Synthesis of Chiral Non Racemic Azetidines

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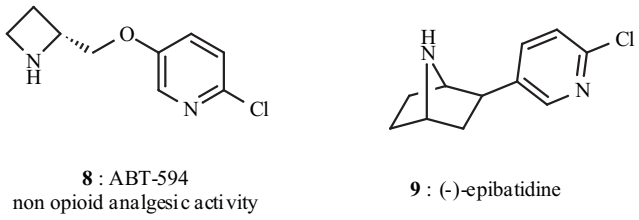
Abstract: This mini-review discusses the different synthetic methodologies used to synthesize azetidines in enantiomerically pure form, as well as the use of these strained aza-heterocycles as ligands for enantioselective catalysis.

Keywords: Azetidines, enantioselective synthesis, enantioselective catalysis.

INTRODUCTION

Functionalized nitrogen-containing heterocycles are among the most ubiquitous building blocks in natural products and synthetic compounds with important biological activities. If the 3-, 5- and 6-membered rings (respectively aziridines, pyrrolidines and piperidines) have been widely studied, less attention has been paid to the four-membered rings, the azetidines [1]. One explanation of this fact would be the scarcity of natural molecules, which include an azetidine ring, some representative examples being shown in Scheme **1.**



8 : ABT-594
non opioid analgesic activity

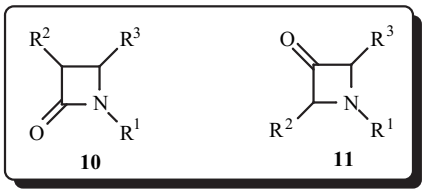
9 : (-)-epibatidine

Fig (1). A synthetic azetidine **8** related to natural (-)-epibatidine is a powerful analgesic.

Obviously, in comparison with the amazing amount of pyrrolidine and piperidine alkaloids, the rarity of natural azetidines has not stimulated synthetic chemists to discover original routes to these heterocylces to the same extent. This is however, surely not the only reason for this apparent disinterest: as a matter of fact azetidines, particularly in enantiomerically pure form, and because of their scarcity and originality, would be ideal subjects of interest in at least two active areas of research. The first one is medicinal chemistry, where nitrogen heterocycles are frequently represented: this area of research is still in need of original molecules, and the success of azetidine ABT-594 **8** discovered through the optimization of non-opioid drugs related to (-)-epibatidine **9** (Fig. (**1**)) should stimulate discoveries in the azetidine series [9]. The second is ligand design for enantioselective catalysis: in this area, the steric demand brought by the strained azetidine compounds employed as chiral ligands on transition metals would be a positive parameter for the optimization of diastereodifferentiation, and enhance the enantioselectivity of these processes.

The scarcity of azetidines in the literature is in fact a reflection of the lack of general and inexpensive synthetic routes to these heterocycles, particularly in enantiomerically pure form. As an illustration, when efficient enantioselective aziridination became available, a boost in interest for these heterocycles naturally followed [10].

The aim of this mini-review is to present an up-to-date (until July 2003) overview of the different methods available to prepare azetidines in enantiomerically pure form, as well as the use of these heterocycles in enantioselective catalysis and medicinal chemistry. Since no recent review has appeared in this field to our knowledge, and because it is intended to restrict the scope of this mini review to the preparation of non-racemic azetidines, it is worth mentioning two important points. First, as will be described later on, azetidines can be prepared by reduction of azetidin-2-ones **10** (β-lactams). Due to their well-known antibiotic properties, synthetic methodologies aimed at the preparation of these heterocycles have been extensively studied and appear in different reviews [11]. Asymmetric syntheses of enantiopure β-lactams will thus not appear herein. Secondly, azetidin-3-ones **11** are another particular class of functionalized azetidines for which an elegant access has been devised notably by De Kimpe's group [12]. The synthesis and chemistry of these heterocycles, prepared mainly in racemic form, has already been reviewed [13] and will not appear here, but one should know that precious general considerations about the chemistry of azetidines can be found in this review.



10 **11**

The chapters are ordered according to the key synthetic steps which allow the stereoselective formation of the azetidine ring system (corresponding to the retrosynthetic disconnections shown in Scheme **1**). Both resolutions, chiral pool-derived routes and asymmetric reactions are discussed in each of the eight sections, as well as the potential applications in medicinal chemistry. An independant section will be devoted to the use of chiral non-racemic azetidines as ligands for enantioselective catalysis.

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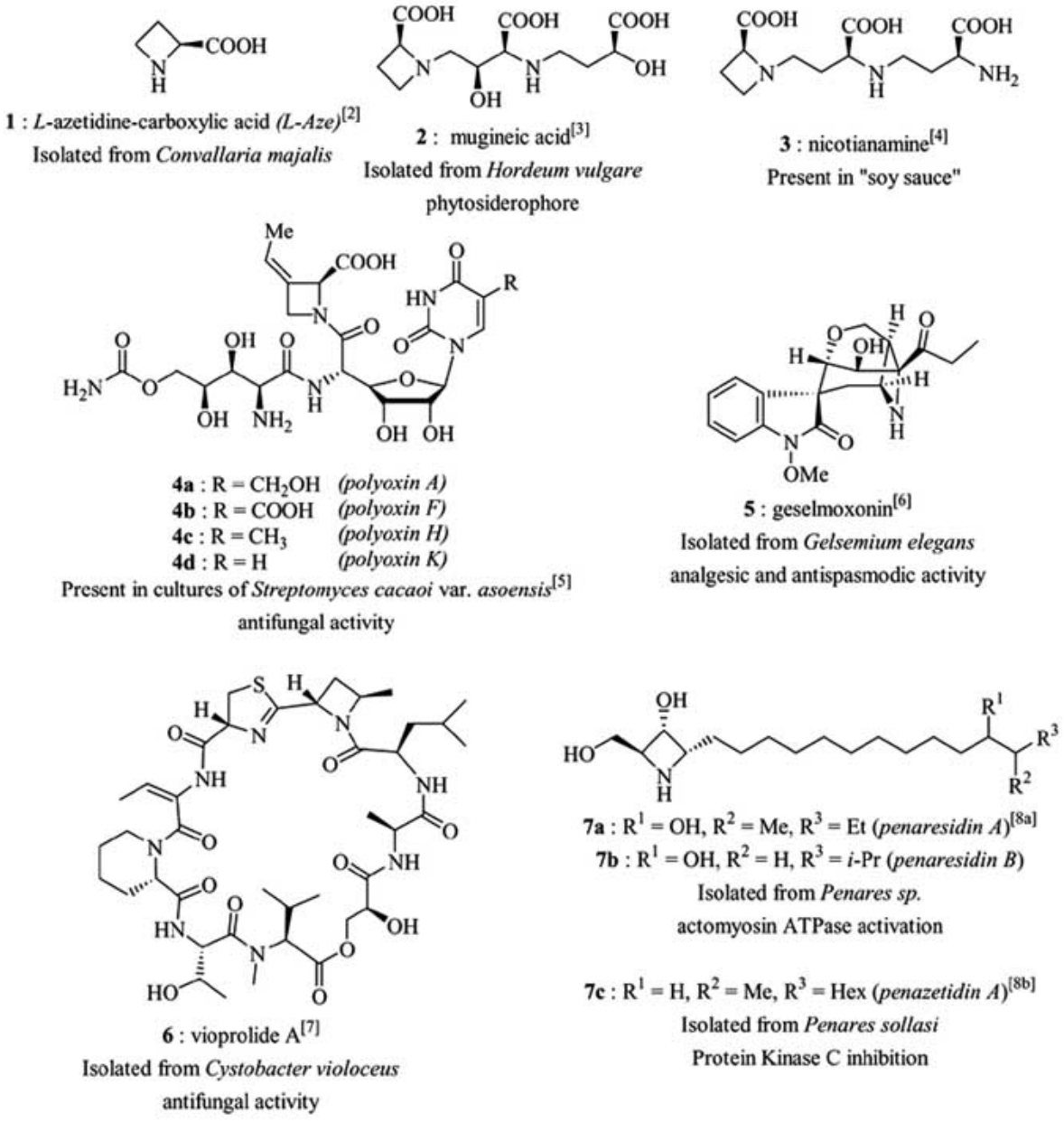
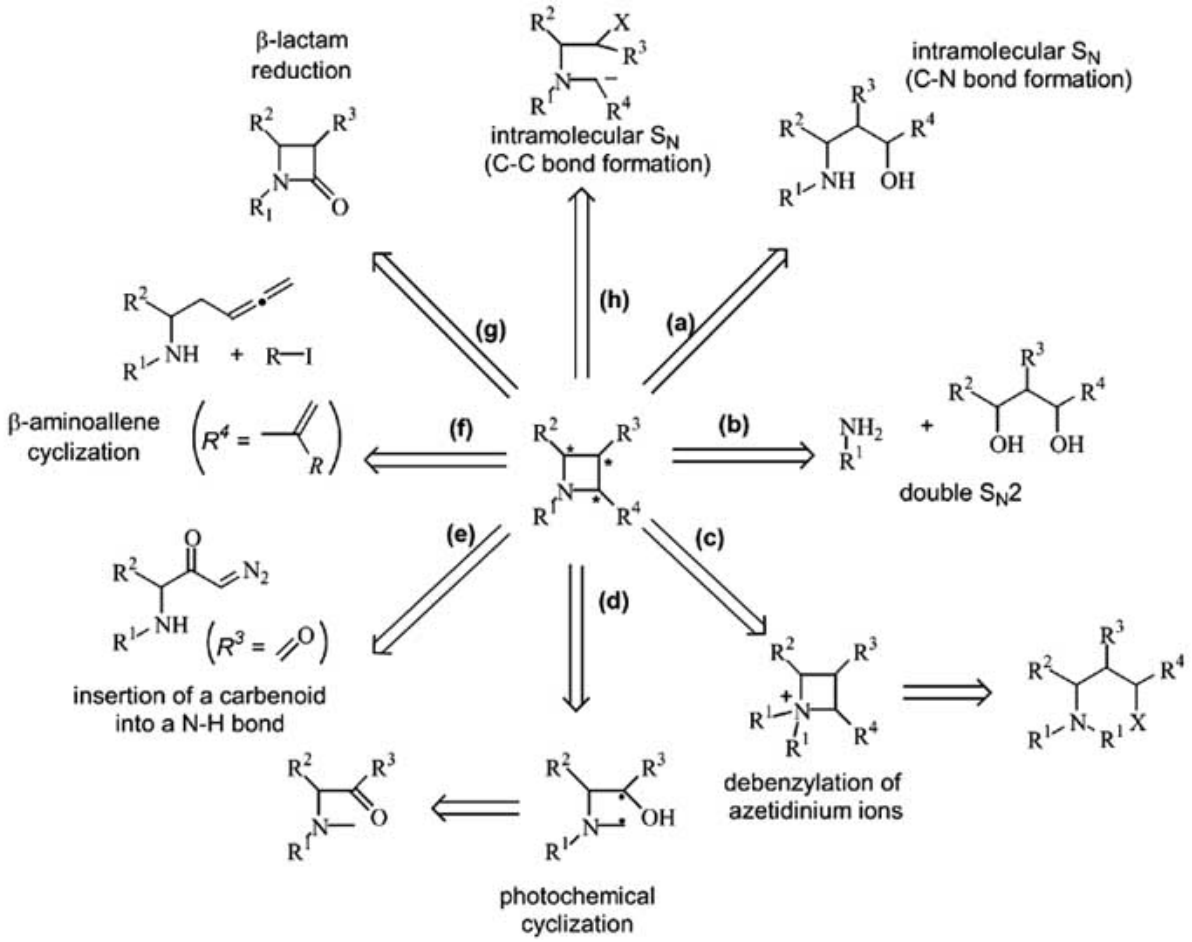


Scheme 1. Natural compounds including an azetidine ring.

I) Azetidines from 1,3-amino Alcohols

The intramolecular nucleophilic displacement of an activated alcohol (e.g., tosylate or mesylate) by an amine is certainly one of the most useful and reliable methods for the preparation of enantiopure azetidines, which makes 1,3-amino alcohols (Scheme **1**, disconnection a) the best substrates for the preparation of these heterocycles. However, this approach requires that the stereochemistry has already been established in previous steps using either chiral pool-derived cyclization precursors or stereoselective synthesis. This approach has been used in the synthesis of nicotianamine derivatives **3** [14], penaresidins **7** [15], conformationally constrained analogues of phenylalanine derived from natural amino acid **1** [16], other azetine 2-

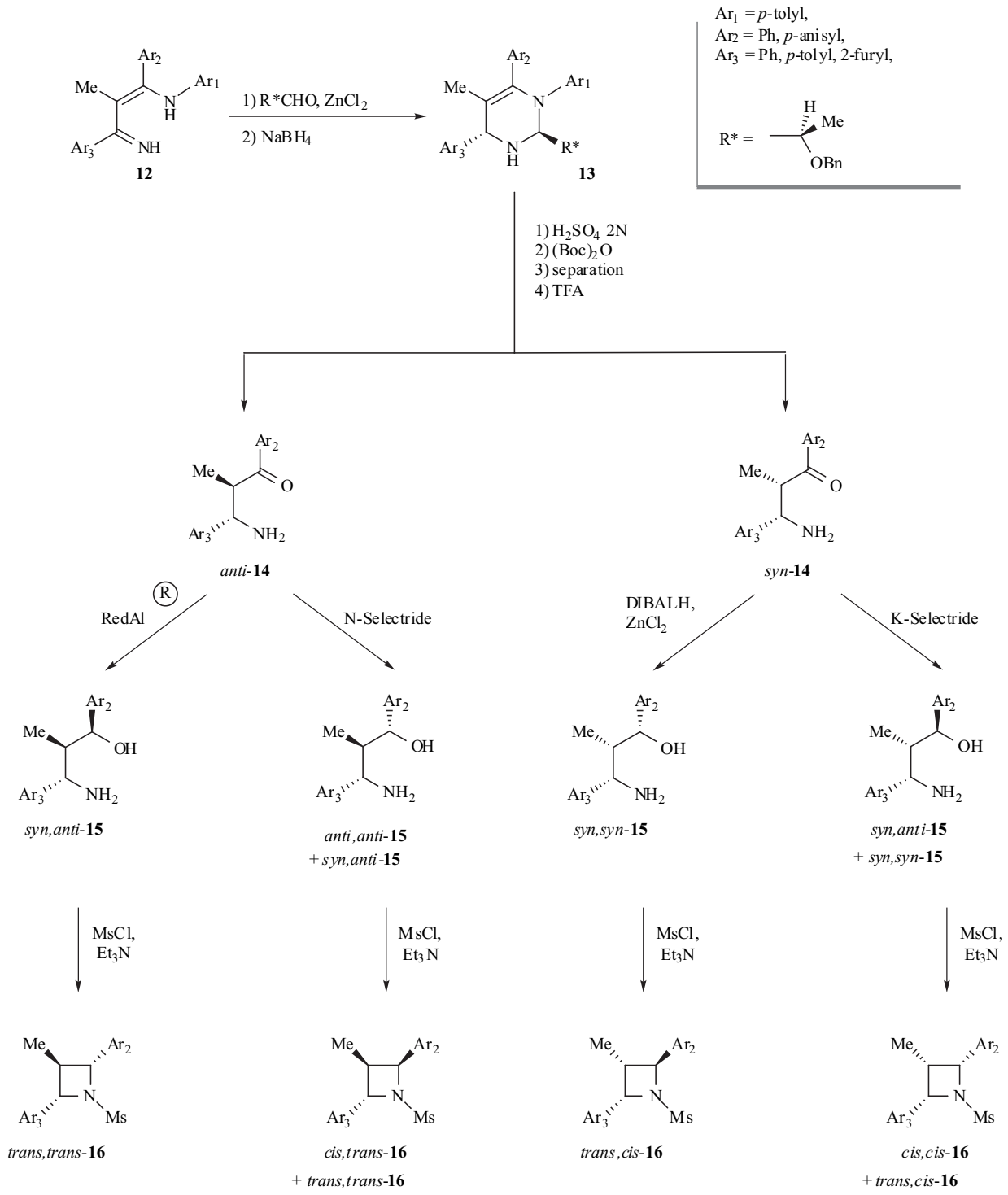


Scheme 2. Major retrosynthetic disconnections for the synthesis of enantiopure azetidines.

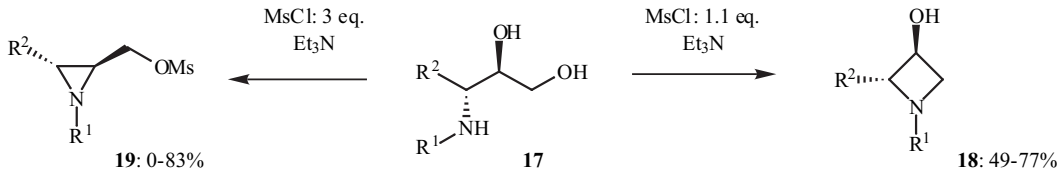
carboxylic acids [17], analogues of biologically active molecules such as Taxol® [18], nucleosides [19], and azetidine 2-phosphonic acids [20]. Barluenga has studied the scope of this intramolecular alkylation [21] in order to prepare all the possible diastereoisomers of a trisubstituted azetidine. For this purpose, all isomers of 1,3-amino alcohols **15** were prepared in enantiomerically pure form [22] starting from (*R*)-O-benzylactaldehyde-derived tetrahydropyrimidine **13** [23] and cyclized (MsCl, Et_3N) to afford azetidines **16**. This study highlights the fact that this cyclization does not always proceed through a stereospecific S_N2 pathway and that a S_N1 process can compete in some cases, especially for the production of the all *cis* isomer **16**.

Another report in this field merits a special comment, as it deals with the regioselectivity of this intramolecular alkylation. Thus, Pericàs [24] described the treatment of amino diol **17** with MsCl. The outcome of the reaction was shown to be highly dependent on the amount of MsCl used: while one equivalent gave the expected azetidine **18** through selective mesylation of the primary alcohol, followed by intramolecular alkylation, the use of three equivalents of MsCl gave aziridine **19**. In this case, bis-mesylation was followed by a 3-*exo*-*tet* intramolecular alkylation, this pathway being favoured compared to the 4-*exo*-*tet* cyclization (Scheme **4**).

The Mitsunobu reaction has also been used to achieve this cyclization. In order to obtain the cyclization precursors, an original and elegant access to enantiopure stereodefined 1,3-amino alcohols **21** was recently reported [25]. These substrates were prepared from enantiopure ethynyl aziridines **19**, readily accessible from amino acids. Generation of allenyl indium derivatives **20a,b** from these substrates followed by reaction with an aldehyde [26] afforded amino 1,3-amino alcohols **21**, which were in turn cyclized under Mitsunobu conditions. It is worth noting that by-products of elimination were obtained in some cases, depending on the



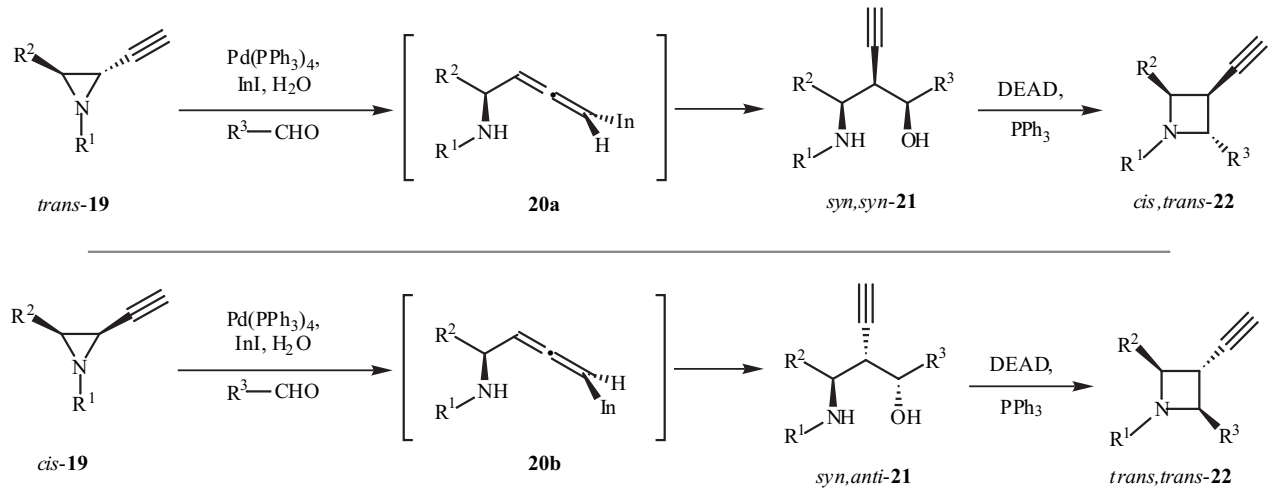
Scheme 3. Synthesis of all possible isomers of a trisubstituted azetidine through an intramolecular alkylation.



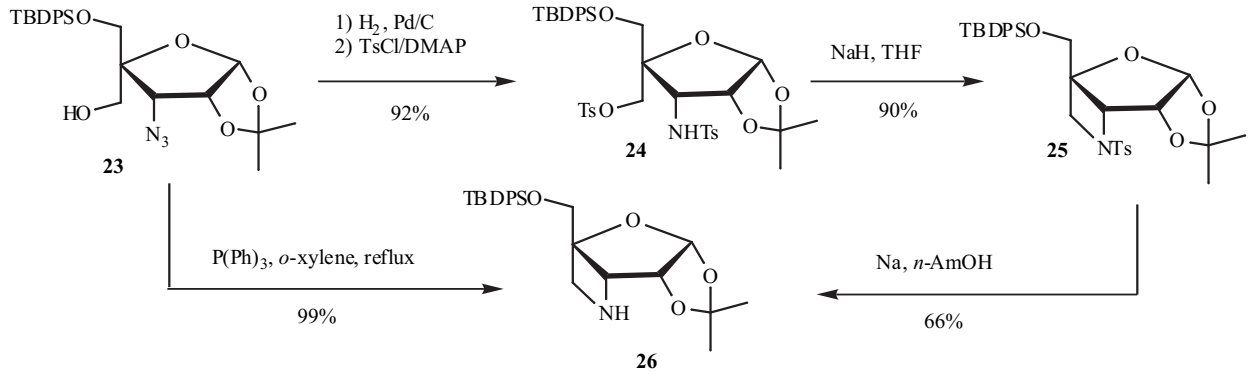
Scheme 4. 3-*exo-tet* cyclization is favoured compared to 4-*exo-tet* pathway.

substitution pattern and relative stereochemistry of the starting amino alcohol **21**. (Scheme **5**).

A Staudinger reaction was also used as a key step in an enantioselective synthesis of Penaresidin A [27]. A very



Scheme 5. Enantioselective synthesis of trisubstituted azetidines from aziridines.

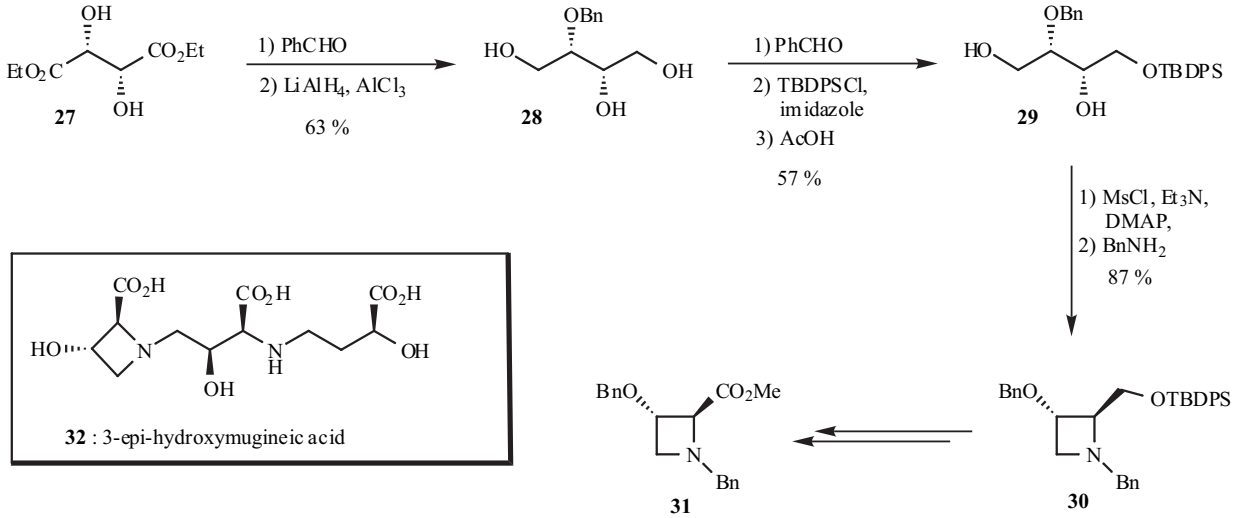


Scheme 6. Synthesis of an azetidine starting from an azido alcohol.

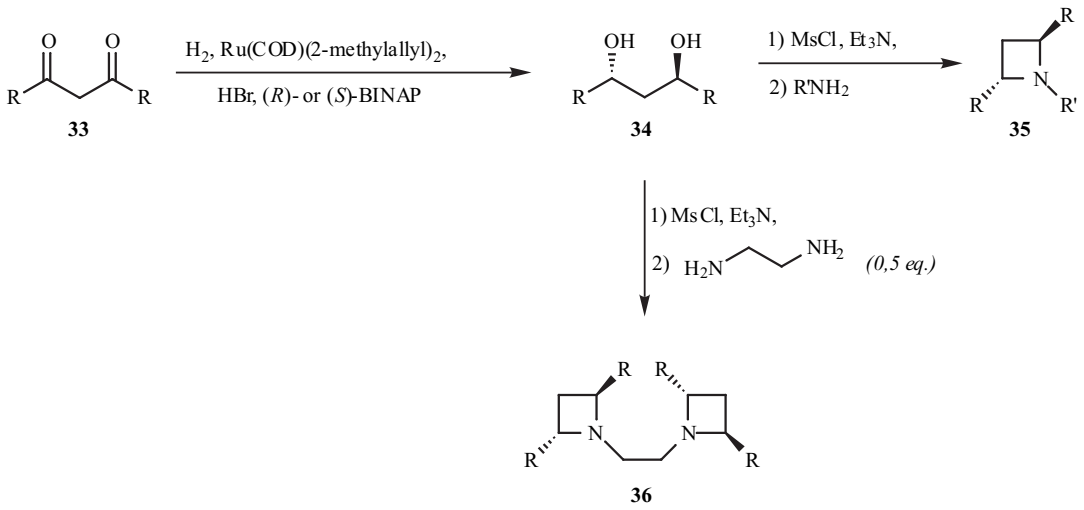
recent example should be described in detail here: Imanishi [19a] described the preparation of fused azetidine nucleoside derivatives. Two routes were employed to prepare azetidine **26**: a "classical" intramolecular alkylation via intermediate **24** and a straightforward one step cyclization from azide **23**. This isolated exemple of azetidine formation from an azido alcohol show an efficiency that surely merits further studies (Scheme **6**).

II) Azetidines Prepared Through Intermolecular Amine Alkylations of 1,3-*bis* Electrophilic Reagents

Retrosynthetic disconnection (b) outlined in Scheme **2** involves *bis*-alkylation of a primary amine using a 1,3-*bis* electrophilic reagent, which can either be a *bis*-sulfonate derived from a 1,3-diol or a 1,3-dibromo compound. Since 1,3-diols are available in enantiomerically pure form, they have been used for the synthesis of enantiopure azetidines.



Scheme 7. Synthesis of an azetidine starting from a 1,3-diol.



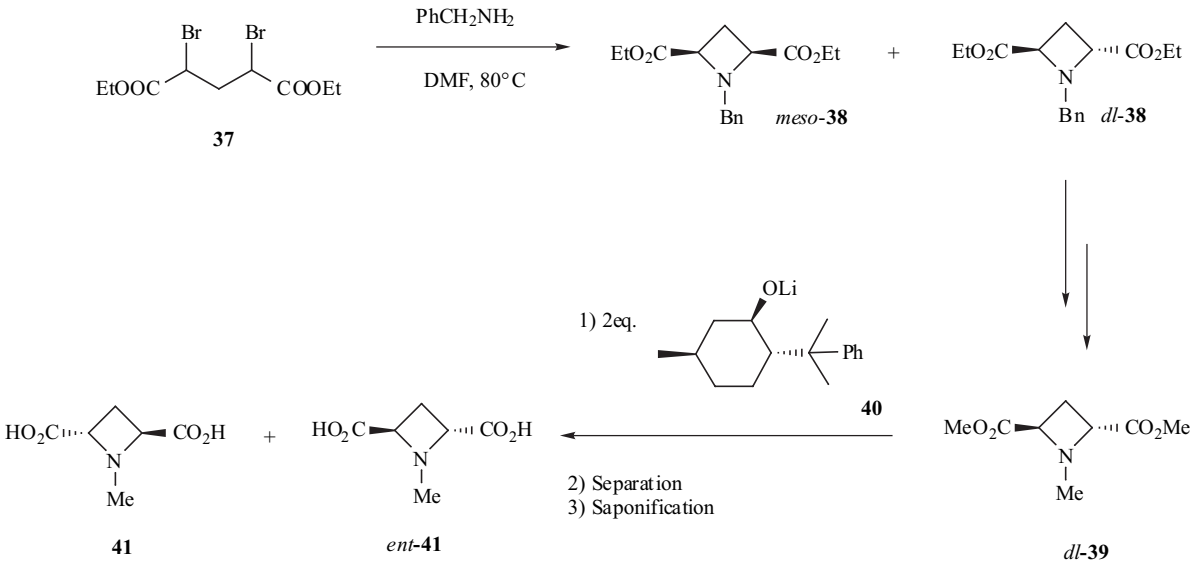
Scheme 8. Synthesis of C_2-symmetric azetidines.

One of the first examples involving this intermolecular alkylation was reported by Depezay [28] who synthetised the azetidinic core of 3-*epi*-hydroxymugineic acid **32** starting from (*L*)-diethyl tartrate **27** as a source of non-racemic material. Transformation of this compound gave diol **29** that was cyclized in good yield *via* its bis-mesylate to give azetidine **30** (Scheme **7**).

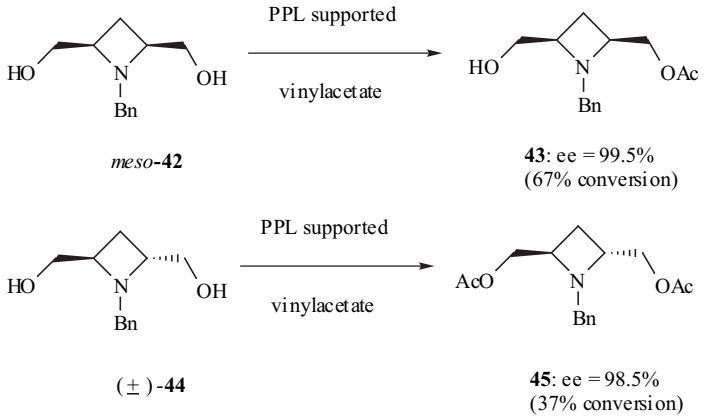
This synthetic strategy is particularly well-suited for the preparation of C_2 symmetric azetidines **35**. In an effort to prepare these azetidines, Genêt and Marinetti [29] recently described their synthesis from *anti*-1,3-diols **34** prepared by enantioselective reduction of the corresponding diketones **33** using [Ru/ (*R*) or (*S*)-BINAP] catalytic systems. After cyclization upon treatment with MsCl, the azetidines were obtained with ee higher than 95%. When 1,2-ethylenediamine was used for the cyclization step, *bis*-azetidine **36** was obtained. However, this *bis*-alkylation did not work with hindered diols (R = *i*-Pr in Scheme **8**).

Bis-electrophiles used for the double nucleophilic displacement can also be 1,3-dibromo derivatives. However, due to the lack of enantioselective access to these compounds, different methods have been employed to produce enantiopure azetidines from these dibromides. Kozikowski [30] first reported the resolution of *trans*-azetidine-2,4-dicarboxylic acids *via* their (-)-8-phenylmenthyl diester derivatives. Thus, alkylation of benzylamine with 1,3-dibromo diester **37** (mixture of *dl*-and *meso* isomers) gave separable isomers *dl*-**38** and *meso*-**38** [30b]. The *dl* isomer was then transformed into diester **39,** which was then transesterified with (-)-8-phenylmenthol alkoxide **40**. The resulting diastereoisomers could be separated and were finally saponified to give **41** and *ent*-**41** (Scheme **9**).

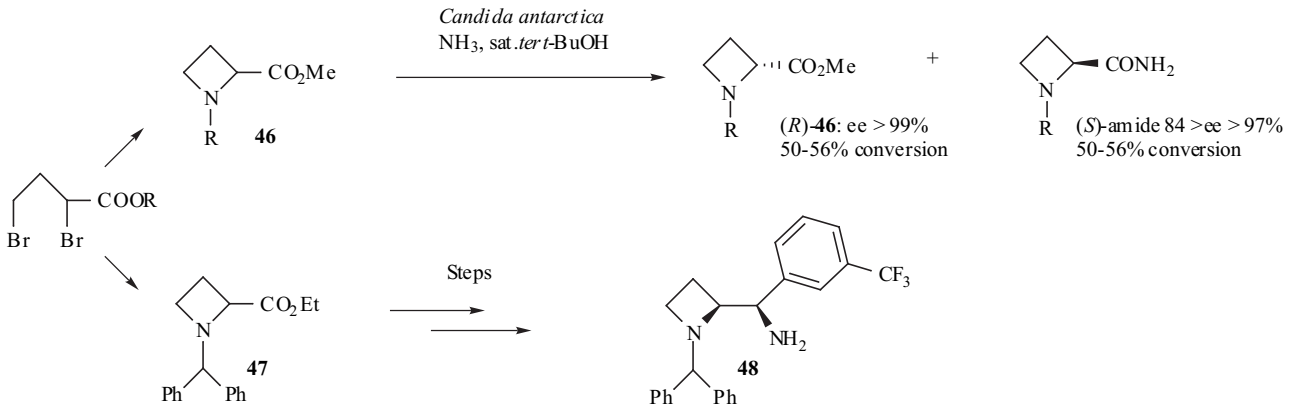
In 1995, two strategies were published in order to produce non-racemic 2,4-disubstituted azetidines. Yamamoto [31] first described the alkylation of **37** with enantiopure phenylethylamine, that is available in both enantiomerically pure forms. The so produced isomers could be separated by chromatography. Later on, Riva [32] devised an enzymatic desymmetrization of diol **42** and resolution of **44** with supported PPL lipase. The absolute configurations of the



Scheme 9. Synthesis of C_2-symmetric azetidines by resolution through their (-)-8-phenylmenthyl diesters.



Scheme 10. Enzymatic resolution of C_2-symmetric azetidines.



Scheme 11. Resolution of azetidines obtained by alkylation of 2,4-dibromobutyrate esters.

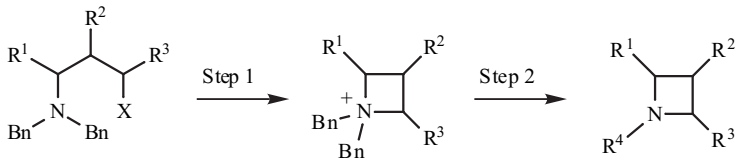
produced azetidines were recently determined (Scheme **10**) [33].

Zwanenburg also described an enzymatic resolution of racemic methyl ester **46**. This compound was produced by alkylation of allylic or benzylic amines with methyl 2,4-dibromobutyrate. Ammoniolysis of these esters catalyzed by *Candida antarctica* gave (*R*)-esters **46** with very high ee's [34]. We should also discuss the resolution of azetidine diamine **48** in this section: this diamine was prepared in a racemic form from azetidine **47**, itself prepared by the methodology described above [35]. In this case, enantiomers of **48** were resolved using chiral HPLC, and the absolute configuration was determined by X-ray crystallography of a tartrate salt. Compound (-)-(2*S*,3*R*)-**48** displayed potent activity as a novel ORL1 receptor ligand (Scheme **11**).

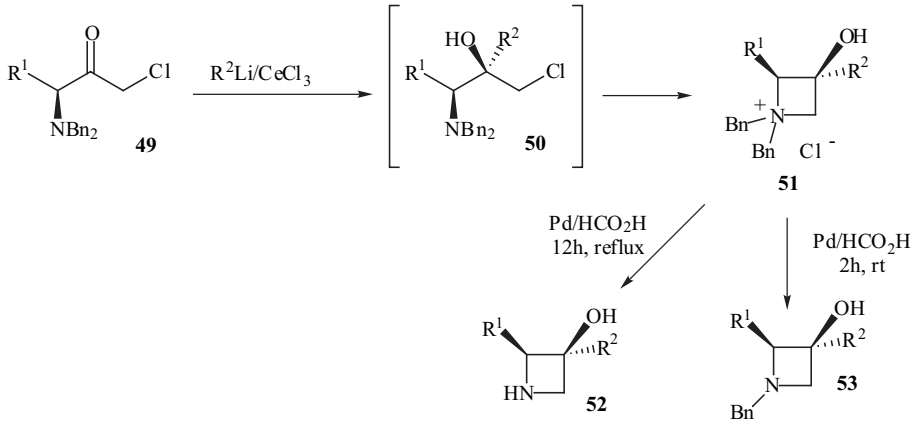
III) Azetidines Prepared through Intermolecular Amine Alkylations followed by Debenzylation of Intermediate Azetidiniums

As detailed above, intramolecular and double inter- and intramolecular nucleophilic substitutions are the two major methods for the synthesis of azetidines. Another approach is based on a two-step methodology (Scheme **12**), involving an internal alkylation of an haloaminohydrins (step 1) followed by debenzylation of an azetidinium salt (step 2) to afford the azetidine skeletton. If this method is conceptually close to the synthesis of azetidines starting from 1,3-amino alcohols, the reactions used are completely different.

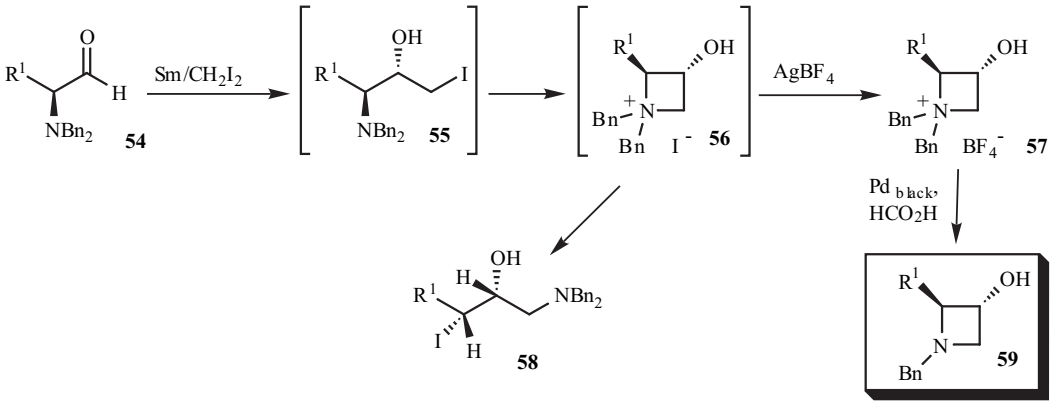
Enantiopure azetidinium salts were first reported by Barluenga in 1997 [36], as shown in Scheme **13**. The reaction of dibenzylaminoalkyl chloromethyl ketones **49** with various organocerium derivatives gave the corresponding chlorohydrins **50** in high yields, which spontaneously cyclized to the azetidinium salts **51** in high yields (74–84 %) and diastereoisomeric excesses (90 to 95%). Deprotection of these compounds was performed in the presence of palladium in HCO_2H (step 2). As shown in scheme **13**, variation of reaction conditions (2h, rt or 12h, reflux) induced a *mono*- or *bis*-debenzylation process and thus allowed for the selective preparation of either azetidinols **52** (90%) or *N*-benzylazetidinols **53** (95%) respectively.



Scheme 12. Debenzylation of azetidiniums produced by intramolecular alkylation.



Scheme 13. Synthesis of 3-hydroxy azetidines through debenzylation of intermediate azetidinium ions.

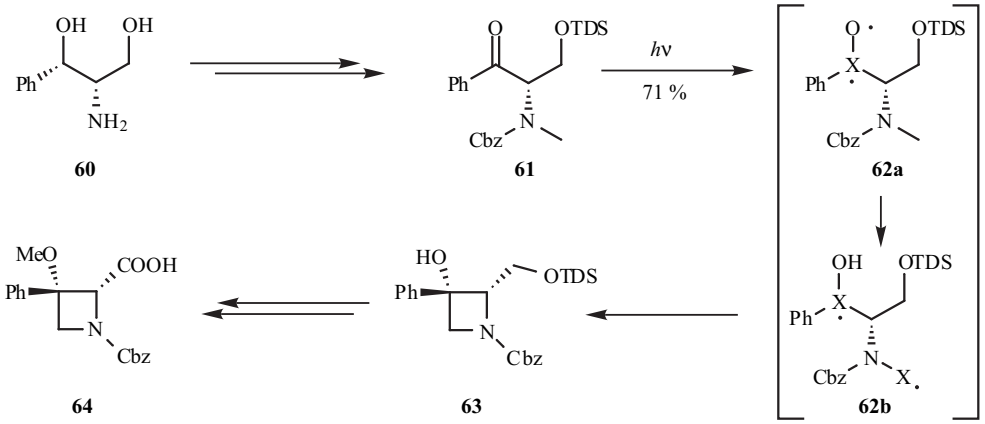


Scheme 14. Synthesis of 3-hydroxy azetidines by debenzylation of intermediate azetidiniums.

More recently, a similar approach has been reported by Concellón [37] (Scheme **14**). In this case, the intermediate azetidinium salts **56** were prepared in two steps starting from 2-dibenzylaminoaldehydes **54**. Upon treatment with diiodomethane and samarium iodide, the intermediate aminoiodohydrins were obtained under mild conditions in a diastereoselective manner (de 80%) and were transformed into enantiopure azetidinium salts by evaporation to dryness. Those azetidinium iodides proved to be highly unstable and were rapidly opened by the iodide, yielding a new iodohydrin **58**. They could however be stabilized using a counterion less nucleophilic than iodide: treatment of the azetidinium salt **56** with $AgBF_4$ afforded the azetidinium tetrafluoroborate salts **57** as stable compounds. Finally, hydrogenolysis gave the monodebenzylated azetidines **59** in almost quantitative yields.

IV) Azetidines Prepared through Photochemical Cyclization

An interesting approach to azetidin-3-ols, based on a photochemical cyclization was disclosed by Schwartz [38]. Although illustrated by a single example, this strategy is the first one in which the azetidine ring is prepared through a



Scheme 15. Synthesis of 3-hydroxy azetidines through photochemical ring-closure.

ring closure involving a C-C bond formation. Apart from disconnection (h), (*vide infra*), this is the only azetidine synthesis based on such bond formation. Thus, commercially available amino diol **60** was converted into amino ketone **61** in 7 steps. This compound cleanly cyclized through diradical intermediate **62b** to stereoselectively give azetidine **63**, which was next converted into azetidine-2-carboxylic acid **64** (Scheme **15**).

V) Azetidines through Insertion of Carbenoids into N-H Bonds

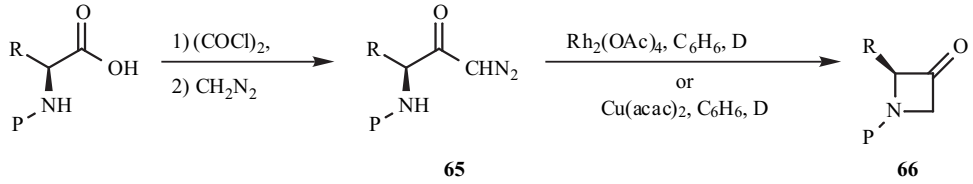
Homochiral 3-oxo-azetidines **66** can be prepared from N-protected α-amino acids, after conversion into a diazoketone **65**. This compound upon heating in the presence of catalytic amounts of $Rh_2(OAc)_4$ [39] or $Cu(acac)_2$ [40] undergoes ring closure through insertion of carbenoid species into the N-H bond, following disconnection (e) in Scheme **2**, to give 3-oxo-azetidines in fair yields (34-66% : Scheme **16**).

It should be noted that this reaction has met with great success over the past few years for the synthesis of β-lactams (2-oxo-azetidines), culminating with Merck's industrial synthesis of thienamycin [41]. Formation of the azetidine ring from the diazoketone may also be catalysed by silver salts, although in this case a Wolf rearrangement leading to the acyclic β-amino acid may compete [42].

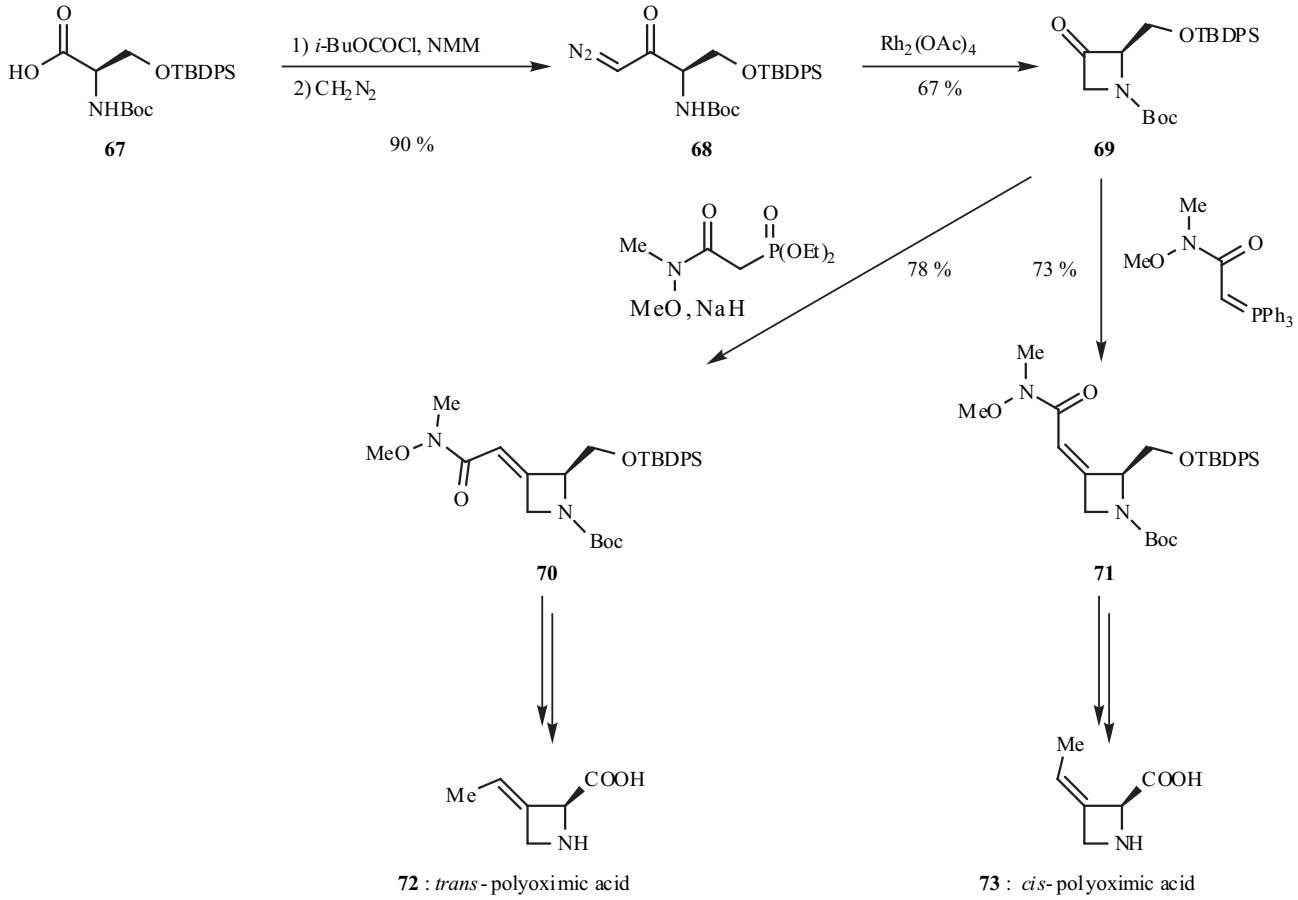
This efficient methodolgy, allowing access in four-steps to homochiral azetidin-3-ones was used by Hanessian [43] in a synthesis of *cis*- and *trans*- polyoxomic acids **72** and **73** (Scheme **17**), thereby establishing the stereochemistry of the exocyclic alkene found in natural polyoxines (Cf. Scheme **1**).

VI) Azetidines Prepared through Cyclization of β-Aminoallenes

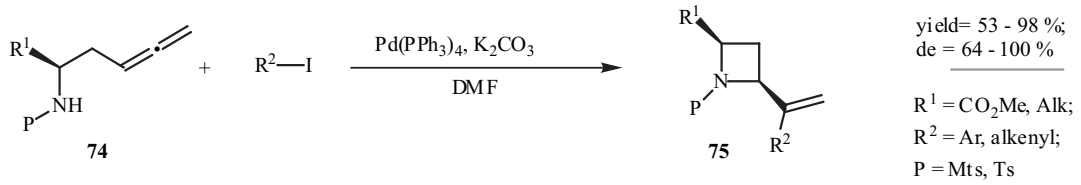
Intramolecular Pd-catalysed aminocyclization of enantiopure β-aminoallenes is an emerging elegant synthetic methodology for the preparation of functionalized azetidines



Scheme 16. Synthesis of 3-oxo azetidines through carbenoid insertion.



Scheme 17. Synthesis of *cis*- and *trans*- polyoximic acids through carbenoid insertion.



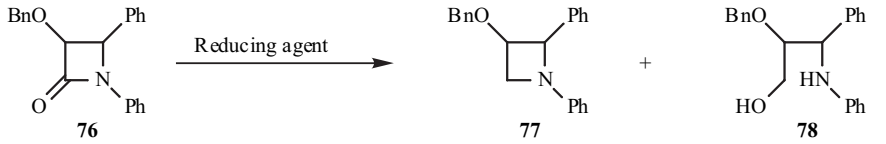
Scheme 18. Synthesis of *cis*-alkenylazetidines through Pd-catalysed cyclization of enantiopure β-aminoallenes.

(disconnection (f) in Scheme **2**). This reaction, depicted in Scheme **18**, was almost simultaneously reported by Hiemstra [44] and Ibuka [45]. It involves the reaction of an enantiopure β-aminoallene with a palladium (0) catalyst, potassium carbonate, and an aryl or alkenyl iodide. This reaction affords in good yields 2,4-*cis* azetidines **75**. The high *cis*- diastereoselectivity observed in this reaction was explained by Ibuka [45b] on the basis of steric interactions in the intermediate π-allyl palladium complexes. The starting enantiopure β-aminoallenes required as substrates were prepared either from available β-aminoalcohols [46] or from enzymatic resolution of allenyl glycine.

It should be noted that in some cases, a 6-*endo-trig* process, leading to a tetrahydropyridine was competitive.

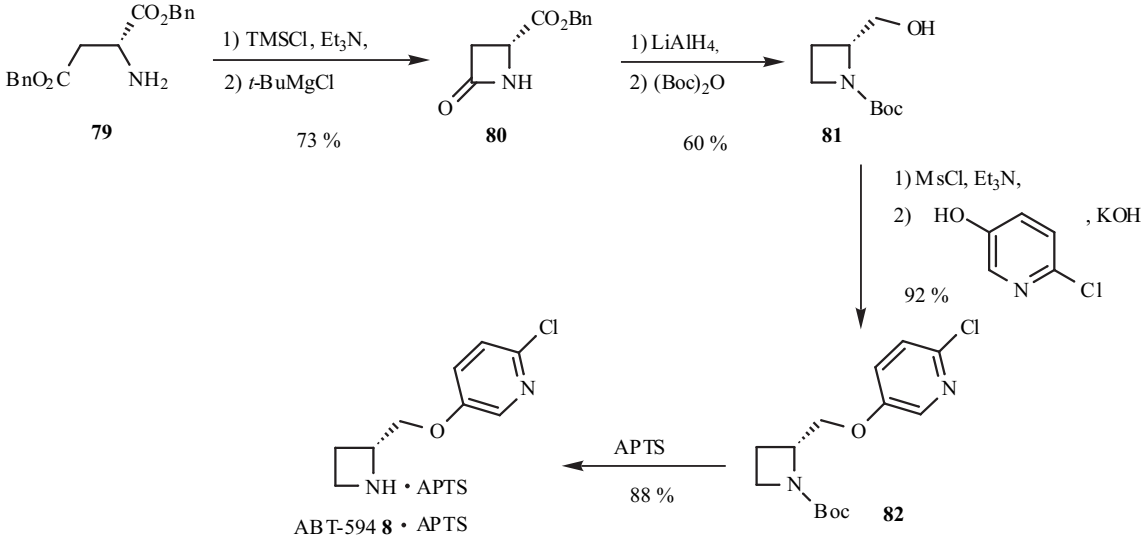
VII) Azetidines Prepared through Reduction of β-Lactams

Due to the huge number of synthetic methodologies available to prepare β-lactams [11], their simple reduction into an azetidine following disconnection (g), (Scheme **2**) is of great interest. However, this reduction can lead either to the desired azetidine or to a γ-amino alcohol, and the optimization of the reaction conditions in order to produce



Reducing agent	77	78
BH_3• THF	No reaction	
$NaBH_4$ - $AlCl_3$	No reaction	
$LiAlH_4$	-	Sole product
$LiBEt_3H$	-	Sole product
$LiB(s\text{-}Bu)_3H$	-	Sole product
DIBALH	73 %	16 %
AlH_2Cl	94 %	-
$AlHCl_2$	94 %	-
AlH_3	29 %	59 %

Scheme 19. Azetidines are produced from β-lactams through reduction with mono or dichloroalane.



Scheme 20. Synthesis of ABT-594 using Ojima's procedure.

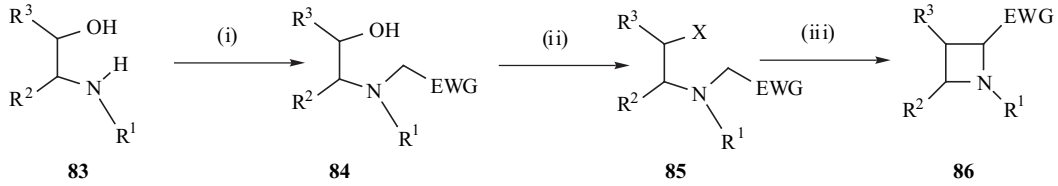
an azetidine was studied by Ojima [47]. As reported by this group, and depicted in Scheme **19**, the nature of the reducing agent employed is very important: monochloro, or dichloroalane gave excellent yields of azetidines **77**, while $LiAlH_4$ exclusively gave ring opening product **78**.

The use of this Ojima's procedure to prepare azetidines is underrated in the literature [48]. It was however, reported [49] to be the key step of an efficient synthesis of ABT-594 **8** and other analogues in the context of a structure-activity research program developed by Abbott (Scheme **20**).

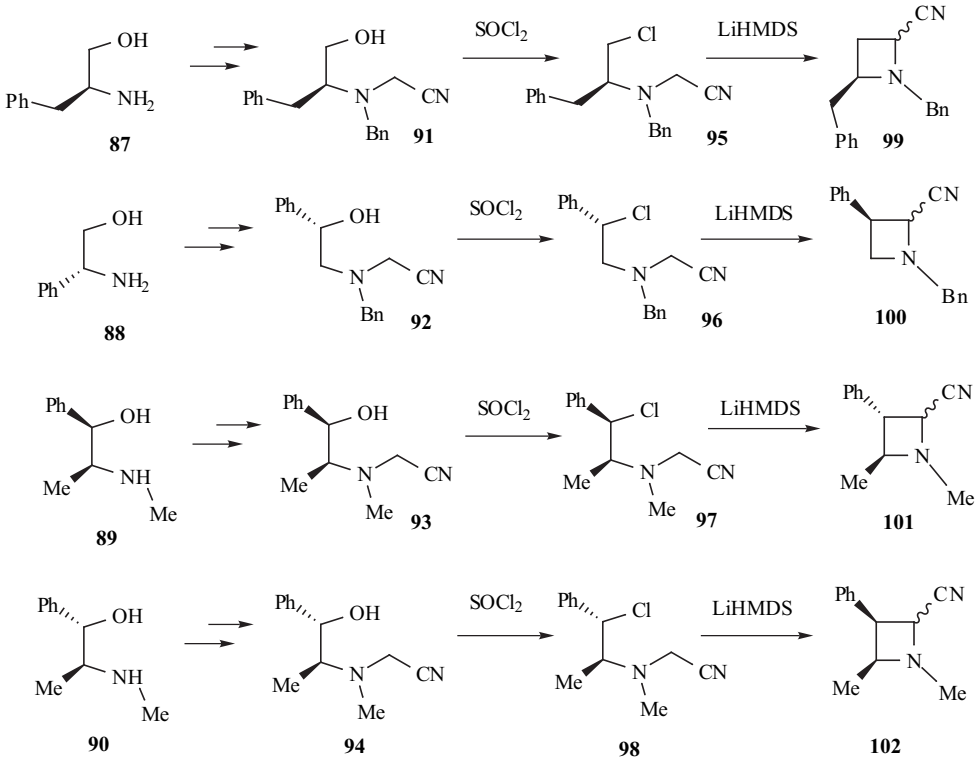
VIII) Azetidines Prepared through Intramolecular C-Alkylations

The last section devoted to the synthesis of non-racemic azetidines details the methodologies based on disconnection (h) in Scheme **2**. With the exception of disconnection (f), which is, as previously mentioned, illustrated by a single example, this last disconnection appears to be the only one based on the formation of a C-C bond. As it will be described hereafter, it is however of broad scope and particularly well-suited to the synthesis of non-racemic azetidines since the required starting material is a β-amino alcohol, easily available in enantiomerically pure form. This methodology requires a three-steps sequence from the latter compound in order to form the azetidine ring: (i) *N*-alkylation with a methylene bearing moiety able to stabilise a carbanionic species, (ii) activation of the β-hydroxyl function that is transformed into a leaving group and (iii) an intramolecular S_N2 C-alkylation (4-*exo*-*tet* cyclization) induced by deprotonation of the methylene adjacent to the electron withdrawing group (Scheme **21**).

This synthetic sequence offers two main advantages over the other routes presented in this review. First, it requires only easily available starting material and a few synthetic steps. Furthermore, the electron-withdrawing group on the azetidine allows for further transformations. Despite its appealing simplicity, this synthesis was only described recently: in 2002, we reported a preparation of 2-cyano azetidines based on this concept [50]. Commercially available β-amino alcohols **87**-**89** were first *N*-benzylated (**87** and **88**) and *N*-cyanomethylated to give **91**-**94**. Chlorination of these alcohols ($SOCl_2$) proved to be highly stereoselective, yielding chlorinated amines **95**-**98** with retention of configuration. Furthermore, (*R*)-phenyl glycinol-derived amino alcohol **92** gave rearranged chloride **96**. These results can be explained by the formation of an intermediate aziridinium ion, which is regioselectively opened by the chloride anion at the benzylic (**A**) or less hindered (**B**) position (Fig (**2**)). Intramolecular alkylation of these



Scheme 21. Disconnection (h) in Scheme **2** requires β-amino alcohols as starting material.



Scheme 22. Synthesis of 2-cyano azetidines from commercially available enantiopure β-amino alcohols.

substrates was achieved by treatment with LiHMDS to give 2-cyano azetidines in good yields (71-91%) but with a low diastereoselectivity, the 2,3-*trans* isomers being usually produced as major isomers. It is worthy to note that all these isomers could be easily (with the exception of **99**) separated by flash chromatography (Scheme **22**).

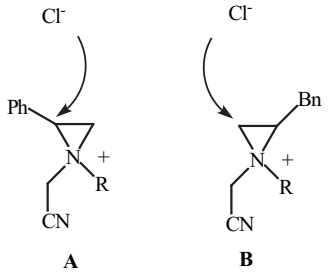
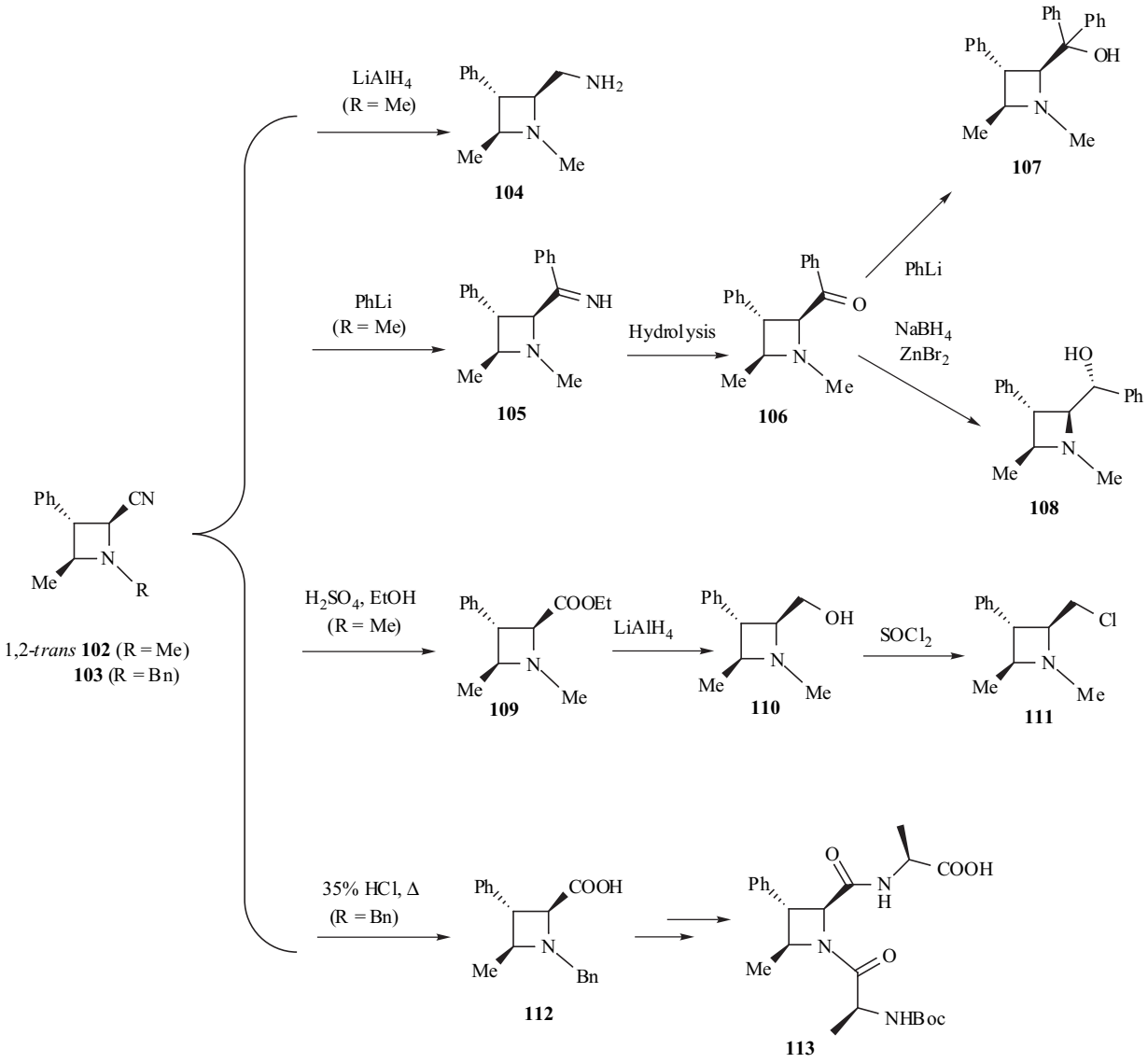


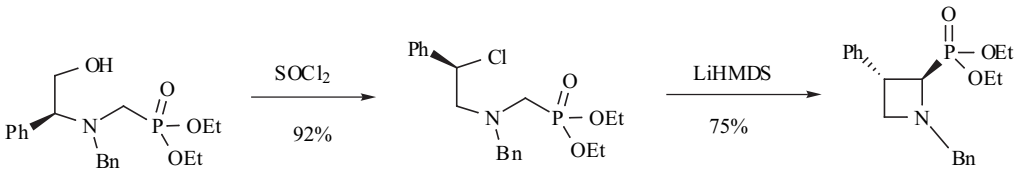
Fig (2). Regioselective opening of intermediate aziridinium ions explains the stereoselectivity of the chlorination observed for benzylic (**A**) or alkyl-substituted (**B**) amino alcohols **91**-**94**.

The cyano moiety introduced into these heterocycles was later shown to be particularly versatile. It could be reduced ($LiAlH_4$) into a primary amine **104** [51], transformed into a ketone **106** by addition of an organolithium reagent, followed by hydrolysis of the intermediate imine **105** [52]. This ketoazetidine **106** could be transformed into α-hydroxyazetidines **107** and **108** respectively by addition of PhLi or diastereoselective reduction [52]. The nitrile could also be transformed into an ester **109** that was reduced into a primary alcohol **110** and transformed into the primary chloride **111** [53]. Finally, and this is the most well-known transformation of amino nitriles, acidic hydrolysis afforded the corresponding amino acid **112** that could be incorporated in a peptidic sequence **113** (Scheme **23**) [54].

The cyano group could also be replaced by other electron withdrawing groups. Esters were operative in this synthetic sequence, but diastereoselectivity was not enhanced. The use of phosphonates allowed the first asymmetric synthesis of azetidinic 2-phosphonic acids [55]. In this case, the bulkiness of the phosphonate moiety induced a high diastereoselectivity for the anionic cyclization, the 2,3-*trans* azetidine **116** being the only observable isomer produced from chloride **115**, as shown in Scheme **24**.

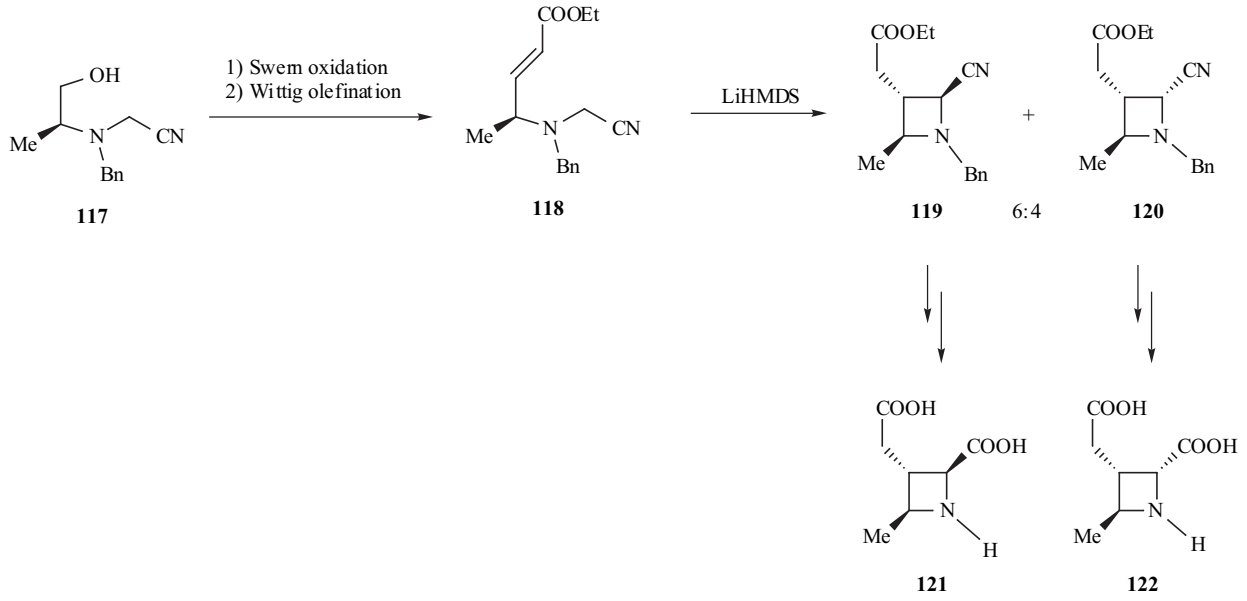


Scheme 23. Synthetic versatility of the 2-cyano azetidines.



114 **115** **116**

Scheme 24. A phosphonate group induces a high diastereoselectivity in anionic cyclization leading to azetidines.



117 **118** **119** **120** **121** **122**

Scheme 25. Synthesis of azetidines by intramolecular Michael addition.

In order to close this section, it should be mentioned that the nature of the electrophilic partner may also vary in this anionic cyclization. Indeed, it was possible to prepare azetidines using an intramolecular Michael addition involving an unsaturated ester as Michael acceptor. For this purpose, amino ester **118** was prepared in a one-pot sequence involving Swern oxidation followed by Wittig olefination. This operation was shown to afford the desired amino ester without racemization. Treatment of this compound with LiHMDS induced a stereoselective 4-*exo*-*trig* cyclization, affording azetidines **119** and **120** as separable products. The diastereoselectivity of this unprecedented intramolecular Michael addition [56] leading to a four-membered heterocycle was shown to be the result of thermodynamic control. The obtained azetidines were then transformed in good overall yields into conformationally constrained analogues of NMDA **121** and **122** (Scheme **25**).

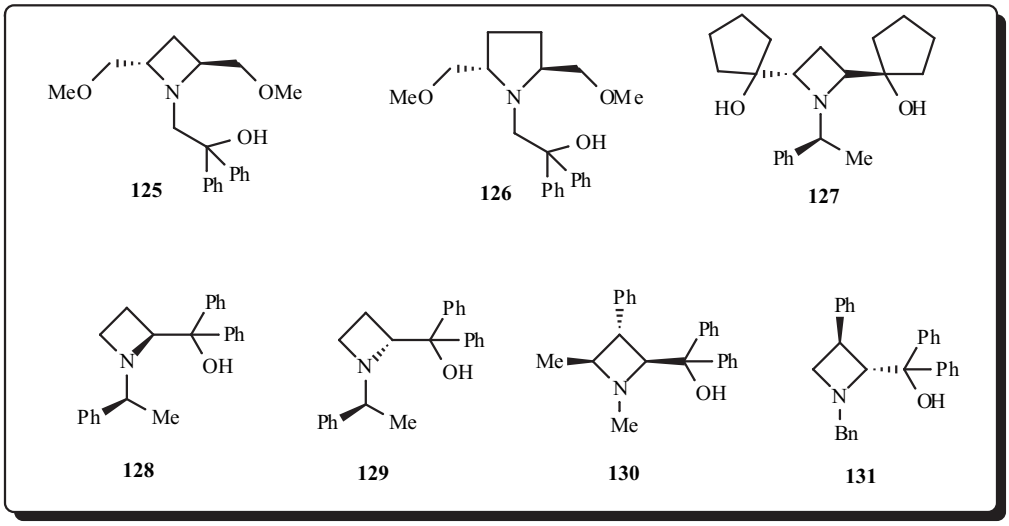
IX) Azetidines Used as Ligands in Enantioselective Catalysis

To date, because of their difficult access in enantiomerically pure form, azetidines have not been much used as ligands in enantioselective catalysis. Yet, the steric congestion brought by the small size of this heterocycle is expected to be a favourable parameter for the discrimination of prochiral moieties and enhance the enantioselectivity of catalytic processes using such ligands. The last section of this review will present an overview on the use of these strained hetereocyles in enantioselective catalysis.

The pioneering work in this field is due to Rama Rao [57a] and Martens [57b] who reported in 1992, the enantioselective reduction of several aromatic ketones catalysed by oxazaborolidine **123**. This compound was prepared following the procedure described above for the preparation of **47**, an intermediate azetidine 2-carboxylic acid being resolved with (*L*)-tyrosine hydrazide. As noticed by the authors [57a], "the steric influence brought by the more rigid four-membered ring compared to the five-membered ring was expected to improve the enantioselectivity of the reduction". This was indeed the case, and oxazaborolidine **123** furnished the reduced ketones with 95-97% ee. Martens reported next year [58] the use of azetidine **124** as a chiral catalyst in the enantioselective addition of diethylzinc onto aromatic aldehydes. He also noticed an improvement of the enantioselectivity compared to the use of the proline-derived homologues.

123 **124**

This last reaction was then extensively studied using azetidine ligands. In 1999, Shi reported [59] the synthesis of various C_2-symmetric 2,4-disubstituted azetidines prepared following Yamamoto's procedure [31], and their use as

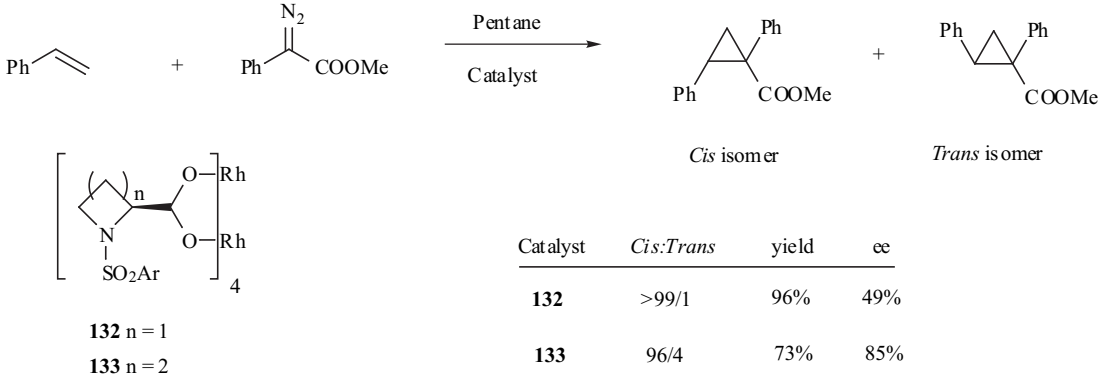


catalysts in this reaction. The best catalyst in terms of enantioselectivity was shown to be the tridentate ligand **125**, which gave alcohols with ee ranging from 63 to 92%. Although this catalyst was less efficient than the tertiary alcohol **124**, Shi again noticed an improvement compared to the five-membered ring homologue **126**: this compound catalysed the enantioselective addition of diethyl zinc onto *p*-chloroacetophenone with a 76% ee while **125** used in this reaction gave a 92% ee. Martens [60] reported the use of other C_2-symmetric azetidines such as **127** in this reaction, but with no improvement.

More recently, Zwanenburg [61] described the use of catalysts **128** and **129**: if **128** gave low selectivity, probably due to a mismatched effect of the external stereocenter, **129** was very efficient and showed a marked improvement compared to **124** for the enantioselective addition of diethyl zinc on aliphatic aldehydes, with ee ranging from 77 to 97%. Finally, we described recently azetidine catalysts **130** and **131** for this reaction [52], these compounds being prepared from 2-cyano azetidines, as depicted in scheme **23**. These ligands were shown to be very efficient catalysts: for example **130** gave enantioselectivities of 98 and 81% respectively for benzaldehyde and nonanal.

Azetidine ligands were also used with more or less success in other catalyzed reactions. Zwanenburg [62] reported the use of homochiral rhodium(II) azetidine-(2*S*)-carboxylate complex **132** for enantioselective cyclopropanation. In this case, compared to the five-membered ring homologue derived from proline, **132** was found to be generally more efficient in terms of diastereoselectivity, providing *cis*- and *trans*-isomers with higher ratios, but with lower enantioselectivity as depicted in Scheme **26**. The same observation was made by Zwanenburg [63] for azetidine based ligands in the BBr_3 catalyzed asymmetric Diels-Alder reactions: while enantioselectivity was lowered compared to the five-membered ring homologues catalysts, the diastereoselectivity (*endo*/*exo* ratio) was increased.

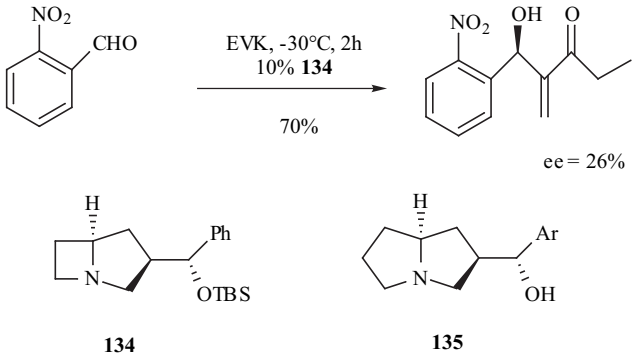
Azetidine catalysts appear in two other reactions: the asymmetric Michael addition of malonate anions to prochiral acceptors catalysed by rubidium salts of amino acids [64] and a Baylis-Hillman reaction [65]. While in the former reaction no improvement was noted compared to proline-derived catalysts, the second reaction merits further details. In this work, Barrett described an isolated example of the use of bicyclic azetidine **134** used as a catalyst for the reaction depicted in Scheme **27**. Although the ee obtained for the Baylis-Hillman adduct was low, the author noticed a marked improvement in kinetic of the reaction, compared to catalyst **135**. This was attributed to the particular strain present in catalyst **134** that induced a pyramidalisation of the lone pair of nitrogen, which is a favourable parameter for the Baylis-Hillman reaction. In this work, although the long and difficult synthesis of **134** precluded further studies, the



Catalyst	*Cis:Trans*	yield	ee
132	>99/1	96%	49%
133	96/4	73%	85%

Scheme 26. Enantioselective cyclopropanation catalysed by azetidine and pyrrolidine-derived rhodium catalysts.

azetidine strain is fully exploited for the preparation of an original and promising catalyst.



134 **135**

Scheme 27. A bicyclic azetidine **134** used as a catalyst in the Baylis-Hillman reaction.

CONCLUSION

As shown in this mini-review, synthetic methodologies used for the preparation of chiral non-racemic azetidines can be discussed in few pages. However, convenient synthetic procedures on a multigram scale of functionalized azetidines from readily available β-amino alcohols and β-amino aldehydes and involving disconnections (h) and (c) in Scheme **2** have appeared quite recently. No doubt these new routes to enantiopure functionalized azetidines will be illustrated in the near future by interesting applications, mainly in the field of medicinal chemistry and enantioselective catalysis.

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