Ring expansions of 1-azabicyclo[n.1.0]alkanes. Recent developments

Dmytro O. Tymoshenko

AMRI, 26 Corporate Circle, Albany, NY 12203, USA
E-mail: Dmytro.tym@gmail.com

DOI: http://dx.doi.org/10.3998/ark.5550190.0012.105

Abstract
In the past decade ring expansion of aziridines and aziridiniums fused to other rings has developed into an attractive alternative method to classical pyrrolidine, piperidine and azepine ring construction approaches. This short review provides an update on recent reports and demonstrates the usefulness and the efficiency of this approach.

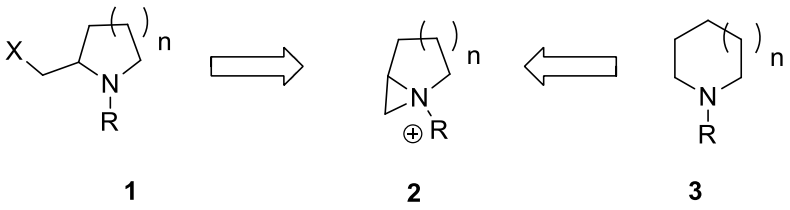
Keywords: 1-Azabicyclo[n.1.0]alkanes, ring expansion, aziridine, aziridinium

Table of Contents

1. Introduction

Non-aromatic aza-heterocycles, such as pyrrolidines, piperidines and azepines, their benzo-, spiro-, bridged and polycyclic derivatives can be found in numerous natural products. They represent a vast variety of cyclic and substitution patterns. Their synthesis, properties, biological activity and isolation from the natural products are well-documented.[1a-d] Several recent reviews have been published covering pharmaceutically active compounds,[2] spiro-derivatives,[3a-b] marine alkaloids,[4] iminosugar di- and oligosaccharides,[5a-b] and alkaloid lipids.[6] Advances in synthetic methods include catalytic asymmetric aza Diels-Alder reactions, [7]benzotriazole mediated syntheses,[8] asymmetric synthesis,[9a-b] and cyclization of allylsilyl-substituted *N*-acyliminium and

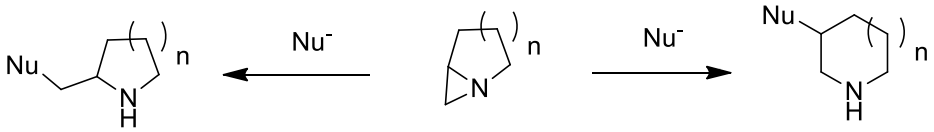
iminium ions.[10] A special case of the preparation of *n*-membered non-aromatic azacycles is a ring expansion of (*n*-1) cyclic precursors fused to aziridine ring. Thus, azabicyclo[3.1.0]hexane **2** (n = 1),[11a-b] serves as a reactive precursor to piperidine **3** (Figure 1). Additional *N*-diversification in aziridinium species (R ≠ H) is a valuable source of *N*-substituted derivatives.



1 **2** **3**

Figure 1

Bicycles **4** are expected to meet the general reactivity profile of aziridines,[12] (Scheme 1) with the unfavorable predominant formation of 2-aminomethyl derivatives **5** due to nucleophilic attack on the least substituted C2-carbon. Strain of the fused ring, nature of the nucleophile and catalyst can significantly further affect the process. Additionally, the high reactivity of the species **2** makes isolation of fused aziridines and aziridiniums difficult to achieve. Nevertheless, ring expansion methodology is of continuous interest as it provides vast opportunities for the transfer of substitution patterns and stereochemistry from more accessible smaller (*n*-1) rings onto *n*-membered aza-cycles.



5 **4** **6**

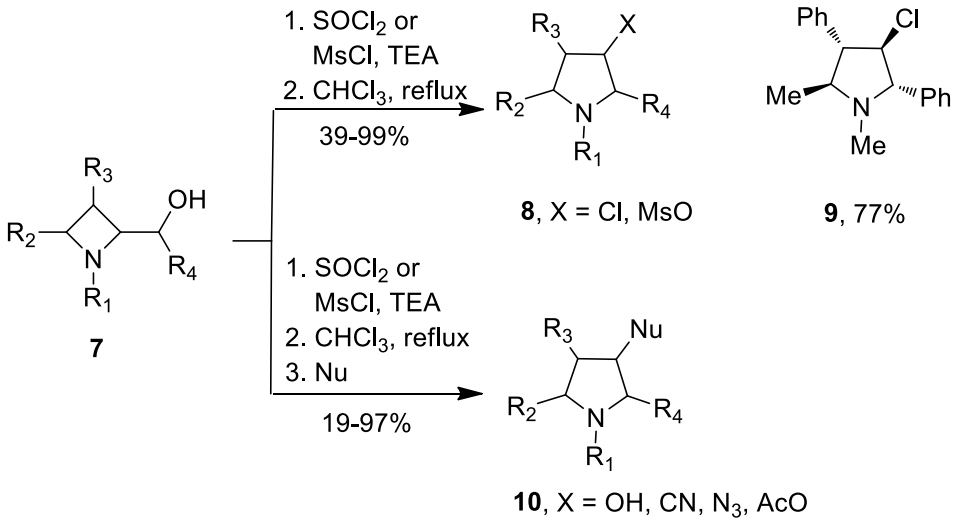
Scheme 1

The current account surveys the literature from 2001 until 2010 on ring enlargement of the systems **2** (n = 1) and includes results of a deeper retrospective literature search for other azabicyclo[3.1.0]alkanes (n ≠ 1). The discussion is organized in the order of ring sizes followed by reactivity of aziridines fused to bridged and polycyclic systems.

2. Ring Expansions of 1-Azabicyclo[2.1.0]pentanes

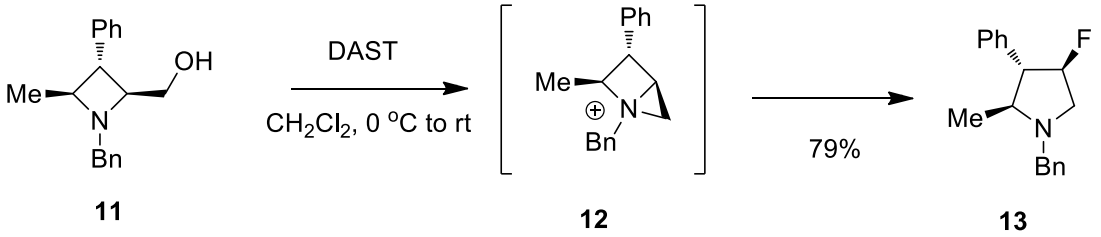
High energy for the strained 1-azabicyclo[2.1.0]pentane **2** (n = 0) results in its instability and isolatable entities are quite rare.[13] At the same time high reactivity of the precursors **1** results in the desired ring expansion process. A series of 2-(α-hydroxyalkyl)azetidines **7** with a variety of

substituents both on the four-membered ring and on the adjacent hydroxy group are treated with either thionyl chloride or methanesulfonyl chloride in the presence of triethylamine (Scheme 2). The obtained intermediate 2-α-chloro- or 2-α-methanesulfonyloxyalkyl azetidines rearrange stereospecifically providing good to excellent yields of 3-(chloro- or methanesulfonyloxy)pyrrolidines **8**. Thus, a single isomer of the highly substituted pyrrolidine **9** was reported in 77% isolated yield. When this rearrangement is conducted in the presence of nucleophile (NaN_3, KCN, KOH, or NaOAc), the produced pyrrolidines **10** stereospecifically incorporate the added nucleophile at C-3.[14a-b] The relative configuration of the substituents in the formed pyrrolidines is consistent with a mechanism involving the formation of an intermediate bicyclic aziridinium ion, which is opened regioselectively at the bridgehead carbon atom.[14b]



Scheme 2

Enantiopure 2-hydroxyalkylazetidine **11** when treated with DAST (*N*,*N*-diethylaminosulfur trifluoride) rearranged into 3-fluoropyrrolidines **13** (Scheme 3). The reaction is stereospecific and involves a 1-azabicyclo[2.1.0]pentane intermediate **12** which is regioselectively opened by a fluoride anion.[15]

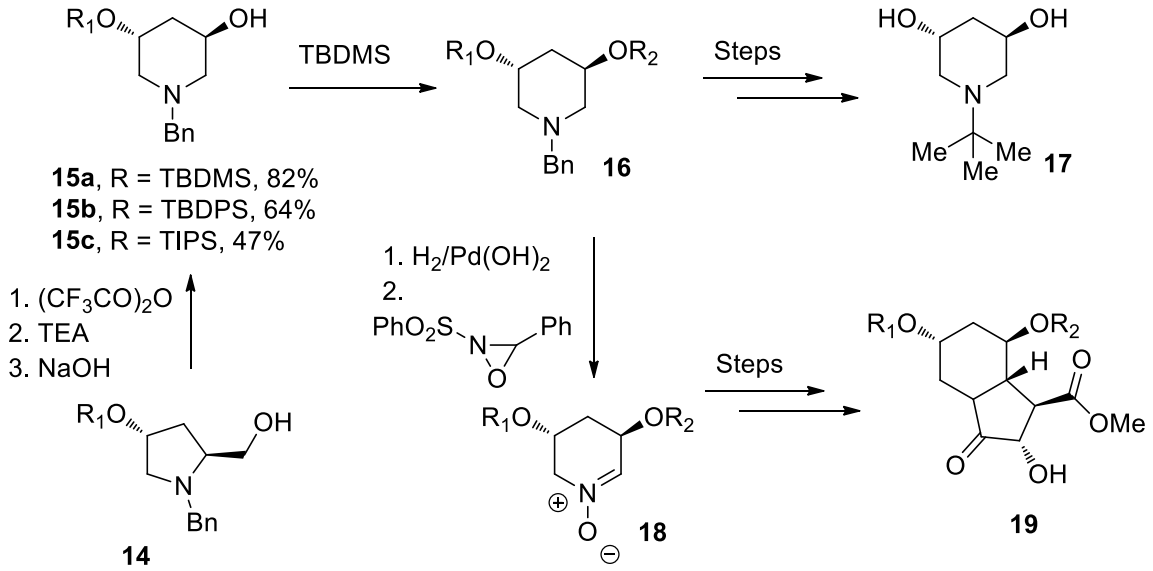


Scheme 3

3. Ring Expansions of 1-Azabicyclo[3.1.0]hexanes

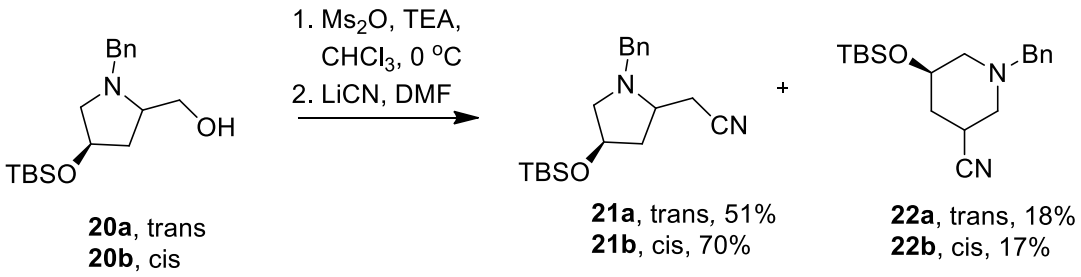
Since an early report by Fuson and Zirkle,[16] ring expansion of 2-substituted pyrrolidines through 1-azabicyclo[3.1.0]hexane intermediates become a useful synthetic tool and the reader is referred to the preceding reviews.[11a-b] Recent reports include further developments of functionalized mono- and polycyclic systems.

Substituted silyl compounds **15a–c** were prepared from the corresponding prolinols **14** by well-established treatment with trifluoroacetic anhydride followed by the addition of triethylamine and then by treatment with sodium hydroxide (Scheme 4).[17a-c] Subsequent reaction and protection/deprotection steps resulted in *N*-*tert*-Bu-piperidine **17** which was applied as a catalyst for enantioselective addition of diethylzinc to aldehydes.[17a] 3,5-Di-TBDMSO-piperidine **16** (R_1 = R_2 = TBDMS) can further undergo oxidation with *C*-phenyl-*N*-phenylsulfonyl oxaziridine to produce corresponding nitrone **18**, a valuable intermediate for the corresponding protected dihydroxyindolizidinone **19**.[17b] Similarly prepared intermediate **15a** was further used for the synthesis of piperidine based peptide nucleic acids.[17]



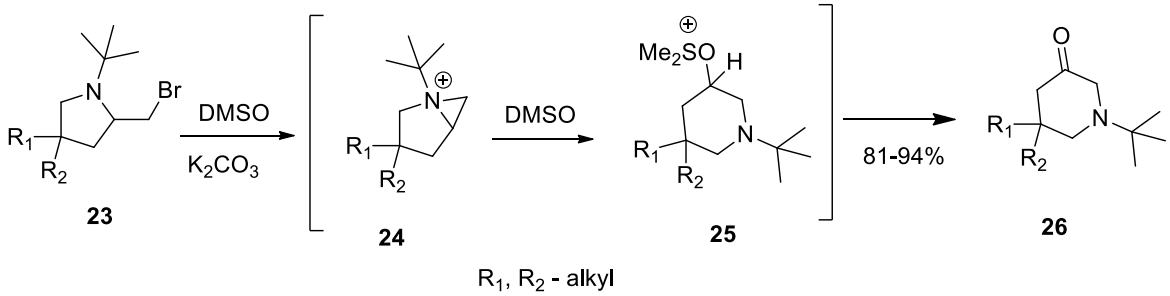
Scheme 4

In a similar manner (Scheme 5),[18] successive *O*-activation of the protected hydroxyproline-derivatives **20a** (trans) and **20b** (cis) followed by nucleophilic displacement using LiCN resulted in formation of the nitriles **21a** and **21b** in 51 and 70% yield, respectively. Under the reported reaction conditions (DMF, 0 °C to rt) rearrangement occurs only to a minor extent giving the piperidine derivatives **22a–b** as side products. In the case of the trans-substituted derivatives, the pyrrolidine- and the piperidine-derivatives were formed in a 7:3 mixture of isomers. For the cis-isomers 4:1 ratio was observed.



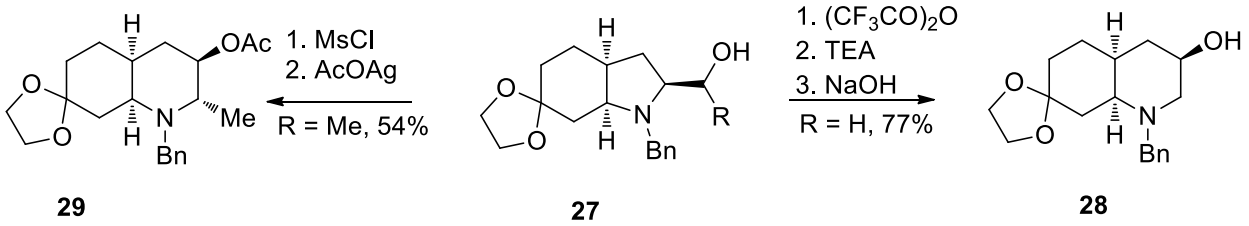
Scheme 5

Attempted Swern oxidation of spiro-2-(bromomethyl)pyrrolidine **23** into corresponding 2-aldehyde (DMSO, 30 °C, 14 h, 2 equiv of potassium carbonate) resulted in piperidin-3-one **26** instead (Scheme 6).[19] The addition of potassium carbonate appeared to be essential, as piperidin-3-one **26** was isolated in very low yields (10%) if no K_2CO_3 was used. According to the suggested mechanism 2-(bromomethyl) pyrrolidines **23** are first transformed into intermediate bicyclic aziridinium salts **24** which are converted into piperidines **26** upon ring opening with dimethylsulfoxide. The last step of the proposed mechanism could occur either via direct nucleophilic ring opening at the less substituted aziridine carbon atom or via spontaneous ring opening and subsequent substitution of the formed carbenium ion. Abstraction of the acidic proton at the oxygenated carbon atom in intermediate **25** by potassium carbonate is important for further liberation of dimethylsulfide and formation of final piperidin-3-ones **26**.



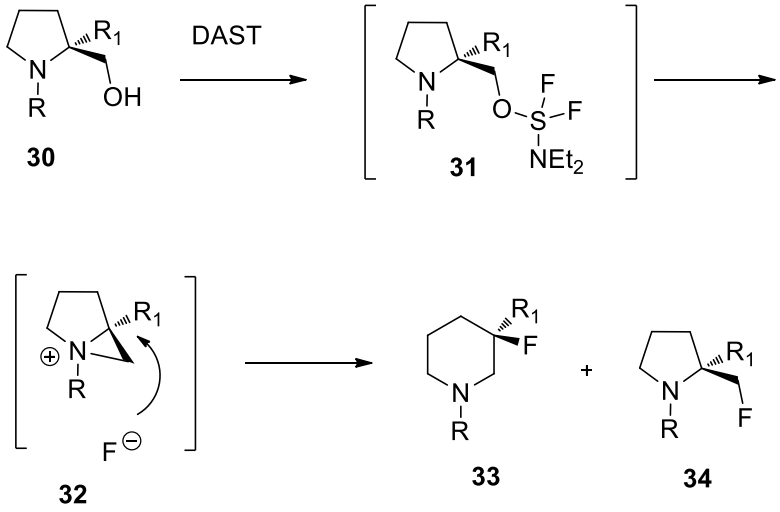
Scheme 6

Synthesis of enantiopure *cis*-decahydroquinoline **28** is performed in a straightforward manner staring from octahydroindole **27** (Scheme 7).[20] As above, reaction conditions include *O*-trifluoroacetylation to form a better leaving group followed by rearrangement in the presence of hydroxy anion as a nucleophile. Interestingly, when hydroxyl group activation is achieved through mesylation, the chloride anion serves as an internally generated nucleophile resulting in high yield of 3-chloro decahydroquinoline which can be subsequently transformed into an acetoxy derivative **29**.



Scheme 7

As previously described for azabicyclopentanes, DAST is a reagent of choice for conversion of the active prolinols **30** into enantiopure 3-fluoropiperidines **33**. The reaction proceeds via aziridinium intermediate **32** and usually produces mixtures of the desired piperidines **33** with 2-fluoromethyl pyrrolidines **34** of variable ratios (Scheme 8).[21a-b] In the case of C-2-alkyl-substituted prolinols **30c**–**d** and *N*-trityl prolinol **30e** piperidines **33c–e** form exclusively. The authors explain such selectivity by an increase in the length of the C-2–N bond in the aziridinium intermediate **32**. Stabilization of a partial positive charge at quaternary C-2 correlates with a weakened C-2–N bond. This results in the nucleophilic attack of the fluoride at the more electrophilic carbon and the cleavage of the C-2–N bond. The selectivity of the rearrangement when the nitrogen atom is substituted by a bulky protecting group can also be explained in terms of lengthening of the C-2–N bond due to steric constraints.



	R	R_1	Yield, %	33	34
a	Bn	H	61	80	20
b	CH_2-*t*-Bu	H	54	60	40
c	CH_2-*t*-Bu	Et	76	100	0
d	CH_2-*t*-Bu	Bn	87	100	0
e	CPh_3	H	64	100	0

Scheme 8

Other examples of the ring expansion of appropriately substituted prolinols to 3-substituted piperidines include (Figure 2) the synthesis of 3-OAc derivative **35** (46%),[22] tetrahydroquinoline **36** (91%, 3:1 mixture with indoline **37**),[23] 3-aminomethyl piperidine **38** (33%),[24] thiazole **39**, as a precursor of glycosidase inhibitor 1-deoxynojirimycin (46%),[25] ester **40** (84%),[26] and chloromethyl derivative **41** (55%).[27]

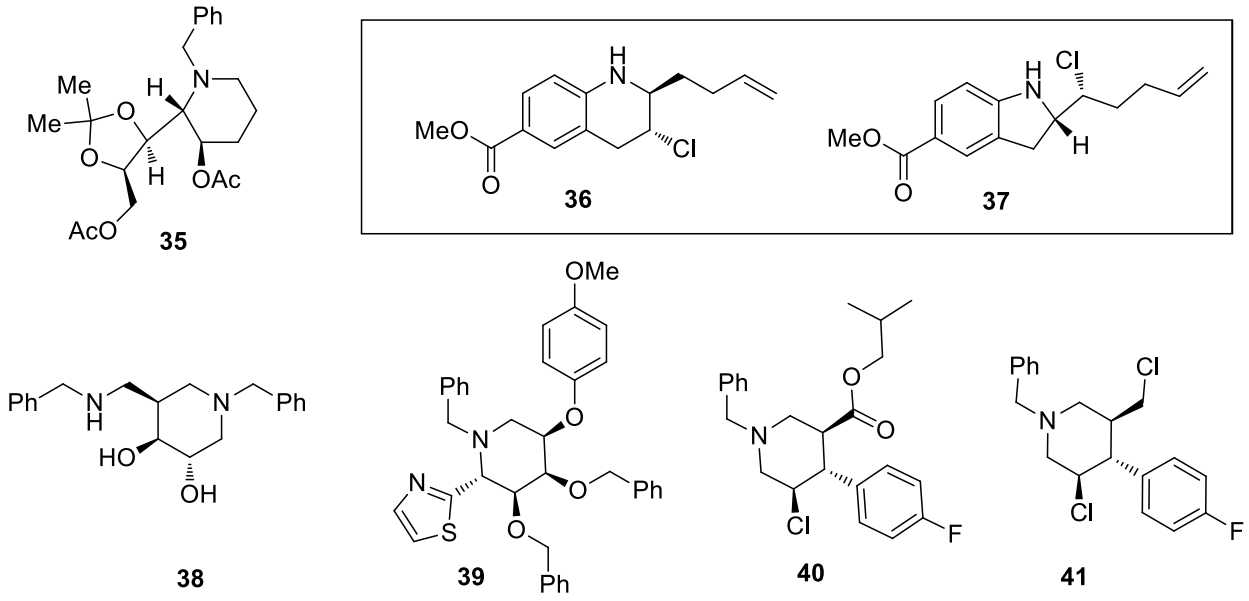
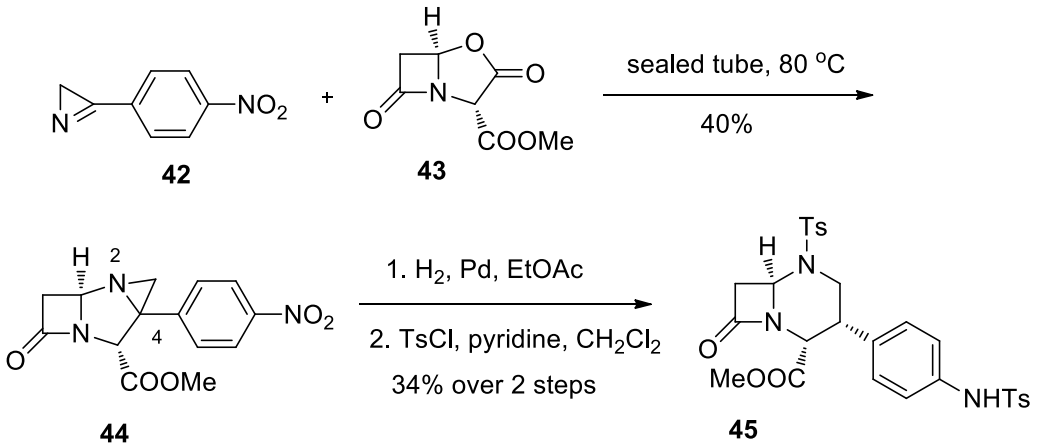


Figure 2

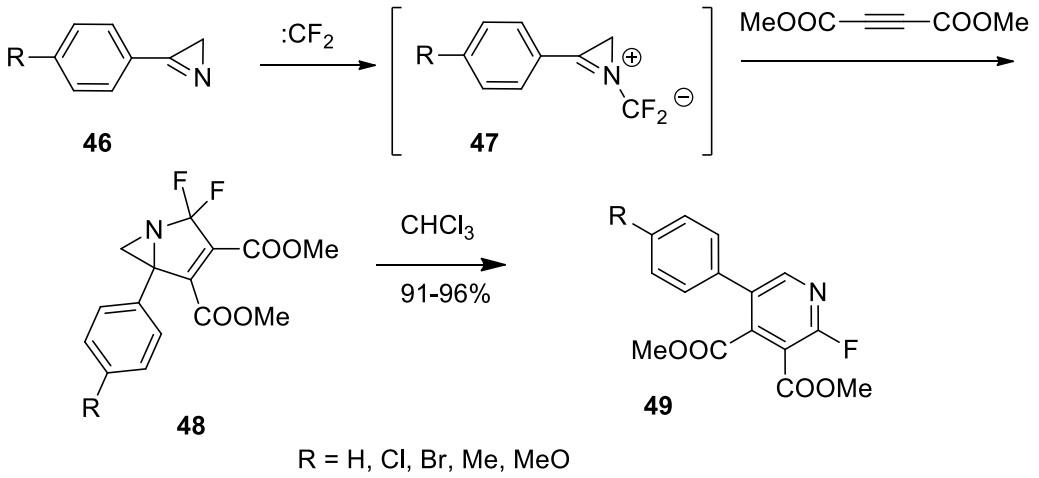
Noteworthy is an alternative method for fused aziridine intermediate preparation involving 2*H*-azirines as precursors. Thus, 4-nitrophenyl substituted azirine **42**, prepared in three steps starting from 4-nitrostyrene, is a highly reactive 1,3-dipolarophile due to the ring strain. Cycloadducts **44** derived from azirine and oxazolidinone **43** incorporates a highly strained C–N bond within 2,6-diazatricyclo[4.2.0.0^{2,4}]octan-7-one ring system **44**. Subsequent reduction is followed by ditosylation/cleavage of the strained C(4)–N(2) bond and produces 1-azacepham (1,5-diazabicyclo[4.2.0]octan-8-one) derivative **45** in 34% yield over two steps (Scheme 9).[28]

Although of less practical significance, azirines can serve as a source of ylides **47** which are suitable reagents for cycloadditions with dipolarophiles.

Dimethyl 2,2-difluoro-1-azabicyclo[3.1.0]hex-3-ene 3,4-dicarboxylates **48** are relatively stable and can be stored at –20 ºC, but (on prolonged storage at room temperature) undergo ring expansion followed by defluorination/aromatization to 2-fluoropyridine derivatives **49** in high yields (Scheme 10).[29a-b]



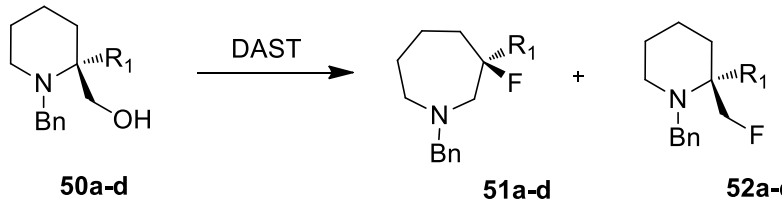
Scheme 9



Scheme 10

4. Ring Expansions of 1-Azabicyclo[4.1.0]heptanes and 1-azabicyclo[5.1.0] octanes

A number of recent publications covers ring expansion of aziridines fused to the medium rings. Thus, similarly to substituted prolinols (Scheme 8, section 2) 3-fluoroazepanes **51** are exclusive ($R_1 \neq H$) products of 2-hydroxymethylpiperidines **50** ring expansion (Scheme 11).[21b] Compound **50a** ($R_1 = H$), unsubstituted at position 2, results upon treatment with DAST in mixture of the corresponding 3-fluoroazepane **51a** and fluoromethyl derivative **52a**.

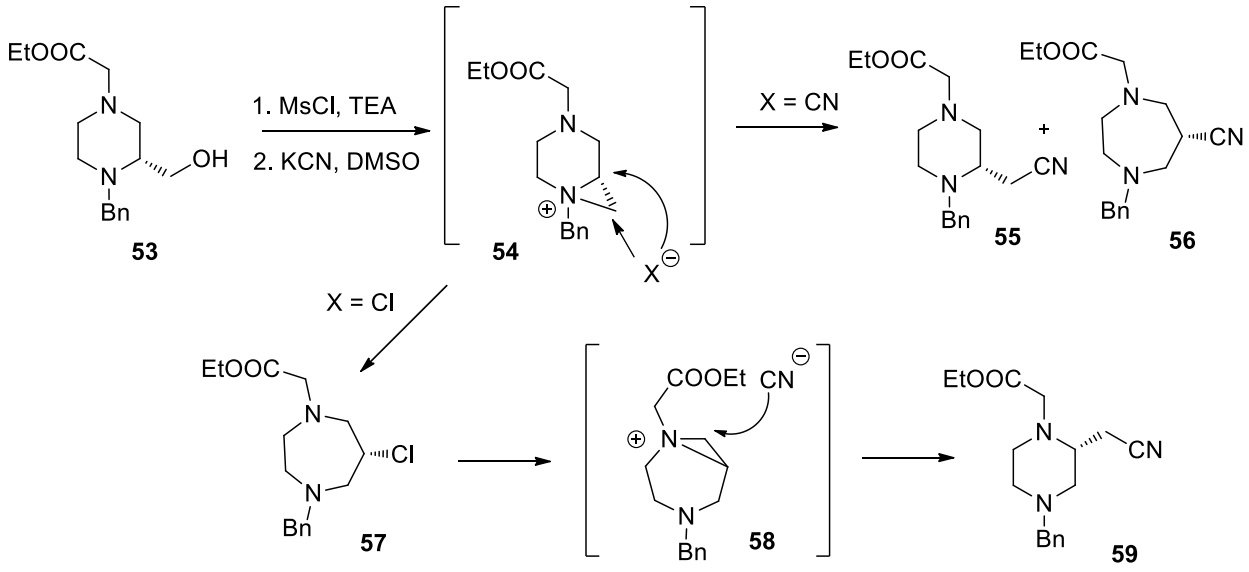


50a-d 51a-d 52a-d

	R_1	Yield, %	51	52
a	H	63	70	30
b	Et	63	100	0
c	Allyl	76	100	0
d	Bn	76	100	0

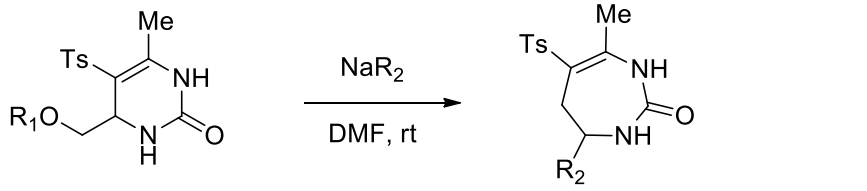
Scheme 11

Reaction of the alcohol **53** with methanesulfonyl chloride and subsequently with KCN in DMSO at room temperature provided 1,4-diazepane derivative **56** as a minor product (11% yield) along with the major cyanomethyl derivative **55** (54% yield). Surprisingly, in addition to these main products, careful chromatographic separation provided the isomeric nitrile **59** (0.4%). The formation of the isomeric nitriles **55** and **56** is apparent through intermediate aziridinium ion **54**. Chloride anion generated during mesylation step competes with cyanide and forms chloro diazepane **57**. The latter undergoes formation of regioisomeric aziridinium ion **58** and subsequent cyanide attack to afford small but detectable amounts of compound **59** (Scheme 12).[30]



Scheme 12

Mesylate **60a** and tosylate **60b** when treated with NaCN in DMF or acetonitrile produce 4-substituted 6-tosyl-2,3,4,5-tetrahydro-1*H*-1,3-diazepin-2-ones **61**. Reaction in acetonitrile requires addition of 18-crown-6 ether. The process apparently proceed through an aziridine intermediate, although an alternative route is theorized by authors. In a similar fashion, mesylate **60a** was reacted with sodium thiophenolate to give diazepinone **61b** in 97% yield (Scheme 13).[31]

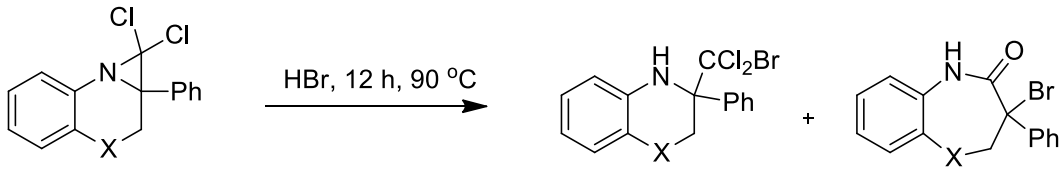


60a, R_1 = Ms
60b, R_1 = Ts

61a, R_2 = CN, 95% (from **60a**)
61a, R_2 = CN, 89% (from **60b**)
61b, R_2 = SPh, 97% (from **60a**)

Scheme 13

Ring opening of 1,1-dichloro-1a-phenyl-1a,2-dihydro-1*H*-azirino[1,2-*d*]benzo[*b*][1,4]oxazine **62a** (X = O) with HBr gives the product **63a** of N-C1 bond scission with no trace of the ring expansion product **64a**. Under the same conditions compound **64b**, the product of 1,5-benzothiazepine **62b** ring enlargement and sequential hydrolysis, was observed and isolated in 5% yield (Scheme 14).[32]



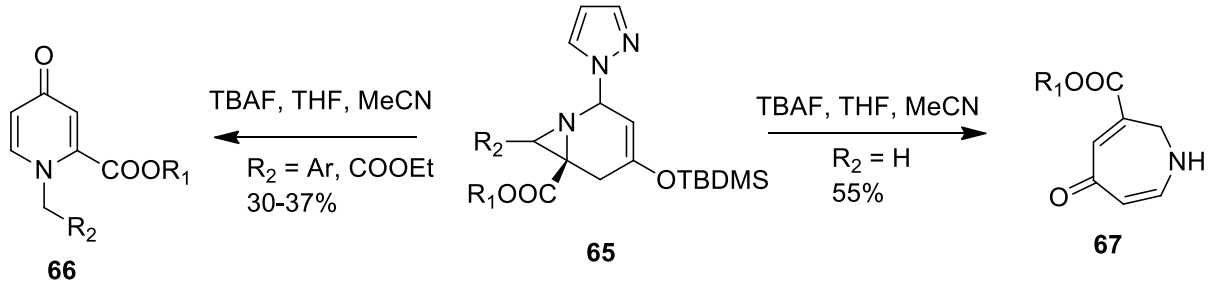
62a, X = O
62b, X = S

63a, X = O, 62%
63b, X = S, 45%

64a,X = O, 0%
64b, X = S, 5%

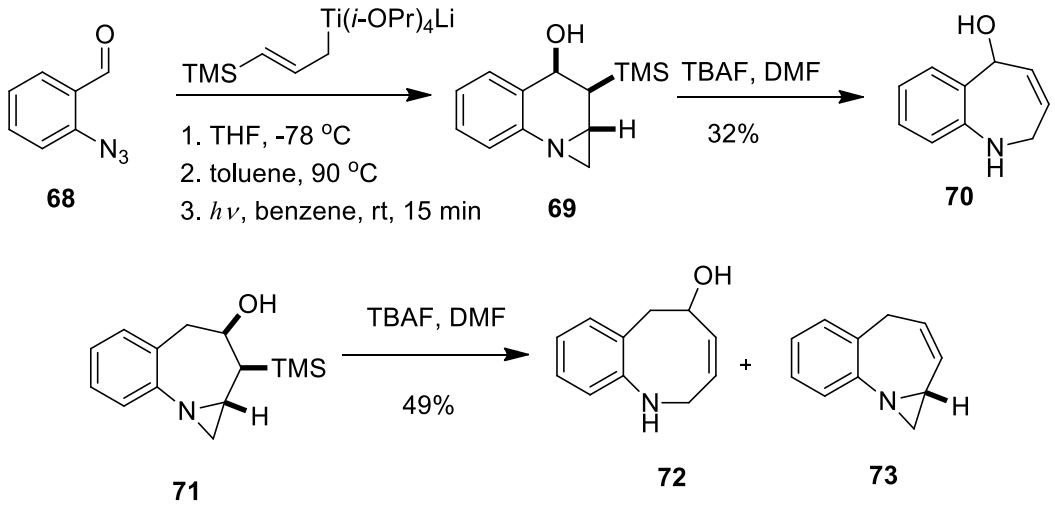
Scheme 14

Compounds **65**,[33] rapidly undergo aziridine ring cleavage followed by elimination of pyrazole leaving group, analogous to previously reported,[34] MeO-derivatives, when treated with tetrabutylammonium fluoride (Scheme 15). Ester and aryl substitution on R_2 stabilize a negative charge and pyridones **66** are formed as exclusive products of C6–C7 bond cleavage. In the case of R_2 = H, the negative charge cannot be delocalized and cleavage of C6–N1 bond occurs with expansion to the seven membered ring **67**.



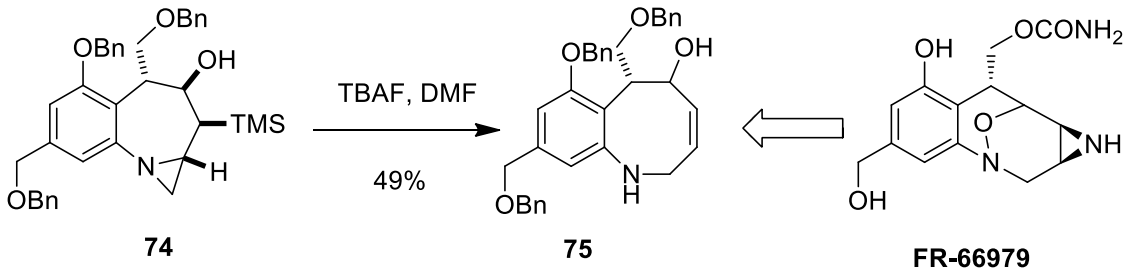
Scheme 15

Synthesis of aziridine **69** was reported starting from *o*-azidobenzaldehyde **68** through a synthetic sequence which includes fully diastereoselective 1,3-dipolar cycloaddition and irradiation of triazoline intermediate. Although compound **69** is surprisingly stable, as compared to other allylsilane-derived aziridines, its exposure to TBAF or Bu_4NOH in DMF at −20 °C promotes conversion to benzazepenol **70** (Scheme 16).[35] Similarly, starting from *o*-azidophenylacetaldehyde through aziridine intermediate **71** azocenol **72** was isolated as ca. 5:1 mixture with unsaturated aziridine **73**. The formation of the latter was attributed to the side Peterson olefination reaction.



Scheme 16

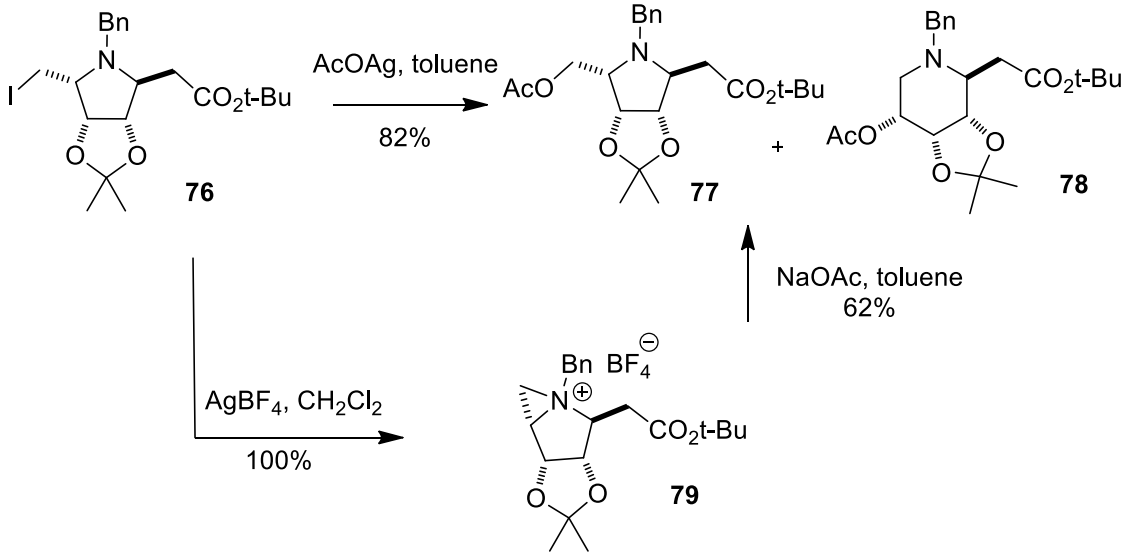
The same ring opening strategy was used in the synthesis of the antitumor agent FR-66979, structurally related to the mitomycins (Scheme 17).[36]



Scheme 17

5. Ring expansions of aziridines fused to bridged and bicyclic ring systems

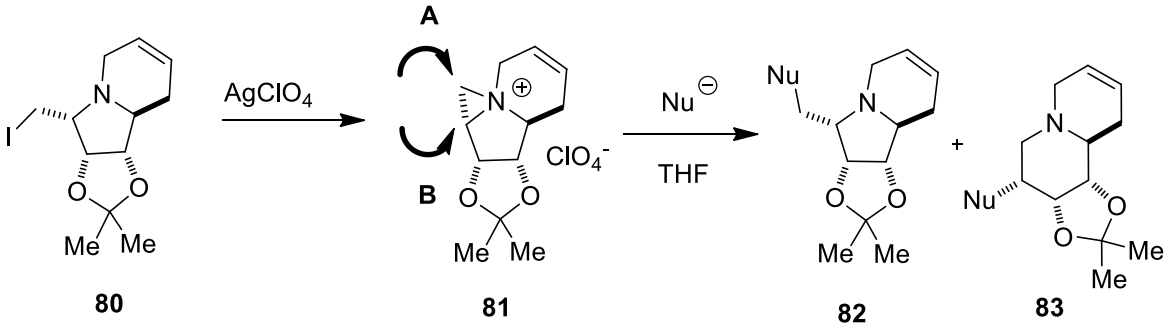
The reactivity of aziridines fused to bicyclic systems is in accordance with the general rules described above. Thus, reaction of diastereomeric iodide **76** with AgOAc in toluene gives an inseparable 45:55 mixture of the pyrrolidine **77** and piperidine **78** acetates in 82% overall yield. The suggested mechanism includes the formation of an intermediate aziridinium ion. In the proof of concept experiment, treatment of the iodide **76** with $AgBF_4$ gave a quantitative yield of aziridinium derivative **79**, which upon reaction with NaOAc in toluene gave a 45:55 mixture of the acetates **77** and **78** in 62% isolated yield (Scheme 18).[37]



Scheme 18

Tricyclic salt **81** bridged through aziridine nitrogen was generated in situ in $CDCl_3$ and characterized by NMR spectroscopy and it demonstrated similar reactivity (Scheme 19). The ring-opening of **81** with the iodide, methylthiolate, and acetate ions gives indolizidines **82** and

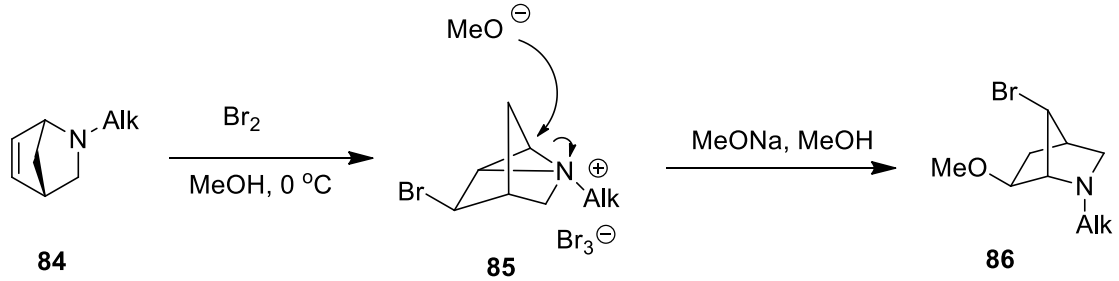
quinolizidines **83** in a 1:2 ratio. The formation of quinolizidines as major products indicates a preferential attack of the nucleophile at the most substituted carbon atom C-3 (pathway B) probably due to the larger relief of ring strain.[38]



Nu	Reagent	Yield (**82**+**83**), %
I	Bu_4NI	76
SMe	NaSMe	59
OAc	Bu_4NOAc	53

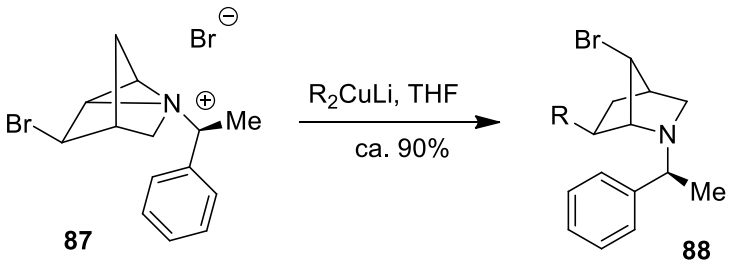
Scheme 19

Bromination of 2-alkyl-2-azabicyclo[2.2.1]hept-5-ene **84** affords 3-bromo-1-alkyl-1-azoniatricyclo 2.2.1.02,6]heptane bromides **85**, and opening of the aziridine ring in this salt with various nucleophiles gives the corresponding 6-substituted 2-alkyl-2-azabicyclo[2.2.1] heptanes as exemplified in Scheme 20 for 6-methoxy derivatives **86**.[39a-b] Complete inversion of configuration of the ring system occurs due to the fact that only the less sterically hindered bond of the aziridinium bromide **85** is available for S_{N2} nucleophilic attack.



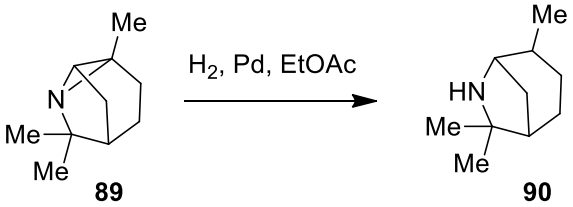
Scheme 20

Similarly, an efficient method for the preparation of 6-substituted 7-bromo-aza-bicyclo[2.2.1]heptanes **88** through the selective opening of the aziridinium **87** with organocuprates was reported in up to 90% yields (Scheme 21).[40]



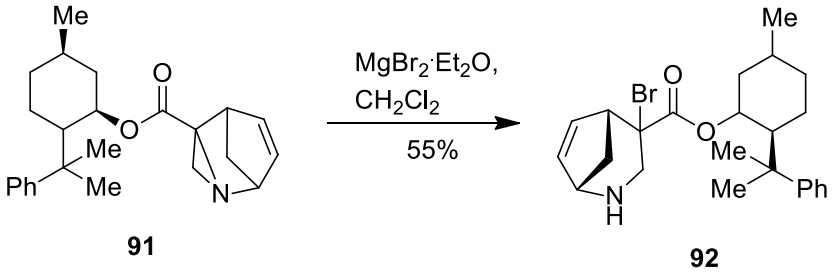
Scheme 21

Hindered aziridine **89** is stable towards nucleophilic attack and in alkaline media. Nevertheless, its hydrogenation occurs quantitatively at the less hindered C2-N bond to afford 1,3,3-trimethyl-2-azabicyclo[2.2.2]octane **90**, azacineole, one of the components of eucalypt leaf oil (Scheme 22).[41]



Scheme 22

On the other hand, more accessible strained aziridine moiety in the bridged 1-azabicyclo[4.1.0]heptane **91** easily undergoes stereoselective ring opening by magnesium bromide (as well as other magnesium halides) to produce chiral ester **92** in 55% yield (Scheme 23).[42a-b]



Scheme 23

6. Summary

The past decade has witnessed a growing interest in non-aromatic cyclic amines as related to natural product synthesis. The need for new and more efficient synthesis has served as the driving force for research efforts and resulted in non-trivial ring construction strategies, and ring expansion of 1-azabicyclo[n.1.0]alkanes is undoubtedly among them. The present review has outlined the importance of this transformation as an advantageous methodology for synthesis of diverse pyrrolidines, piperidines and medium size cyclic amines.

7. Acknowledgments

We thank Dr. Brian Gregg and Dr. Jolicia Gauuan for discussions and advice.

8. References

1. (a) Bremner, J. B. In *Progress in Heterocyclic Chemistry*; Gribble, G. W.; Joule, J. A. Eds.; Elsevier: Oxford, 2004; Vol. 16, p 431. (b) Bremner, J. B. In *Progress in Heterocyclic Chemistry*; Gribble, G. W.; Joule, J. A. Eds.; Elsevier: Oxford, 2005; Vol. 17, p 389. (c) Quirion, J.-C.; Leclerc, E.; Jubault, P. In *Science of Synthesis, Houben-Weyl Methods of Organic Transformations*; Molander, G., Ed.; Georg Thieme Verlag: Stuttgart, 2007; Vol. 20, p 659. (d) Fraser, H. L.; Floyd, M. B.; Hopper, D. W. In *Progress in Heterocyclic Chemistry*; Gribble, G. W.; Joule, J. A. Eds.; Elseveir: Oxford, 2007; Vol. 18, p 310.
2. Kaellstroem, S.; Leino, R. *Bioorg. Med. Chem.* **2008**, *16*, 601.
3. (a) Companyo, X.; Alba, A.-N.; Rios, R. *Targets Heterocycl. Syst.* **2009**, *13*, 147. (b) Troin, Y.; Sinibaldi, M.-E. *Targets Heterocycl. Syst.* **2009**, *13*, 120.
4. Wahba, A. E.; Hamann, M. T. *Marine Drugs* **2010**, *8*, 2395.
5. (a) Merino, P.; Delso, I.; Marca, E.; Tejero, T.; Matute, R. *Curr. Chem. Biology* **2009**, *3*, 253. (b) Vogel, P.; Gerber-Lemaire, S.; Juillerat-Jeanneret, L. In *Iminosugars* Compain, P.; Martin, O. R. Eds.; John Wiley and Sons 2007, 87.
6. Koulocheri, S. D.; Pitsinos, E. N.; Haroutounian, S. A. *Curr. Org. Chem.* **2008**, *12*, 1454.
7. Yamashita, Y.; Kobayashi, S. In *Handbook of Cyclization Reactions* Ma, S., Ed.; Wiley, Inc. 2010, Vol. 1, p 59.
8. Katritzky, A. R.; Rachwal, S. *Chem. Rev.* **2010**, *110*, 1564.
9. (a) Vicario, J. L.; Badia, D.; Carrillo, L.; Ruiz, N.; Reyes, E. *Targets Heterocycl. Syst.* **2008**, *12*, 302. (b) 2009MI139 Troin, Y.; Sinibaldi, M.-E. In *Synthesis of Nitrogen Heterocycles*, Royer, J. Ed.; Wiley-VCH Verlag GmbH and Co KGaA: Weinheim, 2009, 139.
10. Remuson, R.; Gelas-Mialhe, Y. *Mini-Reviews Org. Chem.* **2008**, *5*, 193.

11. (a) Cossy, J.; Pardo, D. G. *Chemtracts* **2002**, *15*, 579. (b) Cossy, J.; Pardo, D. G. *Targets Heterocycl. Syst.* **2002**, *6*, 1.
12. Pearson, W. H.; Lian, B. W. In Comprehensive Heterocyclic Chemistry II, A. R. Katritzky, C. W. Rees, E. F. V. Scriven, Eds.; Pergamon: Oxford, 1996, vol. 1, p 1.
13. Joucla, M.; Fouchet, B.; Hamelin, J. *Tetrahedron* **1985** *41*, 2707.
14. (a) Couty, F.; Durrat, F.; Prim, D. *Tetrahedron Lett.* **2003**, *44*, 5209. (b) Durrat, F.; Sanchez, M. V.; Couty, F.; Evano, G.; Marrot, J. *Eur. J. Org. Chem.* **2008**, *19*, 3286.
15. Drouillat, B.; Couty, F.; David, O.; Evano, G.; Marrot, J. *Synlett* **2008**, *9*, 1345.
16. R. C. Fuson, C. L. Zirkle, *J. Am. Chem. Soc.* **1948**, *70*, 2760.
17. (a) Roudeau, R.; Pardo, D. G.; Cossy, J. *Tetrahedron* **2006**, *62*, 2388. (b) Brandi, A.; Cicchi, S.; Paschetta, V.; Pardo, D. G.; Cossy, J. *Tetrahedron Lett.* **2002**, *43*, 9357. (c) Lonkar, P. S.; Kumar, V. A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2147.
18. Heindl, C.; Hubner, H.; Gmeiner, P. *Tetrahedron: Asymmetry* **2003**, *14*, 3153.
19. D'hooghe, M.; Baele, J.; Contreras, J.; Boelens, M.; De Kimpe, N. *Tetrahedron Lett.* **2008**, *49*, 6039.
20. Mena, M.; Bonjoch, J.; Gomez-Pardo, D.; Cossy, J. *J. Org. Chem.* **2006**, *71*, 5930.
21. (a) Dechamps, I.; Pardo, D. G.; Cossy, J. *Synlett* **2007**, 263. (b) Dechamps, I.; Pardo, D. G.; Cossy, J. *Eur. J. Org. Chem.* **2007**, 4224.
22. Dechamps, I.; Pardo, D. G.; Cossy, J. *Tetrahedron* **2007**, *63*, 9082.
23. Ori, M.; Toda, N.; Takami, K.; Tago, K.; Kogen, H. *Tetrahedron* **2005**, *61*, 2075.
24. Deyine, A.; Delcroix, J.-M.; Langlois, N. *Heterocycles* **2004**, *64*, 207.
25. Dondoni, A.; Richichi, B.; Marra, A.; Perrone, D. *Synlett* **2004**, 1711.
26. Cossy, J.; Mirguet, O.; Pardo, D.G.; Desmurs, J.-R. *Tetrahedron Lett.* **2001**, 42, 5705.
27. Cossy, J.; Mirguet, O.; Pardo, D. G.; Desmurs, J.-R. *Eur. J. Org. Chem.* **2002**, 3543.
28. Brown, D.; Brown, G. A.; Andrews, M.; Large, J. M.; Urban, D.; Butts, C. P.; Hales, N. J.; Gallagher, T. *J. Chem. Soc., Perkin Trans. 1* **2002**, *17*, 2014.
29. (a) Khlebnikov, A. F.; Novikov, M. S.; Amer, A. A. *Russ. Chem. Bull, Int. Ed.* **2004** *53*, 1092. (b) Khlebnikov, A. F.; Novikov, M. S.; Amer, A. A. *Tetrahedron Lett.* **2002**, *43*, 8523.
30. Beduerftig, S.; Wuensch, B. *Eur. J. Med. Chem.* **2006**, *41*, 387.
31. Fesenko, A. A.; Tullberg, M. L.; Shutalev, A. D. *Tetrahedron* **2009**, *65*, 2344.
32. Shinkevich, E. Yu.; Novikov, M. S.; Khlebnikov, A. F. *Synthesis* **2007**, 225.
33. Alves, M. J.; Fortes, A. G.; Costa, F. T.; Duarte, V. C. M. *Tetrahedron* **2007**, *63*, 11167.
34. Alves, M. J.; Gilchrist, T. L. *Tetrahedron Lett.* **1998**, *39*, 7579.
35. Ducray, R.; Cramer, N.; Ciufolini, M. A. *Tetrahedron Lett.* **2001**, 42, 9175.
36. Ducray, R; Ciufolini, M. A. *Angew. Chem. Int. Ed.* **2002**, *41*, 4688.
37. Davies, S. G.; Nicholson, R. L.; Price, P. D.; Roberts, P. M.; Smith, A. D. *Synlett* **2004**, 901.
38. Verhelst, S. H. L.; Martinez, B. P.; Timmer, M. S. M.; Lodder, G.; van der Marel, G. A.; Overkleeft, H. S.; van Boom, J. H. *J. Org. Chem.* **2003**, *68*, 9598.
39. (a) Bulanov, M. N.; Sosonyuk, S. E.; Zyk, N. V.; Zefirov, N. S. *Russ. J. Org. Chem. (Transl. Zhurn. Org. Khimii)* **2003**, *39*, 415. (b) Krow, G. R.; Gandla, D.; Guo, W.; Centafont, R. A.;

Lin, G.; DeBrosse, C.; Sonnet, P. E.; Ross III, C. W.; Ramjit, H. G. Carroll, P. G. Cannon, K. C. *J. Org. Chem.* **2008**, *73*, 2114.
40. Gayet, A.; Andersson, P. G. *Adv. Synth. Catal.* **2005**, *347*, 1242.
41. Carman, R. M.; Derbyshire, R. P. C. *Aust. J. Chem.* **2003**, *56*, 319.
42. (a) Timén, Å. S.; Somfai, P. *J. Org. Chem.* **2003**, *68*, 9958. (b) Timén, Å. S.; Fischer, A.; Somfai, P. *Chem. Commun.* **2003**, 1150.

Author's Biography

Dmytro O. Tymoshenko received his M.S. chemical engineering from the Ukrainian University of Chemical Engineering (UUCE) of Dnepropetrovsk, Ukraine. Later on, as a Scientist at the Department of Macromolecular Compounds of the UUCE, he received his Ph.D. in 1986, with a thesis focused on synthesis and properties of water soluble polymer careers for drug immobilization and transport. His tenure at UUCE included positions of Assistant Professor and Associate Professor, while his research was focused on various aspects of heterocyclic synthesis and synthesis on polymer supports. His postdoctoral experience was gained with Volodymyr Syromyatnikov at the National Taras Shevchenko University of Kiev, Ukraine, and Alan Katritzky at the University of Florida. In 2000, he joined Albany Molecular Research, Inc. in Albany, New York, as Senior Research Scientist, leading parallel synthetic chemistry research program and working in area of medicinal chemistry. His research interests include synthesis and reactivity of heterocycles, polymer supported reagents and their application in organic synthesis.

