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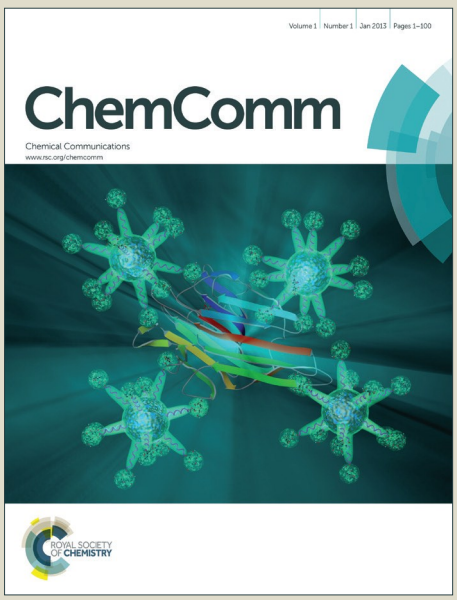

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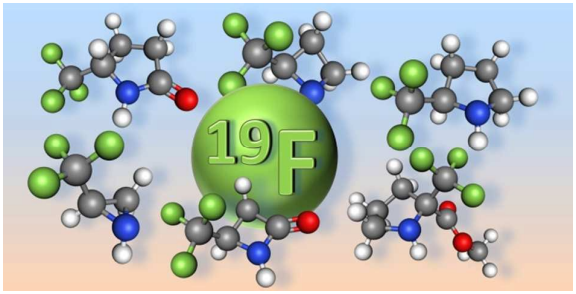
The synthetic methodologies and the potential biological targets of α-trifluoromethylated nitrogen heterocycles are presented.



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ARTICLE

Trifluoromethyl nitrogen heterocycles: synthetic aspects and potential biological targets

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Recent advances regarding the synthetic chemistry of fluorinated aziridines, azetidines, pyrrolidines and their lactam/amino acid counterparts are presented. These heterocycles are of high importance both as building blocks for more complex structures and as active parts of medicinal chemistry-oriented compounds.

Introduction

After the isolation of elemental fluorine in 1886 by Henri Moissan, the development of fluorination methodologies has been an ongoing topic of extensive research.[1] Indeed, fluorinated compounds have opened new opportunities inherent to the remarkable physico-chemical properties of fluorine which stem from the combination of a small size (van der Waals radius ~ 1.47 Å), a strong electronegativity and a low polarizability. For instance, fluorine appears isostere of oxygen but bigger than hydrogen, a CF_3 group is comparable in size to an isopropyl group and the C-F bond possesses one of the highest bond-dissociation energy (~485 kJ.mol^{-1}).[2] Typically, highly fluorinated components exhibit valuable advantages such as high thermal, light and chemical stability, oil and water repellency, low dielectric constants and low flammability. This behaviour appeared profitable in many different fields, ranging from functional materials[3,4] and polymer science,[5,6] to pharmaceuticals and molecular biology.[7,8]

Fluorination also appears of particular relevance in drug design since approximately 25% of all marketed drugs contain fluorine.[9] Thus, the incorporation of a fluorinated group in biologically active molecules will significantly affect their electronic and binding properties, metabolic stability, lipophilicity, and *p*Ka. For instance, a popular trend in drug design lies in the classical bioisostere substitution of hydrogens with fluorines.[10] To address this issue, a great deal of effort is dedicated to the elaboration of new strategies of mono-,[11] di- and trifluoromethylation, a particular attention being devoted to the trifluoromethylated compounds.[12,13]

Nitrogen heterocycles are frequently encountered in natural products and bioactive ingredients. Small nitrogen heterocycles including aziridines[14,15] and azetidines[16,17] exhibit high potential for further design of enantiopure N-containing molecules, owing to their facile ring opening by nucleophiles.[18] These building blocks are also often found in biologically active compounds[19,20] and their fluorinated counterparts can be integrated in the elaboration of amino acids to create modified peptides and proteins with special features.[21] Similarly, five-membered rings containing nitrogen such as pyrrolidine, proline and glutamic acid present a distinct appeal due to their application as pharmaceuticals, catalytic systems[22] and their role in the conformation of peptides.[23,24]

Here, we propose to highlight the current methodologies applied for the synthesis of α-trifluoromethylated nitrogen heterocycles possessing 3 to 5 membered rings. The formation of these fluorinated compounds was carried out according to various racemic and asymmetric strategies. In this regard, the document is divided as a function of ring size and subsections take into consideration the immediate precursor of these α-trifluoromethylated components. In addition, we mention the main biological target and/or the hydrogenated analogue, when reported, in order to shed light on the potential pharmaceutical application of these fluorinated molecules.

1 Trifluoromethyl-aziridines

1.1. Synthesis of trifluoromethyl-aziridines from fluorinated amines

The preparation of trifluoromethyl-aziridines has been widely reported through cyclization reactions of fluorinated amines. According to multistep chemical sequences, these building blocks were mainly obtained from epoxide or imine due to the ease to install a trifluoromethyl group close to a nitrogen atom. Indeed, only few commercially available synthons are at our disposal for the elaboration of complex molecules. For instance, Uneyama and coworkers disclosed the synthesis of trifluoromethyl-aziridines **1** from (*S*)-3,3,3-trifluoropropene oxide as source of chirality. In the presence of benzylamine, a ring opening reaction provided the fluorinated compound **2** in 85% yield with an enantiomeric excess (*e.e.*) of 99.5% after successive recrystallization steps. The subsequent ring closure reaction with dichlorotriphenylphosphorane gave aziridine **1a** in good yield and enantiomerically pure (*e.e.* of 99.5%) (Figure 1).[25] Later, a modified procedure described the ring opening of (*S*)-3,3,3-trifluoropropene oxide with aqueous NH_3, followed

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by a one pot *N*- and *O*-tosylation step. However, cyclization of amine **3a** led to cycloadduct **1b** in only 31% yield[26] but an improved strategy using an intramolecular Mitsunobu reaction provided the desired compound in 91% yield (Figure 1).[27] In 2013, this synthetic approach was employed by Mykhailiuk and coworkers to produce the trifluoromethyl-morpholine unit **4** as a fluorinated analogue core found in several drugs such as Gefitinib or Linezolid. The ring closure of fluorinated amine **2r** allowed for the formation of aziridine **1ar** in 30% yield, but further developments provided the fluorinated morpholine **4** in multigram quantities (Figure 1).[28]

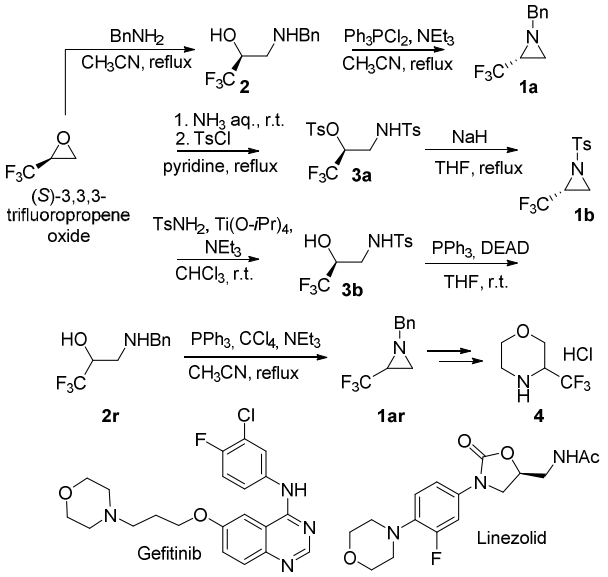

Figure 1. Synthesis of trifluoromethyl-aziridines **1a**, **1b** and **1a**r and structure of trifluoromethyl-morpholine unit.

Aziridines can have an interest as final compound or as building blocks for further regioselective ring-opening. With this in mind, Portella and coworkers promoted a fluorinated chiral alkoxyaldehydes **5** which allowed for the formation of (*R*)-*β*-alkoxysulfonamides **6** by a condensation with *p*-toluenesulfonamide then a reductive amination with $NaBH(OAc)_3$. After a debenzylation step, a Mitsunobu reaction has converted the (*R*)-*β*-alkoxysulfonamides **6** into the corresponding enantiopure heterocycles **7a** in yields higher than 81%. A similar strategy was also applied to the preparation of non-activated *N*-benzylaziridine **7b** starting from amine **8**. In this case, the ring closure arose in good yield after reaction with PPh_3/CCl_4 (Figure 2).[29]

Zanda and coworkers also developed a concise approach to optically active substituted aziridines using chiral sulfoxides. Hence, the procedure involved the formation of *β*-sulfinyl amines **11** by reaction of aldimine **9** with *α*-lithiated sulfoxides **10**. Then, a rearrangement into *β*-chlorosulfenamides **12** operated with a high degree of stereoselectivity (98:2) by treatment with oxalyl chloride in the presence of *sym*-collidine. Cleavage of N-S bond with sodium borohydride ($NaBH_4$) yielded the *β*-chloro amide intermediates **13** as single diastereomers in yields up to 87%. Compound **13** underwent cyclization into enantiomerically pure fluorinated aziridines **14** in 70 and 79% yields, respectively (Figure 3).[30,31]

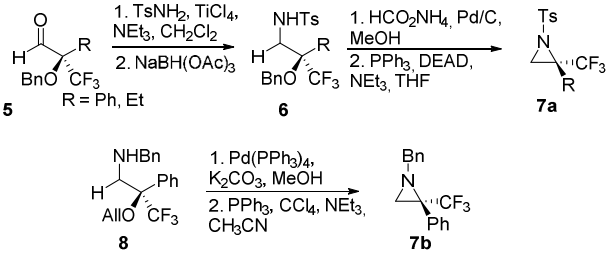

Figure 2. Synthesis of trifluoromethyl-aziridines **7a,b**.

In this case, the method offers the possibility to introduce varied substituents on the heterocycle. Proceeding with a chiral sulfoxide auxiliary, CF_3-substituted imines **15** were involved in Mannich-type reactions with ketones leading to chiral *β*-aryl-*β*-trifluoromethyl-*β*-aminoarones **16** with diastereoisomeric ratios (*d.r.*) up to 93:7 (as determined by ^{19}F NMR) and yields up to 91%. The chiral sulfoxide group was removed under acidic condition, followed by benzoylation of nitrogen with benzoyl chloride. The resulting amine **16a** was expected to form a fluorinated oxazine with phosphorus pentachloride, however, an intramolecular cyclization provided the aziridine **17** (R = Ph) in 73% yield (Figure 3).[32]

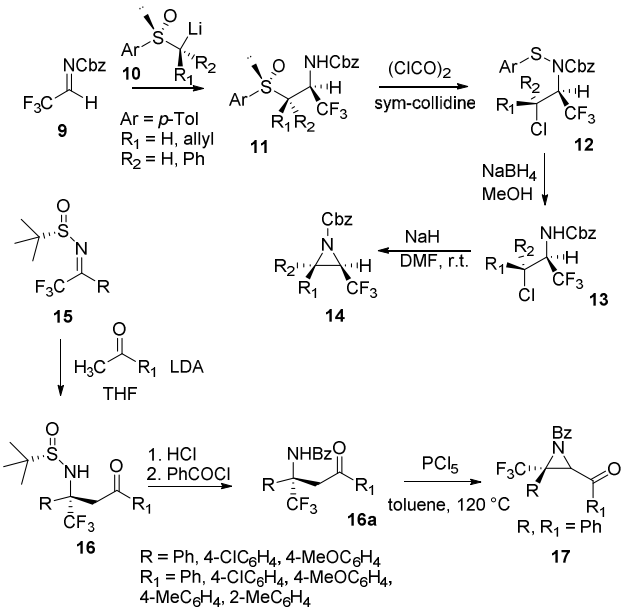

Figure 3. Synthesis of trifluoromethyl-aziridines **14** and **17**.

In 2010, a straightforward and cost-effective strategy afforded the access to racemic trifluoroaziridines through ring closure of *β*-chloroamines. Starting from commercially available 1,1,1-trifluoroacetone, the corresponding fluorinated imines **18**

were converted in *N*-(1-chloromethyl-2,2,2-trifluoroethylidene)alkylamines **19** by chlorination with *N*-chlorosuccinimide (NCS) as reagent. *β*-Chloro compounds were subsequently reduced in moderate yields (54-65%) with $NaBH_4$ but the cyclization using lithium bis(trimethylsilyl)amide (LiHMDS) operated in good yields (78-92%) to provide the aziridines **20** (Figure 4).[33]

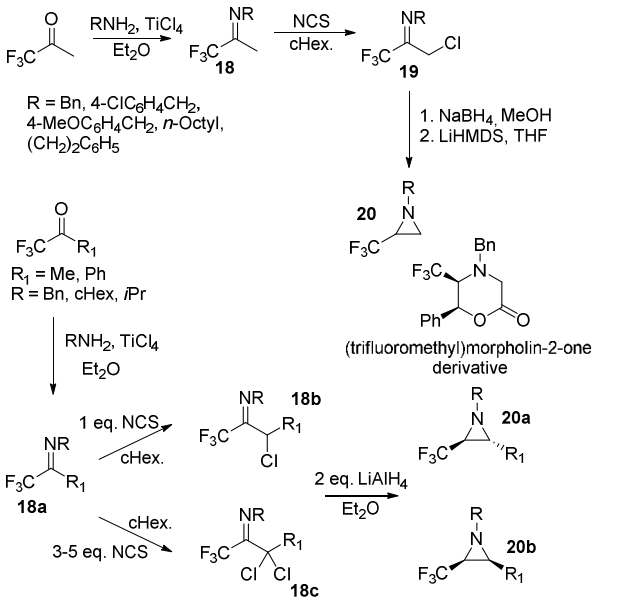

Figure 4. Synthesis of trifluoromethyl-aziridines **17**, **17a** and **17b** and structure of a (trifluoromethyl)morpholin-2-one derivative.

Afterwards, this procedure was extended to the stereoselective synthesis of either *cis*- or *trans*-trifluoromethyl-aziridines **20a** and **20b**, targeting the preparation of (trifluoromethyl)morpholin-2-one derivatives as potential T-type Ca^{2+} channel blockers or tachykinin receptor antagonists (Figure 4). According to the aforementioned methodology, a set of imines **18a** derived from 1,1,1-trifluoro-3-phenylpropan-2-one and 1,1,1-trifluorobutan-2-one was reacted with 1 eq. or 3-5 eq. of NCS to give *α*-monochlorinated or *α*,*α*-dichlorinated imines **18b** and **18c**, respectively. When *α*-monochlorinated imines **18b** are challenged with 2 eq. of lithium aluminum hydride ($LiAlH_4$) in ether at room temperature, *trans*-aziridines **20a** were isolated as the major diastereomers (diastereoisomeric ratio up to 6/94 (*cis*/*trans*)) and yields up to 86%.

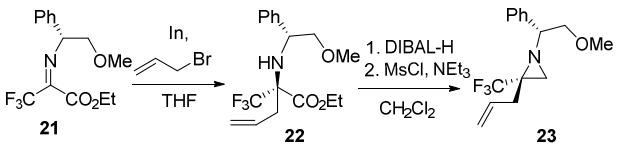

Figure 5. Synthesis of trifluoromethyl-aziridine **23**.

In contrast, the reduction of *α*,*α*-dichlorinated imines **18c** with the same amount of $LiAlH_4$ in refluxing ether yielded the *cis*-aziridines **20b** as the major diastereomers (*cis*/*trans* 97:3) in 57-93% yields (Figure 4).[34]

Finally, a quaternary *α*-trifluoromethyl *α*-amino acid was exploited as intermediate for an aziridine formation. Starting from imine of trifluoropyruvate **21** bearing the (*R*)-phenylglycinol methyl ether group, Zhang and coworkers carried out an allylation with allyl bromide and indium to give the expected *α*-allyl-*α*-trifluoro amino acid **22** in 98% yield (*d.r.*> 20:1). According to a two-step procedure, the reduction of ester group into alcohol and mesylation led to 2-allyl-2-(trifluoromethyl)aziridine **23** in 93% yield (Figure 5).[35]

1.2. Synthesis of trifluoromethyl-aziridines from imines

Aside from the cyclization of fluorinated amines, direct aziridination reactions were developed from imines. For instance, Bégué and coworkers highlighted a straightforward synthesis of aziridine-2-carboxylates as potential precursors of non-proteogenic *α*- and *β*-amino acids. In this respect, varied conditions were studied to promote the reaction between trifluoroaldimines **24** flanked with Bn or para-methoxyphenyl (PMP) groups and ethyl diazoacetate. Hence, the cyclic species **25** were obtained in yields higher than 86% when reactions were performed in ether at -78 °C using $BF_3{\cdot}Et_2O$ as catalyst. Interestingly, in all attempts, the *cis* isomer was predominantly obtained but, in the aforementioned conditions, the *cis*/*trans* ratio reached the higher stereoselectivity (95:5, Figure 6).[36] An improved methodology was developed through reaction of trifluoroaldimines **24** with ethyl diazoacetate in hexafluoroisopropanol (HFIP) as reaction media. Indeed, HFIP is a highly polar solvent which displays a poor nucleophilic behaviour and unique properties like high hydrogen bond donating ability.

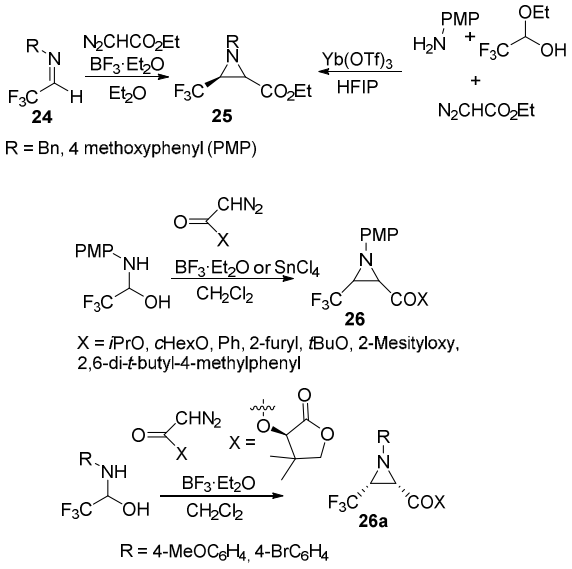

Figure 6. Synthesis of trifluoromethyl-aziridines **25**, **26** and **26a**.

In this case, by adopting $Yb(OTf)_3$ or $BF_3{\cdot}Et_2O$ as catalytic systems, heterocycles were produced in yields higher than 64% with a *cis*/*trans* ratio in the range from 60:40 to 70:30. More strikingly, a two-step one-pot procedure involving an aromatic amine, fluoral ethyl hemiacetal and ethyl diazoacetate gave rise to the fluorinated aziridines **25** in good yields but moderate diastereoselectivity (~6:4) (Figure 6). In opposite, no reaction was observed using hexane or ether as solvents.[37] We can note that De Kimpe and coworkers improved the procedure leading to the same fluorinated aziridines in 62% yield but *d.r.* > 99:1.[38]

Fluorinated hemiacetals are frequently found as building blocks of fluorinated imines. For this reason, the cycloaddition reaction of trifluoroacetaldehyde ethyl hemiacetal with a series of diazoacetates is reported here. The reactions required the assistance of 1 eq. of $BF_3{\cdot}Et_2O$ to give the fluorinated aziridines **26** in yields ranging 56-96%. In all cases, a *cis* selectivity was observed with the exception of the aziridination involving 2,6-di-*tert*-butyl-4-methylphenyl diazoacetate and $SnCl_4$ where the *trans* isomer arose as the major heterocycle (*cis*/*trans* 10:90). Afterwards, a convenient diastereoselective synthesis was implemented using varied chiral diazoacetates. It was determined that (*R*)-pantolactone-containing diazo ester allowed the conversion in heterocycles **26a** with both high *cis* stereoselectivity (up to 99:1) and diastereoselectivity (up to 94%) (Figure 6).[39]

The aza-Darzens reaction can be considered as one of the most direct routes for the formation of aziridine. In this regard, this strategy was employed using a trifluoromethyl diazomethane reagent **27** prepared *in situ* by reaction of trifluoroethylamine hydrochloride and $NaNO_2$ in a mixture water/dichloromethane. When intermediate **27** was exposed to imines **28** (ethyl glyoxal imine and aromatic glyoxylimines) in the presence of $BF_3{\cdot}Et_2O$, the resulting aziridines **29** were isolated in yields from 47 to 78%, together with a *cis*/*trans* diastereoselectivity in going from 11:1 to 19:1 (Figure 7).[40]

According to the same approach, Cahard and coworkers transposed this reaction in an optically active version by means of a chiral phosphoric acid (**(*S*)-TRIP**) catalyst. After the careful analysis of ^1H and ^{19}F NMR data, it came out that successive additions of 2.5 and 2% of chiral catalyst could increase the *cis*-aziridine formation in 65% yield with an *e.e.* of 99% and a diastereoisomeric ratio of 431:1. Under the same conditions, a series of aryl glyoxal monohydrates **28a** conducted to the corresponding aziridines **29a** in yields higher than 65% and *e.e.* up to 99% (Figure 7). Subsequently, aza-Darzens reactions were promoted with *α*-iminoglyoxylic amide and *α*-iminoglyoxalate. Only glyoxylic amides were converted in a 1:1 mixture of *cis*-aziridine (*e.e.* > 98%)/triazoline. The added value of such a three-membered ring was displayed by its ring opening into a fluorinated isocysteine derivative (Figure 7).[41]

One of the unexpected outcomes was viewed in the frame of azirine synthesis from *β*-ketoxime-phosphine oxides and-phosphonates using a modified Neber reaction. After preparation of *β*-keto-phosphine oxides **30** and -phosphonates **31**, a condensation with hydroxylamine and tosylation of corresponding *β*-ketoximes gave rise to the *β*-*p*-toluenesulfonyloximes **32a** and **32b**. In the presence of NaOMe/MeOH, oximes underwent a ring closure reaction providing exclusively *trans*-aziridine derivatives **33a** in yields spanning from 44 to 69%. Subsequent efforts were made to trap the cyclic azirine intermediate but only aziridine heterocycles were formed when reactions were performed with imidazole, benzenethiol or Grignard reagents. In the last case, the resulting aziridines **33b** possessing phosphonate and phosphine oxide functionalities were isolated as *cis*/*trans* mixtures in yields up to 73%, the *cis*-isomers being the major products (Figure 7).[42]

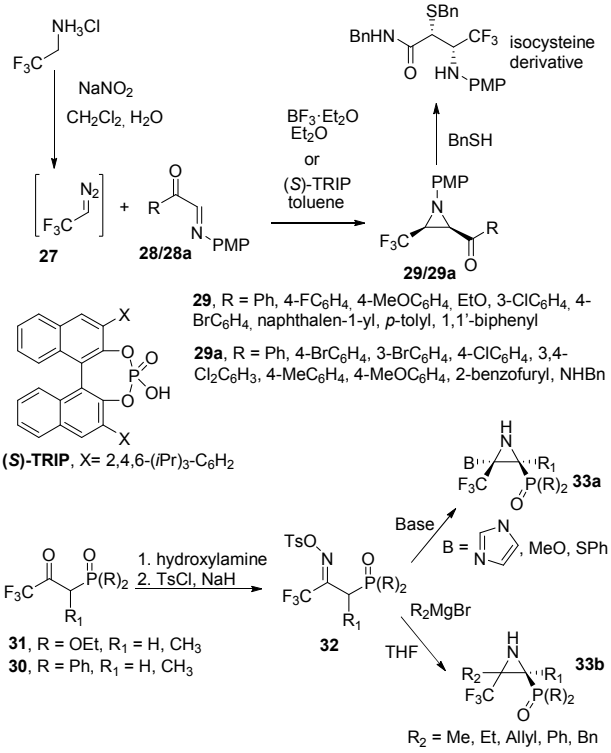

Figure 7. Synthesis of trifluoromethyl-aziridines **29**, **29a**, **33a** and **33b** and structure of an isocysteine derivative.

Other methods took advantage of the electrophilic character of imines using sulphur ylides. In 2002, a series of alkyl, aryl and trifluoroaldimines **34** bearing a (*R*)-phenylglycinol methyl ether group was reacted with butyl lithium (BuLi) as base and trimethylsulfonium iodide in THF at 0 °C. Nucleophilic intermediates were transformed into fluorinated aziridines **35** in good yields with a diastereoisomeric ratio of 92:8 ((*S,R*)/(*R,R*)) (Figure 8). Additional experiments demonstrated the prominent role of the oxygen atom located on the chiral auxiliary group with regard to the reactivity.[43] To address the issue of reactivity, a new Corey-Chaykovsky aziridination reaction relied on a new source of sulphur ylide. Hence, new chiral CF_3-substituted (*S*)-*N*-*tert*-butylsulfinylketimines **36** were synthesized by condensation of (*S*)-*tert*-butylsulfinyl amide **37** and fluorinated ketones **38** in the presence of $Ti(OiPr)_4$ as

catalyst. In contrast to the previous case, the *in situ* generation of sulphur ylide from trimethylsulfoxonium iodide (**TMSOI**) under addition of NaH led to a much less reactive sulphur ylide intermediate. This method allowed for an increased reactivity and conversion rate into aziridines **39** and slightly improved the diastereoselectivity up to 99:1 (Figure 8). Further developments aimed at producing the chiral *α*-trifluoromethylallylamine building block **40** by oxidation with *m*CPBA of aziridine **39** (R = Ph) followed by ring opening with dimethylsulfonium methylide (Figure 8).[44]

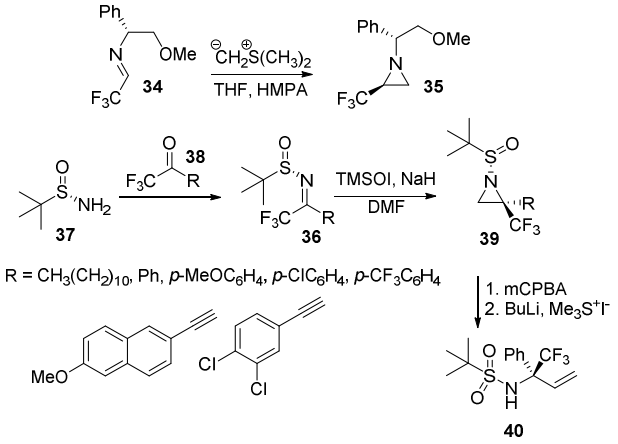

Figure 8. Synthesis of trifluoromethyl-aziridines **35** and **39** and structure of the chiral *α*-trifluoromethylallylamine building block **40.**

1.3. Synthesis of trifluoromethyl-aziridines from heterocyclic precursors

In some cases, fluorinated compounds present a distinct reactivity with respect to their hydrogenated counterparts. This aspect was highlighted by a ring contraction by an unexpected pathway starting from trifluoromethylated selena- and thiazetidine precursors. Synthesis of *β*-aminoalkyl selenide **42** was performed according to a three-step procedure by treatment of a fluorinated benzyl selenide **41** with lithium diisopropylamide (LDA), (hexafluoroisopropylidene) aniline (HFIA), and NH_4Cl aq. Removal of *tert*-butyldimethylsilyl group using tetrabutyl ammonium fluoride (TBAF) and oxidation with *m*CPBA yielded the tetracoordinate 1,2-selenazetidines **43** in 40 and 8% yields as a diastereomeric mixture which were separated after further purification. Under thermolysis at 210 °C, no expected olefin was formed but only the 2,2-bis(trifluoromethyl)aziridine **44** was isolated in 78% yield (Figure 9).[45] According to a similar chemical sequence, the tetracoordinate $1\lambda^4$,2-thiazetidine **46** was synthesized from a benzyl sulfide **45** bearing a Martin ligand, and converted by oxidization with RuO_4 into the corresponding pentacoordinate $1\lambda^6$,2-thiazetidine in only 15% yield. Upon heating at 160 °C in toluene-d_8, the thiazetidine was transformed in aziridine **44** in 94% yield due to a mechanistic pathway similar to that of the aza-Corey-Chaykovsky reaction (Figure 9).[46] Finally, Kawashima and coworkers applied the same approach in order to form fluorinated azetidines bearing two chiral centers. In this regard, a mixture of *cis* and *trans* selenazetidines **47** was obtained from *N*-(2,2,2-trifluoro-1-phenylethylene)-aniline and separated by chromatography in 8 and 77% yields, respectively. Whereas the reaction of *trans*-cycloadduct **47** with dimethyl acetylenedicarboxylate (DMAD) provided the aziridines **49** in very low yields (<5%), oxidation of *β*-aminoalkyl selenide intermediate **48** with 2-benzenesulfonyl-3-phenyloxaziridine provided unexpectedly a *cis*-aziridine **49** in 69% yield (Figure 9).[47] Further investigations were conducted through the thermal treatment of *trans*-thiazetidine **50** but the *cis*- and *trans*-aziridines **49** were produced in only 34 and 4% yields (preparation of *trans*-thiazetidine followed the same method reported above).[48]

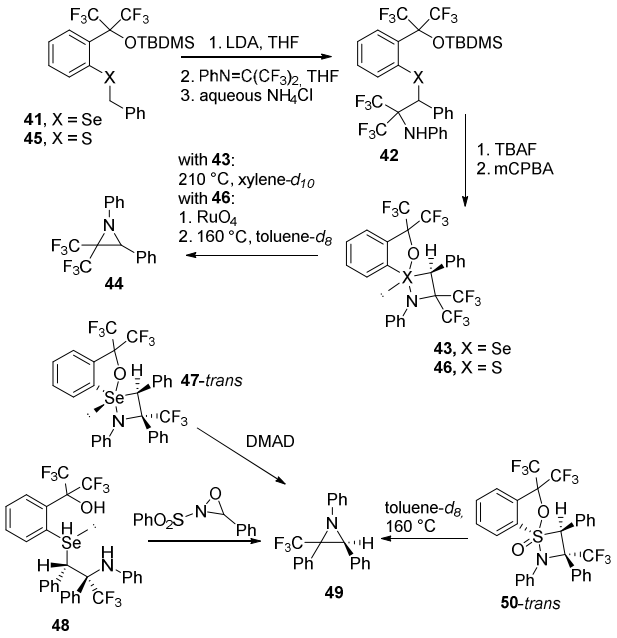

Figure 9. Synthesis of trifluoromethyl-aziridines **44** and **49**.

Another original synthetic pathway concerned the thermal elimination of nitrogen from fluorinated triazoles. After a [2+3] cycloaddition reaction occurring between imines **51** derived from hexafluoroacetone and diazomethane or diazoethane, the resulting 1,2,4-triazoles **52** were heated in neat condition for 10 h at 150 °C, promoting aziridine **53** in 37% yield by ring contraction (Figure 10).[49] Similarly, a heterocyclic production was carried out using *N*-trifluoroacetylimines of trifluoropyruvate **54** in the presence of diazomethane, but a mixture of triazolines **55** and aziridines **56** was obtained (Figure 10). However, elimination of nitrogen from triazole ring occurred in high yields upon heating in the presence, in some cases, of CF_3COOH or HCl. Interestingly, the authors reported a spontaneous triazoline to aziridine transformation which was complete after several months at room temperature.[50]

Finally, the structural design of fluorinated aziridines can be envisaged through modification of pre-formed CF_3-aziridine. In this sense, Uneyama and coworkers demonstrated that *N*-

tosylaziridine **1b** could easily generate an aziridinyl anion by deprotonation with BuLi.[26]

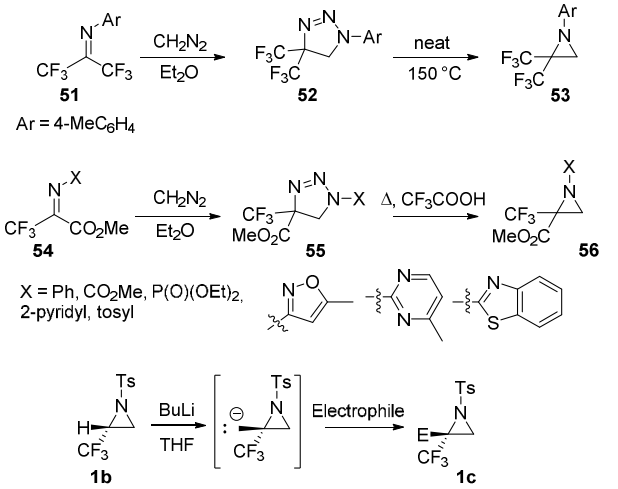

Figure 10. Synthesis of trifluoromethyl-aziridines **53**, **56** and **1c**.

The anionic intermediate showed its versatile reactivity with various electrophiles such as acyl chloride, aldehydes, ketones, haloformate and bromoalkane to yield new CF_3-aziridines **1c** as potential precursors of *α*-hydroxy-*β*-trifluoromethyl-*β*-amino acids or *α*-trifluoromethyl-*α,β*-diamino acids (Figure 10).[51] In 2011, an improved methodology was developed regarding the synthesis of *N*-tosyl-2-trifluoromethyl-2-alkyloxycarbonyl aziridine with *e.e.* higher than 98%.[27]

1.4. Synthesis of trifluoromethyl-aziridines from olefins

Fluorinated olefins represent an important class of commercially available intermediates which found application for the elaboration of CF_3-containing heterocycles. For instance, 4,4,4-trifluorocrotonate underwent a bromination and a treatment with ammonia, to give the *trans*-3-trifluoromethyl-2-carbamoylaziridine **57a** in 46% yield, whereas cyclization with benzylamine led to *trans*-3-trifluoromethyl-2-methoxycarbonylaziridine **57b** in 70% yield (Figure 11). Further investigations aimed at creating Cl-N and F-N bonds by treatment of *N*-deprotected aziridines with chlorinating or fluorinating agents, namely *tert*-butyl-hypochlorite and F_2/NaF, respectively.[52] Considering the ethyl nosyloxycarbamate as a relevant aziridine precursor, Tardella and coworkers evaluated its reactivity with a set of fluorinated olefins possessing varied ester functions. With the assistance of NaH as base, an aza Michael reaction occurred which was immediately followed by a ring closure into aziridines **58** in yields up to 90% (Figure 11). Interestingly, with CaO or LiOH as a base, the corresponding *α*-trifluoromethyl-*β*-amino esters were isolated. Afterwards, syntheses proceeded with chiral fluorinated olefins capped with the (-)-8-phenylmenthol or Helmchen's auxiliaries. In both cases, aziridines were obtained in yields higher than 70%, however only the Helmchen's group allowed a significant induction, the diastereoisomeric excess reaching 72% (Figure 11).[53] In the same vein, attention was turned toward precursors **59** of fluorinated alkenes which were capable of reacting directly with the nosyloxycarbamate derivatives in the presence of a large amount of CaO, achieving the heterocycles **58a** in up to 78% yields (Figure 11). The authors demonstrated that such a reaction requires the use of a trifluoromethylated compound since the absence of reactivity was observed with non-fluorinated molecules.[54]

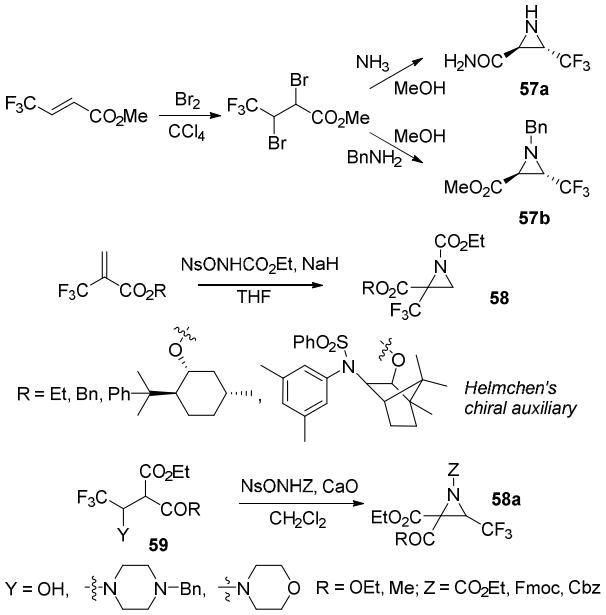

Figure 11. Synthesis of trifluoromethyl-aziridines **57a**, **57b**, **58** and **58a**.

An alternative approach has concerned an intermolecular aziridination under oxidative condition using iodobenzene diacetate ($PhI(OAc)_2$). Typically, fluorinated olefins were reacted with carbazate or phtalimide reagents in the presence of $PhI(OAc)_2$ and an excess of potassium carbonate in dichloromethane. The resulting (*E*) *N*-aminoaziridines **60** were generated in 37 to 76% yields (Figure 12). In addition, other fluorinated compounds derived from amino acids allowed an *N*-aminoaziridination in yields higher than 64%. The peptidomimetic diastereomers **60a** were considered as a good entry to *α*-substituted *β*-CF_3-hydrazino acids through ring-opening reactions (Figure 12).[55] Recently, the promotion of (*β*-trifluoromethyl)vinylsulfonium salts derived from fluorinated olefins was also proposed. After quarternization of (*β*-trifluoromethyl)vinyl sulfides with diphenyliodonium triflate, in the presence of CuCl(I), the corresponding sulfonium salts were challenged with a series of amines in DMSO providing the fluorinated cycloadducts **61** in yields up to 94% (Figure 12). An asymmetric variation using (*S*)-1-phenethylamine proceeded in good yield but with very poor diastereocontrol (54:46).[56]

At last, it can be reported the access to enantiomerically pure fluorinated aziridines through resolution processes using chiral

chromatography or lipase-catalyzed acetylation of aziridines.[57,58]

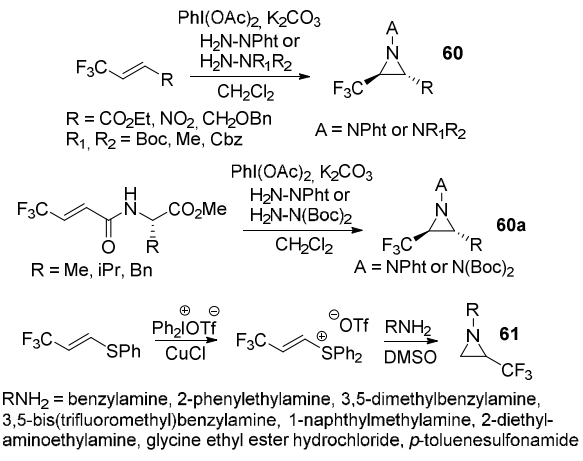

Figure 12. Synthesis of trifluoromethyl-aziridines **60**, **60a** and **61**.

2 Trifluoromethyl-azetidines

2.1. Synthesis of trifluoromethyl-azetidines from fluorinated amines

By comparison with their three-membered ring counterparts, less synthetic strategies afforded the preparation of azetidines. Back in 1999, Zanda and coworkers selected the non-racemic *α*-trifluoromethyl-*β*-hydroxyaspartic acid as starting materials for further development of peptidomimetic derivatives. In this regard, the synthetic strategy exploited a stereoselective Mannich-type reaction involving (*S*)-(*α*-benzyloxy)acetyl-2-oxazolidinone **62** and an imine derived from ethyl trifluoropyruvate. The "Evans" *anti*-adduct **63** was thereby isolated in 88% yield as major isomer (91:9 ratio). The subsequent removal of chiral auxiliary with $NaBH_4$ provided the diastereomerically pure carbinol amino acid (87% yield). After tosylation, an intramolecular cyclization with BuLi yielded azetidine **64** in 85% yield (Figure 13).[59] More recently, De Kimpe and coworkers described a straightforward access to racemic azetidines. In practice, a set of fluorinated enamines **65** obtained by condensation of ethyl 4,4,4-trifluoroacetoacetate with primary amines, was subjected to $NaBH_4$ reduction and chlorination with thionyl chloride, giving rise to *N*-alkyl-4-chloro-1,1,1-trifluorobutan-2-amines **66** in yields higher than 50%. The ring closure reaction required a treatment with LiHMDS to lead to 1-alkyl-2-(trifluoromethyl)azetidines **67** in 59 to 90% yields (Figure 13). Further investigations focused on a C_4 regiospecific ring-opening in the presence of nucleophiles through an azetidinium intermediate, in contrast with non-fluorinated azetidines.[60]

In 2014, a simple cylization reaction mediated by iodination of homoallylic amines was proposed in racemic and optically pure versions. Under Barbier condition, the unsaturated amines **68** were produced in good yields through the reaction of trifluoroaldimines bearing either a benzyl group or (*R*)-phenylglycinol methyl ether with allyl bromide and zinc in THF.[61] Although the iodine-mediated cyclization of *N*-benzyl amine was supposed to give a fluorinated pyrrolidine, a *cis*-azetidine **69** was obtained in 61% yield as major stereoisomer. When the ring closure was carried out with the chiral compound, a mixture of diastereomers (*cis*/*trans* 81:19) was isolated in 71% yield (Figure 13). An additional purification step and X-ray diffraction analysis confirmed both the *cis*-stereoselectivity and the absolute configuration of the chiral centers; molecules also developed a halogen bonded polymer.[62] This heterocyclic derivative demonstrated its versatile reactivity by displacement of the iodide atom at position 4 by nucleophilic substitution or Huisgen 1,3-dipolar cycloaddition.[63]

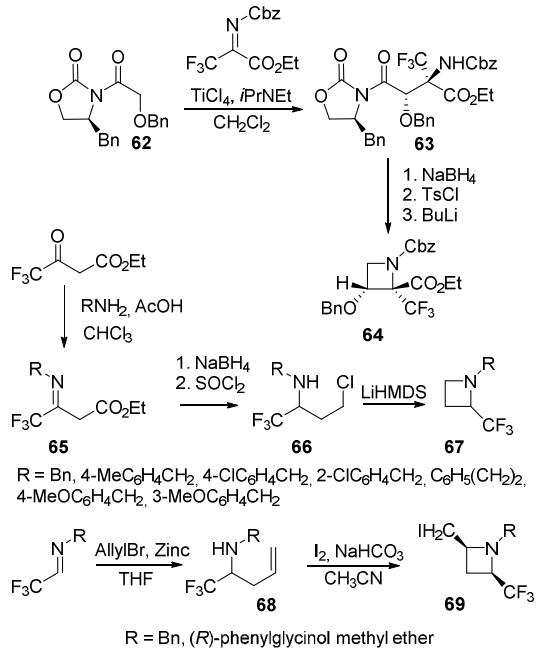

Figure 13. Synthesis of azetidines **64**, **67** and **69**.

2.2. Synthesis of trifluoromethyl-azetidines from heterocycles

Similarly to aziridines, the transformation of four-membered rings into azetidines was considered as a key strategy owing to the complexity of obtaining such small rings. De Vita and coworkers studied the structural modification of a fluorinated lactam into its corresponding azetidine by means of a Wittig reaction. Hence, the commercially available 3-amino-4,4,4-trifluorobutyric acid was converted in 4-trifluoromethyl-*β*-lactam in 45% yield followed by *N*-Boc protection. The resulting lactam **70** was reacted with varied Wittig reagents, producing azetidines **71** flanked with ester or nitrile functionalities in good yields (78-85%). These fluorinated cycloadducts were also capable of undergoing other hydrogenation or alkylation reactions. According to the same procedure, the optically pure 3-amino-4,4,4-trifluorobutyric

acid conducted to azetidines **71** as pure diastereomers (Figure 14).[64]

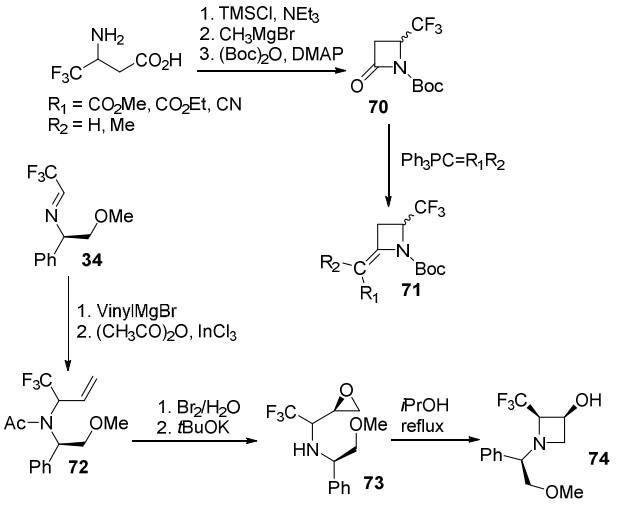

Figure 14. Synthesis of trifluoromethyl-azetidines **71** and **74**.

Another four-membered ring construction was presented in the frame of the synthesis of new fluorinated protease inhibitors. Purposely, trifluoroaldimine **34** bearing the (*R*)-phenylglycinol methyl ether group was alkylated with a Grignard reagent and acetylated with acetic anhydride attaining allylamine **72** in good overall yields and high diastereoselectivity (>98%). Then, the chemical sequence proceeded by an epoxidation with Br_2/H_2O, followed by ring closure in the presence of potassium *tert*-butoxide to achieve the targeted epoxide **73**. Finally, when heated in refluxing isopropanol, compound **73** was transformed quantitatively in the corresponding azetidinol **74** as a single diastereomer (Figure 14). The subsequent crystallization of heterocycle **74** allowed the determination of the *syn* configuration of asymmetric carbons C_2 and C_3 together with their absolute configuration.[65]

As aforementioned, the conversion of one heterocyclic ring to another can proceed according to unexpected pathways. This aspect was observed owing to a tandem ring opening/ring closure. Whilst *N*-tosyl aziridine **75** could be converted in new aziridines by tosylate substitution with varied sulfur nucleophiles, the attack of phenolate anions occured regiospecifically through displacement of the OTs group. The resulting *cis*-azetidines **76** were formed by an intramolecular cyclization in 56-95% yields when the reaction was conducted in refluxing DMF (Figure 15).[38] Finally, Brigaud and coworkers investigated the formation of constrained peptides incorporating novel *α*-trifluoromethyl-amino acids. Starting from diastereomerically pure oxazolidine **77**, the four-membered core of oxazolidine **78** was prepared as a single diastereomer according to a three-step procedure, *i.e.* an ester reduction with $NaBH_4$ in the presence of $CaCl_2$, conversion of alcohol function into iodo derivative using I_2/PPh_3/imidazole and cyclization with NaH in refluxing THF. When challenged with TMSCN and $BF_3{\cdot}Et_2O$ in dichloromethane, compound **78** underwent a Strecker-type reaction, giving rise to a 58:42 mixture of diastereomers of azetidine-2-carbonitriles **79** in 99% yield (Figure 15). After separation by chromatography, both diastereomers allowed the formation of (*R*) and (*S*) *α*-trifluoromethyl homoserines by treatment with HCl.[66]

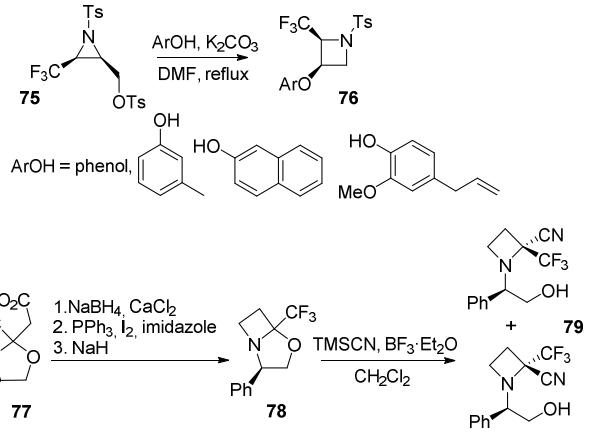

Figure 15. Synthesis of trifluoromethyl-azetidines **76** and **79**.

3 Trifluoromethyl-β-lactams

3.1. Synthesis of trifluoromethyl-*β*-lactams from fluorinated imines

The *β*-lactam class of compounds belongs to an important family of natural products of which the penicillin group accounts for more than half of antibiotic prescriptions. In addition, these four-membered rings represent a good entry to *β*-amino acid moieties by ring opening, as found in paclitaxel or docetaxel. With this in mind, one of the very first syntheses of fluorinated *β*-lactams was performed in 1997 by Ojima in the frame of the preparation of CF_3-containing baccatins, these taxoids possessing significant anticancer properties (Figure 16). In this context, treatment of benzyloxyacetyl chloride with triethylamine generated a ketene which was condensed *in situ* with trifluoroaldimine **24** capped with the PMP group. The Staudinger reaction yielded fluorinated *β*-lactam **80** in 51% yield, followed by a structural adaptation in order to be coupled with various C-10 modified baccatins. The authors also developed an asymmetric version using (–)-*trans*-2-phenylcyclohexyl triisopropylsilyloxyacetate **81**, achieving thus the fluorinated heterocycle **82** in 62% yield but *e.e.* of only 50% (Figure 16).[67] To address the issue of enantioselectivity, another asymmetric strategy consisted in a [2+2] cycloaddition using a ketene and an imine derived from (*S*)-phenylethylamine. *Cis*-azetidinones were synthesized in 90% yield, but with very poor diastereocontrol (15%). However, both isomers were easily separated by crystallization and their further ring opening afforded the formation of enantiomerically pure *N*-Boc-isoserinates as fluorinated analogues of nonproteogenic *α*-hydroxy-*β*-amino acids (Figure 16).[68] Later, Ojima and coworkers investigated the enzymatic optical resolution of racemic 3-AcO-4-CF_3-*β*-lactam prepared

from fluorinated lactam **80** in two steps. When the reaction was conducted at 0-5 °C for 12h in the presence of the ''PS-Amano'' lipase (pH 7), fluorinated lactams **83** and **84** were isolated in good yields (45 and 36%, respectively) and *e.e.* higher than 97% (Figure 16).[69,70]

Targeting the development of fluorinated *β*-anilino carboxylic esters with antibacterial and antimalarial properties, Reformatsky reactions involving imine **24**, zinc dust and *α*-bromocarboxylic esters was supposed to provide a series of *β*-aminoesters, but surprisingly enough, these compounds were accompanied with fluorinated lactams **85** (as major products) in 28 to 46% yields (Figure 16).[71]

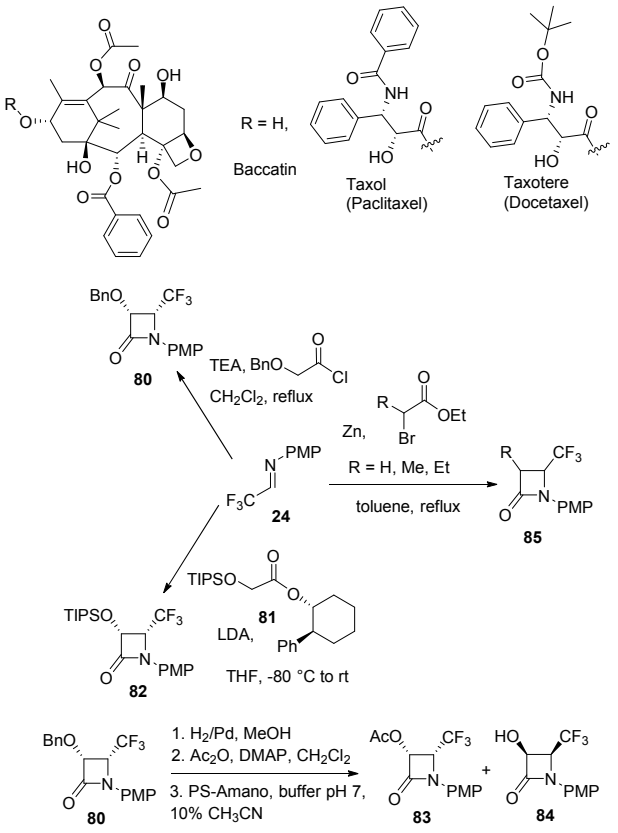

Figure 16. Synthesis of trifluoromethyl azetidinones **80-85** and structures of paclitaxel, docetaxel and baccatin.

3.2. Synthesis of trifluoromethyl-*β*-lactams from fluorinated amines

Since *β*-lactams represent a convenient building block for the preparation of *β*-aminoesters, the latters can be used for a ring closing in azetidinones. Following this principle, Prati and coworkers disclosed a two-step synthesis of *trans*-azetidinones from trifluoromethylaziridine-2-carboxylate **25**. Typically, the ring opening of three-membered rings operated regio- and stereoselectively by nucleophilic attack of HCl or trifluoroacetic acid. Subsequently, a Grignard-mediated cyclization transformed the *anti*-*α*-chloro-*β*-trifluoromethyl-*β*-alanine **86** and *anti*-3-(trifluoromethyl)isoserinate derivative **87** in the corresponding azetidinones **88** and **89** in 96 and 68% yields, respectively (Figure 17).[72] Several years later, the preparation of enantiomerically pure lactam **92** relied on the cyclization of (*R*)-ethyl-3-amino-4,4,4-trifluorobutanoate **91** in good yield (80%), according to conditions reported above. Starting from ethyl-4,4,4-trifluoroacetoacetate **90** as commercially available building block, the key aspect of this synthesis lied in the resolution of aminoester **91** with (2*R*, 3*R*)-tartaric acid (Figure 17).[73]

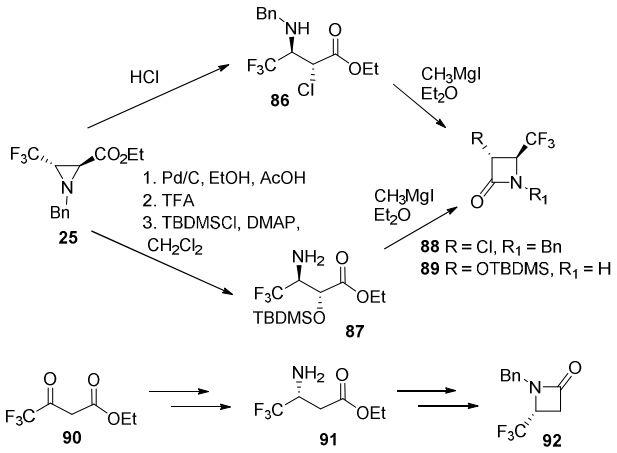

Figure 17. Synthesis of trifluoromethyl azetidinones **88**, **89** and **92**.

Other research works aimed at preparing fluorinated analogues of known pharmaceuticals. In this sense, Qing and coworkers turned their attention toward optically pure counterparts of ezetimibe, a strong cholesterol absorption inhibitor (Figure 18). Thus, a three-step sequence started from trifluoroacetic acid (TFA) which led to the chiral *α*-trifluoromethyl amines **93** bearing an oxazolidinone chiral auxiliary with diastereoisomeric ratios higher than 87:13. After removal of chiral group, the formation of the fluorinated *β*-lactams **94** relied on a cyclization using a Grignard reagent (Figure 18).[74] Recently, the same approach demonstrated that a chiral fluorinated acrylate **95** could react through an aza-Michael reaction with 4-fluoroaniline in neat condition to give amine **93** (R = F) as a mixture of diastereomers (2.8:1, determined by ^{1}H NMR) (Figure 18).[75] As far as the cycloadduct formation is concerned, the cyclization of a *β*-aminoester by means of NaH was also reported, but the resulting fluorinated lactam was isolated in poor yield.[76]

Finally, Cahar and coworkers demonstrated that fluorinated azetidinones could be prepared straightforwardly from *N*-tosyl-1-chloro-2,2,2-trifluoroethylamine **96** and acid chlorides. Cyclocondensations operated at -78 °C in dichloromethane in the presence of a base with a high level of diastereoselectivity (*trans*/*cis* from 94:6 to 99:1). The desired heterocycles **97** were thereby isolated in 63 to 80% yields (Figure 18).[77]

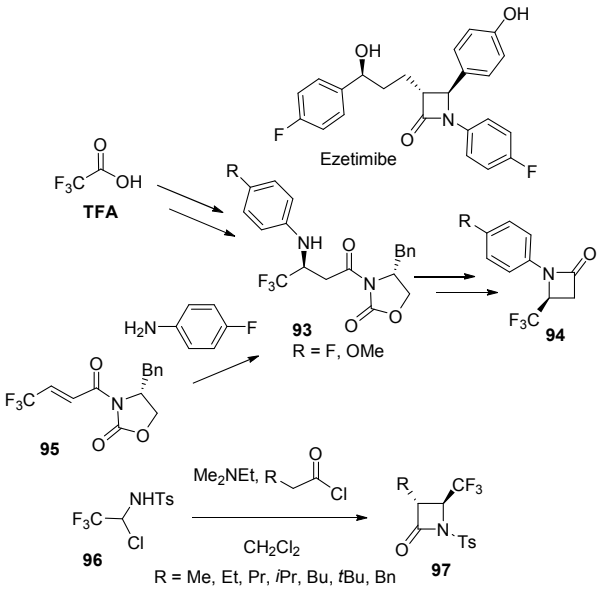

Figure 18. Synthesis of trifluoromethyl azetidinones **94**, and **97** and structure of ezetimibe.

3.3. Synthesis of trifluoromethyl-*β*-lactams from heterocycles

The preparation of fluorinated azetidinones from heterocycles is less common. For instance, Bégué and coworkers demonstrated that the structural modification of fluorinated lactams **98** and **99** could occur by deprotonation with 2.5 eq. of LiHMDS and quenching with methyl iodide. The corresponding azetidinone analogues **100** were produced stereoselectively in very good yields (> 90%). Further works aimed at investigating the Wittig rearrangement of enolate intermediates. When heterocycle **98** is challenged with LiHMDS, the variation of temperature (from -30 °C to r.t.) allowed for the formation of a single diastereomer **101** in 63% yield.

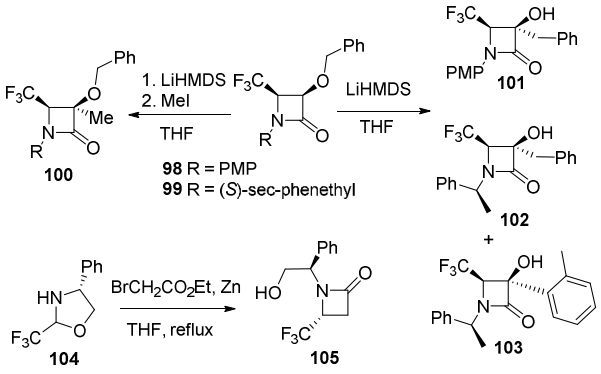

Figure 19. Synthesis of trifluoromethyl azetidinones **101**, **102**, **103** and **105**.

As far as *N*-[(*S*)-*sec*-phenethyl]-(*R*,*R*)-*β*-lactam **99** is concerned, the enolate rearranged into two lactams **102** and **103** (40:60 ratio, 65% yield), both as a single diastereoisomer, due to [1,2]- and [2,3]-Wittig rearrangements (Figure 19).[78] We can note that a ring contraction due to a Reformatsky reaction involved chiral 2-trifluoromethyl-1,3-oxazolidines **104** (2.5:1 mixture of diasteromers), ethyl bromoacetate and zinc dust in refluxing THF. The resulting azetidinones **105** were formed in 42% yield as a 74:26 mixture of diastereomers (Figure 19).[79] Amongst the most convenient and efficient ring expension pathways, Crousse and coworkers elaborated the transformation of azetidines into halogenated *trans* or *cis*-azetidinones. Starting from *trans*-azetidine **106**, a stereospecific conversion provided the corresponding *trans*-chloro-*β*-lactam **107** in 55% yield using NaH and thionyl chloride in toluene at 70 °C. Similarly, chlorinated azetidinone **110** was attained as a unique *cis*-isomer in 76 % yield when *cis*-aziridine **109** was challenged with $POCl_3$ and NaH in toluene at 80 °C. As concerns the bromination reaction, triphenylphosphine dibromide was employed as reagent to convert compounds **106** and **109** into *trans*- and *cis*-bromo-*β*-lactams **108** and **111**, respectively, in yields up to 85% with the same selectivity (Figure 20).[80]

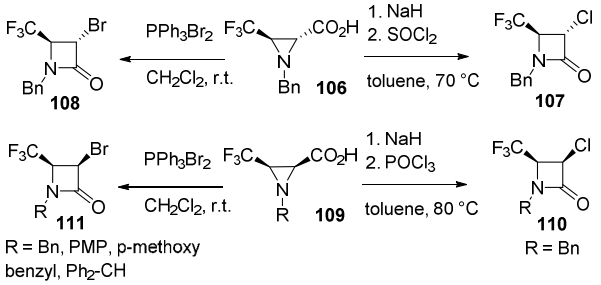

Figure 20. Synthesis of trifluoromethyl azetidinones **107** and **110**.

4. Trifluoromethyl-pyrrolidines

4.1. Synthesis of trifluoromethyl-pyrrolidines from amines

Five-membered rings such as pyrrolidines are also found in natural products and bioactive compounds and therefore their fluorinated analogues represent a potential target as building block. In addition, these less constrained heterocycles allowed for the development of a larger number of chemical pathways compared to aziridines and azetidines. In this spirit, *β*-trifluoroalkyl-*β*-amino alcohols were selected as targeted units for their introduction in a peptide sequence as isostere. Purposely, a stereoselective synthesis of *syn*-homoallylic *β*-trifluoromethyl-*β*-amino alcohol **113** initiated by the reaction of (*R*)-trifluoromethyl aldehyde **112** with allylmagnesium chloride in THF at -78 °C, followed by separation of *syn*/*anti* isomers (9:2, 85 % yield) by chromatography. Afterwards, *syn*-derivative **113** underwent an esterification, a reductive desulfenylation with $NaBH_4$/pyridine and methanolysis of ester group to give *syn*-amino alcohol **114** as the major isomer. Finally, under oxidative conditions (OsO_4/$NaIO_4$), a spontaneous intramolecular cyclization provided the

fluorinated pyrrolidines **115** quantitatively as a 1:1 mixture of isomers (Figure 21).[81] Another strategy dealt with an original sequence relying on a cross metathesis intramolecular aza-Michael tandem reaction, with a second generation Hoveyda-Grubbs catalyst[82] (5% mol) with the assistance of BF_3-Et_2O (1% mol). Hence, methyl vinyl ketone was allowed to react with (*R*)-fluorinated pentenamine **116** in refluxing dichloromethane or under microwave irradiation to lead to fluorinated diastereomers **117** in yields higher than 76% but moderate stereoselectivity (up to *trans*/*cis*, 5:1) (Figure 21).[83]

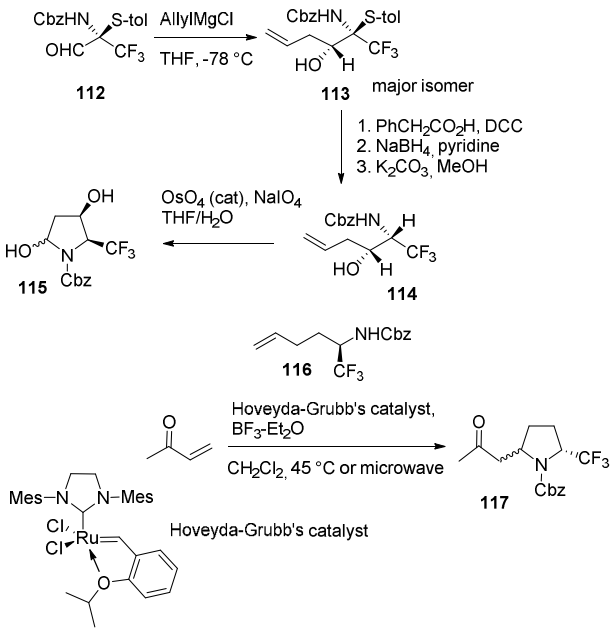

Figure 21. Synthesis of trifluoromethyl-pyrrolidines **115** and **117**.

Taking advantage of the wide reactivity of olefinic amines, Uneyama and coworkers proposed an access to fluorinated pyrrolidines for further application in bioactive peptides or their beneficial effect on the 3D structure of elastatin polypeptides and collagens. Starting from hexafluoroacetone imine, a four-step procedure provided the fluorinated homoallylic amine **118** in good overall yields. Then, displacement of PMP group by Cbz group using cerium ammonium nitrate (CAN) and reprotection with benzylchloroformate achieved intermediate **119** in 58 % overall yield. Finally, Treatment of compound **119** with ozone and triethylsilane/BF_3-Et_2O provoked a cyclization reaction (92% yield) and a dehydroxylative hydrogenation (74% yield), respectively, to give the *N*-Cbz-3,3-difluoro-2-trifluoromethylpyrrolidine **120** (Figure 22).[84] At the same time, fluorinated amines **121a,b** were produced in ~55% yields by reaction of xanthate **122** with olefins **123** in the presence of lauroyl peroxide in refluxing 1,2 dichloroethane (DCE). The subsequent cyclization with potassium *tert*-butoxide in THF provided the fluorinated heterocycles **124** in ~45% yields as mixtures of diastereomers. Interestingly, compound **124a** was considered as a potential analogue of epibatidine which possesses very powerful non-opioid analgesic and nicotinic agonist properties (Figure 22).[85]

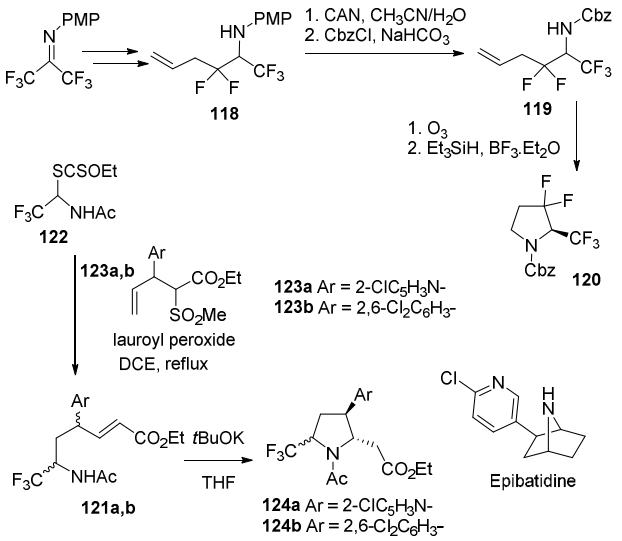

Figure 22. Synthesis of trifluoromethyl-pyrrolidines **120** and **124** and structure of epibatidine.

The Ruppert's reagent ($TMSCF_3$) is a well-established source of nucleophilic CF_3 species which can react with a wide variety of electrophilic substrats. In 2011, a cyclization reaction was achieved by a tandem addition relying on an intramolecular hydroamination followed by a second *in situ* addition of a nucleophile on the intermediate. Practically, aminoalkynes **125** were able to react with $TMSCF_3$ in the presence of AgF and water in dioxane at 100 °C under microwave condition, to provide the fluorinated pyrrolidines **126** in yields higher than 90% (Figure 23).[86]

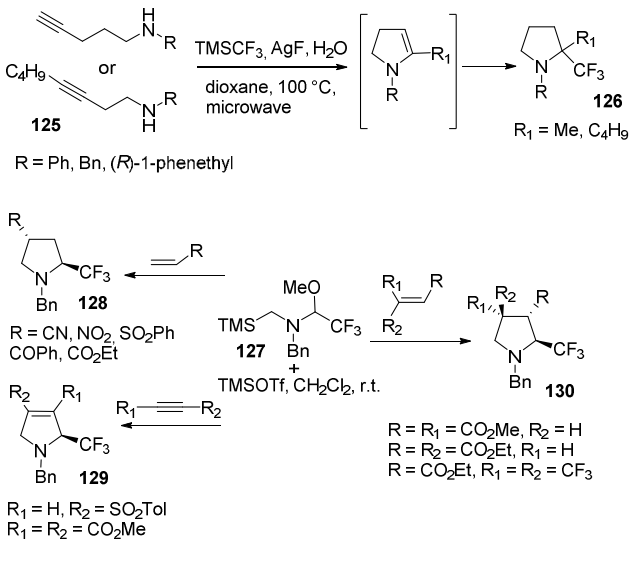

Figure 23. Synthesis of trifluoromethyl-pyrrolidines **126**, **128**, **129** and **130**.

Azomethine ylides also came out as very appealing precursors of pyrrolidine heterocycles thanks to their ability to make [3+2] cycloaddition with varied olefins. The fluorinated amine **127** was thereby allowed to generate an ylide intermediate by reaction with trimethylsilyl triflate in dichloromethane. The versatile reactivity was addressed through a series of cycloaddition reactions with different unsaturated partners. When challenged with mono-, di- and tri-substituted alkenes, the resulting five-membered rings **128** and **130** were obtained with a regioselectivity higher than 6:1 and yields up to 91%. Finally, a cycloaddition with electron-deficient alkynes led to compounds **129** in very high yields and regioselectivity (Figure 23).[87]

4.2. Synthesis of trifluoromethyl-pyrrolidines from fluorinated precursors

Preparation of pyrrolidines from fluorinated precursors has been less reported. Among these strategies, Aggarwal and coworkers proposed the synthesis of trifluoromethyl pyrrolidines with a ring-fused epoxide. Purposely, the fused ring system was obtained by reaction of trifluoromethylvinyl sulfonium salt **131** with aminoketones **132** according to the combination of a Michael-type reaction and an annulation. The heterocycles **133** were isolated in yields in the range of 49 to 90% with a diastereoisomeric ratio of 20:1. Further investigations demonstrated the regioselective ring opening of epoxide, highlighting these compounds as valuable building blocks for superior pharmacophores (Figure 24).[88] Aside, Johnson and coworkers developed a straightforward access to fluorinated pyrrolidines through an asymmetric Michael addition/reductive cyclization pathway. The Michael addition of 1,1,1-trifluoromethylketones **135** to nitroolefins **134** in the presence of a chiral catalyst (2.5 mol %) has conducted to γ-nitro trifluoromethyl ketones **136** with highly diastereo- and enantioselectivity. Subjecting compounds **136** to Raney-Ni hydrogenation conditions resulted in the clean formation of heterocycles **137** in good yields (73 to 87 %) with excellent levels of diastereocontrol (>20:1) (Figure 24).[89]

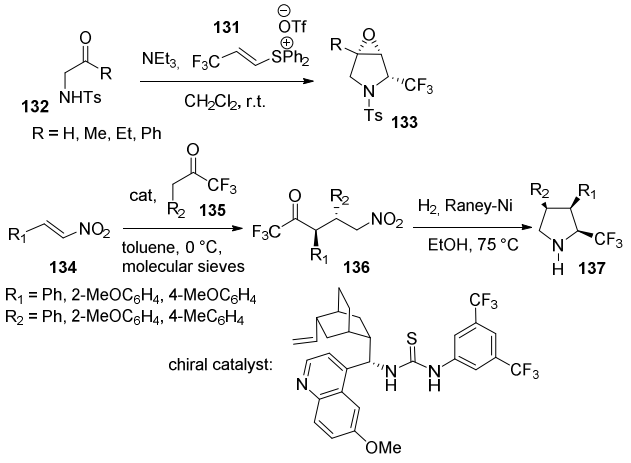

Figure 24. Synthesis of trifluoromethyl-pyrrolidines **133** and **137**.

4.3. Synthesis of trifluoromethyl-pyrrolidines from heterocycles

The formation of pyrrolidines from heterocycles will consist in a ring expension/contraction, or the structural variation of a preformed core. As far as the ring expension is concerned, an original approach lied in the generation of an azomethine ylide from an aziridine. Hence, a 1,3 dipolar cycloaddition took place by heating heterocycle **138** in refluxing xylene with varied olefins bearing electron donating or accepting groups. Starting from styrene and methyl acrylate, heterocycles **139** were isolated with complete *trans* regioselectivity for 2,5 substituents in 81 and 39% yields, respectively, whereas cyano cycloadduct **139** possessed a *cis* regioselectivity (83% yield). In opposite, the reaction involving butoxyethene gave rise to a mixture (*cis*/*trans* 53:47) of pyrrolidines **139** in 89% yield (Figure 25).[90] While addressing the ring expansion, aziridines **140** were able to react with a large array of nucleophiles for achieving the trifluoromethyl pyrrolidines **141** in yields up to 98% (Figure 25).[91]

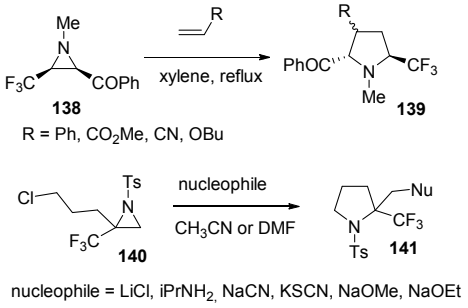

Figure 25. Synthesis of trifluoromethyl-pyrrolidines **139** and **141**.

Considering *N*-benzylpyrrolidone **142** as precursor, it was demonstrated that *α*-methoxy-*α*-trifluoromethylpyrrolidine **143** could be achieved in 80% yield by the combination of a methylation with methyl triflate and a nucleophilic trifluoromethylation with $TMSCF_3$. Afterwards, 2-trifluoromethylpyrrolidine **144** was attained in 87% yield by removal of methoxy group with $NaBH_4$ and BF_3-Et_2O. In addition, replacement of methoxy group operated using varied trimethylsilyl nucleophiles which resulted in cycloadducts **145** in 71 to 85% yields (Figure 26).[92] The structural modification of five membered rings was also investigated from cyclic nitrones targeting the formation of fluorinated analogues of natural polyhydroxylated pyrrolidines such as codonopsine, codonopsinine and 3,4-dihydroxy-2-hydroxymethyl-6-methylpyrrolidine (6-deoxy- DMDP), DMDP being an inhibitor of *β*-mannosidase, *β*-galactosidase, and *α*-fucosidase (Figure 26). Typically, pyrrolidinol **147** was prepared in 60% yield by reaction of cyclic nitrone **146** with $TMSCF_3$ and tetrabutylammonium fluoride in THF at 0 °C. The subsequent reduction with Zn and In cleaved the N-O bond and provided the desired pyrrolidine **148** in 90% yield. As concerns pyrrolidine **149**, its synthesis was carried out through

debenzylation by hydrogenation with $Pd(OH)_2/C$ in MeOH/HCl in 95% yield (Figure 26). In this work, the authors also described the preparation of a series of similar fluorinated heterocycles from different sugar-derived cyclic nitrones using the same procedure.[93]

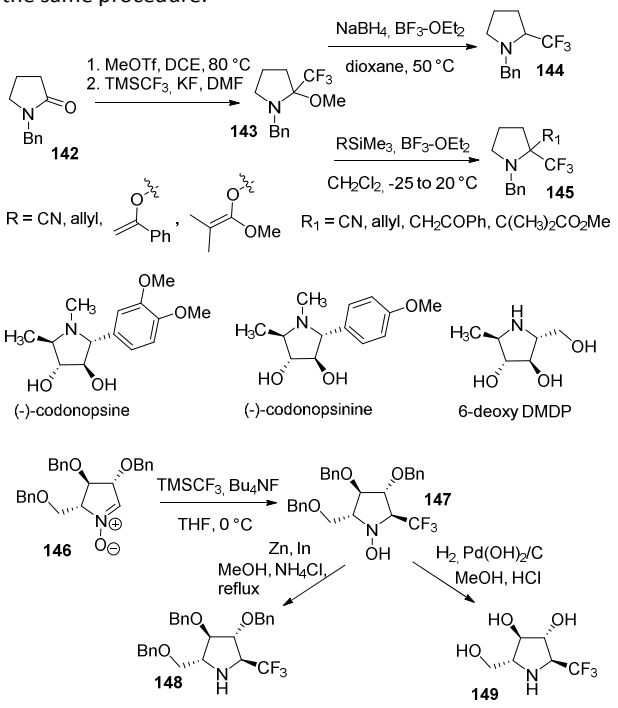

Figure 26. Synthesis of trifluoromethyl-pyrrolidines **143**, **144**, **145**, **147**, **148** and **149** and structures of codonopsine, codonopsinine and 6-deoxy- DMDP.

Until now, the CF_3 group was introduced on a heterocycle due to a fluorinated reagent or trifluoromethylated building block. Here, Haufe and coworkers reported the formation of trifluoromethylated analogues of pyrrolidinylsulfonyl isatin (a potent inhibitor of caspase-3 and -7) by an oxidative desulfurization-fluorination reaction. This method relied on the transformation of dithiane precursor **150** by the sequential addition of dibromohydantoin/pyridine.9HF at -70 °C in dichloromethane. Hence, the isatin derivative **151** was obtained in ~50% yield, as determined by ^{19}F NMR spectroscopy (Figure 27).[94,95]

More conventional approaches lied in the connection of a preformed trifluoromethyl-pyrrolidine ring thank to the creation of a C-N bond. For instance, in the frame of the preparation of GN8 analogues with antiprion properties, (*S*)-(+)-2-(trifluoromethyl)pyrrolidine was appended to bromo derivative **152** in the presence of K_2CO_3 in refluxing THF. The resulting active product **153** was isolated in 73% yield (Figure 27).[96]

Following the same principle, fluorinated cholesteryl ester transfer protein inhibitors **154**[97] and antibacterial 8-aminomethyltetracycline derivative **155**[98] were synthesized and their biological activities were subsequently evaluated (Figure **28**).

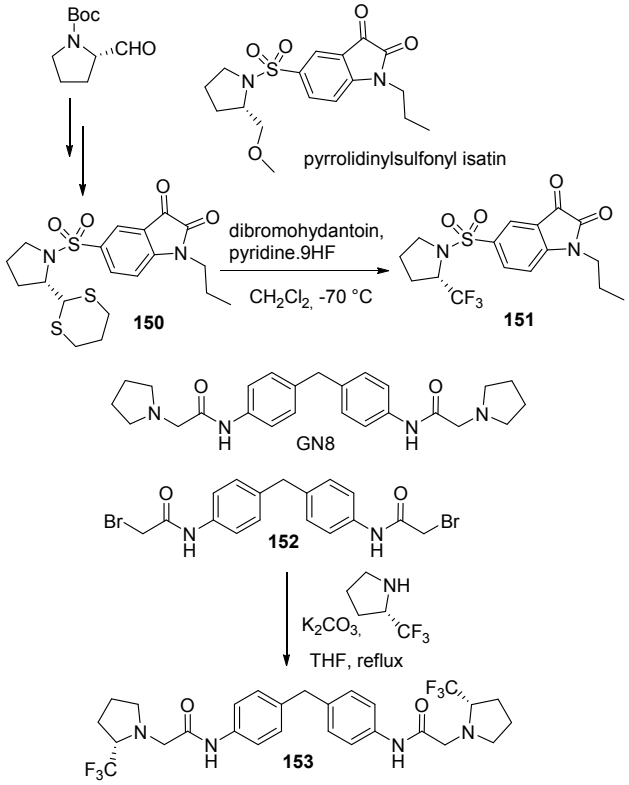

Figure 27. Synthesis of trifluoromethyl-pyrrolidines **151** and **153** and structures of GN8 and pyrrolidinylsulfonyl isatin.

Finally, the arylation of fluoroalkyamines was recently investigated by metal-catalyzed coupling reaction. Indeed, the strong electron-withdrawing effect of CF_3 group tends to retard reductive elimination to form the C–N bond. Purposely, it was demonstrated that such a coupling reaction could occur using $[Pd(allyl)Cl]_2$ (0.375 mol%) as catalyst in the presence of CyBippyPhos (1.5 mol%) as ligand and NaO*t*Bu as base at 65 °C. Starting from a set of chloro or bromo aryl derivatives **156** and (*S*)-(+)-2-(trifluoromethyl)pyrrolidine hydrochloride, the resulting heterocycles **157** were produced in 21 to 95% yields with an *e.e.* higher than 99 % (Figure **28**).[99]

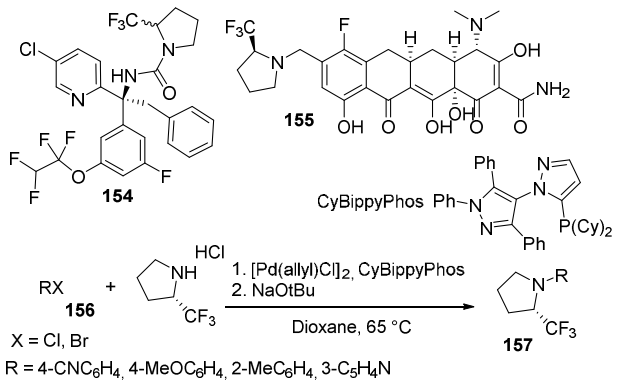

Figure 28. Synthesis of trifluoromethyl-pyrrolidines **157** structures of compounds **154** and **155**.

4.4. Synthesis of trifluoromethyl-pyrrolidines from imines

Röschenthaler and coworkers have extensively explored the added value of CF_3-pyrrolines which can be prepared from *N*-vinylpyrrolidin-2-one and ethyl trifluoroacetate.[100] As first target, the authors prepared almost quantitatively the pyrrolidinylphosphonate **159** by addition of diethyl phosphite to cyclic imine **158** in the presence of BF_3-Et_2O. This compound was considered as a phosphonate analogue of prolines with a potential therapeutic effect to prevent the rejection of transplanted tissues (Figure 29).[101] The same methodology was subsequently extended to the preparation of fluorinated analogues of biologically active compounds containing a pyrrole, indole or tetrazole unit. As concerns the pyrrole group, the fluorinated derivatives **160** were prepared in yields spanning from 69 to 87%, some of them were derived from amino acids (Figure 29).[102,103] For indole derivatives **161**, the authors show that a wide variety of heterocycles could be appended in very good yields (>60%) (Figure 29).[104] Finally, an azido-Ugi reaction with benzyl isocyanide and $TMSN_3$ achieved the formation of the tetrazole ring, thus giving compound **162** in 54% yield (Figure 29).[105] As aforementioned, the Ruppert's reagent is a powerful source of trifluoromethyl anion. Hence, it was challenged with a series of cyclic imines **163** with the aim to prepare fluorinated analogues of nicotine and anabasine with potential application for treatment of central nervous system disorders. The reaction was achieved with $TMSCF_3$ and potassium hydrofluoride in a mixture CH_3CN/DMF to give the corresponding pyrrolidines **164** in the range of 49 to 79% yield (Figure 29).[106,107]

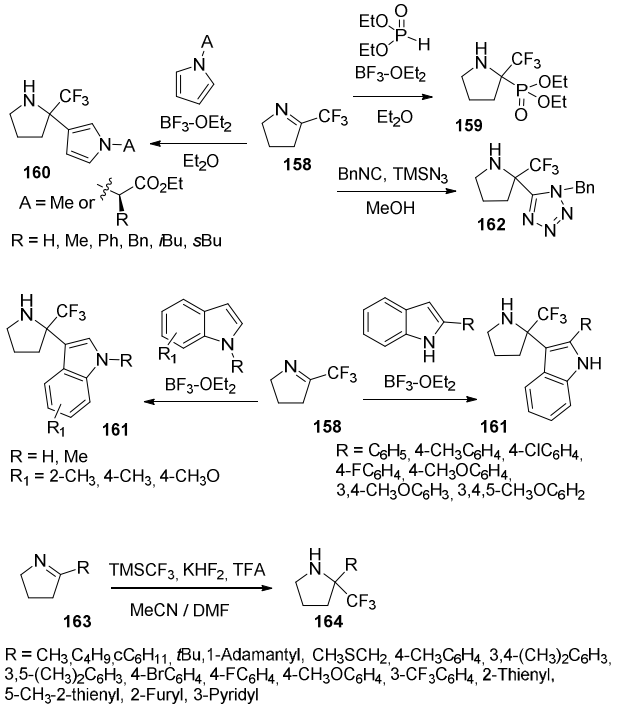

Figure 29. Synthesis of trifluoromethyl-pyrrolidines **159**, **160**, **161**, **162** and **164**.

5. Trifluoromethyl five membered ring amino acids

5.1 Synthesis of trifluoromethyl amino acids from amines

Fluorinated amino acids have been the subject of intense researches since their incorporation in a peptide sequence can dramatically improve the hydrolytic stability and the secondary structure. In this spirit, the synthesis of a trifluoroglutamic acid was proposed in order to make an analogue of thyreotropin releasing hormone (pGlu-His-Pro-NH_2), which controls the release of thyroid stimulating hormone. The reaction of butenylmagnesium bromide with imine of 3,3,3-trifluoropropanoate **165** followed by oxidation of double bond with $KMnO_4$ provided the trifluoromethyl glutamate intermediate **166** in yield higher than 70%. Then, a saponification step followed by a debenzylation by hydrogenation with Pd/C gave the corresponding amino acid which readily underwent a spontaneous cyclization at room temperature into trifluoro pyroglutamic acid **167** in 96% yield (Figure 30).[108] In 2008, Brigaud and coworkers developed an asymmetric version starting from oxazolidine **168** derived from ethyl trifluoropyruvate and (*R*)-phenylglycinol. Its conversion into hydroxymorpholinone **169** (75:25 diastereomeric mixture) proceeded according to a three-step synthesis (allylation, lactonisation and hydroboration). Subjecting compound **169** to a Jones oxidation afforded to form the diastereomers **170** in 61 and 20% yields after a separation step. Finally, (*R*) and (*S*)-pyroglutamic acids **167** were achieved in 69 and 49% overall yields, respectively, according to a three-step sequence involving a saponification, acidification and reductive cleavage of benzyl group with lithium ammonia (Figure 30).[109] Uneyama and coworkers also demonstrate that *N*-tosylaziridine could give a straightforward access to trifluoromethyl pyroglutamic acid. Using (*S*)-ethyl 1-tosyl-2-(trifluoromethyl)aziridine-2-carboxylate **1c** as starting material, its addition with the carbanion of dimethyl malonate provoked a ring opening in 67% yield.

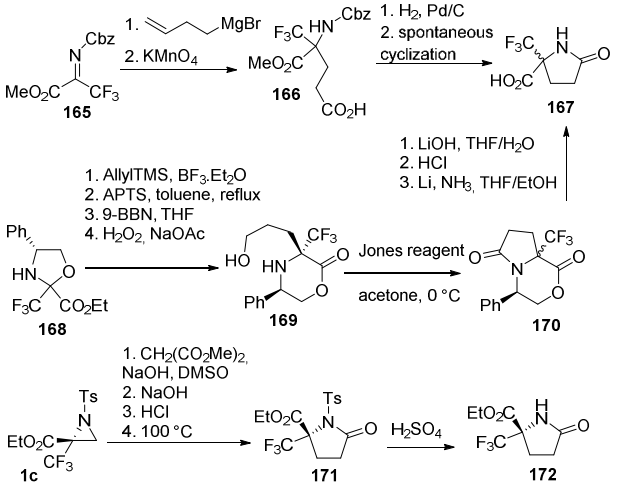

Figure 30. Synthesis of trifluoromethyl-pyroglutamic acids **167** and **172**.

Afterwards, cycloadduct **171** was obtained in 32% yield by saponification and acidification. Finally, detosylation was attained with concentrated H_2SO_4 to give the (*S*) cycloadduct **172** in 92% yield (Figure 30).[27]

Fluorinated prolines are also appealing building blocks which can potentially assume the same chemico-physical properties as CF_3-pyroglutamic acids. In 1998, Dixneuf and coworkers disclosed a simple and effective synthesis of trifluoromethyl prolines by ring closing metathesis. Imines **165** bearing tosyl or Cbz groups were able to react successively with vinyl magnesium bromide at -90 °C and allylbromide in the presence of NaH to provide the amines **173** in 81 and 65% yields, respectively. The ring closure required 10% mol of first generation Grubbs catalyst to reach trifluoro dehydroprolinates **174** in ~50% yields (Figure 31).[110] Later, this strategy was applied to the structural modification of 5,6-dichloro-benzimidazoles **175** which are selective androgen receptor antagonists.[111] In 2006, oxazolidine **168** was also used as starting building block for the stereoselective preparation of trifluoroprolines. Starting from intermediate **169**, the combination of a cyclization reaction with PPh_3/I_2 imidazole or mesyl chloride then removal of chiral auxiliary group by hydrogenation furnished enantiopure (*R*) and (*S*) trifluoromethyl prolines **177**.[112]

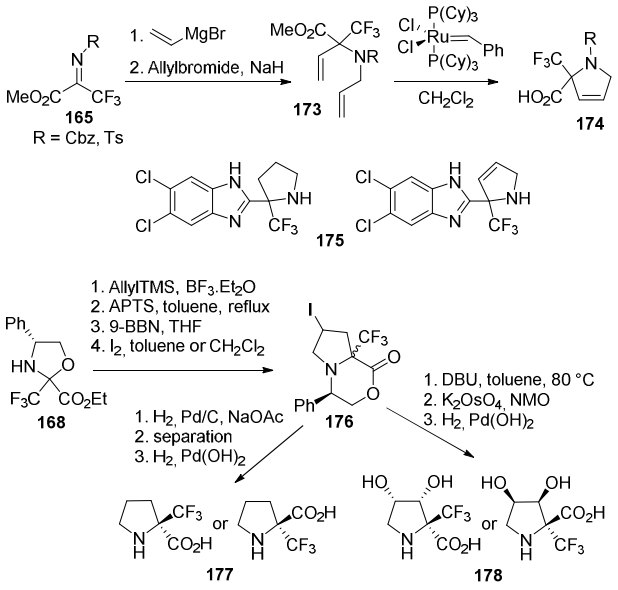

Figure 31. Synthesis of trifluoromethyl-proline derivatives **174**, **177** and **178**.

According to a similar chemical pathway, a modified synthetic approach was developed using an iodine-mediated cyclization. Iodo oxazinone derivatives **176** were thereby formed as a mixture of diastereoisomers in up to 87% yield. A reductive deiodination afforded to separate both diastereomers which underwent a hydrogenolysis with $H_2/Pd(OH)_2$ to give rise to (*R*) and (*S*) fluorinated prolines **177** in 45 and 68% yields, respectively. Focusing on dihydroxylated analogues of prolines **177**, the successive treatment of diastereomers **176** with 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) and dihydroxylation of resulting alkenes with osmium tetroxide/ NMO yielded the diol intermediates in good yields. Finally, the dihydroxyprolines **178** were produced in 92% yield by hydrogenation of phenylglycinol group (Figure 31).[113,114]

In 2013, another asymmetric version based on the cyclization of an optically pure homoserine derivative was presented. Alkylation of aryl imine ester **165** with alkyne and Me_2Zn in the presence of (*R*)-3,3'-TMS_2-BINOL allowed for the formation of chiral propargyl amine **179** in 93% yield and *e.e.* of 95%. Chiral compound **179** was subsequently converted into heterocycle **180** by a three-step procedure involving a hydrogenation of triple bond, removal of (*tert*-butyldimethylsilyl) moiety with HCl, and a cyclization after conversion of alcohol into mesylate functional group. At last, treatment with CAN and HCl produced (*R*)-α-trifluoromethyl-proline hydrochloride **181** in 66% yield (Figure 32).[115]

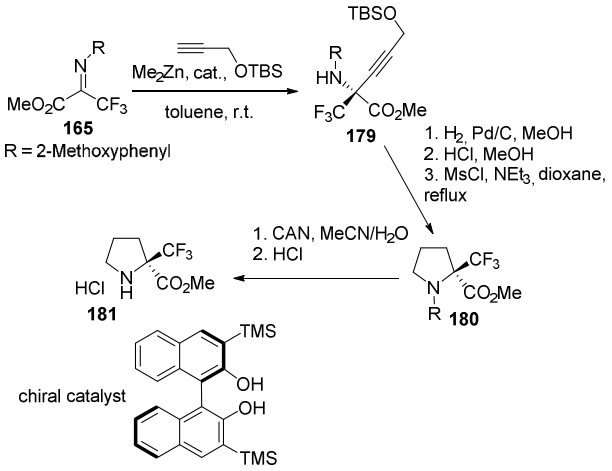

Figure 32. Synthesis of trifluoromethyl-proline derivative **181**.

5.2. Synthesis of trifluoromethyl-amino acids from cyclic imines

We already mentioned that cyclic imines were conveniently used for the formation of trifluoromethyl pyrrolidines. Nenajdenko and coworkers also demonstrated that imine **158** could be involved in a multicomponent reaction with an isocyanide and a strong acid (CF_3COOH) to form trifluoroproline derivatives **182** in ~80% yields. In the presence of isocyanoacetic acid derivatives, Ugi reactions allowed to prepare dipeptides **183** in 51 to 67% yields (Figure 33).[100] Aside, an original strategy concerned the preparation of cyclic trifluoromethyl imines from propargylic compounds. Alkynes **184** possessing carboxylate or phosphonate groups were end-functionalized with an aryl group through palladium catalyzed Sonogashira cross coupling in yields around 70%.[116] *N*-Boc deprotection occurred in the presence of trifluoroacetic acid but the resulting amine was accompanied with imine **185**. A complete conversion was attained by reaction of crude materials with AgOTf (5 mol.%) in MeCN, compounds **185** being isolated in 72 to 90% yields. As far as phosphonates are concerned, removal of Cbz group was carried out with a

mixture CF_3COOH/APTS which underwent a spontaneous cyclization into cyclic imines **186** in yields higher than 75%. The subsequent hydrogenation of cycloadduct **185** in conventional conditions yielded trifluoro 5-arylproline **187** in 65% yield (Ar = PMP) (Figure 33).[117]

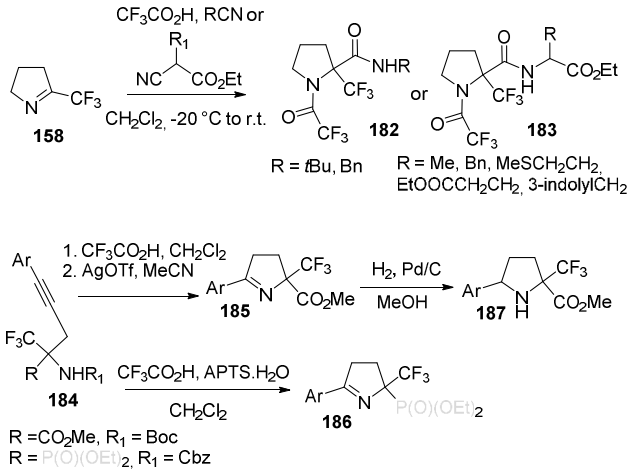

Figure 33. Synthesis of trifluoromethyl-proline derivatives **182**, **183** and **187**.

At this stage, it can be observed that all synthetic strategies lied in the preparation of cyclic species with CF_3-containing quaternary carbon centers. In 2014, an approach aimed at synthesizing a *cis*-trifluoroproline from L-glutamic acid. Ester end-chain of fully protected amino ester **188** was thereby modified by reduction with diisobutylaluminium hydride (DIBAL-H) (84% yield), trifluoromethylated with $TMSCF_3$ (95% yield) and oxidized with Dess-Martin reagent (79% yield), leading to amino ester **189**. Afterwards, *N*-Boc deprotection and saponification of amino ester **189** provided an intermediate which spontaneously cyclized in imine **190** after treatment with an acidic resin. At this stage, the authors mentioned the isomerization of double bond and loss of chirality at position 2. Unstable heterocycle **190** was hydrogenated in conventional conditions and converted quantitatively into trifluoroproline **191** as a diastereomeric mixture (*cis*/*trans* 87:13) (Figure 34).[118]

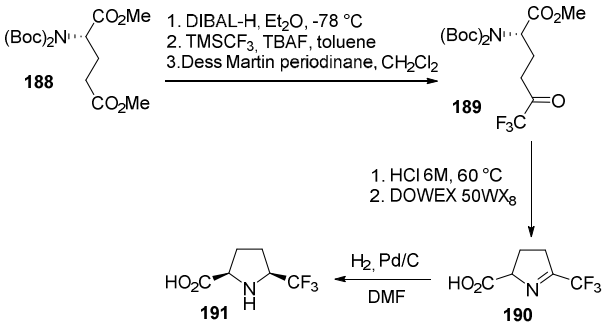

Figure 34. Synthesis of trifluoromethyl-proline derivative **191**.

6. Trifluoromethyl five membered ring lactams

6.1. Synthesis of trifluoromethyl five membered ring lactams from amines

Fluorinated five membered ring lactams can mimic several analogues such as proline or pyroglutamic acid. Thus, aside from the disappointing cyclization of amino ester into *β*-lactams, Hao and coworkers revealed that the ring closure of longer amino esters (prepared in 2 steps from precursor **192**) with NaH as base afforded the preparation of corresponding lactams **193** in 85 to 94% yields (Figure 35).[76] Following the same principle, cycloadducts bearing phosphonate groups were investigated owing to their biological activities found in the treatment of cancer, HIV and brain diseases. A [2 + 2] cycloaddition reaction between phosphazenes **194** and polyfluoroacetylenephosphonates **195** created an ylide which readily reacted with ethyl glyoxalate to form 1-azadienes **196** in yields higher than 65%. Unsaturated compounds were reduced with $NaBH_4$ giving rise to a mixture of diastereomers **197**. Interestingly, its reaction with NaH provoked a cyclization into lactams **198** which were isolated as a unique *trans* isomer (Figure 35).[119]

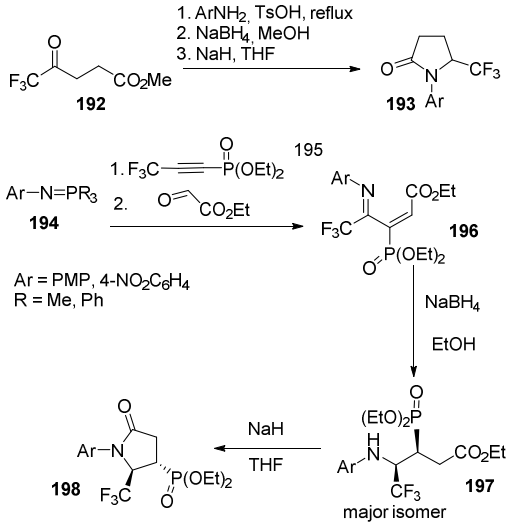

Figure 35. Synthesis of trifluoromethyl five membered ring lactams **193** and **198**.

6.2. Synthesis of trifluoromethyl five membered ring lactams from heterocycles and imines

Among unusual syntheses of fluorinated lactams, we can note the conversion of acidic function of (*S*)-pyroglutamic acid into trifluoromethyl group by means of sulphur tetrafluoride in the presence of anhydrous HF. The corresponding cycloadduct **199** was obtained in 92% yield with an *e.e.* of >99%.[120] Fluorinated five membered rings **200** were also prepared by reaction of imine **24** bearing Bn or phenyl glycinol methyl ether group with ethyl 2-(bromomethyl)acrylate and Zn under Barbier conditions in up to 60% yields.[121]

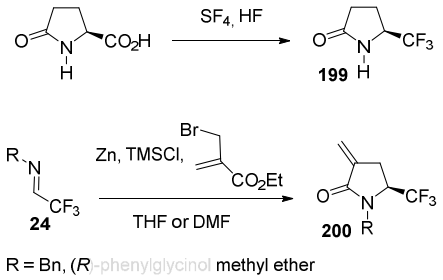

Figure 36. Synthesis of trifluoromethyl five membered ring lactams **199** and **200**.

Conclusions

The development of new strategies targeting fluorine-containing compounds is an ongoing field of research which also includes small nitrogen heterocycles. In this paper, we provide an overview regarding the synthetic methodologies aiming at preparing fluorinated aziridines, azetidines and pyrrolidines and their lactam/amino acid analogues. Hence, these cycloadducts were attained through elegant synthetic methodologies with potential high regio- and diastereoselectivities. In most cases, their hydrogenated counterparts have inspired the formation of these fluorinated compounds for biological purposes. As a result, the synthetic approaches have sometimes demonstrated a higher or unique reactivity regardless the chemical pathways and, in some cases, with unexpected chemical sequences. Interestingly, three membered rings have been the subject of intense efforts which contributed to the development of varied chemical approaches; these aziridines acting as building blocks through ring opening. Azetidines and *β*-lactams were much less reported, probably due to a high ring tension in addition to the destabilizing effect of the strong electronwithdrawing CF_3 group. However, the combination of the unique properties of fluorine and a small size should give rise to relevant intermediates particularly active in medicinal chemistry and ligand design. For instance, some non-fluorinated azetidine-containing molecules exhibit potent biological activities such as nanomolar selective CB2 receptor agonists,[122] or Syk kinase inhibitors.[123] At last, five-membered rings allowed for the development of many different synthetic pathways owing to the ease to install the CF_3 moiety. Taking into consideration the role of proline-containing motifs in the 3D organization of peptides, we can note that some fluorinated nitrogen heterocycles are already considered in the rational design of analogues.[124] Beyond the challenging aspects of heterocyclic chemistry, the development of new fluorination methodologies appears highly desirable for selective mono-, di- or trifluoromethylation at specific positions. The exceptional potential of fluorinated compounds in biochemistry and pharmaceutical industry should be sufficient to convince academic and private stakeholders to combine their efforts to deal with this issue.

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