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Recent advances in synthetic facets of immensely reactive azetidines

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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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1. 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 azetid-2-carboxylic acid is a proline antagonist in plant tissue



Dr Vishu Mehra obtained his Master's degree in Applied Chemistry with first division in 2007 from Guru Nanak Dev University, Amritsar. In 2007, he joined Jubilant Chemsys (R & D) at Noida and worked as a Trainee Research Associate in the field of organic synthesis. He joined the research group of Dr Vipin Kumar in 2009 in the Department of Chemistry, Guru Nanak Dev University, and

worked extensively on the synthetic transformations of C-3 functionalized azetid-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.



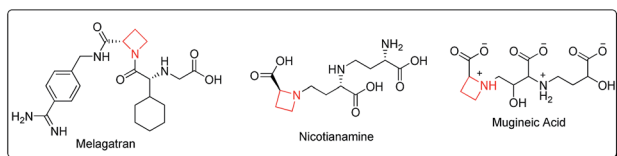


Fig. 1 Azetidine based biologically active scaffolds.

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-acids^{3a} 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 ring-opening 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- CF_3 -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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istry, GNDU, Amritsar in 2009. His research interest includes designing and synthesis of diverse heterocyclic compounds with biological and medicinal potential utilising the well documented β -lactam synthon strategy. 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.



Dr Vipin kumar Ph.D. has been working as an Assistant Professor in the Department of Chemistry, Guru Nanak Dev University, Amritsar since 2009. He obtained his Ph.D with Prof. Mohinder P Mahajan, in the Department of Applied Chemistry, GNDU. In 2007, he moved to the University of Cape Town (UCT), South Africa to pursue his postdoctoral studies with Prof. Kelly Chibale. In 2015, he

was awarded research fellowship from Carl Tryggers research foundation, Sweden to carry out research at University of Umea, Sweden. His research interests include the development of diverse synthetic protocols for synthesis of novel molecular frameworks targeting tropical infections. He has also been engaged in the utilization of β -lactam synthon protocols for the synthesis of functionally decorated and biologically relevant heterocycles with medicinal potential.



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)azetidines 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).

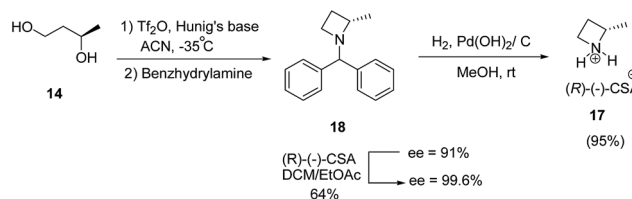
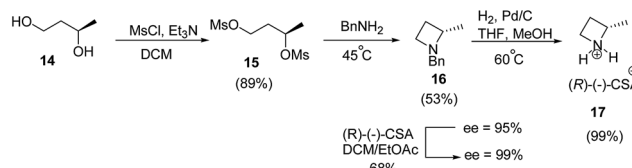
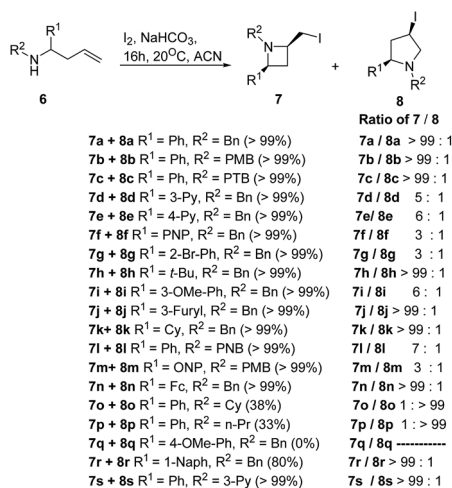
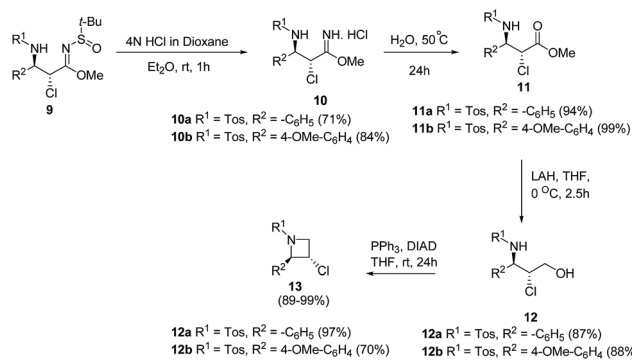
De Kimpe and co-workers⁹ have utilized α -chloro- β -amino-sulfinyl imidates **9** for the synthesis of enantiopure *trans*-2-aryl-3-chloroazetidines **13**. The key step involved the deprotection of α -chloro- β -aminosulfinyl imidates **9** with 4 N HCl in dioxane to afford the corresponding imidate 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 -sulfonfylamino 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 bis-triflate under different conditions. Best results in terms of yield was obtained *via* dropwise addition of Tf₂O to a premixed solution of (*R*)-1,3-butanediol **14** and Hunig's base at -35 °C followed by treatment with benzhydrlamine 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 azetidines **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** ($R^1 = \text{Et}$, $R^2 = t\text{-Bu}$, $\text{Nu} = \text{N}_3$) 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 3-azidoazetidine-3-carboxylates **24** ($R^1 = \text{Et}$, $R^2 = t\text{-Bu}$, $\text{Nu} = \text{N}_3$) with Pd/C yielded the corresponding 3-aminoazetidine-3-carboxylate **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-(4-methylbenzyl)-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*-*t*-butylimine **32** with NaBH₄ selectively gave *N*-(*t*-butyl)-2,3-dibromo-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 7

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

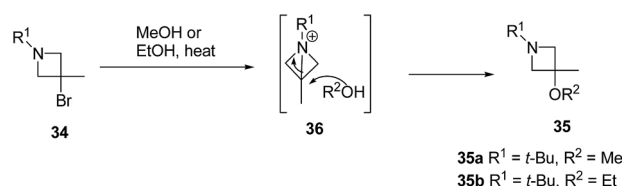
Szymoniak *et al.*¹⁵ have recently explored the stereoselective synthesis of *cis*-2,3-disubstituted azetidines through diastereoselective hydrozirconation. The synthetic approach involved the treatment of **37** with Schwartz reagent to yield the hydrozirconated intermediate which on reaction with iodine 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** ($R^1 = i\text{-Pr}$, Ph and $R^2 = \text{Me}$) could be attributed due to steric hinderance created by the bulky substituents. When ($R^1 = \text{allylamine}$, $R^2 = \text{Ph}$) dehydrozirconation turned out to be more favorable pathway and the reaction did not lead to iodination/cyclisation product (Scheme 11).

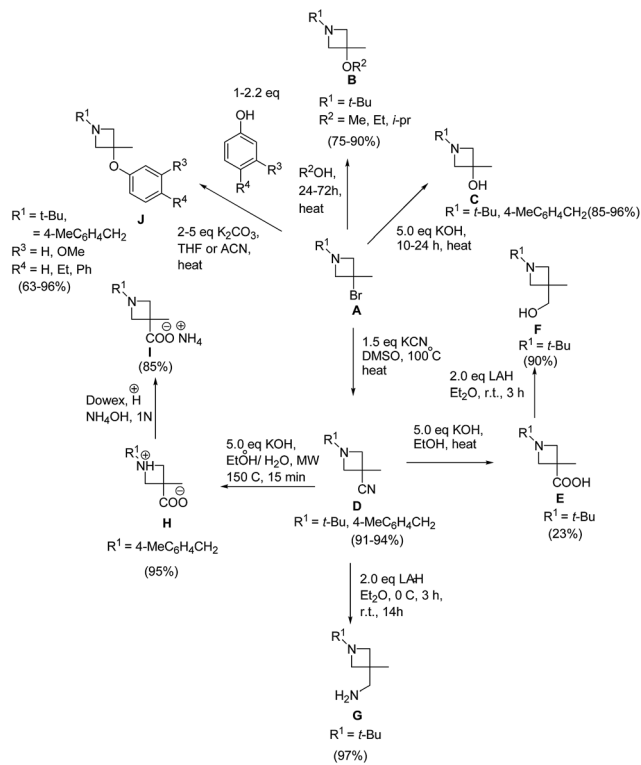


Scheme 6

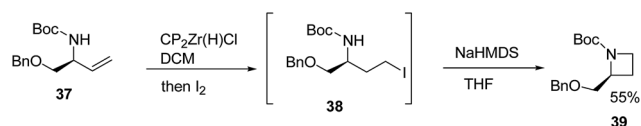


Scheme 8

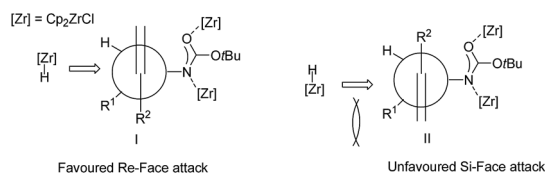
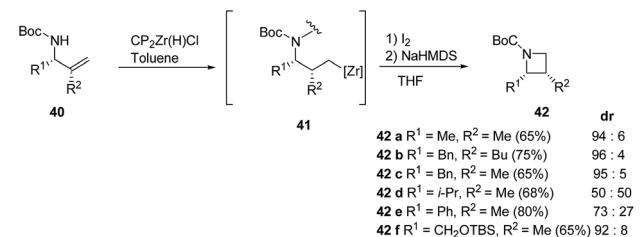




Scheme 9

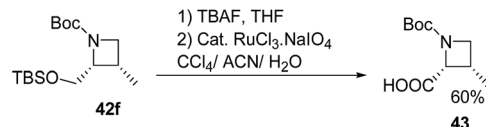


Scheme 10



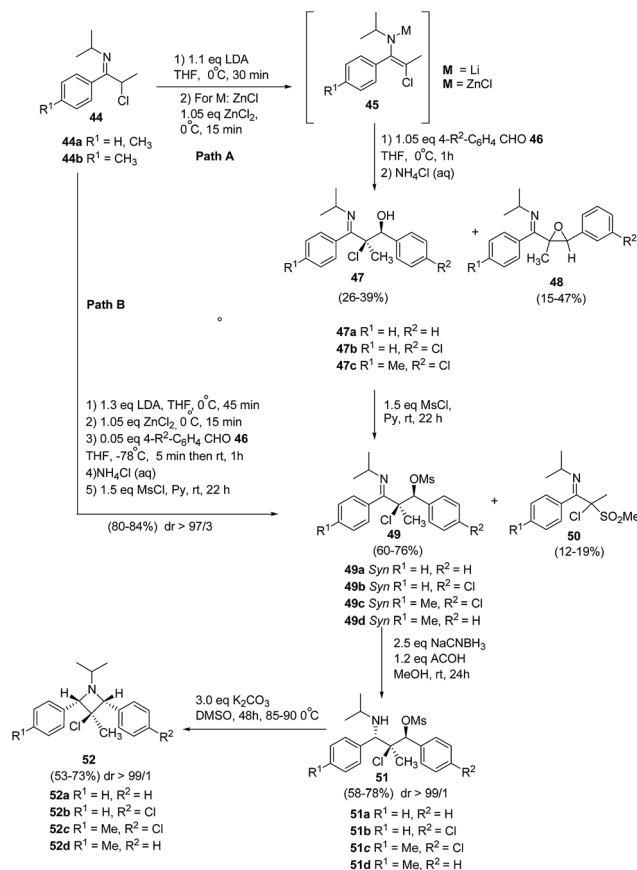
Scheme 11

Deprotection of **42f** with TBAF and subsequent ruthenium promoted oxidation led to *cis*-azetid-2-carboxylic acid **43** which is a key constituent of a number of natural products and their derivatives (Scheme 12).^{2,16}



Scheme 12

De Kimpe and co-workers¹⁷ have utilized the zincated 3-chloro-3-methyl-1-azaallylic anions **45** in stereoselective aldol condensation with aromatic aldehydes and subsequent mesylation to produce *syn*- α -chloro- β -mesyloxyketimines **49**. This upon stereoselective reduction and cyclisation afforded 1,2,3,4-tetrasubstituted 3-chloroazetidines **52** having three stereogenic centers as depicted in Scheme 13. The synthetic protocol involved the treatment of *N*-isopropyl- α -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*-imidoyloxides **48a** as the side products. The transmetalation of the lithiated anion with ZnCl_2 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



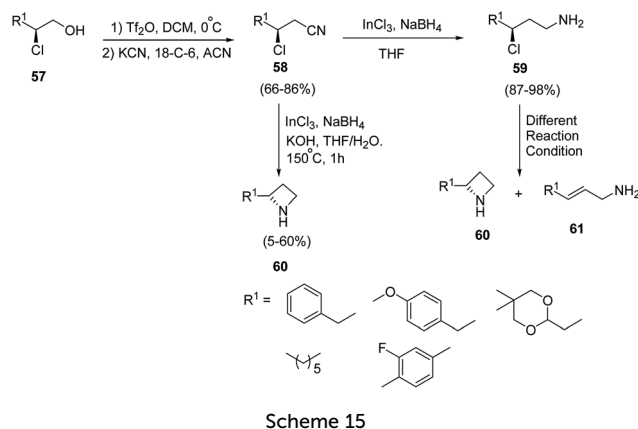
Scheme 13



amounts of the epoxide **48a**. Further lowering the reaction temperature to $-78\text{ }^{\circ}\text{C}$ 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 α -chloro- α -methanesulfonylketimines **50a** isolated as a by product in low yield (**Path B**). The stereoselective reduction of β -mesyloxyketimines **49** with NaCNBH_3 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 $50\text{ }^{\circ}\text{C}$, however yielded the corresponding imine which subsequently was cyclized in the presence of NaCNBH_3 affording chiral azetidine-piperidines **56** as depicted in Scheme 14.

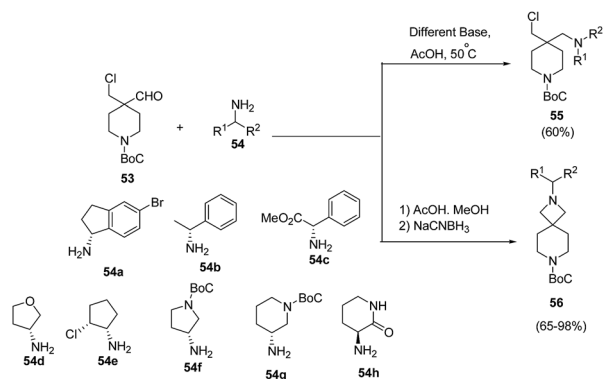
Lindsley and co-workers¹⁹ have devised an enantioselective synthesis of C2-functionalized azetidines from β -chloroalcohol. The methodology involved the initial activation of β -chloro alcohol **57** as triflate with subsequent displacement of triflate ion with cyanide in presence of 18-crown-6 to afford β -chloronitrile **58**. The synthesized β -chloronitrile **58** was reduced with indium(III)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(III)chloride-sodium borohydride. Different reaction conditions (K_2CO_3 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.



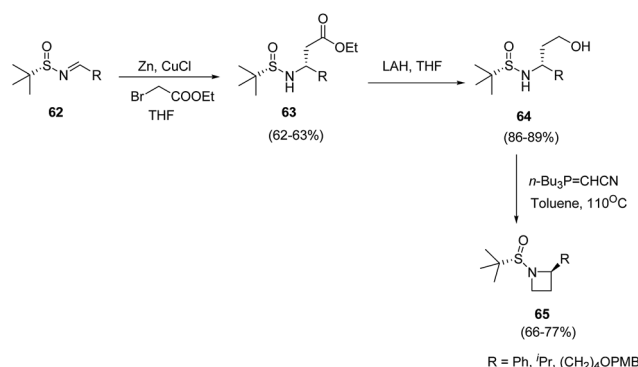
Scheme 15

Voss and co-workers²⁰ described the synthesis of C-2-substituted 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 $110\text{ }^{\circ}\text{C}$ 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 α -trifluoromethylated azetidine-2-carboxylic 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 $\text{NaBH}_4/\text{CaCl}_2$ (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** respectively (Scheme 17).

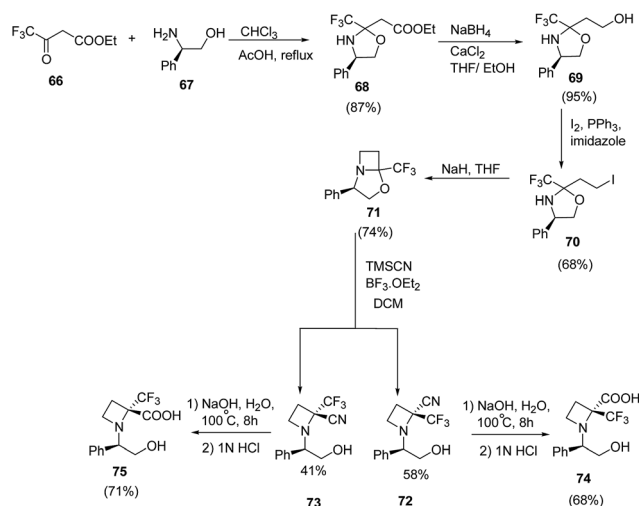


Scheme 14

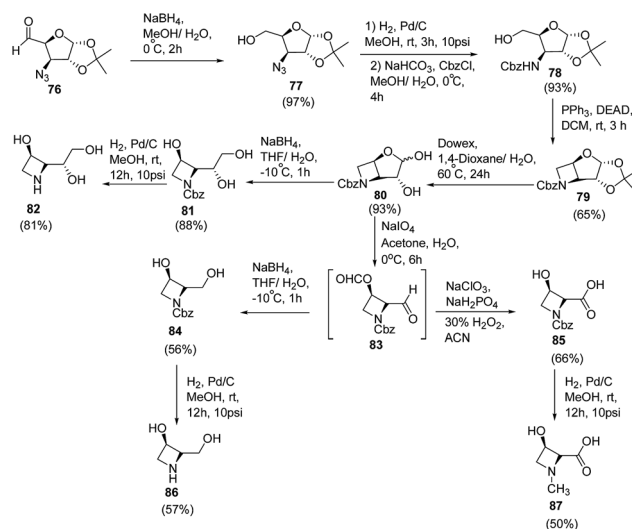


Scheme 16





Scheme 17



Scheme 18

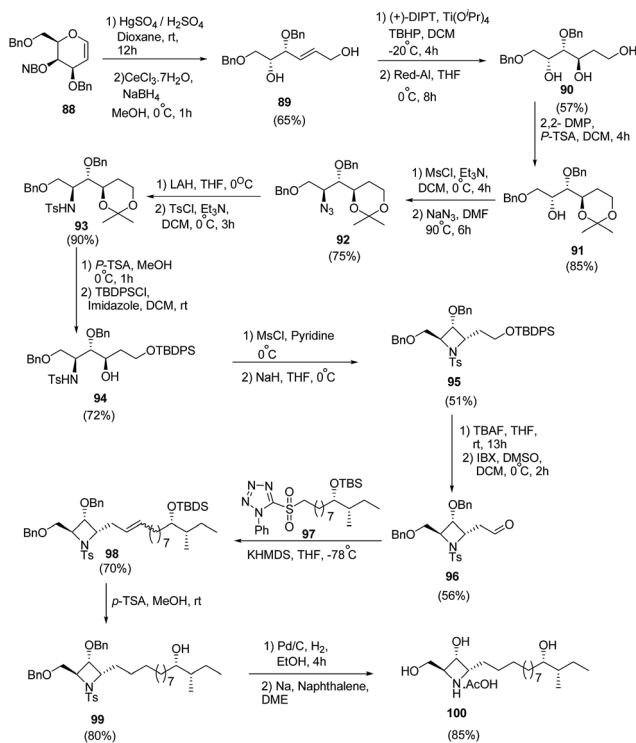
Polyhydroxylated nitrogen containing compounds popularly known as iminosugars are well known glycosidase inhibitors.^{23,24} Shinde *et al.*²⁵ have developed a convenient methodology for the synthesis of azetidines and 3-hydroxy-*N*-methylazetidines-2-carboxylic acid from *D*-glucose using intramolecular 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 azetidines **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 (2*S*,3*R*)-2-((*R*)-1,2-dihydroxyethyl)azetid-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 (2*R*,3*R*)-2-(hydroxymethyl)azetid-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 yielded (2*S*,3*R*)-3-hydroxy-*N*-methylated azetidines-2-carboxylic acid **87** (Scheme 18).

Reddy *et al.*²⁷ have developed a synthetic methodology for the stereoselective synthesis of azetidines 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 **96**. Julia-Kocienski olefination of **96** with sulfone fragment **97** in presence of KHDMS afforded olefin **98**. Further, desilylation 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 azetidines analogues of mannosidase inhibitor swainsonine and 1,4-dideoxy-1,4-imino-*D*-mannitol (DIM) through bicyclic azetidines. The methodology involved the protection of *D*-altrose **101** with acetone in the presence of sulfuric acid and anhydrous copper(II)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 silyl 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 azetidines intermediate **107**. Further, hydrolysis of **107** with aqueous trifluoroacetic acid resulted in the **108** which upon reduction with sodium borohydride in water, yielded *N*-benzylazetidines **109**. Hydrogenation of **109** with ammonium formate in the presence of palladium on



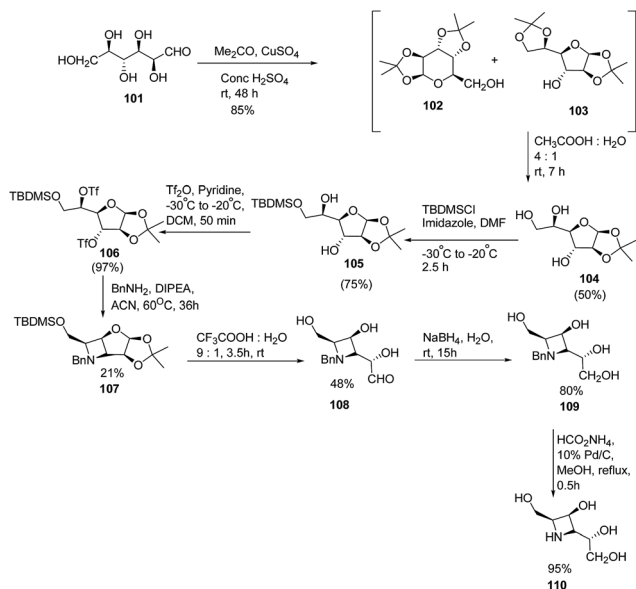


Scheme 19

carbon yielded the desired azetidine analogue of DIM (1,4-dideoxy-1,4-imino-D-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

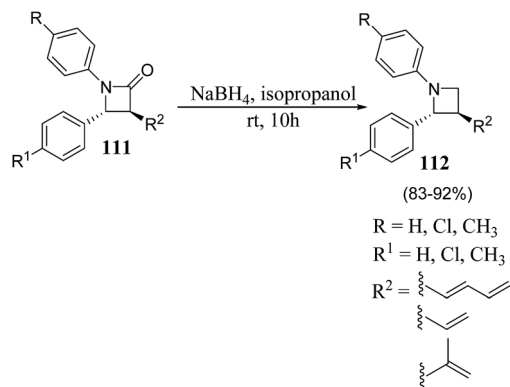
safety of this type of antibacterials.²⁹ Besides their biological relevance, the stereocontrolled transformation of β -lactam ring provides efficient access to a variety of non-protein amino acids, functionalized piperazines, 1,4-diazepanes, quinolones, isoquinolones, isoquinolines, enantiopure succinimides, oligopeptides, peptidomimetics and biologically 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



Scheme 21





Scheme 22



Scheme 23

aziridine **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



Scheme 24



Scheme 25

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 Ac_2O afforded **128** which underwent Pd-catalyzed allylic amination resulting in the enantioselective formation of azetidine **129** as depicted in Scheme 26.



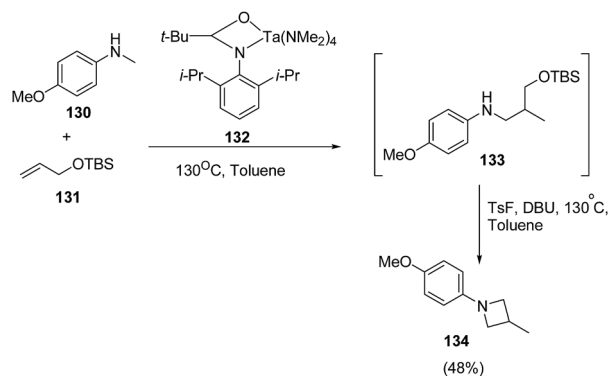
Scheme 26



Schafer *et al.*³⁷ have utilized tantalum catalyzed hydro-aminoalkylation 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 **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.

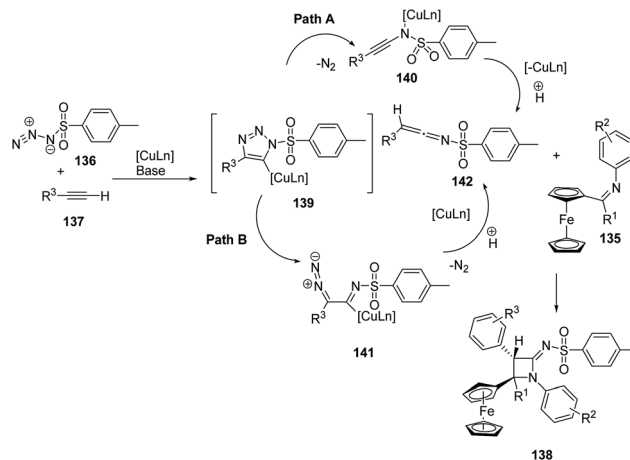
Mechanistically the alkyne **137** reacted with sulfonyl azide **136** to afford intermediate **139** which could follow two different pathways leading to azetidinimine **138**. Nitrogen extrusion of intermediate **139** generated ring opened intermediate **140** which upon protonation afforded ketenimine 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 **142** (**Path B**). [2 + 2]-Cycloaddition of **142** with ferrocenylimine **135** led to the diastereoselective synthesis of ferrocenyl substituted azetidinimine **106** (Scheme 29).⁴¹



Scheme 27



Scheme 28



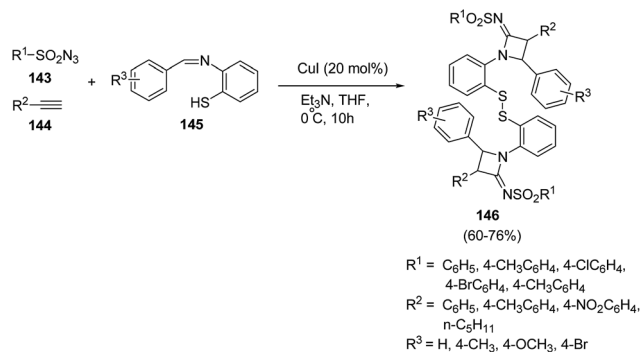
Scheme 29

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 afford 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

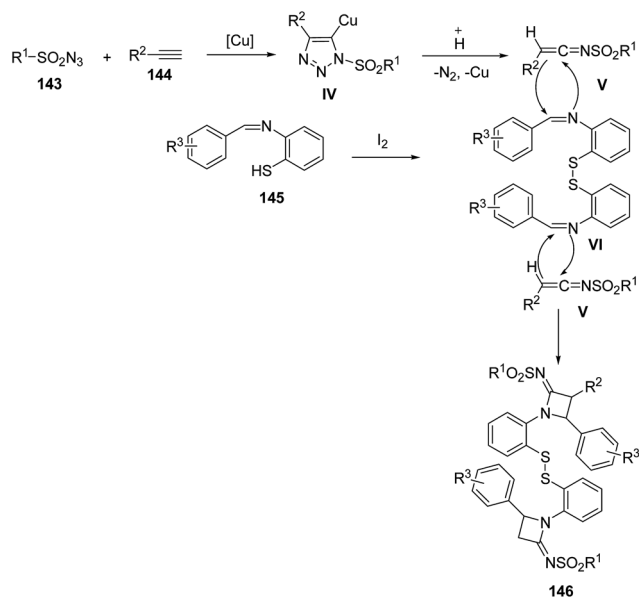
2.5 Synthesis of azetidines *via* organocatalysis

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



Scheme 30



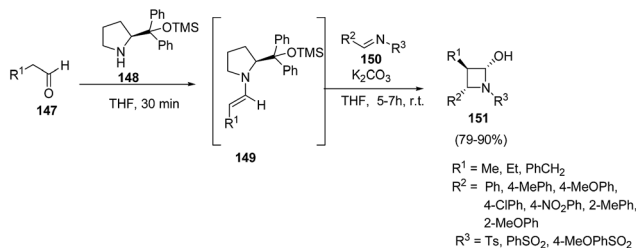


Scheme 31

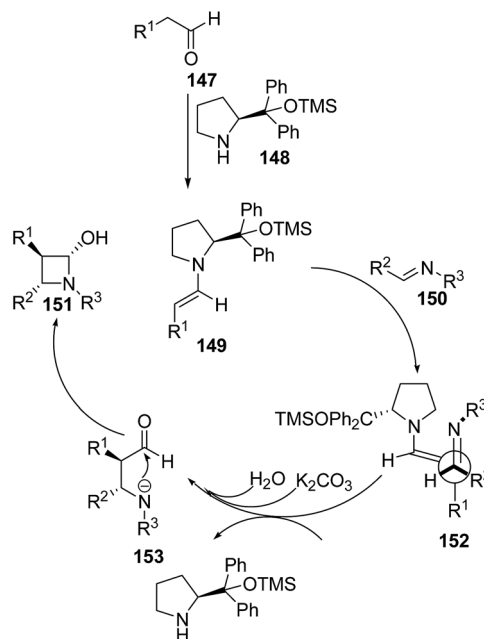
azetidin-2-ols. The key step in the synthesis involved the treatment of aldehyde **147** with pyrrolidine based catalysts **148** to afford chiral enamine intermediate **149** which upon [2 + 2] annulation reaction with aldimines **150** in presence of K_2CO_3 resulted in the diastereoselective synthesis 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, Et_3N and $NaHCO_3$. Best results in terms of yields were obtained using **116** as the catalyst and K_2CO_3 as base.

Mechanistically it was found that the catalyst diphenylprolinol trimethylsilyl ether **148** activated the aldehyde **147**, generating the corresponding enamine **149**. Stereoselective 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 allenolate **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)



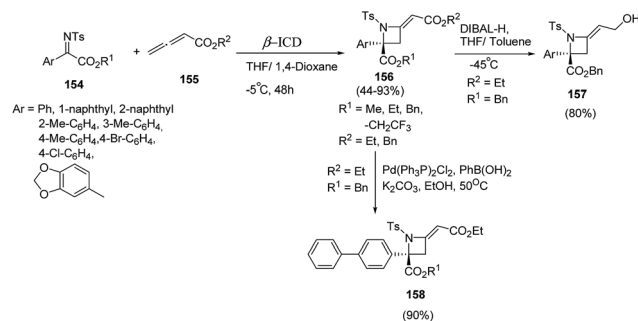
Scheme 32



Scheme 33

as catalyst in the presence of MS 3 Å. Azetidine **156** was reduced using DIBAL-H affording allyl alcohol **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 poly-substituted azetidines demands greater exploration as compared to aziridines, pyrrolidines and piperidines. Kaufman *et al.*⁴⁵ have developed an 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 $-20^\circ C$ afforded intermediate **163** which upon reduction with $NaBH_4$ 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-



Scheme 34





Scheme 35

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 K_2CO_3 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 K_2CO_3 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* TiCl_4 promoted [3 + 3] cycloaddition reaction. The synthetic methodology involved the treatment of cyclopropane 1,1-diester **170** with alkyl azide **169** in presence of catalytic amount of TiCl_4 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-diester **170** gave corresponding triazines **171** in good yields. The synthesized triazine **171**



Scheme 36



Scheme 37

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

Mechanistically, it was found that TiCl_4 , promoted the ring-opening 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

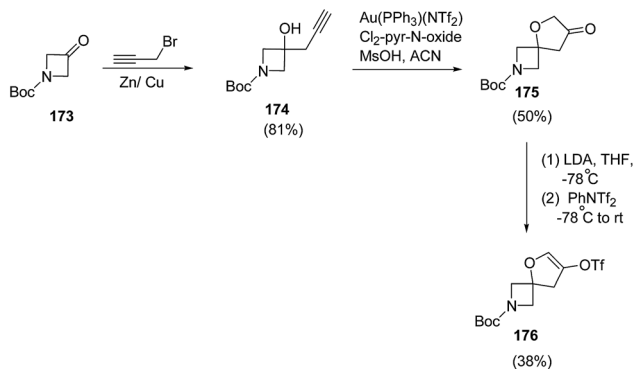
Santini and co-workers⁴⁸ reduced the 3-oxo-azetidine **176** into corresponding alcohol in the presence of Zn/Cu couple⁴⁹ which was subsequently utilized in spirocyclization. The synthetic methodology involved the reduction of 3-oxo-azetidine **173** with propargyl bromide in the presence of Zn/Cu couple resulting into azetidine **174**. The treatment of azetidine **174** with catalytic amount of $\text{Au}(\text{PPh}_3)(\text{NTf}_2)$ 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 allenates has experienced a great expansion over the past few decades.⁵¹ Ma *et al.*⁵² introduced Lewis bases promoted [2 + 2] annulation reaction of allenates 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

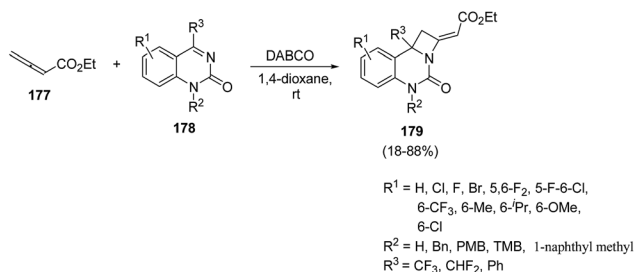


Scheme 38





Scheme 39



Scheme 40

aromatic ring afforded the cycloadducts **179** in high yields whereas ketimine bearing electron-donating groups at 6th-position 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 CF₃-group in the [2 + 2] annulation reaction (Scheme 40).

The plausible mechanism involved an initial 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



Scheme 41

3. Azetidines as versatile synthons

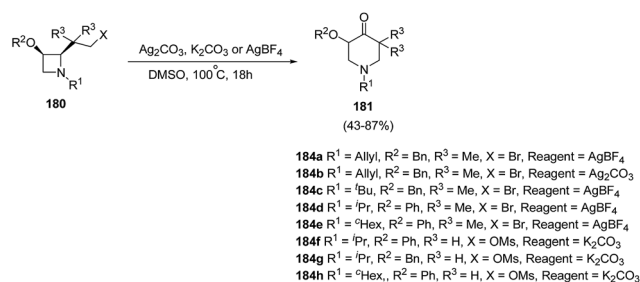
Azetidines played an important role in medicinal chemistry programs.⁵³ In recent years, ring transformations of azetidines has been exploited widely through nucleophilic ring-opening, cycloaddition, and rearrangement reactions which makes them highly valuable in organic synthesis.⁵⁴

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 expansion-oxidation of corresponding azetidines. The key step in the synthesis involved the treatment of *cis*-2-(2-bromo-1,1-dimethylethyl)azetidines **180a-e** with silver salt in DMSO at 100 °C for 18 h to afford the corresponding 5,5-dimethylpiperidin-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 (bis-trichloromethylcarbonate, 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





Scheme 43

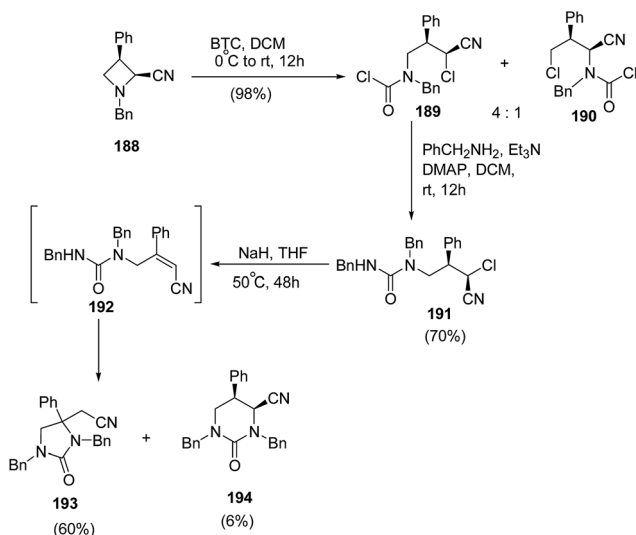


Scheme 44

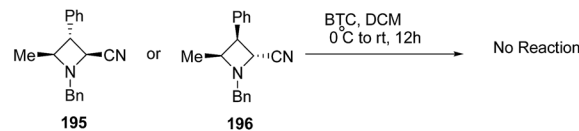
along with formation of tetrahydropyrimidin-2-one **194**, as the minor product as illustrated in Scheme 45.⁵⁶

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

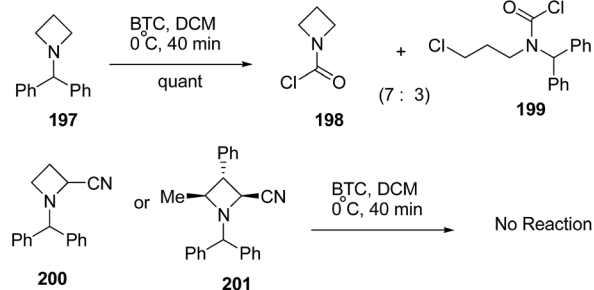


Scheme 46

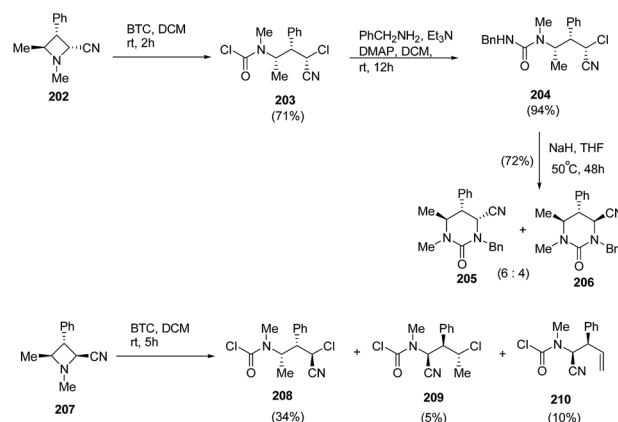
chloride **198** and ring opened product **199** in ratio 7 : 3. Further, *N*-benzhydryl 2-cyano azetidine **200** or trisubstituted *N*-benzhydrylazetidine **201** were found to be completely inert due to steric crowding around the nitrogen atom (Scheme 47).⁵⁶

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 γ -lactams *via* tandem intramolecular azetidine ring-opening/closing cascade reaction. The key step involved the SN²-type ring-opening of TMSOTf-activated 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



Scheme 47



Scheme 48

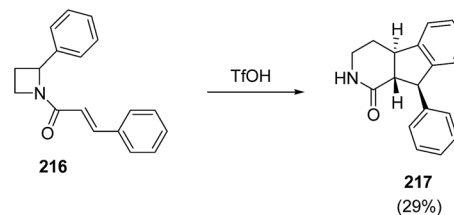


formation of spirocyclopropyl- γ -lactam **212** in highly regio and stereoselective manner. Further reduction of the ester group with superhydride resulted into primary alcohol **213** while pyrrolidine analogue **214** was achieved by using LAH. The pyrrolidine analogue, **213** was efficiently converted to corresponding bromide **215** by using PPh_3/Br_2 and pyridine (Scheme 49).

Mechanistically S_{N}^2 -type ring-opening^{1f,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 $\text{Na}_2\text{WO}_4 \cdot 2\text{H}_2\text{O}$ 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

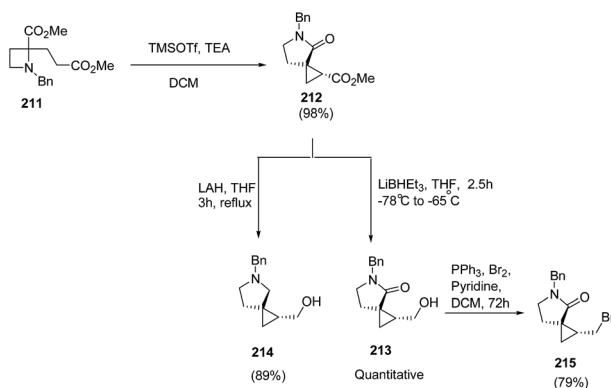


Scheme 51

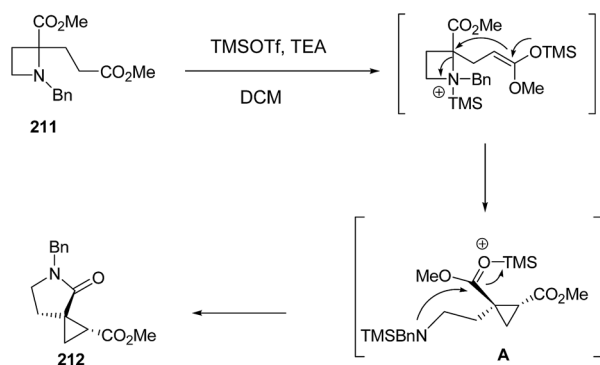
presence of Na_2CO_3 yielded 2-benzyl-isoxazolidine-5-carbonitrile **222** and 2-benzyl-isoxazolidine-5-carboxylic acid ethyl ester **224**, respectively (Scheme 52).⁶²

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



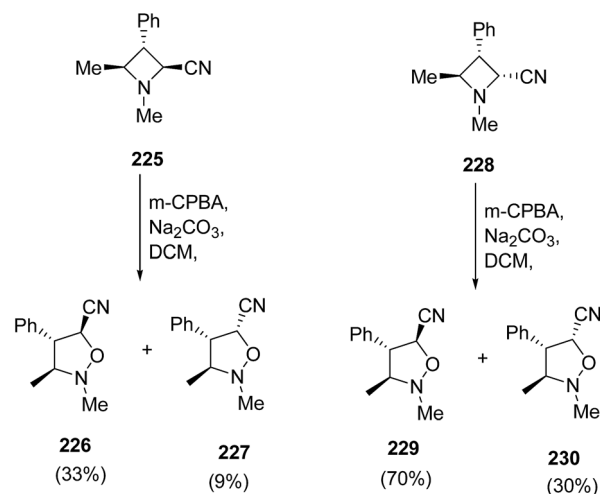
Scheme 49



Scheme 50



Scheme 52



Scheme 53



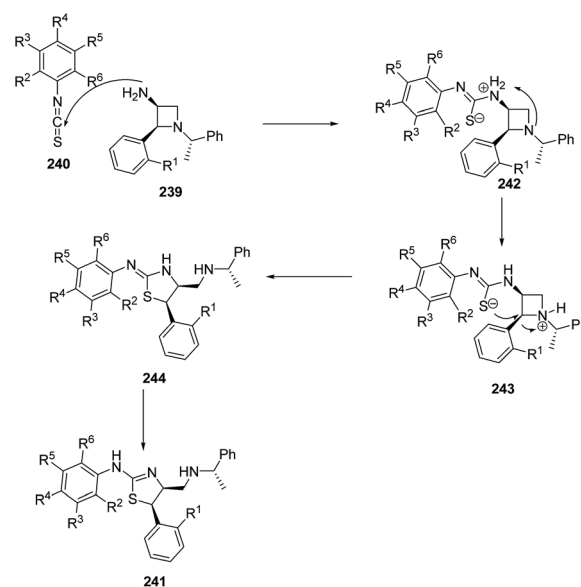
azetidine ester **231**. Furthermore, the nature of substituent on nitrogen also play a crucial role, since extensive epimerization was observed in case of *N*-Me azetidine **234**. Moreover, it was found that when *N*-oxide has *cis* relationship to the 4-methyl substituent, Cope elimination took place 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 regio- and stereoselective manner *via* ring opening of azetidines. The synthetic protocol involved the treatment of 3-amino-4-aryl-azetidine **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).

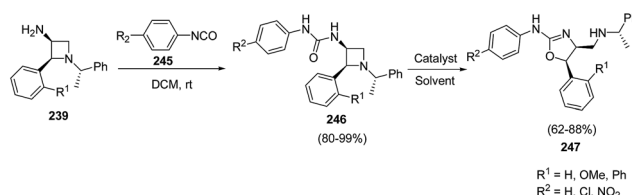
Mechanistically, the reaction was thought to proceed *via* the formation of thiourea as an intermediate which underwent intramolecular cyclization to afford corresponding dihydrothiazoles **241** as depicted in Scheme 56.⁶³

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

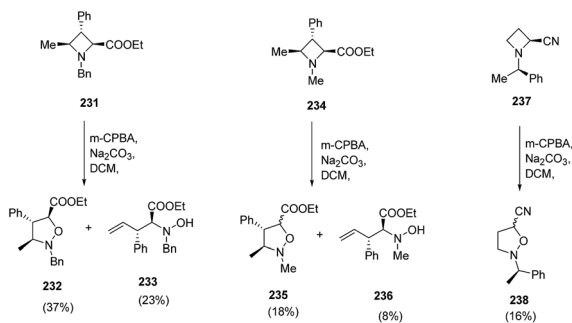
The pyrrole ring is one of the basic heteroaromatic motifs in numerous biologically active alkaloids, pharmaceutical products, or even in conducting polymers.⁶⁴ 2,4-Disubstituted



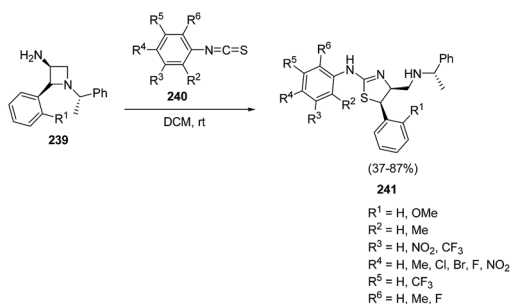
Scheme 56



Scheme 57



Scheme 54



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.

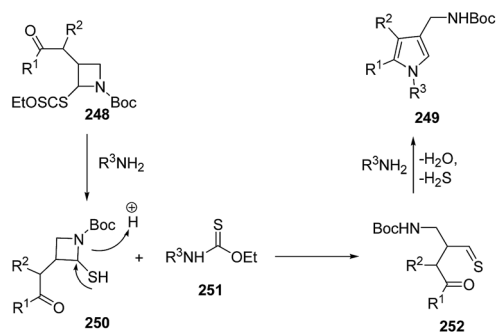
Mechanistically, the aminolysis of azetidine **248** resulted in the formation of thiol **250**, which underwent ring-opening to generate thioaldehyde **252**. The intramolecular condensation of amine with both the reactive thioaldehyde and the ketone afforded the desired pyrroles **249** (Scheme 59).⁶⁷

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-





Scheme 58



Scheme 59

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 (H_2SO_4 , TfOH and CF_3COOH) in presence of different solvents (DCE, DCM and toluene) resulting in a mixture of tetrahydrobenzazocines **256** and 3-vinyl-1,2,3,4-tetrahydroquinolines **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 H_2SO_4 (Scheme 62).⁶⁹



Scheme 60



Scheme 61

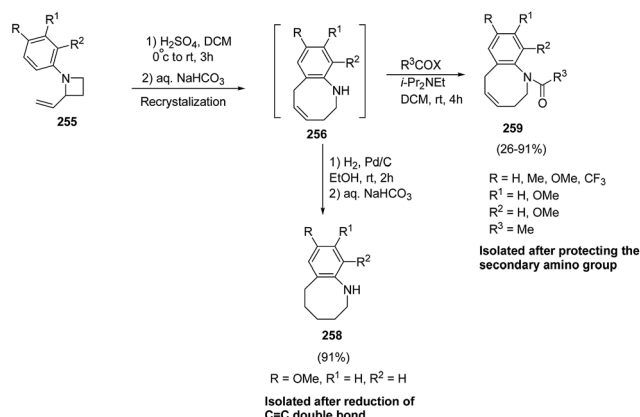


Scheme 62

The stability of **256** was enhanced either *via* catalytic hydrogenation to afford hexahydrobenzazocine **258** or by protection of amino group through acylation to yield the acetylated benzazocine derivatives **259** (Scheme 63).⁶⁹

The treatment of **256** with silica gel gave 6,7-dimethoxy-3-vinyl-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 room temperature yielded 6,7-dimethoxy-3-vinyl-1,2,3,4-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

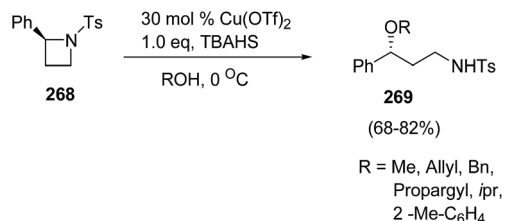


Scheme 63





Scheme 64

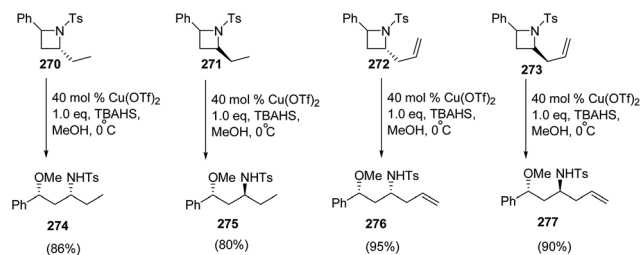


Scheme 67

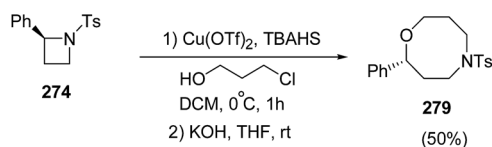
addition of amines yielding 4-amino-2-aminomethylbutyronitriles **263**–**265**. The synthetic methodology involved the treatment of azetidinium ion **260** with LiHMDS in THF at $-78\text{ }^{\circ}\text{C}$ with subsequent methylation resulting in the synthesis of acrylonitrile **261** which underwent 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)triflate-catalyzed 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 $0\text{ }^{\circ}\text{C}$ to afford γ -amino ethers **269** (Scheme 67).



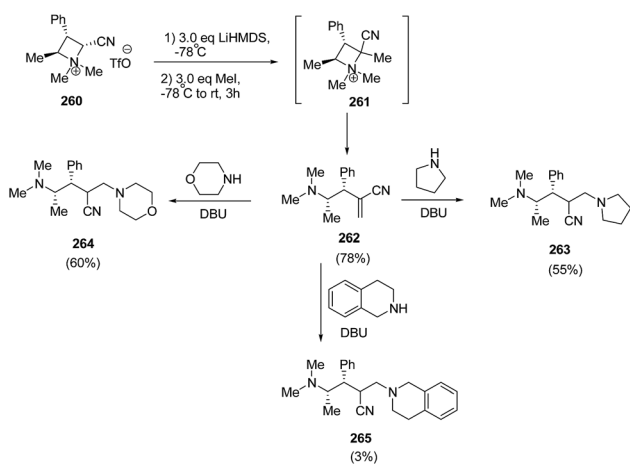
Scheme 68



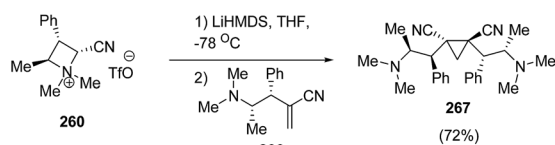
Scheme 69

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 $0\text{ }^{\circ}\text{C}$ in dichloromethane, afforded oxazocane **279**, having two carbon higher homologue of morpholines (Scheme 69).⁷¹



Scheme 65



Scheme 66

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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Notes and references

- (a) D. Antermite, L. Degennaro and R. Luisi, *Org. Biomol. Chem.*, 2017, **15**, 34; (b) J. Dolfen, N. De Kimpe and M. D'hooghe, *Synlett*, 2016, **27**, 1486; (c) F. Couty, B. Drouillat, G. Evano and O. David, *Eur. J. Org. Chem.*, 2013, 2045; (d) B. Alcaide, P. Almendros and C. Aragoncillo, *Curr. Opin. Drug Discovery Dev.*, 2010, **13**, 685; (e) A. Brandi, S. Cicchi and F. M. Cordero, *Chem. Rev.*, 2008, **108**, 3988; (f) F. Couty and G. Evano, *Synlett*, 2009, **19**, 3053; (g) G. S. Singh, M. D'Hooghe and N. De Kimpe, Azetidines, Azetines and Azetes: Monocyclic, in *Comprehensive Heterocyclic Chemistry III*, ed. A. R. Katritzky, Elsevier, 2008, vol. 2, ch. 2.01, pp. 1–110; (h) G. B. Evans, R. H. Furneaux, B. Greatrex, A. S. Murkin, V. L. Schramm and P. C. Tyler, *J. Med. Chem.*, 2008, **51**, 948; (i) T. M. Bott and F. G. West, *Heterocycles*, 2012, **84**, 223; (j) G. B. Evans, R. H. Furneaux, B. Greatrex, A. S. Murkin, V. L. Schramm and P. C. Tyler, *J. Med. Chem.*, 2008, **51**, 948; (k) D. Honcharenko, J. Barman, O. P. Varghese and J. Chattopadhyaya, *Biochemistry*, 2007, **46**, 5635; (l) J. Slade, J. Bajwa, H. Liu, D. Parker, J. Vivel, G. P. Chen, J. Calienni, E. Villhauer, K. Prasad, O. Repic and T. J. Blacklock, *Org. Process Res. Dev.*, 2007, **11**, 825; (m) N. Kolocouris, G. Zoidis, G. B. Foscolos, G. Fytas, S. R. Prathalingham, J. M. Kelly, L. Naesense and E. De Clercq, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 4358.
- F. Couty and G. Evano, *Org. Prep. Proced. Int.*, 2006, **38**, 427.
- (a) H. Brauner-Osborne, L. Bunch, N. Chopin, F. Couty, G. Evano, A. A. Jensen, M. Kusk, B. Nielsen and N. Rabasso, *Org. Biomol. Chem.*, 2005, **3**, 3926; (b) B. Drouillat, K. Wright, J. Marrot and F. Couty, *Tetrahedron: Asymmetry*, 2012, **23**, 690; (c) D. Honcharenko, C. Zhou and J. Chattopadhyaya, *J. Org. Chem.*, 2008, **73**, 2829; (d) O. Plashkevych, S. Chatterjee, D. Honcharenko, W. Pathmasiri and J. Chattopadhyaya, *J. Org. Chem.*, 2007, **72**, 4716; (e) D. Honcharenko, O. P. Varghese, O. Plashkevych, J. Barman and J. Chattopadhyaya, *J. Org. Chem.*, 2006, **71**, 299.
- C. Agami, F. Couty and N. Rabasso, *Tetrahedron Lett.*, 2002, **43**, 4633.
- (a) T. M. Bott, J. A. Vanecko and F. G. West, *J. Org. Chem.*, 2009, **74**, 2832; (b) W. Van Brabandt, Y. Dejaegher, R. Van Landeghem and N. De Kimpe, *Org. Lett.*, 2006, **8**, 1101; (c) F. Couty, F. Durrat, G. Evano and J. Marrot, *Eur. J. Org. Chem.*, 2006, 4214.
- (a) S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320; (b) W. K. Hagmann, *J. Med. Chem.*, 2008, **51**, 4359.
- S. Kenis, M. D'hooghe, G. Verniest, T. A. D. Thi, C. P. The, T. V. Nguyen and N. De Kimpe, *J. Org. Chem.*, 2012, **77**, 5982.
- A. Feula, S. S. Dhillon, R. Byravan, M. Sangha, R. Ebanks, M. A. H. Salih, N. Spencer, L. Male, I. Magyary, W.-P. Deng, F. Muller and J. S. Fossey, *Org. Biomol. Chem.*, 2013, **11**, 5083.
- F. Colpaert, S. Mangelinckx, S. De Brabandere and N. De Kimpe, *J. Org. Chem.*, 2011, **76**, 2204.
- M. S. Dowling, D. P. Fernando, J. Hou, B. Liu and A. C. Smith, *J. Org. Chem.*, 2016, **81**, 3031.
- A. Zukauskaitė, S. Mangelinckx, V. Buinauskaitė, A. Sackus and N. De Kimpe, *Amino Acids*, 2011, **41**, 541.
- L. Provins, B. Christophe, P. Danhaive, J. Dulieu, M. Gillard, L. Quere and K. Stebbins, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 3077.
- S. T. Murphy, H. L. Case, E. Ellsworth, S. Hagen, M. Huband, T. Joannides, C. Limberakis, K. R. Marotti, A. M. Ottolini, M. Rauckhorst, J. Starr, M. Stier, C. Taylor, T. Zhu, A. Blaser, W. A. Denny, G. L. Lu, J. B. Smaill and F. Rivault, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 2150.
- S. Stankovic, M. D'hooghe, K. A. Tehrani and N. De Kimpe, *Tetrahedron Lett.*, 2012, **53**, 107.
- T. K. Pradhan, K. S. Krishnan, J.-L. Vasse and J. Szymoniak, *Org. Lett.*, 2011, **13**, 1793.
- (a) H. O'Dowd, J. G. Lewis, J. Trias, R. Asano, J. Blais, S. Lopez, C. K. Park, C. Wu, W. Wang and M. F. Gordeev, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 2645; (b) M. R. Faust, G. Hoefner, J. Pabel and K. T. Wanner, *Eur. J. Med. Chem.*, 2010, **45**, 2453.
- S. Mangelinckx, B. D. Sterck, F. Colpaert, S. Catak, J. Jacobs, S. Rooryck, M. Waroquier, V. V. Speybroeck and N. De Kimpe, *J. Org. Chem.*, 2012, **77**, 3415.
- S. T. M. Orr, S. Cabral, D. P. Fernando and T. Makowski, *Tetrahedron Lett.*, 2011, **52**, 3618.
- T. J. Senter, M. C. O'Reilly, K. M. Chong, G. A. Sulikowski and C. W. Lindsley, *Tetrahedron Lett.*, 2015, **56**, 1276.
- A. A. Kudale, P. Anaspure, F. Goswami and M. Voss, *Tetrahedron Lett.*, 2014, **55**, 7219.
- N. Lensen, J. Marais and T. Brigaud, *Org. Lett.*, 2015, **17**, 342.
- Y. Ishida, N. Iwahashi, N. Nishizono and K. Saigo, *Tetrahedron Lett.*, 2009, **50**, 1889.
- G. Horne, F. X. Wilson, J. Tinsley, D. H. Williams and R. Storer, *Drug Discov. Today*, 2011, **16**, 107.
- P. R. Markad, D. P. Sonawane, S. Ghosh, B. A. Chopade, N. Kumbhar, T. Louat, J. Herman, M. Waer, P. Herdewijn and D. D. Dhavale, *Bioorg. Med. Chem.*, 2014, **22**, 5776.
- P. P. Lawande, V. A. Sontakke, R. J. Nair, A. Khan, S. G. Sabharwal and V. S. Shinde, *Tetrahedron*, 2015, **71**, 5085.
- V. U. Pawar, S. T. Chavan, S. G. Sabharwal and V. S. Shinde, *Bioorg. Med. Chem.*, 2010, **18**, 7799.
- B. V. S. Reddy, C. Kishore and A. S. Reddy, *Tetrahedron Lett.*, 2014, **55**, 49.



- 28 N. Araujo, S. F. Jenkinson, R. F. Martinez, A. F. G. Glawar, M. R. Wormald, T. D. Butters, S. Nakagawa, I. Adachi, A. Kato, A. Yoshihara, K. Akimitsu, K. Izumori and G. W. J. Fleet, *Org. Lett.*, 2012, **14**, 4174.
- 29 A. Weber, *J. Med. Chem.*, 2004, **47**, 4135.
- 30 (a) C. M. L. Delpiccolo, M. M. Amezaga and E. G. Mata, Recent Approaches Toward the Generation of Molecular Diversity Based on β -Lactam Structures, in *Beta-Lactams-Novel Synthetic Pathway and Applications*, ed. B. K. Banik, Springer International Publishing AG, 2017, pp. 129–162; (b) B. Alcaide, P. Almendros and C. Aragoncillo, Synthesis of Five-Membered Heterocycles Through β -Lactam Ring-Expansion Reaction, in *Beta-Lactams-Novel Synthetic Pathway and Applications*, ed. B. K. Banik, Springer International Publishing AG, 2017, pp. 163–218.
- 31 (a) V. Mehra, P. Singh, K. Bisetty and V. Kumar, *RSC Adv.*, 2014, **4**, 41793; (b) V. Mehra and V. Kumar, *Tetrahedron Lett.*, 2014, **55**, 845; (c) V. Mehra, P. Singh, N. Manhas and V. Kumar, *Synlett*, 2014, **25**, 1124; (d) V. Mehra and V. Kumar, *Tetrahedron*, 2013, **69**, 3857; (e) A. Anand, V. Mehra and V. Kumar, *Synlett*, 2013, **24**, 865; (f) V. Mehra, P. Singh and V. Kumar, *Tetrahedron*, 2012, **68**, 8395; (g) A. Kamath and I. Ojima, *Tetrahedron*, 2012, **68**, 10640; (h) S. Dekeukeleire, M. D'hooghe, M. Vanwalleghe, W. V. Brabandt and N. De Kimpe, *Tetrahedron*, 2012, **68**, 10827; R. Raj, V. Mehra, P. Singh, V. Kumar, G. Bhargava, M. P. Mahajan, S. Handa and L. Slaughter, *Eur. J. Org. Chem.*, 2011, 2697.
- 32 (a) B. Van Driessche, W. Van Brabandt, M. D'Hooghe, Y. Dejaegher and N. De Kimpe, *Tetrahedron*, 2006, **62**, 6882; (b) L. Kvaerno, M. Werder, H. Hauser and E. M. Carreira, *Org. Lett.*, 2005, **7**, 1145.
- 33 V. Mehra, Neetu and V. Kumar, *Tetrahedron Lett.*, 2013, **54**, 4763.
- 34 S. Stankovic, H. Goossens, S. Catak, M. Tezcan, M. Waroquier, V. V. Speybroeck, M. D'hooghe and N. De Kimpe, *J. Org. Chem.*, 2012, **77**, 3181.
- 35 T. Soeta, Y. Miyamoto, S. Fujinami and Y. Ukaji, *Tetrahedron*, 2014, **70**, 6623.
- 36 X. Wei, D. Liu, Q. An and W. Zhang, *Org. Lett.*, 2015, **17**, 5768.
- 37 P. R. Payne, P. Garcia, P. Eisenberger, J. C.-H. Yim and L. L. Schafer, *Org. Lett.*, 2013, **15**, 2182.
- 38 *Ferrocenes: Ligands, Materials and Biomolecules*, ed. P. Stepnicka, John Wiley & Sons, New York, 2008, p. 39.
- 39 (a) V. S. Sudhir, N. B. R. Baig and S. Chandrasekharan, *Eur. J. Org. Chem.*, 2009, 5365; (b) J. Tauchman and P. Stepnicka, *Inorg. Chem. Comm.*, 2010, **13**, 149; (c) A. Garcia, B. Insuasty, M. A. Herranz, R. Martinez-Alvarez and N. Martin, *Org. Lett.*, 2009, **11**, 5398.
- 40 (a) Q. Li, C.-H. Ding, X.-L. Hou and L.-X. Dai, *Org. Lett.*, 2010, **12**, 1080; (b) S. L. Marquard, D. C. Rosenfeld and J. F. Hartwig, *Angew. Chem., Int. Ed.*, 2010, **49**, 793.
- 41 S. Gouthaman, P. Shanmugam and A. B. Mandal, *Tetrahedron Lett.*, 2013, **54**, 3007.
- 42 Y. Shang, K. Liao, X. He and J. Hu, *Tetrahedron*, 2013, **69**, 10134.
- 43 A. Rai and L. D. S. Yadav, *Tetrahedron Lett.*, 2013, **54**, 3127.
- 44 S. Takizawa, F. A. Arteaga, Y. Yoshida, M. Suzuki and H. Sasai, *Org. Lett.*, 2013, **15**, 4142.
- 45 M. Amongero and T. S. Kaufman, *Tetrahedron Lett.*, 2013, **54**, 1924.
- 46 N. Kern, A.-S. Felten, J.-M. Weibel, P. Pale and A. Blanc, *Org. Lett.*, 2014, **16**, 6104.
- 47 H.-H. Zhang, Y.-C. Luo, H.-P. Wang, W. Chen and P.-F. Xu, *Org. Lett.*, 2014, **16**, 4896.
- 48 T. O. Painter, J. R. Bunn, F. J. Schoenen, J. T. Douglas, V. W. Day and C. Santini, *J. Org. Chem.*, 2013, **78**, 3720.
- 49 X. Ma, J.-X. Wang, S. Li, K.-H. Wang and D. Huang, *Tetrahedron*, 2009, **65**, 8683.
- 50 S. E. Denmark and G. L. Beutner, *Angew. Chem., Int. Ed.*, 2008, **47**, 1560.
- 51 (a) F. Lopez and J. L. Mascarennas, *Chem.-Eur. J.*, 2011, **17**, 418; (b) C.-K. Pei and M. Shi, *Chem.-Eur. J.*, 2012, **18**, 6712; (c) Q.-Y. Zhao, Z. Lian, Y. Wei and M. Shi, *Chem. Commun.*, 2012, **48**, 1724; (d) Y. Wei and M. Shi, *Chem. Rev.*, 2013, **113**, 6659.
- 52 L.-J. Yang, S. Li, S. Wang, J. Nie and J.-A. Ma, *J. Org. Chem.*, 2014, **79**, 3547.
- 53 (a) T. A. Brandt, S. Caron, D. B. Damon, J. Di Brino, A. Ghosh, D. A. Griffith, S. Kedia, J. A. Ragan, P. R. Rose, B. C. Vanderplas and L. Wei, *Tetrahedron*, 2009, **65**, 3292; (b) Y. Han, M. Han, D. Shin, C. Song and H.-G. Hahn, *J. Med. Chem.*, 2012, **55**, 8188.
- 54 (a) J. Xiao and S. W. Wright, *Tetrahedron Lett.*, 2013, **54**, 2502; (b) P.-A. Nocquet, D. Hazelard and P. Compain, *Eur. J. Org. Chem.*, 2011, 6619.
- 55 K. Mollet, M. D'hooghe, L. Broeckx, B. Danneels, T. Desmet and N. De Kimpe, *Tetrahedron*, 2013, **69**, 2603.
- 56 L. Menguy, B. Drouillat and F. Couty, *Tetrahedron Lett.*, 2015, **56**, 6625.
- 57 P.-A. Nocquet, D. Hazelard and P. Compain, *Tetrahedron*, 2012, **68**, 4117.
- 58 F. Couty, F. Durrat and G. Evano, in *Targets in Heterocyclic Systems-Chemistry and Properties*, ed. O. A. Attanasi and D. Spinelli, Italian Society of Chemistry, Rome, 2005, **9**, p. 186.
- 59 (a) D. C. Blakemore, J.-Y. Chiva and I. Thistlethwaite, *Synlett*, 2011, 1101; (b) K. Mollet, S. Catak, M. Waroquier, V. Van Speybroeck, M. D'hooghe and N. De Kimpe, *J. Org. Chem.*, 2011, **76**, 8364; (c) K. Mollet, L. Broeckx, M. D'hooghe and N. De Kimpe, *Heterocycles*, 2012, **84**, 431.
- 60 T. R. Hoye, V. Dvornikovs and E. Sizova, *Org. Lett.*, 2006, **8**, 5191.
- 61 F. D. King, A. Aliev, S. Caddick and D. Tocher, *Tetrahedron*, 2015, **71**, 3411.
- 62 L. Menguy, B. Drouillat, J. Marrot and F. Couty, *Tetrahedron Lett.*, 2012, **53**, 4697.
- 63 X. Zhou, X. Xu, Y. Li, Z. Zhang and Z.-B. Zheng, *Tetrahedron Lett.*, 2016, **57**, 1236.
- 64 (a) I. S. Young, P. D. Thornton and A. Thompson, *Nat. Prod. Rep.*, 2010, **27**, 1801; (b) H. Fan, J. Peng, M. T. Hamann and J.-F. Hu, *Chem. Rev.*, 2008, **108**, 264.
- 65 (a) S. Han, D. S. Siegel, K. C. Morrison, P. J. Hergenrother and M. Movassaghi, *J. Org. Chem.*, 2013, **78**, 11970; (b)



- R. Raju, A. M. Piggott, L. X. Barrientos Diaz, Z. Khalil and R. J. Capon, *Org. Lett.*, 2010, **12**, 5158.
- 66 (a) R. Yan, X. Kang, X. Zhou, X. Li, X. Liu, L. Xiang, Y. Li and G. Huang, *J. Org. Chem.*, 2014, **79**, 465; (b) M.-C. P. Yeh, M.-N. Lin, C.-H. Hsu and C. J. Liang, *J. Org. Chem.*, 2013, **78**, 12381; (c) Y. Zhou, X. Yan, C. Chen and C. Xi, *Organometallics*, 2013, **32**, 6182; (d) Y. Shi and V. Gevorgyan, *Org. Lett.*, 2013, **15**, 5394; (e) R. Chaudhuri and U. Uli Kazmaier, *Organometallics*, 2013, **32**, 5546.
- 67 S. Han and S. Z. Zard, *Org. Lett.*, 2014, **16**, 1992.
- 68 (a) J. L. Acena, A. E. Sorochinsky and V. A. Soloshonok, *Synthesis*, 2012, **44**, 1591; (b) X.-L. Qiu and F.-L. Qing, *Eur. J. Org. Chem.*, 2011, 3261.
- 69 T. Shimizu, S. Koya, R. Yamasaki, Y. Mutoh, I. Azumaya, K. Katagiri and S. Saito, *J. Org. Chem.*, 2014, **79**, 4367.
- 70 C. Lo, O. David and F. Couty, *Tetrahedron Lett.*, 2014, **55**, 535.
- 71 M. K. Ghorai, D. Shukla and A. Bhattacharyya, *J. Org. Chem.*, 2012, **77**, 3740.

