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Recent advances in synthetic facets of immensely reactive azetidines

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1.

The synthetic chemistry of azetidine constitutes an important yet undeveloped research area, in spite of their ubiquity in natural products and importance in medicinal chemistry. Their aptness as amino acid surrogates along with their potential in peptidomimetic and nucleic acid chemistry is considered remarkable. Azetidines also possess important prospects in other settings such as catalytic processes including Henry, Suzuki, Sonogashira and Michael additions. They also represent an important class of strained compounds making them excellent candidates for ring-opening and expansion reactions. With this in mind, the present review article addresses the recent developments in synthetic strategies towards functionalized azetidines along with their versatility as heterocyclic synthons.

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Introduction

Azetidines constitute a vital class of aza-heterocyclic scaffolds with prevalence in diverse natural and synthetic products exhibiting a wide range of biological activities.¹ α -Amino azetidin-2-carboxylic acid is a proline antagonist in plant tissue



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worked extensively on the synthetic transformations of C-3 functionalized azetidin-2-ones leading towards the synthesis of functionally decorated heterocyclic compounds. He has also received the best poster presentation award in an international conference held at Punjab University, Chandigarh in 2011. He has published fourteen research papers in journals of international repute and is currently working as an Assistant Professor at Hindu College, Amritsar. His research interests include utilization of β -lactam synthon protocol for the preparation of functionally enriched heterocyclic scaffolds having biological relevance. He is also working on designing synthetic conjugates of medicinally active compounds to architect novel hybrid pharmacophores with higher potential and efficacy as compared to their analogues.

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characterization and crystal structure determination of amide based polydentate ligands and their complexes with different transition metals. During her doctoral work, she has published four research papers in journals of international repute. Her research interest includes the designing and synthesis of polydentate ligands along their complexes with different metals and characterized them with different spectroscopic techniques including X-ray crystallography. She is also working on designing synthetically medicinally active complexes, having high potential and efficacy against antimicrobial and antifungal activities.



Fig. 1 Azetidine based biologically active scaffolds.

cultures, exenta and melagatran act as thrombin inhibitors, while nicotianamine acts as a phytosiderophore, and mugineic acid and 2"-hydroxynicotianamine are ACE-inhibitors² (Fig. 1).

The modern mimicking approaches for recognition enhancement by biological receptors suffer from conformational constraints. Small size rings especially the azetidine framework, provide the necessary size for complementary receptor binding and achieving a high level of activity. The usefulness of azetidines as surrogates of natural amino-acids3a and as a tool in peptidomimetics^{3b} is highly commendable.^{3c-e} Their use as ligands in various catalytic processes including reductions, cycloadditions, cyclopropanation and C-C bond forming reactions is endowed with promising results.⁴ Moreover, azetidines belong to the class of strained compounds which makes them excellent candidates for nucleophilic ringopening or ring-expansion reactions yielding highly substituted acyclic amines or expanded ring systems. As a result, substituted azetidines have proven to be excellent synthons for rearrangements towards pyrroles, pyrrolidines, pyrrolidinones, imidazolidinones, isoxazolidines, piperidines, 1,2-oxazines, piperidin-2-ones, 2-iminopiperidines, azepanes and azepan-2-ones.⁵ The purpose of the present review is therefore to address the audience of synthetic chemists about the recent developments (2011-2016) in strategies for the preparation of this four-membered ring along with its role as

versatile synthon in heterocyclic chemistry. For the sake of convenience, the review article is divided into following sections and subsections:

• Intramolecular cyclization enroute to racemic-/enantio-/ diastereoselective access to azetidines.

• C-3 functionalized azetidines *via* β -lactam synthon approach.

- Nucleophilic ring opening of aziridines.
- Metal-catalyzed synthesis of azetidines.
- Synthesis of azetidines via organocatalysis.
- Miscellaneous syntheses.
- Azetidines as versatile synthons.

2. Synthetic approaches to functionalized azetidines

2.1 Intramolecular cyclization enroute to racemic-/enantio-/ diastereoselective access to azetidines

The selective introduction of fluorine, as a trifluoromethyl (CF_3) group strongly alters the biological and pharmacological properties such as pK_a , lipophilicity, toxicity and metabolic stability of bioactive compounds.6 The chemistry of 2-CF3-azetidines has largely remained unexplored both in terms of their synthesis and reactivity. De Kimpe et al.7 has developed protocol for the synthesis 1-alkyl-2-(trifluoromethyl)azetidines 5 starting from ethyl 4,4,4-trifluoroacetoacetate via imination, hydride reduction, chlorination and base-induced ring closure. Thus, the treatment of ethyl 4,4,4-trifluoroacetoacetate 1 with a primary amine in the presence of acetic acid yielded the enamine 2 which upon reduction with sodium borohydride afforded the corresponding 3-alkylamino-4,4,4-trifluorobutan-1-ol 3. Further, treatment of γ -amino alcohol 3 with thionyl chloride in dichloromethane resulted in isolation of N-alkyl-4-chloro-1,1,1-



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trifluorobutan-2-amine **4**. The intramolecular cyclization of **4** in the presence of LiHMDS in THF under refluxing for 4 h, resulted in the formation of 1-alkyl-2-(trifluoromethyl)azetidines **5** as depicted in Scheme **1**. The electron-withdrawing nature of trifluoromethyl substituent reduced the nucleophilicity of nitrogen atom, thus requiring a strong base (LiHMDS) to achieve this cyclization.

Fossey and co-workers⁸ have explored the iodocyclization of homoallyl amines enroute to functionalized 2-(iodomethyl) azetidine derivatives. The synthetic protocol involved the treatment of homoallyl amine **6** with three equivalents of iodine in acetonitrile in the presence of sodium hydrogen carbonate at room temperature resulting in the stereoselective synthesis of *cis*-azetidine 7 along with pyrrolidine **8** as depicted in Scheme 2. It was observed that the nature of substituent (electron releasing/withdrawing) affected the relative ratio of products *viz.* azetidine 7 and pyrrolidine **8** (Scheme 2).

De Kimpe and co-workers⁹ have utilized α -chloro- β -aminosulfinyl imidates **9** for the synthesis of enantiopure *trans*-2-aryl-3-chloroazetidines **13**. The key step involved the deprotection of α -chloro- β -aminosulfinyl imidates **9** with 4 N HCl in dioxane to afford the corresponding imidate hydrochloride **10** which underwent hydrolysis at 50 °C to yield ester **11**. Reduction of ester **11** using LAH in dry THF at low temperature yielded β chloro- γ -sulfonylamino alcohol **12** which underwent intramolecular cyclization under Mitsunobu conditions to afford *trans*-2-aryl-3-chloroazetidines **13** (Scheme 3).

Smith and co-workers¹⁰ have recently reported the synthesis of (*S*)-2-methylazetidine(*R*)-(-)-camphorsulfonate (CSA) from 1,3-butanediol. The synthetic protocol involved an initial mesylation of (*R*)-(-)-1,3-butanediol **14** to yield bis-mesylated product **15** which on treatment with benzylamine afforded the desired azetidine **16** in 53% yield with 95% ee. Recrystallization of (*R*)-(-)-CSA salt of azetidine **16** in ethyl acetate : dichloromethane mixture improved the enantiopurity from 95% to >99%. Subsequent hydrogenolysis of **16** afforded (*S*)-2-methylazetidine **17** as shown in Scheme 4.

Further, enantioenriched (*S*)-2-methylazetidine **17** was prepared through one-pot generation and cyclization of a bistriflate under different conditions. Best results in terms of yield was obtained *via* dropwise addition of Tf_2O to a premixed solution of (*R*)-1,3-butanediol **14** and Hunig's base at -35 °C followed by treatment with benzhydrylamine resulted in the formation of **18** which upon hydrogenolysis in the presence of palladium hydroxide to afford (*S*)-2-methylazetidine(*R*)-(–)-camphorsulfonate (CSA) **17** (Scheme 5).¹⁰

De Kimpe and co-workers¹¹ have developed thermal isomerization of aziridines for the synthesis of 3-bromoazetidine-3-



carboxylic acid derivatives. The key step involved the base promoted cyclization of dibromo amino esters 21 to yield the desired aziridines 22 and/or azetidines 23. Thermal isomerization of kinetically controlled product aziridine to azetidine was carried out by refluxing in DMSO at 70 °C. Further, treatment of 3-bromoazetidines 23 with different nucleophiles viz. potassium cyanide, potassium thiocyanate, sodium azide and potassium phenoxide in DMSO at 60 °C yielded the corresponding 3-cyano, 3-thiocyano, 3-azido and 3-phenoxy azetidine-3-carboxylic acid esters 24. These compounds are imperative in the preparation of libraries of bioactive compounds like bronchodilating and anti-inflammatory drugs¹² and antibacterial agents.13 Hydrolysis of ethyl 3-azidoazetidine-3-carboxylate 24 ($R^1 = Et$, $R^2 = t$ -Bu, *t*-pentyl, Nu = N₃) with 2 N NaOH solution at room temperature yielded the corresponding acid 25 which upon hydrogenolysis afforded 3-aminoazetidine-3-carboxylic acid 27. The hydrogenolysis of ethyl 3azidoazetidine-3-carboxylates 24 ($R^1 = Et, R^2 = t$ -Bu, Nu = N₃) with Pd/C yielded the corresponding 3-aminoazetidine-3carboxylate 26 (Scheme 6).11

The above methodology was further extended by De Kimpe and co-workers14 to afford a facile access to 1-t-butyl- and 1-(4methylbenzyl)-3-bromo-3-methylazetidines as shown in Scheme 7. The synthetic approach followed a sequence of synthetic events with the key step involving the thermal isomerisation of aziridine 30 in acetonitrile to afford 3-bromoazetidine 31 (Path A). Further, room temperature stirring of N-tbutylimine 32 with NaBH₄ selectively gave N-(t-butyl)-2,3dibromo-2-methylpropanamine 33 instead of azetidine derivative (Scheme 7, Path B). Refluxing of 33 in ethanol or methanol for 12 h yielded a mixture of thermodynamically preferred azetidines 34 and 35. The refluxing of 33 in a less nucleophilic solvent such as isopropanol afforded 3-bromoazetidine 34 as the sole product. Further treatment of imine 32 with LAH in diethyl ether gave 3-bromoazetidine 34 as the major product without the traces of corresponding aziridine (Scheme 7, Path C).



Scheme 6



The plausible mechanism for the formation of side product 3-alkoxyazetidines 35 might involve an initial intramolecular nucleophilic displacement in 34 to yield bicyclic aziridinium ion 36, which underwent alcoholysis (methanolysis or ethanolysis) (Scheme 8).

The synthetic potential of 3-bromo-substituted azetidines was further explored by its reaction with different nucleophiles resulting in the formation of C-3-substituted azetidines as depicted in Scheme 9.¹⁴

Szymoniak *et al.*¹⁵ have recently explored the stereoselective synthesis of *cis*-2,3-disubstituted azetidines through diastereoselective hydrozirconation. The synthetic approach involved the treatment of **37** with Schwartz reagent to yield the hydrozirconated intermediate which on reaction with iodine afforded iodocarbamate intermediate **38**. The base promoted intramolecular nucleophilic ring closure of intermediate **38** afforded enantiopure azetidine **39** as elucidated in Scheme **10**.

A range of substituents were explored leading to diastereoselective access of *cis*-2,3-disubstituted azetidine **42** in as depicted in Scheme $11.^{15}$

However the lack of diastereoselectivity was observed in case of **42d** and **42e** ($R^1 = i$ -Pr, Ph and $R^2 = Me$) could be attributed due to steric hinderance created by the bulky substituents. When ($R^1 =$ allylamine, $R^2 =$ Ph) dehydrozirconation turned out to be more favorable pathway and the reaction did not lead to iodonation/cyclisation product (Scheme 11).









Deprotection of 42f with TBAF and subsequent ruthenium

promoted oxidation led to cis-azetidin-2-carboxylic acid 43

which is a key constituent of a number of natural products and



De Kimpe and co-workers¹⁷ have utilized the zincated 3chloro-3-methyl-1-azaallylic anions 45 in stereoselective aldol condensation with aromatic aldehydes and subsequent mesylation to produce $syn-\alpha$ -chloro- β -mesyloxyketimines 49. This upon stereoselective reduction and cyclisation afforded 1,2,3,4tetrasubstituted 3-chloroazetidines 52 having three stereogenic centers as depicted in Scheme 13. The synthetic protocol involved the treatment of N-isopropyl-a-chloro imine 44a with lithium diisopropylamide in tetrahydrofuran at 0 °C to yield lithiated 3-chloro-3-methyl-1-azaallylic anion 45a, which on aldol condensation with arylaldehyde 46 at 0 °C resulted in a mixture of syn-α-chloro-β-hydroxyketimine 47a as major product along with the corresponding cis- and trans-imidoylepoxides 48a as the side products. The transmetalation of the lithiated anion with ZnCl₂ at 0 °C, resulted in zincated 3-chloro-3-methyl-1-azaallylic anion 45a, which proved to be beneficial as it led to slight improvement in the diastereoselectivity of the aldol reaction with benzaldehyde and afforded only smaller



Scheme 13

their derivatives (Scheme 12).2,16

amounts of the epoxide 48a. Further lowering the reaction temperature to -78 °C led to the vast improvement in *syn*-diastereoselectivity of aldol reaction. Nevertheless, it was not possible to effectively separate the syn-α-chloro-β-hydroxyketimine 47a from its anti-adduct via crystallization due to the occurrence of concomitant retro-aldol reaction. However during workup, almost all of the zincated anti-adduct got converted into syn isomer. Subsequent treatment of 47a with mesyl chloride in pyridine yielded the corresponding syn- α -chloro- β mesyloxyketimines 49a in 80% yield along with a-chloro-amethanesulfonylketimines 50a isolated as a by product in low yield (Path B). The stereoselective reduction of β -mesyloxyketimines 49 with NaCNBH₃ resulted in the formation of β chloro- γ -mesyloxypropylamines 51 which upon heating in DMSO followed by base-induced cyclization, stereoselectively generated 1,2,3,4-tetrasubstituted 3-chloroazetidines 52.

Makowski *et al.*¹⁸ have developed a convenient access to spiro-azetidine-piperidine ring system *via* reaction of piperidine chloroaldehyde with chiral amines. Initial attempts involving heating of **53** with chiral amines in the presence of base afforded the uncyclized reductive amination chloroamine product **55**. The treatment of **53** with chiral amine **54** in AcOH and methanol at 50 °C, however yielded the corresponding imine which subsequently was cyclized in the presence of NaCNBH₃ affording chiral azetidine-piperidines **56** as depicted in Scheme **14**.

Lindsley and co-workers19 have devised an enantioselective synthesis of C2-functionalized azetidines from β-chloroalcohol. The methodology involved the initial activation of β-chloro alcohol 57 as triflate with subsequent displacement of triflate ion with cyanide in presence of 18-crown-6 to afford β-chloronitrile 58. The synthesized β -chloronitrile 58 was reduced with indium(m)chloride-sodium borohydride with simultaneously achievement of 4-exo-tet cyclization in the presence of KOH/THF to afford the desired azetidine 60 without the isolation of γ chloroamine 59. It has been found that the reduction of β chloronitrile 58 to γ -chloroamine 59 was achieved using indium(m)chloride-sodium borohydride. Different reaction conditions (K₂CO₃ in NMP, NaH in DMF, LHMDS in DMF and K_2CO_3 in DMF) were attempted for 4-exo-tet cyclization of γ chloroamine 59 but it led to olefin 61 along with small quantities of desired azetidine 60 as depicted in Scheme 15.



Voss and co-workers²⁰ described the synthesis of C-2substituted azetidines by using chiral *tert*-butanesulfinamide as auxiliary to achieve high levels of stereoselectivity. The synthetic methodology involved Reformatsky reaction of sulfinimines **62** yielding **63** followed by LAH promoted reduction to yield corresponding alcohol **64**. The treatment of **64** with Tsunoda reagent in toluene at 110 °C resulted in the formation of C-2-substituted azetidines **65** as depicted in Scheme 16.

Brigaud et al.21 have recently developed a route for the synthesis of enantiopure *a*-trifluoromethylated azetidine-2carboxylic acid from chiral oxazolidine. The synthetic methodology involved the condensation reaction of ethyl trifluoroacetoacetate 66 with (R)-phenylglycinol 67 to yield the oxazolidine 68 as a single diastereomer. This on selective reduction with NaBH₄/CaCl₂ (ref. 22) in a freshly distilled ethanol/THF (2:1) solution resulted in desired alcohol 69 without any degradation of the oxazolidine moiety (Scheme 17). The alcohol 69 was converted to corresponding iodo derivative 70 which upon NaH promoted cyclization in refluxing THF afforded bicyclic trifluoromethylated oxazolidine 71. The synthesized oxazolidine 71 was subjected to Strecker-type reaction using TMSCN to afford C-2 substituted azetidine as a diastereomeric mixture of 72 and 73. Sodium hydroxide promoted hydrolysis of 72/73 yielded the α-trifluoromethylated azetidine-2-carboxylic acids viz. 74 and 75 repectively (Scheme 17).





Polyhydroxylated nitrogen containing compounds popularly known as iminosugars are well known glycosidase inhibitors.^{23,24} Shinde et al.²⁵ have developed a convenient methodology for the synthesis of azetidine iminosugars and 3-hydroxy-N-methylazetidine-2-carboxylic acid from D-glucose using intramolecular Mitsunobu reaction. The synthetic methodology involved the treatment of azido aldehyde 76 with sodium borohydride in aqueous methanol at 0 °C to afford the corresponding azido alcohol 77. The reduction of C3-azido functionality was achieved by using 10% Pd/C in methanol to afford the corresponding amine, which on protection with benzyl chloroformate (CbzCl) resulted in carbamate derivative 78. Further, reaction of 78 with triphenylphosphine and diethyl azodicarboxylate (DEAD) under Mitsunobu condition yielded cyclic azetidine intermediate 79. Deprotection of 1,2-acetonide group of 79 with the Dowex (H^+) resin gave anomeric mixture of hemiacetals 80 which on treatment with sodium borohydride in THF/H₂O generated N-Cbz protected triol 81. Hydrogenolysis of 81 using 10% Pd/C in methanol afforded (2S,3R)-2-((R)-1,2dihydroxyethyl)azetidin-3-ol 82. Synthesized hemiacetal 80 also underwent oxidative cleavage with sodium metaperiodate, to yield the corresponding dialdehyde 83. This upon reduction with sodium borohydride in methanol afforded N-Cbz protected diol 84 which upon hydrogenolysis using 10% Pd/C in methanol yielded (2R,3R)-2-(hydroxymethyl)azetidin-3-ol 86. The hemiacetal 80 upon treatment with sodium metaperiodate, followed by the Pinnick oxidation²⁶ using sodium chlorite and hydrogen peroxide afforded N-Cbz protected acid 85 which on subsequent hydrogenolysis vielded (2S,3R)-3-hydroxy-N-methylated azetidine-2-carboxylic acid 87 (Scheme 18).

Reddy *et al.*²⁷ have developed a synthetic methodology for the stereoselective synthesis of azetidine analogue of natural product penaresidin A. Key step involved the treatment of 3,4,6-tri-*O*-benzyl-D-galactal **88** with HgSO₄ in the presence of H₂SO₄ afforded the hydroxy-*trans*-enal which upon chemoselective reduction with CeCl₃·7H₂O/NaBH₄ yielded the allyl alcohol **89**. Sharpless epoxidation of **89** with subsequent ring opening using

Red-Al generated triol 90. The triol 90 was protected with 2,2-DMP to yield 1,3-acetonide 91. Mesylation of 91 with subsequent treatment with NaN₃ led to azide 92. The reduction of azide 92 with LAH and subsequent tosylation yielded tosyl intermediate 93. Removal of acetonide group of 93 was carried out with p-TSA in methanol while subsequent protection of primary hydroxyl group with tert-butyldiphenylsilyl chloride afforded the TBDPS ether intermediate 94. This upon a sequence of mesylation and cyclization afforded 95. Desilylation of 95 with TBAF followed by oxidation of the hydroxyl group with IBX in DMSO yielded the corresponding aldehyde Julia–Kocienski olefination of 96 with sulfone fragment 97 in presence of KHDMS afforded olefin 98. Further, desiylation of 98 with p-TSA led to the formation of 99. The utilization of 99 in the formation of penaresidin A 100 was achieved via its reduction with 10% Pd/C followed by treatment with Na/ naphthalene (Scheme 19).

Fleet and co-workers²⁸ have developed a route for the synthesis of azetidine analogues of mannosidase inhibitor swainsonine and 1,4-dideoxy-1,4-imino-p-mannitol (DIM) through bicyclic azetidine. The methodology involved the protection of *D*-altrose 101 with acetone in the presence of sulfuric acid and anhydrous copper(n)sulfate to yield an inseparable mixture of pyranose 102 and furanose 103 diacetonides. Further, selective hydrolysis of the side chain acetonide of 103 was achieved with acetic acid resulting in monoacetonide 104 along with pure pyranose diacetonide 102. Further, treatment of 104 with TBDMS chloride in the presence of imidazole yielded the silvl ether 105 while the remaining two hydroxyl groups underwent esterification with triflic anhydride to afford the ditriflate 106. Reaction of 106 with benzylamine resulted in the formation of bicyclic azetidine intermediate 107. Further, hydrolysis of 107 with aqueous trifluoroacetic acid resulted in the 108 which upon reduction with sodium borohydride in water, yielded N-benzylazetidine 109. Hydrogenation of 109 with ammonium formate in the presence of palladium on



carbon yielded the desired azetidine analogue of DIM (1,4dideoxy-1,4-imino-p-mannitol) **110** as depicted in Scheme 20.

2.2 C-3 functionalized azetidines via β -lactam synthon approach

 β -Lactam antibiotics is generally recognized as a cornerstone of human health care due to the unparalleled clinical efficacy and



Scheme 20

safety of this type of antibacterials.²⁹ Besides their biological relevance, the stereocontrolled transformation of β -lactam ring provides efficient access to a variety of non-protein amino acids, functionalized piperazines, 1,4-diazepanes, quinolones, isoquinolones, isoquinolines, enantiopure succinimides, oligopeptidomimetics biologically peptides, and relevant heterocycles, such as indolizidines, paclitaxel, docetaxel, taxoids, cryptophycins, lankacidins. Such transformation is popularly known as β-lactam-synthon protocol.^{30,31} Reduction of β-lactams (azetidin-2-ones) with DIBAL-H and chloroalanes is considered as one of the most convenient approach for the chemoselective synthesis of azetidines.32 However, the presence of a Lewis acid and alanes could result in the ring opening of the strained four membered ring. The effect is generally more pronounced with electron rich phenyl group substituents on azetidine nucleus. Kumar et al.33 have recently developed a protocol for the diastereoselective synthesis of 2,3-disubstituted 1-arylazetidines via NaBH4 promoted reduction of C-3 functionalized azetidin-2-ones. The synthetic protocol involved the treatment of azetidin-2-ones 111 with sodium borohydride in isopropanol to afford the diastereoselective formation of trans-azetidines 112 (Scheme 21).33

The developed protocol was further extended towards the synthesis of a series of C-3 azido/amino azetidines as depicted in Scheme 22.³³

2.3 Nucleophilic ring opening of aziridines

The thermodynamically controlled rearrangement of aziridine to azetidine has very few precedents in the chemical literature and hence provides a window of opportunities for the selective synthesis of 3-substituted azetidines. De Kimpe *et al.*³⁴ explored the intrinsic reactivity of 2-bromomethyl-2-methylaziridines **117** to ring enlargement in different solvents with a variety of nucleophiles such as thiocyanate, cyanide, phenoxide and acetate in order to assess the scope of the developed transformation (Scheme 23).³⁴

Ukaji and co-workers³⁵ have recently developed the route for the synthesis of four-membered heterocyclic azetidines *via* [3 + 1] cycloaddition reaction of azomethine ylide with aromatic isocyanides. The key step of reaction involved the treatment of



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azridine **120** having dicarboxylate moiety with aromatic isocyanide **121** in the presence of $Y(OTf)_3$ to afford azetidine derivatives **122/123** in good yields as depicted in Scheme 24. It has been found that the aliphatic isocyanides could not initiate the reaction due to its low reactivity. Aromatic isocyanides, irrespective of electron-withdrawing or donating substituents led to the formation of desired four membered heterocycle in reasonably good yields.

Mechanistically, it has been found that $Y(OTf)_3$, coordinated with the oxygen atom of dicarboxylate moiety **120**, to generate complexed intermediate **I** which undergoes C–C bond cleavage to afford the corresponding azomethine ylide **II**. The Ugi-type nucleophilic attack of the isocyanide **121** generated the nitrilium intermediate **III** which subsequently underwent internal trapping by α -anion of the azomethine ylide resulting in the formation of azetidine derivatives **122** as shown in Scheme 25.

2.4 Metal-catalyzed synthesis of azetidines

Zhang *et al.*³⁶ have recently reported the synthesis of chiral azetidine using Pd-catalyzed asymmetric allylation of



azalactones **124** with 4-styryl-1,3-dioxolan-2-one **125** via **127** as intermediate. Different ligands, additives and solvents were attempted to increase the yield and enantioselectivity of **127** but the best results were obtained when reaction was carried out in presence of ligand **126** and NaBAr_F as additive. The acetylation of **127** with Ac₂O afforded **128** which underwent Pd-catalyzed allylic amination resulting in the enantioselective formation of azetidine **129** as depicted in Scheme 26.



Scheme 26

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Schafer *et al.*³⁷ have utilized tantalum catalyzed hydroaminoalkylation reaction for the synthesis of azetidines. The protocol involved hydroaminoalkylation reaction of between **130** with **131** in presence of tantalum catalyst **132** to form an intermediate intermediate **133** which underwent cyclization in presence of TsF and DBU at 130 °C to afford the corresponding azetidine **134** as shown in Scheme 27.

Ferrocene has drawn the attention of chemists due to its various applications in organic synthesis^{38,39} and asymmetric catalysis.⁴⁰ Mandal and co-workers⁴¹ have developed a protocol for the diastereoselective synthesis of ferrocenyl azetidinimines *via* copper catalyzed alkyne–azide cascade reaction as shown in Scheme 28. The synthetic approach involved the cascade reaction of ferrocenylimine **135**, *p*-toluenesulfonyl azide **136** and substituted acetylene **137** yielding the ferrocenyl azetidinimines **138**. Best result in terms of yields was obtained using 10% CuI (catalyst) or with 1.5 equiv. of Et₃N at ambient temperatures.

Mechanistically the alkyne 137 reacted with sulfonyl azide 136 to afford intermediate 139 which could follow two different pathways leading to azetidinimine 138. Nitrogen extrusion of intermediate 139 generated ring opened intermediate 140 which upon protonation afforded ketenimine intermediate 142 (Path A). Alternatively intermediate 139 could result in the intermediate 141 which on protonation and nitrogen extrusion led to the formation of ketenimine 135 led to the diastereoselective synthesis of ferrocenyl substituted azetidinimine 106 (Scheme 29).⁴¹





Scheme 28



Hu *et al.*⁴² has developed an efficient method for the synthesis of disulfide-linked *N*-sulfonylazetidin-2-imines. The synthetic methodology involved the multicomponent reaction between different sulfonyl azides **143**, phenylacetylenes **144** and benzenethiol Schiff bases **145** in presence of CuI and Et₃N at 0 °C as depicted in Scheme 30. The reaction was optimised in different bases and solvents but best results were obtained using Et₃N as base and THF as solvent. The presence of electron donating substituents, both on sulfonyl azides **143** and Schiff bases **145** led to the formation of corresponding azetidines **146** in good yields.

Mechanistically, sulfonyl azide 143 reacted with the alkyne 144 in the presence of CuI to afforded intermediate IV which on protonation gave the ketenimine V. Meanwhile, in presence of trace amounts of I₂, the intermolecular dimerization of benzenethiol Schiff base 145 was achieved to generate intermediate VI. Further, [2 + 2] cycloaddition reaction of V with iminic component VI afforded the desired azetidinimine 146 (Scheme 31).⁴²

2.5 Synthesis of azetidines via organocatalysis

Yadav and co-workers⁴³ have utilized [2 + 2] annulation of aldehydes with aldimines for stereoselective synthesis of





azetidin-2-ols. The key step in the synthesis involved the treatment of aldehyde **147** with pyrrolidine based catalysts **148** to afford chiral enamine intermediate **149** which upon [2 + 2]annulation reaction with aldimines **150** in presence of K₂CO₃ resulted in the diastereoselective synthesis of corresponding azetidin-2-ols **151** as depicted in Scheme 32. The reaction was optimized with substituted pyrrolidine based catalysts and bases *viz.* DBU, DABCO, Et₃N and NaHCO₃. Best results in terms of yields were obtained using **116** as the catalyst and K₂CO₃ as base.

Mechanistically it was found that the catalyst diphenylprolinol trimethylsilyl ether **148** activated the aldehyde **147**, generating the corresponding enamine **149**. Stereoselectively reaction of **149** with aldimine **150** yielded the intermediate **152**. Hydration of **152** afforded another intermediate **153**, which underwent intramolecular cyclization to give the desired azetidin-2-ols **151** depicted in Scheme **33**.⁴³

Sasai and co-workers⁴⁴ have developed an enantioselective synthesis of azetidines **156** using aza-Morita–Baylis–Hillman (MBH) reaction of ketimines **154** and allenoate **155** in the presence of organocatalyst. The reaction was optimized using range of chiral amines as organocatalysts with the best results in terms of yields were obtained using β -isocupreidine (β -ICD) as catalyst in the presence of MS 3 Å. Azetidine **156** was reduced using DIBAL-H affording allylalcohol **157** while Suzuki Miyaura cross-coupling of **156** with phenylboronic acid afforded the corresponding biphenyl azetidine **158** as depicted in Scheme 34.

Synthetic approaches towards optically active polysubstituted azetidines demands greater exploration as compared to aziridines, pyrrolidines and piperidines. Kaufman *et al.*⁴⁵ have developed on organocatalytic approach for the synthesis of optically pure 1,2,3-trisubstituted azetidines. The synthetic protocol involved sequence of synthetic steps as shown in Scheme 35, the key step being L-proline catalysed condensation reaction of substituted aldehydes **159** with substituted anilines **160** to yield Schiff bases **161**. The reaction of **161** with aldehyde **162** in presence of NMP at -20 °C afforded intermediate **163** which upon reduction with NaBH₄ in MeOH led to the corresponding γ -aminoalcohols **164**. Microwave promoted intramolecular cyclization of **164** in presence of tosyl chloride led to the enantioselective synthesis of 1,2,3-





trisubstituted azetidines **165**. The steric as well as electronic nature of substituents both on aldehyde and amine has a profound role on the outcome of the reaction. The presence of substituent *ortho* to the formyl moiety resulted in intermediate imine **161** but failed to form the desired azetidine **165**. 2-Phenylaniline failed to react while the reaction with α -naphthylamine and 2-methoxyaniline furnished the corresponding Schiff bases, but failed to form the desired product (Scheme 35).

2.6 Miscellaneous syntheses

Blanc and co-workers⁴⁶ have reported the synthesis of α -carbonylated *N*-sulfonylazetidines *via* ring contraction of α -bromo *N*-sulfonylpyrrolidinones (Scheme 36). The synthetic methodology involved the ring contraction of α -bromo *N*-sulfonylpyrrolidinone **166** with K₂CO₃ in presence of acetonitrile : methanol (9 : 1) to yield the α -carbonylated *N*-sulfonylazetidine **167** exclusively. A variety of bases and solvents were tried and the best results in terms of yields were obtained using K₂CO₃ as base. Interestingly, no conversion was observed in the absence of base (Scheme 37).

Xu and co-workers⁴⁷ have described the synthesis of C-4 substituted azetidines *via* TiCl₄ promoted [3 + 3] cycloaddition reaction. The synthetic methodology involved the treatment of cyclopropane 1,1-diesters **170** with alkyl azide **169** in presence of catalytic amount of TiCl₄ in hexafluoro-2-propanol (HFIP), resulting in the synthesis of substituted triazines **171**. The presence of electron withdrawing as well as electron donating substituent in cyclopropane 1,1-diesters **170** gave corresponding triazines **171** in good yields. The synthesized triazine **171**





was subsequently refluxed in xylene to afford the corresponding C-4 substituted azetidines 172 in good yields (Scheme 37).

Mechanistically, it was found that TiCl₄, promoted the ringopening of cyclopropane **170** to afford **1**,3-zwitterionic intermediate **VII** which underwent nucleophilic addition of an azide **169** to yield another zwitterionic intermediate **VIII** with subsequent intramolecular ring closure to afford the triazine **171**. Refluxing of **171** in xylene generated intermediate **IX** which upon intramolecular cyclization and nitrogen extrusion yielded desired azetidine **172** as depicted in Scheme 38.⁴⁷

Santini and co-workers⁴⁸ reduced the 3-oxo-azetidine **176** into corresponding alcohol in the presence of Zn/Cu couple⁴⁹ which was subsequently utilized in spirocyclization. The synthetic methodology involved the reduction of 3-oxoazetidine **173** with propargyl bromide in the presence of Zn/ Cu couple resulting into azetidine **174**. The treatment of azetidine **174** with catalytic amount of Au(PPh₃)(NTf₂) in presence of 3,5-dichloropyridine *N*-oxide and methanesulfonic acid resulted in the synthesis of spiro-3-furanone **175** which underwent LDA-promoted enolization to afford enol triflate **176** (Scheme 39).

Lewis base catalyzed⁵⁰ nucleophilic activation of allenoates has experienced a great expansion over the past few decades.⁵¹ Ma *et al.*⁵² introduced Lewis bases promoted [2 + 2] annulation reaction of allenoates and cyclic ketimines for the synthesis of fused azetidines in good yields. The synthetic protocol involved DABCO catalysed [2 + 2] annulation reaction of ethyl 2,3-butadienoate 177 with cyclic ketimine 178 in presence of 1,4-dioxane to afford the azetidine derivatives 179 in good yields (Scheme 40). It has been found that ketimine 178 having electron-withdrawing groups at 5th and/or 6th-position of the









aromatic ring afforded the cycloadducts **179** in high yields whereas ketimine bearing electron-donating groups at 6thposition of the aromatic ring gave products **179** in moderate to good yields. A decrease in yield was observed with the introduction of a free NH group. The conversion of trifluoromethyl to difluoromethyl or phenyl group also resulted in the decrease in yields, confirming the role of CF_3 -group in the [2 + 2] annulation reaction (Scheme 40).

The plausible mechanism involved an intial addition of DABCO to the electrophilic β carbon of ethyl 2,3-butadienoate 177 to form the zwitterionic intermediate **X** which reacts with ketimine 178 through γ addition to give the intermediate **XI**. This upon intramolecular nucleophilic addition led to the formation of intermediate **XII**, which *via* subsequent catalyst elimination yielded fused azetidine 179 (Scheme 41).⁵²

Azetidines as versatile synthons

Azetidines played an important role in medicinal chemistry programs.⁵³ In recent years, ring transformations of azetidines has been exploited widely through nucleophilic ring-opening, cycloaddition, and rearrangement reactions which makes them highly valuable in organic synthesis.⁵⁴

Piperidin-4-ones represent an important class of bioactive heterocycles due to their observed biological and pharmaceutical properties along with their use as intermediates in the synthesis of a variety of biologically active compounds such as functionalized piperidines through the reduction of the carbonyl moiety. De Kimpe et al.55 have recently explored the synthesis of functionalized piperidin-4-ones via ring expansionoxidation of corresponding azetidines. The key step in the synthesis involved the treatment of cis-2-(2-bromo-1,1dimethylethyl)azetidines 180a-e with silver salt in DMSO at 100 °C for 18 h to afford the corresponding 5,5dimethylpiperidin-4-one 181a-e. It has been found that same reaction when carried out with K2CO3 in DMSO did not result in the desired conversion and complex reaction mixtures were obtained. cis-2-(2-Mesyloxyethyl)azetidines 180f-h, however underwent similar ring expansion-oxidation in presence of K₂CO₃ and DMSO resulting in the synthesis of desired piperidin-4-ones 181f-h in good yields (Scheme 42).

Mechanistically, it was suggested that azetidine **180** was transformed into reactive bicyclic azetidinium salts **XIV** through intramolecular nucleophilic displacement with subsequently conversion into piperidine intermediate **XV** *via* ring enlargement with dimethylsulfoxide. The abstraction of acidic proton at the oxygenated carbon atom resulted in the liberation of dimethylsulfide *via* α -elimination affording the formation of corresponding piperidin-4-ones **181** (Scheme 43).⁵⁵

Couty and co-workers⁵⁶ have reported BTC (bistrichloromethylcarbonate, triphosgene) promoted selective bond cleavage of azetidine resulting in the formation of five or six membered urea. The synthetic protocol involved regioselective C-2 cleavage of azetidine **182** with BTC to afford **183** and **184** in ratio of 1 : 2. The reaction of **183** and **184** with benzylamine afforded the mixture of regioisomeric ureas **185** and **186**, which underwent base promoted intramolecular ring closure to yield the pyrimidin-2-ones **187** (Scheme 44).

Further extension of the above protocol to azetidine **188** led to the formation of imidazolidin-2-one **193** as the major product





Scheme 42



along with formation of tetrahydropyrimidin-2-one 194, as the minor product as illustrated in Scheme 45.56

The above protocol, when attempted with trisubstituted azetidines viz. 195 or 196 did not result in any conversion due to its high sensitivity towards steric crowding around the nitrogen atom (Scheme 46).56

The treatment of N-benzhydryl azetidine 197 with BTC however, resulted in the isolation of a mixture of carbamoyl



Scheme 45



chloride 198 and ring opened product 199 in ratio 7 : 3. Further, N-benzhydryl 2-cyano azetidine 200 or trisubstituted N-benzhydrylazetidine 201 were found to be completely inert due to steric crowding around the nitrogen atom (Scheme 47).56

Finally, the reaction of BTC with encumbered trisubstituted azetidines 202 and 207 having N-methyl substituent was carried out. Compound 202 having cis-configuration reacted rapidly to give good yield of ring-opened regioisomer 203 while the reaction with 207 having trans-configuration gave mixture of compounds, 208-210. Further, treatment of 204 with NaH in THF resulted in the synthesis of tetrahydropyrimidinones, 205 and 206 as a 6 : 4 epimeric mixture (Scheme 48).56

Compain and co-workers⁵⁷ have developed the route for the synthesis of spirocyclopropyl y-lactams via tandem intramolecular azetidine ring-opening/closing cascade reaction. The key step involved the SN²-type ring-opening of TMSOTfactivated azetidine ring by silyl ketene acetals. Thus, the treatment of azetidine 211 with 2 equiv. of TMSOTf in the presence of 2.5 equiv. of TEA in dichloromethane resulted in the





formation of spirocyclopropyl- γ -lactam **212** in highly regio and stereoselective manner. Further reduction of the ester group with superhydride resulted into primary alcohol **213** while pyrrolidine analogue **214** was achieved by using LAH. The pyrrolidine analogue, **213** was efficiently converted to corresponding bromide **215** by using PPh₃/Br₂ and pyridine (Scheme 49).

Mechanistically SN²-type ring-opening¹,^{58,59} of azetidine **211** with silyl ketene acetal, generated by treatment with TMSOTf and TEA,⁶⁰ resulted in amino ester **A** which underwent intramolecular cyclization to afford the five membered lactam **212** as depicted in Scheme 50.

King *et al.*⁶¹ have recently explored triflic acid promoted conversion of *N*-cinnamoyl azetidine **216** into fused tricyclic product **217** having biological relevance (Scheme 51).

Couty and co-workers⁶² have utilized [1,2] Meisenheimer rearrangement of functionalized azetidines to isoxazolidines without trapping of the transient *N*-oxide. It was found that with an unsubstituted azetidine, the rearrangement took place very efficiently and the ring cleavage was highly regioselective when an ester or nitrile was present at C-2 position. The treatment of azetidine **218** with hydrogen peroxide in the presence of Na₂-WO₄·2H₂O resulted in the formation of *N*-benzhydryl isoxazolidine **219**. The nitrile substituted azetidine **220** under basic condition led to the synthesis of isoxazolidinyl amide **221**. Further, the reaction of azetidine **220** and **223** with *m*-CPBA in







Scheme 50



presence of Na_2CO_3 yielded 2-benzyl-isoxazolidine-5carbonitrile **222** and 2-benzyl-isoxazolidine-5-carboxylic acid ethyl ester **224**, respectively (Scheme 52).⁶²

The exposure of diastereomeric azetidines **225** and **228** under similar conditions led to epimeric mixture of products. Thus, the treatment of azetidine **225** with *m*-CPBA in presence of Na_2CO_3 resulted in the synthesis of isoxazolidines **226** and **227** in ratio 3 : 1, while azetidine **228** gave isoxazolidines **229** and **230** in ratio 7 : 1 as depicted in Scheme 53.⁶²

The degree of epimerization was found to depend on the nature of the substituent *viz.* nitrile or ester at C-2 position while no epimerization was observed with N-Bn analogue



Scheme 53

azetidine ester **231**. Furthermore, the nature of substituent on nitrogen also play a crucial role, since extensive epimerization was observed in case of *N*-Me azetidine **234**. Moreover, it was found that when *N*-oxide has *cis* relationship to the 4-methyl substituent, Cope elimination took place to yield hydroxylamine **233** and **236** along with isoxazolidines, **232** and **235** respectively (Scheme 54).⁶²

Zhang *et al.*⁶³ have recently developed the route for the chiral synthesis of dihydrothiazoles and dihydro-oxazoles in a regioand stereoselective manner *via* ring opening of azetidines. The synthetic protocol involved the treatment of 3-amino-4-arylazetidine **239** with isothiocyanates **240** in DCM at ambient temperature resulting in the synthesis of dihydrothiazoles **241** without the formation of corresponding thiourea. The reaction was carried out under different conditions but best results in term of yields were obtained in dichloromethane (Scheme 55).

Mechanistically, the reaction was thought to proceed *via* the formation of thiourea as an intermediate which underwent intramolecular cyclization to afford corresponding dihydrothiazoles **241** as depicted in Scheme $56.^{63}$

When 3-amino-4-aryl-azetidines 239 was treated with isocyanates 245 in dichloromethane at ambient temperature overnight, ureas 246 were the exclusive products without the isolation of corresponding dihydrooxazole 247 due to less nucleophilicity of oxygen than that of sulfur. The refluxing of 246 in dichloroethane in the presence of TFA, afforded the corresponding dihydrooxazole 247 as depicted in Scheme 57.⁶³

The pyrrole ring is one of the basic heteroaromatic motifs in numerous biologically active alkaloids, pharmaceutical products, or even in conducting polymers.⁶⁴ 2,4-Disubstituted





Scheme 55





pyrroles are useful intermediates for the synthesis of highly substituted pharmacologically relevant scaffolds.⁶⁵ There are a plethora of methods such as the classical Hantzsch, Knorr, and Paal–Knorr reactions, and metal-based or 1,3-dipolar cycloadditions strategies⁶⁶ for the synthesis of pyrroles. Zard *et al.*⁶⁷ have developed a protocol for the synthesis of functionalized pyrroles having protected aminomethyl group at C-4 position *via* ring opening of Boc-protected azetidine. The treatment of Boc protected azetidine **248** with a range of primary amines or ammonia in presence of *p*-TsOH in hot dioxane furnished the corresponding pyrroles **249** as depicted in Scheme 58.

Mechanistically, the aminolysis of azetidine **248** resulted in the formation of thiol **250**, which underwent ring-opening to generate thioaldehyde **252**. The intramolecular condensation of amine with both the reactive thioaldehyde and the ketone afforded the desired pyrroles **249** (Scheme 59).⁶⁷

The synthesis of α -trifluoromethylated peptides, is still a challenging task⁶⁸ due to steric hindrance and low nucleophilicity of the nitrogen atom. Stringent reaction conditions are required for the introduction of these amino acids into peptides. Brigaud and his co-workers have developed a convenient method for the syntheses of new enantiomerically pure nonproteogenic quaternary amino acid, α -Tfm-homoserines. The methodology involved the acidic hydrolysis of azetidine-2-



carbonitriles viz. 72 and 73 resulting in concomitant hydrolysis of nitrile along with the removal of the phenylethanol (Scheme 60).21

Azumaya et al.69 have recently explored the acid promoted aza-Claisen rearrangement of N-aryl-2-vinylazetidines into corresponding tetrahydrobenzazocines, which being unstable gets isomerized to vinyltetrahydroquinolines. The synthetic protocol involved the treatment of N-aryl-2-vinylazetidines 255 with different acids (H₂SO₄, TfOH and CF₃COOH) in presence of different solvents (DCE, DCM and toluene) resulting in a mixture of tetrahydrobenzazocines 256 and 3-vinyl-1,2,3,4tetrahydroquinolines 257 (Scheme 61).69

Many attempts were made to improve the yield of tetrahydrobenzazocines 256 and the best results were achieved via stirring at 0 °C with subsequent stirring for 3 h at room temperature in presence of H₂SO₄ (Scheme 62).⁶⁹



Scheme 60

hydrogenation to afford hexahydrobenzazocine 258 or by protection of amino group through acylation to yield the acetvlated benzazocine derivatives 259 (Scheme 63).69

The treatment of 256 with silica gel gave 6,7-dimethoxy-3vinyl-1,2,3,4-tetrahydroquinoline 257 in 81% yield. It was found that ring-contraction reaction was dramatically accelerated in the presence of formaldehyde. Thus, the treatment of 256 with formaldehyde in presence of triflic acid at temperature yielded 6,7-dimethoxy-3-vinyl-1,2,3,4room tetrahydroquinoline 257 in 76% yield (Scheme 64).69

Couty and co-workers⁷⁰ have utilized azetidinium triflate in a one-pot two-steps sequence to generate azetidinium ylides 261 with subsequent regioselective Hofmann elimination to yield acrylonitrile 262 which was utilized in DBU-catalyzed conjugate



NHTs

OR

Ph



addition of amines yielding 4-amino-2-aminomethylbutyronitriles **263–265**. The synthetic methodology involved the treatment of azetidinium ion **260** with LiHMDS in THF at -78 °C with subsequent methylation resulting in the synthesis of acrylonitrile **261** which underwent ring opening to yield alkene **262**. It has been found that 3 equiv. of base and 3 equiv. of methyl iodide resulted in good yields of alkene **262**. DBU catalyzed conjugate addition of secondary amines to acrylonitrile **262** gave good yields of diamines **263–265**, having fair levels of diastereoselectivity (Scheme 65).

Further, the conjugate addition of azetidinium ylide derived from **260** on **266** yielded the C2 symmetrical cyclopropanes **267** in good yield as depicted in Scheme 66.⁷⁰

Bhattacharya and co-workers⁷¹ have developed a route for synthesis of enantiopure γ -amino ethers *via* copper(II)triflatecatalyzed ring-opening of chiral azetidines with alcohols. The synthetic methodology involved the ring-opening of enantiopure (*S*)-2-phenyl-*N*-tosylazetidine **268** with different alcohols in the presence of catalytic amount of Lewis acid and stoichiometric amount of quaternary ammonium salt at 0 °C to afford γ amino ethers **269** (Scheme 67).



Scheme 65





30 mol % Cu(OTf)₂

1.0 eq, TBAHS

ROH. 0 ^OC

Ts

The methodology was further extended towards methanol promoted ring-opening of enantiopure *cis-* and *trans-*2,4-disubstituted azetidines **270–273** affording the corresponding 1,3-amino ethers **274–277**. The ring-opening of enantiomerically pure *trans-*(2*R*,4*S*)-2-allyl-4-phenyl-*N*-tosyl-azetidine **272** afforded amino ether **276** as the major diastereomer having *syn* configuration, whereas *cis-***273** afforded amino ether **277** having *anti* configuration as the major product as depicted in Scheme 68.⁷¹

The ring-opening of **268** with 3-chloropropanol in the presence of 40 mol% of Cu(OTf)₂ with stoichiometric amount of TBAHS at 0 °C in dichloromethane, afforded oxazocane **279**, having two carbon higher homologue of morpholines (Scheme 69).⁷¹

4. Conclusion

The inspiring work contained in the present review article attests the importance of azetidine in heterocyclic synthesis. Literary rationale has witnessed a recent upsurge of different synthetic methods including intramolecular ring closure, β lactam-synthon approach as well as the use of metal/ organocatalysis for their stereoselective synthesis. Nevertheless, this synthetically arduous four-membered ring with immense importance both in biological/medicinal chemistry and as a versatile synthon will continue to pose challenges to synthetic chemists for developing efficient strategies.

Conflicts of interest

There are no conflicts to declare.

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