stability of the piperidin-3-ylum cation 13 (n = 2) can account for the formation of the piperidine ring as the major end product.

In accordance with these results, the reactivity of trifluoromethylated prolinols 131 and 134 to a variety of nucleophiles has recently been elucidated (Scheme 34).[39] Due to the presence of a trifluoromethyl substituent, the proposed ring-transformation reactions proceeded with complete regioselectivity. Furthermore, these aziridinium-interceded ring expansions occurred with excellent diastereoselectivity.

A similar pyrrolidine-to-piperidine rearrangement protocol has been developed by Davies et al. as a key step in the synthesis of polyhydroxylated piperidines.[40] This ring-expansion chemistry has also been employed by Bilke et al. in the synthesis of the neurokinin-1-receptor antagonist (+)-L-733,060.[41]

Besides the overwhelming number of examples dealing with 1-azoniabicyclo[3.1.0]hexane-interceded pyrrolidine-to-piperidine transformations, ring-contraction reactions from 3-substituted piperidines to 2-substituted pyrrolidines, involving analogous bicyclic intermediates, are known in the literature as well. Recently, Cossy and co-workers have developed a general protocol for the ring contraction of 3-hydroxy-3-(trifluoromethyl)piperidines 137 into a broad library of 2-substituted 2-(trifluoromethyl)piperidines 139, using a variety of halogen, nitrogen, oxygen, carbon and sulfur nucleophiles to trigger this ring transforma-

Scheme 33. DAST-promoted ring expansion of pyrrolidines 127 and 129.

Scheme 34. Ring expansion of trifluoromethylated prolinols 131 and 134.

Scheme 35. Ring contraction of 3-hydroxy-3-(trifluoromethyl)piperidines 137.
$R^2 = \text{CF}_3$ as compared to its isomeric azacyclocarbennium ion 13 ($n=2$, $R^2 = \text{CF}_3$) possibly accounts for the pyrrolidine formation as well due to the electron-withdrawing character of the trifluoromethyl group.

A piperidine-to-pyrrolidine ring contraction has also been observed in the preparation of 2-(bromomethyl)pyrrolidines 143 (Scheme 36).[43] Reaction of 3-methoxypiperidines 140 with BBr$_3$ in dichloromethane and subsequent treatment with aqueous NaOH afforded 2-(bromomethyl)pyrrolidines 143. Formation of the kinetically favored pyrrolidines 143 could be attributed to the use of an apolar solvent (CH$_2$Cl$_2$), as more polar solvents favored the production of the corresponding piperidines.

Apart from the well-documented formation of 1-azoniabicyclo[3.1.0]hexanes via an intramolecular S$_N$2-mediated expulsion of a terminal leaving group in cyclic substrates, an analogous bicyclic intermediate has also been produced from an acyclic precursor, further supporting the stability and feasibility of 1-azoniabicyclo[3.1.0]hexane formation.[44] In that respect, treatment of $\beta$-(N,N-diallylamino)acetals 144 with TMSOTf produced enantiopure 1-azoniabicyclo[3.1.0]hexanes 145 via a cationic cyclization reaction (Scheme 37). The 1-azoniabicyclo[3.1.0]hexanes 145 were isolated and characterized as the corresponding tetraphenylborate salts 146. The subsequent ring-opening reactions, induced by the addition of an appropriate nucleophile, showed to be mainly regiospecific affording 1,2,4-trisubstituted pyrrolidines 147. However, treatment of intermediates 145 with oxygen nucleophiles also delivered a small amount of the isomeric piperidine structures 148.

Scheme 36. Conversion of 3-methoxypiperidines 140 to 2-(bromomethyl)pyrrolidines 143.

Scheme 37. Preparation of 1-azoniabicyclo[3.1.0]hexane intermediates 145 and subsequent conversion to pyrrolidines 147 and piperidines 148.
1-Azoniabicyclo[3.1.0]hexanes have also been involved in the preparation of functionalized pyrrolidines 153 and piperidines 154 (Scheme 38).\cite{45} Bromination of \( \gamma,\delta \)-unsaturated aldimines 149 with bromine resulted in 5-bromomethyl-1-pyrrolinium bromides 150 via an electrophile-induced cyclization. Immediate reaction of these reactive intermediates 150 with hydride or alkoxides as nucleophiles afforded pyrrolidines 151, which underwent intramolecular ring closure to furnish bicyclic intermediates 152. Finally, ring opening of aziridinium ions 152 furnished the corresponding pyrrolidines 153 or piperidines 154.

The presence of two methyl substituents at C-6 in azabicycles 152 clearly has a profound effect on the regioselectivity of the ring-opening process, resulting in either the thermodynamically favored piperidines 154 (\( R^3 = H \), route ii) or the kinetically controlled pyrrolidines 153 (\( R^3 = Me \), route i).

Hydride-promoted ring opening of 1-azoniabicyclo[3.1.0]hexanes has also been investigated for the synthesis of \((-\)\)-nitramine.\cite{46} Analogous to the bromine-induced cyclization of aldimines 149 (Scheme 38), aldimines 155 were treated with bromine under the same reaction conditions (Scheme 39). Subsequent addition of two equiv. of LiAlH4 resulted in a higher production of the corre-
sponding pyrrolidines 157 as compared to their six-membered regioisomers 158. Finally, debenzylation of benzyl-protected piperidine 158 (PG = Bn) afforded the desired (−)-nitramine.

As illustrated by several examples, the regioselectivity of the ring-opening process of 1-azoniabicyclo[3.1.0]hexanes is dependent upon the nature of the applied nucleophile, yielding either a pyrrolidine ring or a piperidine scaffold. The outcome of the premised ring transformation is also influenced by the starting substrate, which is predictable to a certain extent by comparison of the stabilities among four possible cat-ionic isomers (10, 13, 14 and 15, n = 2, Scheme 4).

2.4 Preparation and Synthetic Utility of 1-Azoniabicyclo[4.1.0]heptanes

The intermolecular preparation of 1-azoniabicyclo[4.1.0]heptanes and their subsequent ring-opening reactions have been scarcely described in the literature so far. To illustrate this methodology, the synthesis of benzo-fused six- and seven-membered heterocycles will be discussed here as an example (Scheme 40). Activation of the starting material 159 was accomplished upon heating with HBr, resulting in tricyclic aziridinium intermediates 160. Whereas benzofused morpholine 159a (Y = O) was regioselectively ring opened affording new morpholine 161a as the sole reaction product, bromide-promoted ring opening of benzo-fused thiomorpholine 159b (Y = S) afforded mainly the analogous thiomorpholine 161b together with a small amount (5%) of its ring-expanded product 163b after hydrolysis. The production of this seven-membered thiazepine derivative 163b is reasonable considering the resonance stabilization of the developing benzylic carbenium ion in the corresponding azepin-3-ylium cation 13 (n = 3, R² = Ph), which is in equilibrium with aziridinium cation 160.

In contrast to the small number of studies regarding the preparation of 1-azoniabicyclo[4.1.0]heptanes via intermolecular activation, more research has been performed dealing with the synthesis of these bicyclic intermediates via intramolecular reactions. Analogous to the previous sections, these intramolecular methods can again be subdivided into two approaches, depending on whether the starting material involves an aziridine scaffold or a piperidine skeleton. Both methodologies have been applied in a study on the preparation of stereodefined piperidines and azepanes starting from diastereomerically pure aziridines. Microwave-assisted intramolecular cyclization of 2-(2-cyanoethyl)aziridines 164 resulted in 1-azoniabicyclo[4.1.0]heptanes 165, which subsequently underwent a regioselective ring opening to afford 2-chloromethyl-4-phenylpiperidine-4-carbonitriles 166 (Scheme 41). Taking advantage of the chloride leaving group in piperidines 166, the latter piperidines were heated to regenerate bicyclic intermediates 165. Upon addition of KCN in DMSO, the latter salts were regioselectively opened at the less-substituted carbon atom, affording 2-cyanomethyl-4-phenylpiperidine-4-carbonitriles 167 in high yields (88–92%). However, reaction with NaOAc in EtOH also furnished the regioisomeric azepanes 168. Surprisingly, the regioselectivity of these ring-opening reactions was strongly influenced by the relative stereochemistry of the substrates and could presumably be attributed to π–π interactions between the phenyl substituent on the piperidine core and the N-aryl substituent.

A 1-azoniabicyclo[4.1.0]heptane intermediate was also involved in the transformation of aziridine 169 upon treatment with MsCl and Et₃N in acetonitrile (Scheme 42). The resulting tricyclic intermediate 170 was consecutively subjected to regioselective ring opening to give 3,4-dihydroisoquinolines 171 upon reaction with acetate and azide as nucleophiles.

In comparison to their lower homologues (especially bicyclic butanes and pentanes), the formation of a 1-azoniabicyclo[4.1.0]heptane skeleton is energetically more favored because of associated ring strain energy differences. As a consequence, also activated

Scheme 40. Conversion of 1-azabicyclo[4.1.0]heptanes 159 to (thio)morpholines 161 and (thi)azepanes 163.

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aziridines, bearing a less nucleophilic nitrogen atom than their non-activated counterparts, can be converted into 1-azoniabicyclo[4.1.0]heptanes. In that respect, treatment of Boc-protected aziridines with NBS and NsNH₂ in ethyl acetate afforded 3-nosylazepanes in excellent enantioselectivity (Scheme 43). From a mechanistic point of view, aziridines were transformed into bicyclic intermediates upon reaction with NBS, followed by NsNH₂-induced nucleophilic ring opening.

A similar ring expansion has also been applied as a key step in the synthetic pathway to the alkaloid (+)-castanospermine. As depicted in Scheme 44, treatment of methyl hydroxamates with bis(trifluoroacetoxy)iodo]benzene (PIFA) generated 1-azoniabicyclo[4.1.0]heptanes, which underwent nucleophilic attack across the less-hindered carbon atom upon reaction with trifluoroacetic acid (TFA).

The influence of the nitrogen-protecting group on the premised bicyclic aziridinium ion-interceded reactions has also been studied by Chong et al. To that end, cis-2,6-di(chloromethyl)piperidines bearing different protecting groups (R = Bn, CBz, Ts) were treated with an excess of NaN₃ in DMSO, furnishing either ring-expanded cis-azepanes or chloride-by-azide substituted diazidopiperidine. As anticipated, reaction of benzyl-protected piperidine with an excess of NaN₃ resulted in the regioselective formation of the corresponding azepane. Although the CBz-protecting group rendered the nitrogen atom less nucleophilic for intramolecular expulsion of the leaving group in piperidine, it could be produced, probably due to the small amount of energy needed to create the 1-azoniabicyclo[4.1.0]heptane intermediate. Furthermore, the piperi-
DAST-promoted ring expansion of 2-(hydroxymethyl)piperazines/morpholines 182.

Scheme 46. DAST-promoted ring expansion of 2-(hydroxymethyl)piperazines/morpholines 182.
extra stabilized, favoring the regioselective fluoride attack towards seven-membered ring formation.

In addition, the same reaction conditions have also been applied to \((S)-\text{piperidine 186a}\) (Scheme 47). Although the anticipated \((R)-\text{azepane 189a}\) was obtained, the enantioselectivity of this reaction was decreased compared to the ring expansion of \((S)-\text{pyrrolidine 129}\) to the corresponding \((R)-\text{piperidine 130}\) (see Scheme 33). This phenomenon is attributed to the structure of the involved bicyclic aziridinium intermediates. Because of the larger ring of 1-azoniabicyclo[4.1.0]heptane 187a compared to its lower homologue, the C-6–N bond is longer, causing a higher incidence of the azepan-3-yl cation 188a. This hypothesis was further confirmed by reaction of \((S)-\text{azepane 186b}\) with DAST, yielding the corresponding \((R)-\text{azo-

cane 189b}\) in an enantiomeric excess of only 52%.

Besides the involvement of 1-azoniabicyclo[4.1.0]heptane intermediates in ring-expansion reactions, these intermediates have also been employed in ring-contraction reactions for the conversion of azepanes to the corresponding piperidine scaffolds, for example, as a key step in the synthesis of \((\pm)-1\text{-deoxynojir-

nymycin and \((\pm)-1\text{-deoxyaltronojirimycin}.\[

Treatment of azepane 190 with mesyl chloride resulted in aziridinium salt 191, which was immediately converted into the kinetically controlled piperidines 192 in an excellent diastereoselectivity (Scheme 48). The same procedure was performed starting from tetrahydroazepine 193, affording the corresponding tetrahydropiperidine structure 194, whereas an additional step was required to obtain the diastereomeric counterpart of 192.

As elucidated by a selection of examples, the 1-azoniabicyclo[4.1.0]heptane intermediates are able to be converted into 2-substituted piperidines and/or 3-substituted azepanes, either with or without high enantioselectivity. The ratio of piperidine versus azepane formation is dependent on the structural features of the substrate and the applied nucleophile. Furthermore, 1-azoniabicyclo[4.1.0]heptanes can be produced bearing a less nucleophilic nitrogen atom as well, which is reasonable from the lower energy input needed to create this intermediate in contrast to their lower homologues. Comparison of the stability among all possible isomeric cationic intermediates (10, 13, 14 and 15, \(n=3\), Scheme 4) should provide the reader the possibility to predict the regiochemical outcome of the aimed transformations to a large extent.

3 Conclusions and Future Prospects

Ring enlargements associated with transient bicyclic aziridinium ions are governed by the high reactivity (electrophilicity) of aziridinium ions towards incoming nucleophiles, involving sequential transition states without intervening intermediates. Mechanistically, the actual intermediacy of strained bicyclic aziridinium ions, as compared to other possible ionic inter-

Scheme 47. DAST-promoted ring expansion of \((S)-\text{piperidine 186a}\) and \((S)-\text{azepane 186b}\).

Scheme 48. Diastereoselective ring contraction of azepane 190 and tetrahydroazepine 193.
mediates, is often a matter of debate. However, the regio- and stereoselectivity associated with many ring expansions can be conveniently explained by the formation of bicyclic aziridinium intermediates, which also have been observed and characterized in a few cases (mostly dealing with 1-azoniabicyclo[3.1.0]hexanes)).

1-Azoniabicyclo[n.1.0]alkanes 198 can be generated intramolecularly from either aziridines 196 appended with a terminal leaving group X within their alkyl chain (route a, Scheme 49) or from azaheterocycles 197 with a β-carbon-attached leaving group X (route b, Scheme 49). Once this cationic intermediate 198 is produced, nucleophilic attack can occur either at the less- (pathway i) or at the more-substituted carbon atom (pathway ii), affording regioisomeric azaheterocycles 199 and 200, respectively (Scheme 49). The ratio of these two possible pathways will depend largely on the features of the involved intermediates (198) and the selected nucleophiles.

Importantly, starting from the initially generated 1-azoniabicyclo[n.1.0]alkane intermediate 198, three other isomeric cations (201, 202 and 203) can be drawn, which is key to determine the regioselectivity of the reaction (Scheme 50). The cation 203 is unfavorable in most cases because of the high ring-strain energy in the aziridine core combined with the presence of a primary carbenium ion. Therefore, most reactions involving a bicyclic aziridinium intermediate do not culminate in a three-membered aziridine end product (unless other intermediates/factors are in place) and, as a consequence, the contribution of isomeric cations 201 and 202 is more substantial. As elucidated in the above-mentioned literature examples, compounds with a quaternary center at the bridgehead carbon atom of intermediates 198 affect the regioselectivity in favor of the ring-expansion product (pathway ii, Scheme 49). After all, extra stabilization of this quaternary carbenium ion by an aryl substituent (mesomeric effect) or an alkyl group (inductive effect, hyperconjugation) results in a larger contribution of 201 compared to 202. Furthermore, the electrostatic gauche effect of a fluorine substituent can influence the regioselectivity of the reaction outcome by favoring a boat-like or a chair-like conformation of the involved bicyclic intermediate.[55]

The reaction pathway is not only dependent on the structural features of the starting material, but is influenced by the nature of the nucleophiles as well. However, it is not possible to identify a general tendency concerning the experimental reaction outcomes based on the characteristics of the nucleophiles alone. In specific examples, the thermodynamic or kinetic behavior of the reaction induced by a certain nucleophile is possibly predictable.[59] In most cases, pathway i in Scheme 49 is kinetically advantageous whereas the pathway ii (Scheme 49) is thermodynamically favorable, and the pathway that will be pursued will be predetermined by the applied nucleophiles. However, the small difference between the two pathways, especially for medium-sized bicyclic ring systems, sometimes makes the reaction outcome more sensitive to the reaction medium (e.g., solvent dependency) and the reaction temperature.

Although there is still a knowledge deficiency concerning the exact details of the involved mechanistic aspects, a broad diversity of useful synthetic applications of ring expansion involving 1-azoniabicyclo[n.1.0]alkane intermediates has been exploited to date. However, more extensive research, both experimentally and computationally, is required to obtain a full and comprehensive picture of the regioselectivity of ring transformations involving transient bicyclic aziridinium ions in a predictable manner. Considering

Scheme 49. Preparation of 1-azoniabicyclo[n.1.0]alkane intermediates 198 via intramolecular activation followed by kinetic (pathway i) or thermodynamic (pathway ii) controlled ring opening.

Scheme 50. Possible isomerizations of bicyclic aziridinium intermediates 198.
the relative easiness and the extent of the discussed ring-expansion reactions, more efficient and versatile methods to systematically develop broad libraries of valuable azaheterocycles with useful substituents along the ring system are expected to emerge in the near future, and aziridinium ion intermediates will undoubtedly continue to play a key role in contemporary heterocyclic chemistry.

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