PREPARATION OF RACEMIC AND OPTICALLY ACTIVE TRIFLUOROMETHYL AZIRIDINES AND AZETIDINES

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Abstract. *Recent advances regarding the synthetic chemistry of fluorinated aziridines and azetidines are presented in this chapter. These small heterocycles are of high importance both as building blocks for more complex structures and as active parts of medicinal chemistry-oriented compounds. Methods are presented according to the precursors used for the synthesis.*

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1. Introduction

The fluorine atom occupies a very special place in the classification of elements, at the top-right corner of Mendeleev's table; this position is associated with strong electronegativity and a low polarizability. In addition, its small size (van der Waals radius ~ 1.47 Å) makes fluorine isostere of oxygen but bigger than hydrogen. The CF_3 group is also comparable in size to an isopropyl group. Hence, the C-F bond is very stable, corresponding to the strongest bond in organic chemistry with a bond-dissociation energy around 485 $kJ.mol^{-1}$. This combination of remarkable properties gives to fluorinated compounds a high added value in many domains, ranging from materials and polymer science, to pharmaceuticals and molecular biology.[1-5]

The physico-chemical properties of the C-F bonds confer materials valuable advantages such as high thermal, light and chemical stability, oil and water repellency, low dielectric constants and low flammability. On the other hand, the introduction of a fluorinated group in biologically active compounds will significantly influence their lipophilicity, electronic and binding properties, metabolic stability, and *p*Ka; the replacement

of H-atoms by F-atoms being one of the best known bioisosteric conversions in drug design. As a consequence, unabated interest in fluorination methods has been seen in the literature, and more particularly trifluoromethylation is the subject of intense research.[6-8]

Chiral aziridines and azetidines have high potential for further elaboration of enantiopure N-containing molecules. Their facile opening by nucleophiles arising from the release of their strain energy opens the way to facile preparation of 1,2-disubstituted chiral building blocks.[9-17] Small heterocycles are also often found in biologically active compounds.[18,19] These fluorinated building blocks can be incorporated in the preparation of amino acids to produce modified peptides and proteins, thereby conferring special features to the resulting species.[20] Here, we decided to present an overview of current methodologies applied for the synthesis of trifluoromethylated aziridines and azetidines. The preparation of these fluorinated heterocycles was performed according to various chemical pathways including those using racemates or optically active compounds. In this regard, the document was organized by taking into consideration the immediate precursor of these fluorinated cycles, therefore, racemic and asymmetric pathways will be described under the same subsection.

2. Trifluoromethylaziridines

2.1. Synthesis of trifluoromethylaziridines from trifluoromethylated amines

In 1997, Uneyama and coworkers reported an elegant asymmetric synthesis of trifluoromethylaziridines **1** from optically pure (*S*)-3,3,3-trifluoropropene oxide. Its ring opening reaction with benzylamine gave rise to the corresponding fluorinated amine **2** in 85% yield with an enantiomeric excess (*e.e.*) of 75%. However, successive recrystallization steps afforded to improve the enantiomeric purity up to 99.5%. Finally, the ring closure reaction with dichlorotriphenylphosphorane provided aziridine **1a** in good yield and an *e.e.* of 99.5% (Figure 1).

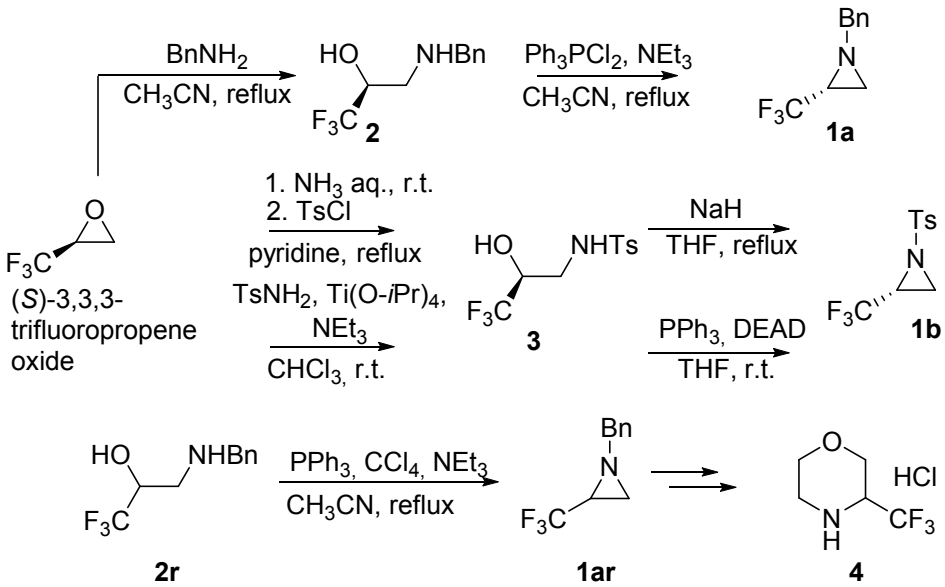


Figure 1. Synthesis of trifluoromethylaziridines **1a**, **1b** and **1ar** from amines.

The absolute configuration of the fluorinated cycle was further determined by a similar reaction in the presence of (*S*)-1-phenylethylamine.[21] Later, the same procedure was exploited for the preparation of

racemic 2-phenyl- and 2-(4-methoxyphenyl)-2-(trifluoromethyl)-aziridine derivatives.[22] Another approach has consisted in the ring opening of (*S*)-3,3,3-trifluoropropene oxide precursor with aqueous NH_3. The resulting amine **3** underwent a one pot *N*- and *O*-tosylation step followed by an intramolecular S_N2 substitution into *N*-Tosylaziridine **1b** in 31% yield (Figure 1).[23] Finally, this last strategy was improved by an aziridine (**1b**) formation in 91% yield from amine **3** using an intramolecular Mitsunobu reaction.[24] It is worth pointing out that in the frame of the preparation of trifluoromethylmorpholines **4**, PPh_3/CCl_4 reagents have promoted the ring closure of fluorinated amine **2r** in racemic trifluoromethylaziridine **1ar** (Figure 1).[25]

The preparation of enantiomerically pure aziridines with *N*-substituent variations was considered of relevant interest owing to their regioselective ring-opening. In this regard, Portella and coworkers reported the synthesis of aziridines from chiral alkoxyaldehydes **5**. Purposely, a one pot procedure relied on a condensation reaction between *p*-toluenesulfonamide and (*R*) fluorinated **5a** in the presence of $TiCl_4$, followed by a reductive amination with $NaBH(OAc)_3$. After removal of benzyl group, (*R*)-β-alkoxysulfonamides **6** were involved in a cycloaddition under classical Mitsunobu conditions, providing the enantiopure cycloadducts **7a** in good yields (>81%). Following the same principle, a non-activated *N*-benzylaziridine **5b** was prepared according to a similar pathway, however, the ring closure of *N*-benzyl β-aminoalcohol (after removal of O-allyl group of **8**) arose in 80% yield after reaction with PPh_3/CCl_4.[26]

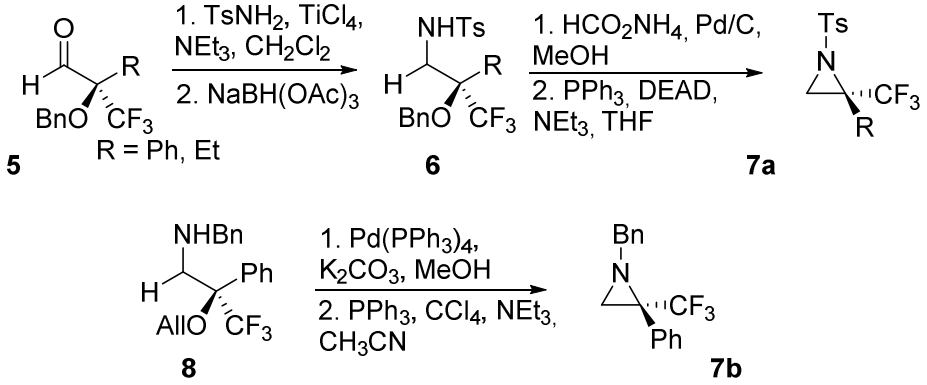


Figure 2. Synthesis of trifluoromethylaziridines **7a,b** from amines.

As far as optically active aziridines are concerned, a synthetic strategy has evaluated the use of amines bearing sulfoxides as chiral auxiliary groups. Hence, the chemical sequence started by treatment of the trifluoroaldimine **9** with α-lithiated sulfoxides **10** to give β-sulfinyl amines **11**. These compounds underwent a rearrangement into β-chlorosulfenamides**12** with a high degree of stereoselectivity (98:2) by reaction with oxalyl chloride in the presence of *sym*-collidine. Subsequently, the cleavage of N-S bonds with sodium borohydride ($NaBH_4$) afforded the formation of β-chloro amides **13** as single diastereoisomers in yields up to 87%. Finally, the chloro derivatives reacted with NaH to give the enantiomerically pure trifluoroaziridines **14** in 70 and 79% yields, respectively (Figure 3).[27,28]

In 2010, De Kimpe and coworkers developed a straightforward and cost-effective access to racemic fluorinated aziridines following a similar pathway, *i.e.* the ring closure of β-chloro amines. In this case, a set of trifluoro imines **15** was prepared by condensation of commercially available 1,1,1-trifluoroacetone with alkylamines in the presence of titanium(IV) chloride as catalyst. The procedure proceeded by a chlorination

step using *N*-chlorosuccinimide (NCS) as reagent, providing the corresponding *N*-(1-chloromethyl-2,2,2-trifluoroethylidene)alkylamines **16**. Then, the reduction of imines with $NaBH_4$ operated in moderate yields (54-65%) and the ring closing reaction required the use of lithium bis(trimethylsilyl)amide (LiHMDS) as strong base to give the fluorinated aziridines **17** in yields higher than 78% (Figure 4 and Table 1).[29]

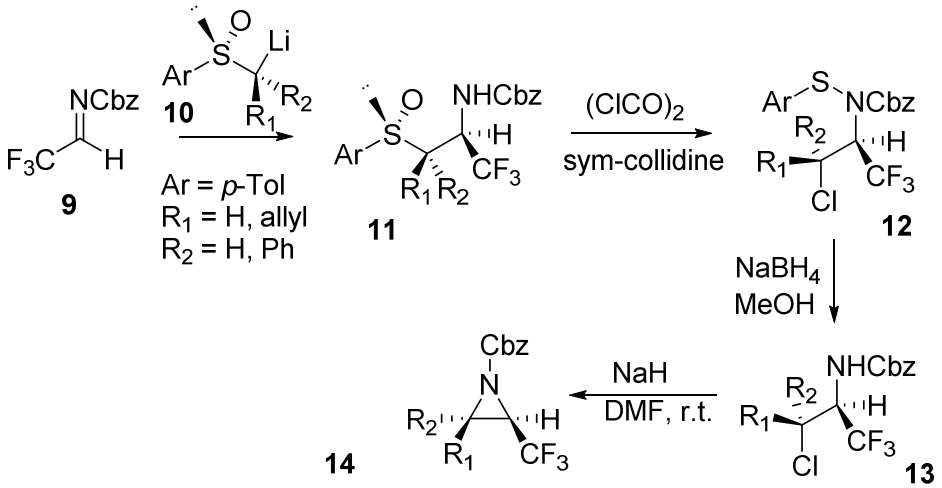
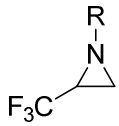


Figure 3. Synthesis of trifluoromethylaziridines **14** from amines.

Table 1. Synthesis of 1-alkyl-2-(trifluoromethyl)aziridines **17**.

1-alkyl-2-(trifluoromethyl)aziridines**17**	R	yield[a]
	Bn	92%
	4-$ClC_6H_4CH_2$	78%
	4-$MeOC_6H_4CH_2$	80%
	n-Octyl	83%
	$(CH_2)_2C_6H_5$	81%

[a]*Yield after column chromatography (SiO_2).*

Proceeding with the ring closure of β-chloro-trifluoromethyl amines, a convenient and stereoselective strategy achieved the access to either *cis*- or *trans*-(trifluoromethyl) aziridines **17a** and **17b**.

According to the procedures previously described, a set of trifluoromethylated imines **15a** was prepared by condensation of 1,1,1-trifluorobutan-2-one and 1,1,1-trifluoro-3-phenylpropan-2-one with primary amines functionalized with Bn, cHex and *i*-Pr groups. Then, chlorination with 1 eq. or 3-5 eq. of *N*-chloro-succinimide provided the corresponding α-monochlorinated or α,α-dichlorinated imines **15b** and **15c**, respectively. Interestingly, treatment of α-monochlorinated imines **15b** with 2 eq. of lithium aluminum hydride ($LiAlH_4$) in ether at room temperature led to *trans*-aziridines **17a** as the major diastereomers in 65-86% yields and diastereoisomeric ratio up to 6/94 (*cis*/*trans*). In contrast, the reduction of α,α-dichlorinated imines **15c** with the same amount of $LiAlH_4$ in refluxing ether yielded the *cis*-aziridines **17b** as the major diastereomers in 57-93% yields with high diastereoselectivity (*cis*/*trans* 97:3, Figure 4). Further investigations allowed the preparation of (trifluoromethyl)morpholin-2-one derivatives as potential T-type Ca^{2+} channel blockers or tachykinin receptor antagonists.[30] Recently, an optically active synthesis of fluorinated aziridines was carried out from chiral aryl CF_3-substituted *N*-*tert*-butylsulfinylketimines **18**.

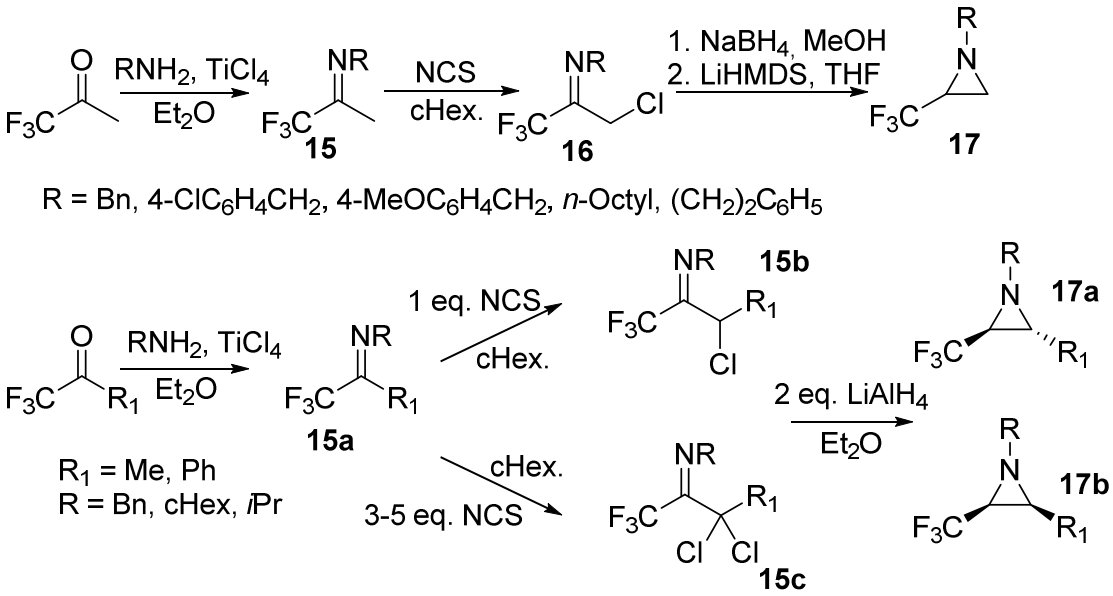


Figure 4. Synthesis of trifluoromethylaziridines **17**, **17a** and **17b** from amines.

Here, chiral β-aryl-β-trifluoromethyl-β-aminoarone intermediates **19** were obtained according to Mannich-type reactions involving ketone-derivative enolates. The resulting compounds were isolated with diastereoisomeric ratios ranging from 55:45 to 93:7 (as determined by ^{19}F NMR) and yields up to 91%. Then, removal of chiral sulfoxide group under acidic condition and benzoylation of nitrogen with benzoyl chloride proceeded with retention of configuration. Finally, treatment of amine **19a** with phosphorus pentachloride was expected to form a fluorinated oxazine. However, only an aziridine **20** was obtained in 73% yield by intramolecular cyclization (Figure 5).[31]

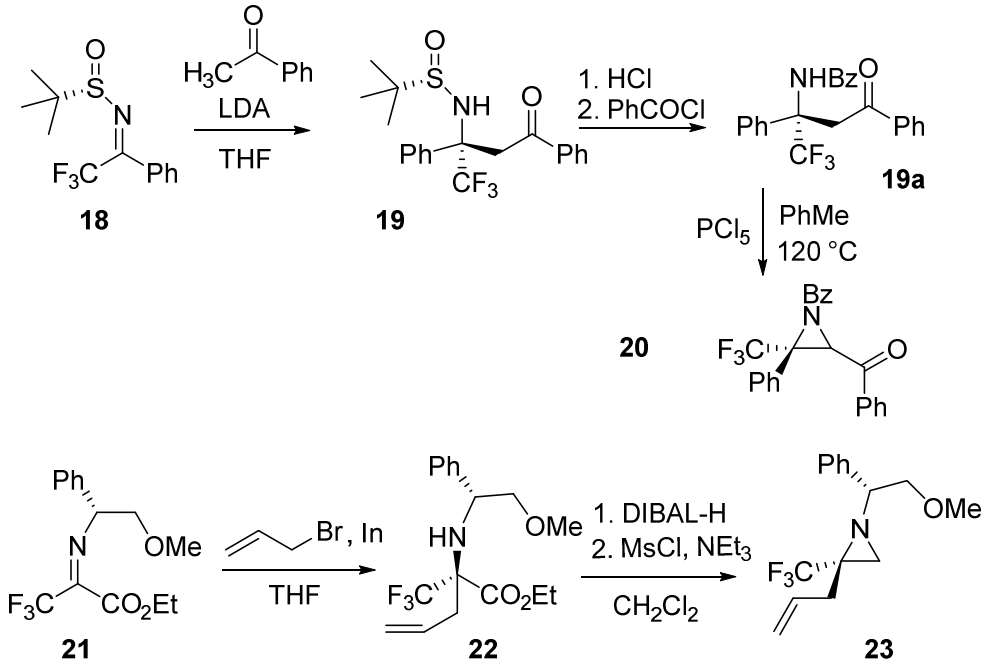


Figure 5. Synthesis of trifluoromethylaziridines **20** and **23** from amines.

In the frame of the diastereoselective formation of quaternary α-trifluoromethyl α-amino acids, Zhang and coworkers developed an efficient method for preparing optically active aziridines. Typically, an imine

(**21**) of trifluoropyruvate flanked with (*R*)-phenylglycinol methyl ether as chiral auxiliary group was able to react with indium and allylic bromide derivatives to give the corresponding quaternary α-allyl-α-trifluoro amino acids **22** in yields up to 98%. The coupling reactions operated with high diastereoselectivities (20:1) as already reported with similar chiral components.[32,33] Afterwards, a three-step procedure which consisted in the reduction of ester group into alcohol, a mesylation and chromatographic purification led to the 2-allyl-2-(trifluoromethyl)aziridine **23** in 93% yield (Figure 5).[34]

2.2. Synthesis of trifluoromethylaziridines from imines

Imines represent versatile building blocks with a wide range of reactivity, allowing a straightforward access to aziridines. In 2001, Bégué and coworkers disclosed the aziridination from trifluoroaldimines, targeting the synthesis of aziridine-2-carboxylates as potential precursors of non-proteogenic α- and β-amino acids. In this regard, varied conditions were investigated to promote the reaction between fluorinated imines **24** bearing benzyl (Bn) or para-methoxyphenyl (PMP) groups and ethyl diazoacetate. It came out that the three membered rings **25** were isolated in yields higher than 86% when reactions were carried out in ether at -78 °C using $BF_3{\cdot}Et_2O$ as Lewis acid 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).

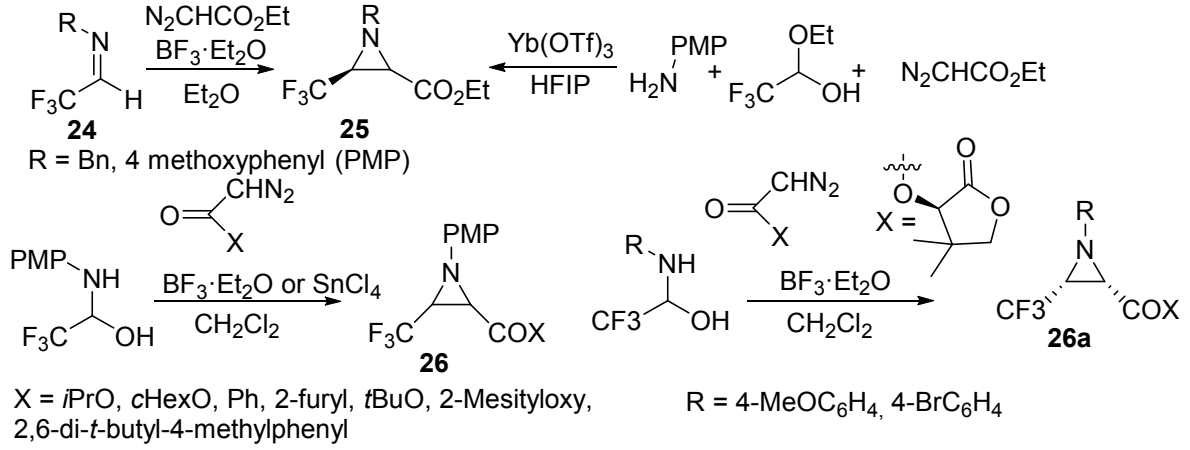


Figure 6. Synthesis of trifluoromethylaziridines **25**, **26** and **26a** from imines.

The nucleophilic ring-opening of aziridines afforded an elegant entry to fluorinated β-amino esters.[35] Hexafluoroisopropanol (HFIP) is a highly polar solvent which displays a poor nucleophilic behaviour and unique properties like high hydrogen bond donating ability. With this in mind, aziridination was investigated through reaction of trifluoroaldimines **24** bearing PMP, Bn and Ph_2-CH groups with ethyl diazoacetate in HFIP as reaction media.

Hence, when the reactions were conducted in the presence of a catalyst (10 mol%) such as $Yb(OTf)_3$ or $BF_3{\cdot}Et_2O$, heterocycles were produced in 64 to 90% yields with a *cis*/*trans* ratio spanning from 60:40 to 70:30. However, a two-step one-pot procedure afforded a very efficient and straightforward access to aziridine formation. The three component system composed of fluoral ethyl hemiacetal, aromatic amine and ethyl diazoacetate in the presence of either $Yb(OTf)_3$ or $BF_3{\cdot}Et_2O$ in HFIP, afforded the formation of fluorinated cycle **25** in good yields but moderate diastereoselectivity (~6:4) (Figure 6). In contrast, no

reaction was observed using hexane or ether as solvents.[36] According to the same chemical pathway, De Kimpe and coworkers prepared the same fluorinated aziridines in 62% yield with high diastereoisomeric ratios (>99:1). This compound was used as starting building block for the preparation of a wide range of fluorinated heterocycles in the presence of nucleophiles, *i.e.* benzodithiin, benzoxathiin, benzothiazine, benzodioxine, benzoxazine and azetidines whose synthetic procedures will be presented later.[37] We can also mention that a *N*,*O*-hemiacetal derived from trifluoroacetaldehyde ethyl hemiacetal underwent cycloaddition to afford the aziridine through reaction with diazoacetate derivatives. Catalytic systems such as $BF_3{\cdot}Et_2O$ or $SnCl_4$ were particularly tailored for the aziridination with high level of stereoselectivity. Reactions operated in the presence of 1 eq. of Lewis acid in refluxing dichloromethane, giving rise to the trifluorinated heterocycles **26** in yields ranging 56-96%. A *cis* selectivity was observed in all cases with the exception of the reaction involving 2,6-di-*tert*-butyl-4-methylphenyl diazoacetate and $SnCl_4$ where the *trans* isomer arose as the major compound (*cis*/*trans* ratio 10:90). Subsequently, a convenient diastereoselective approach was studied using varied chiral diazoacetates. It was found that (*R*)-pantolactone-containing diazo ester allowed the conversion in aziridines **26a** with both high *cis* stereoselectivity (up to 99:1) and diastereoselectivity (up to 94%) (Figure 6).[38]

In 2012, a trifluoromethyl diazomethane was studied as a fruitful reagent for aziridination through aza-Darzens reaction. Here, the fluorinated intermediate was generated *in situ* by reaction of trifluoroethylamine hydrochloride and $NaNO_2$ in a mixture water/dichloromethane. The resulting diazomethane derivative **27** was thereby challenged with imines **28** (aromatic glyoxylimines and ethyl glyoxal imine) in the presence of $BF_3{\cdot}Et_2O$ as catalyst. The corresponding fluorinated 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).[39]

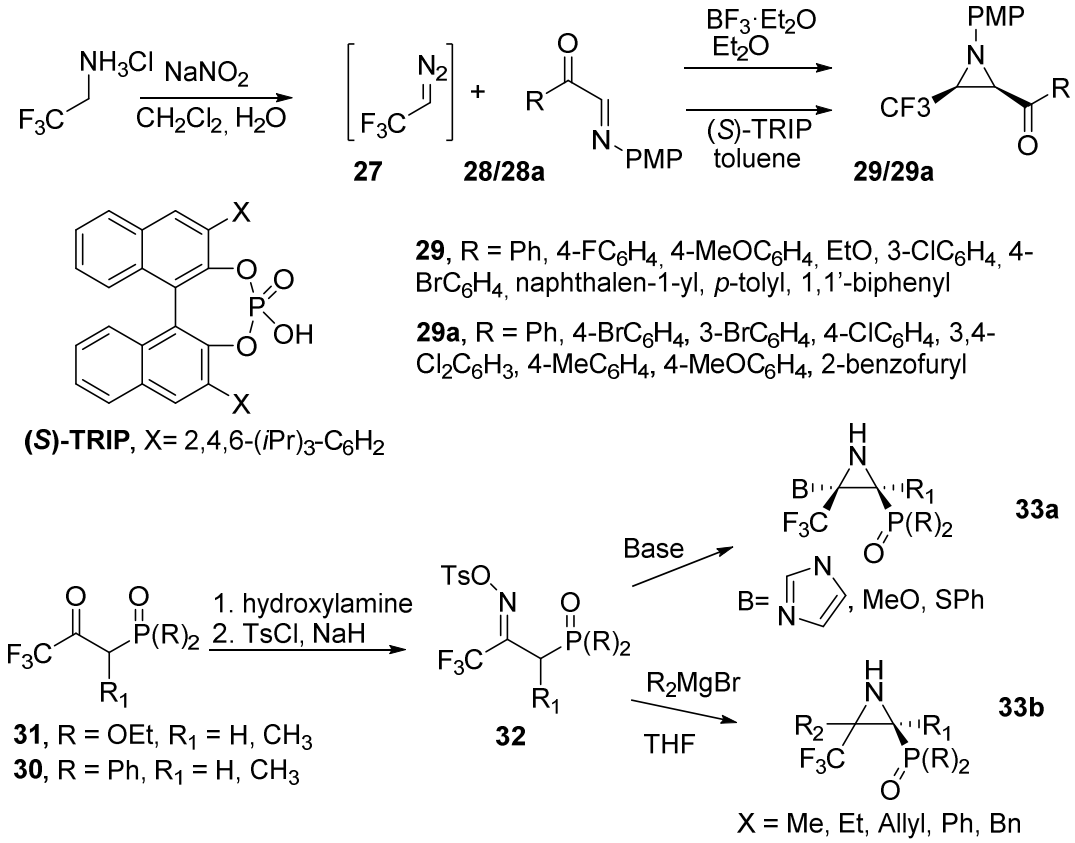


Figure 7. Synthesis of trifluoromethylaziridines **29**, **29a**, **33a** and **33b** from imines.

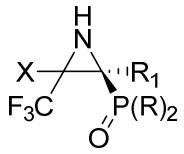
Following the same principle, Cahard and coworkers demonstrated that similar reactions could occur in the presence of a chiral phosphoric acid ((***S*)-TRIP**) catalyst. Hence, experimental conditions were carefully monitored by ^{1}H and ^{19}F NMR, showing that successive additions of 2.5 and 2% of chiral catalyst could improve the *cis*-aziridine formation in 65% yield with a diastereoisomeric ratio of 431:1 and an *e.e.* of 99%. In that way, a series of aryl glyoxal monohydrates **28a** was evaluated in the same conditions, giving rise to the corresponding aziridines **29a** in yields higher than 65% and *e.e.* up to 99% (Figure 7). Afterwards, aza-Darzens reactions were investigated with α-iminoglyoxalate and α-iminoglyoxylic amide. In the case of glyoxalate compounds, *cis*-triazolines were isolated as the major products whereas a mixture of *cis*-aziridine/triazoline was obtained in a 1:1 ratio when glyoxylic amide derivatives were used as reagents. However, fluorinated aziridines obtained from glyoxylic amide derivatives displayed very high enantiomeric ratios (>98%).[40]

In the frame of the formation of new amino phosphorus derivatives targeting pharmaceutical and agrochemical applications, an original synthetic strategy aimed at using a modified Neber reaction for ring closure of β-ketoxime-phosphine oxides and-phosphonates into azirines. After synthesis of β-keto-phosphine oxides **30** and -phosphonates **31**, phosphorous compounds underwent a condensation reaction with hydroxylamine to give the corresponding β-ketoximes which were readily transformed into β-*p*-toluenesulfonyloximes **32a** and **32b** by tosylation. Subsequently, treatment of oximes with NaOMe/MeOH mediated a ring closure reaction giving rise to exclusive *trans*-aziridine derivatives **33a** in yields in the range 44-69%. Good evidences of an azirine intermediate were obtained but this compound was probably unstable, including when reactions were carried out with imidazole or benzenethiol. In order to trap the cyclic intermediate, β-ketoximes were reacted with a set of Grignard reagents, namely methyl-, ethyl-, allyl-, phenyl and benzyl-magnesium bromide

Table 2). The resulting aziridines **33b** bearing phosphine oxide and phosphonate functionalities were isolated as *cis*/*trans* mixtures in yields up to 73%, the *cis*-isomers being the major products (Figure 7).[41]

Table 2. Synthesis of aziridines **33b** using a Grignard reagent.

Compounds **33b**



R	R_1	X	*Cis*/*trans*[a]	yield[b]
Ph	H	Methyl	75/25	58
Ph	H	Ethyl	84/16	69
Ph	H	Allyl	66/34	63 (44)[c]
Ph	H	Phenyl	95/5	73
OEt	H	Ethyl	71/29	57
OEt	H	Benzyl	55/45	56
OEt	H	Phenyl	100/0	60
OEt	CH_3	Allyl	60/40	59

*[a]The ratio of cis/trans isomers was determined by ^{31}P NMR. [b]Yield of isolated purified compounds. [c]Yield of isolated purified compounds from oximes **32a** and **32b**.*

In 2002, the versatile reactivity of chiral imines was evaluated toward dimethylsulfonium methylide in a diastereoselective fashion. In this regard, a series of chiral alkyl, aryl and trifluoroaldimines **34** flanked

with (*R*)-phenylglycinol methyl ether was able to react with trimethylsulfonium iodide and butyl lithium (BuLi) as base in THF at 0 °C, providing the corresponding aziridines **35** (Figure 8).

The fluorinated compound was isolated in good yield with a diastereoisomeric ratio of 92:8 ((*S,R*)/(*R,R*)). Additional experiments demonstrated the prominent role of the oxygen atom located on the chiral auxiliary group with regard to the reactivity.[42] Following the same approach, Corey-Chaykovsky aziridination reaction was investigated, relying on a new source of sulphur ylide. First, new chiral CF_3-substituted (*S*)-*N*-*tert*-butylsulfinylketimines **36** were prepared by condensation of (*S*)-*tert*-butylsulfinyl amide **37** and fluorinated ketones **38** in the presence of $Ti(OiPr)_4$ as catalyst. With respect to the previous case, an improved reactivity was obtained due to a much less reactive sulphur ylide intermediate derived from trimethylsulfoxonium iodide (**TMSOI**). Hence, the *in situ* generation of sulphur ylide from **TMSOI** under addition of NaH dramatically increased conversion rate into aziridines **39** and slightly improved diastereoselectivity (Figure 8).

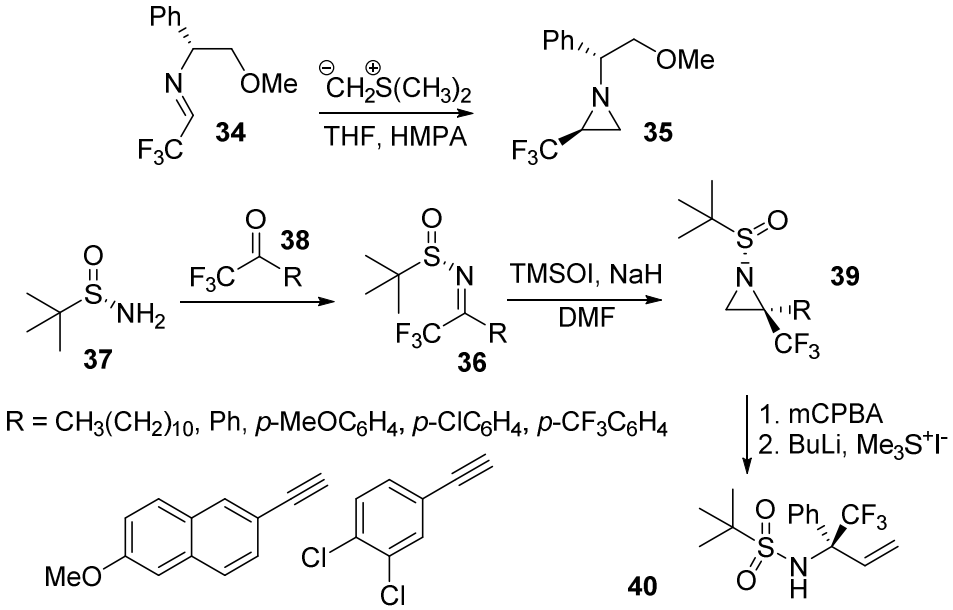


Figure 8. Synthesis of trifluoromethylaziridines **35** and **39** from imines.

Further developments allowed the determination of optimal parameters such as a low temperature (-45 °C) and the dropwise addition of sulphurylide to the reaction medium. The resulting fluorinated rings were isolated in moderate to excellent yields with *d.r.* up to 99:1. Targeting the formation of relevant chiral α-trifluoromethylallylamine synthons **40**, aziridine **39** (R = Ph) was firstly converted into its sulfonyl aziridine analogue by oxidation with mCPBA followed by ring opening in the presence of dimethylsulfonium methylide (Figure 8).[43]

2.3. Synthesis of trifluoromethylaziridines from heterocyclic precursors

Preparation of aziridines from heterocyclic systems is probably less intuitive yet original approaches afforded the three membered ring formation successfully. In the course of new four-membered heterocycles, the preparation of 1,2-selenazetidines was envisaged from fluorinated benzyl selenide as precursors. The synthetic procedure started by treatment of a fluorinated benzyl selenide **41** with lithium diisopropylamide (LDA), (hexafluoroisopropylidene) aniline (HFIA), and NH_4Cl aq., providing thus a β-aminoalkyl selenide

42. Removal of *tert*-butyldimethylsilyl group with tetrabutyl ammonium fluoride (TBAF) followed by oxidation with mCPBA, yielded a diastereomeric mixture (40 and 8% yields) of tetracoordinate 1,2-selenazetidines **43**, which were separated by a purification step. Under thermolysis at 210 °C, the heterocyclobutanes were expected to form an olefin. However, only 2,2-bis(trifluoromethyl)aziridine **44** was isolated in good yield (Figure 9).[44] Taking into consideration the aforementioned results, a new four-membered ring was studied as an aziridine source. In this regard, the chemical sequence regarding the tetracoordinate 1λ^4,2-thiazetidine synthesis initiated from a benzyl sulfide **45** bearing a Martin ligand, in conditions mirroring those for **41**. Then, the tetracoordinate 1λ^4,2-thiazetidine **46** was oxidized with RuO_4 into the corresponding pentacoordinate 1λ^6,2-thiazetidine **47** in only 15% yield. In contrast, upon heating at 160 °C in toluene-d_8, the thiazetidine was converted in aziridine **44** in very high yield (94%) according to a mechanistic pathway similar to that of the aza-Corey-Chaykovsky reaction, as reported above (Figure 9).[45] Finally, Kawashima and coworkers envisaged the same strategy in order to form azetidines bearing two chiral centers. New selenazetidines **48** were prepared using *N*-(2,2,2-trifluoro-1-phenylethylene)-aniline as starting materials. A mixture of *cis* and *trans* diastereomers **48** was separated by chromatography in 8 and 77% yields, respectively.

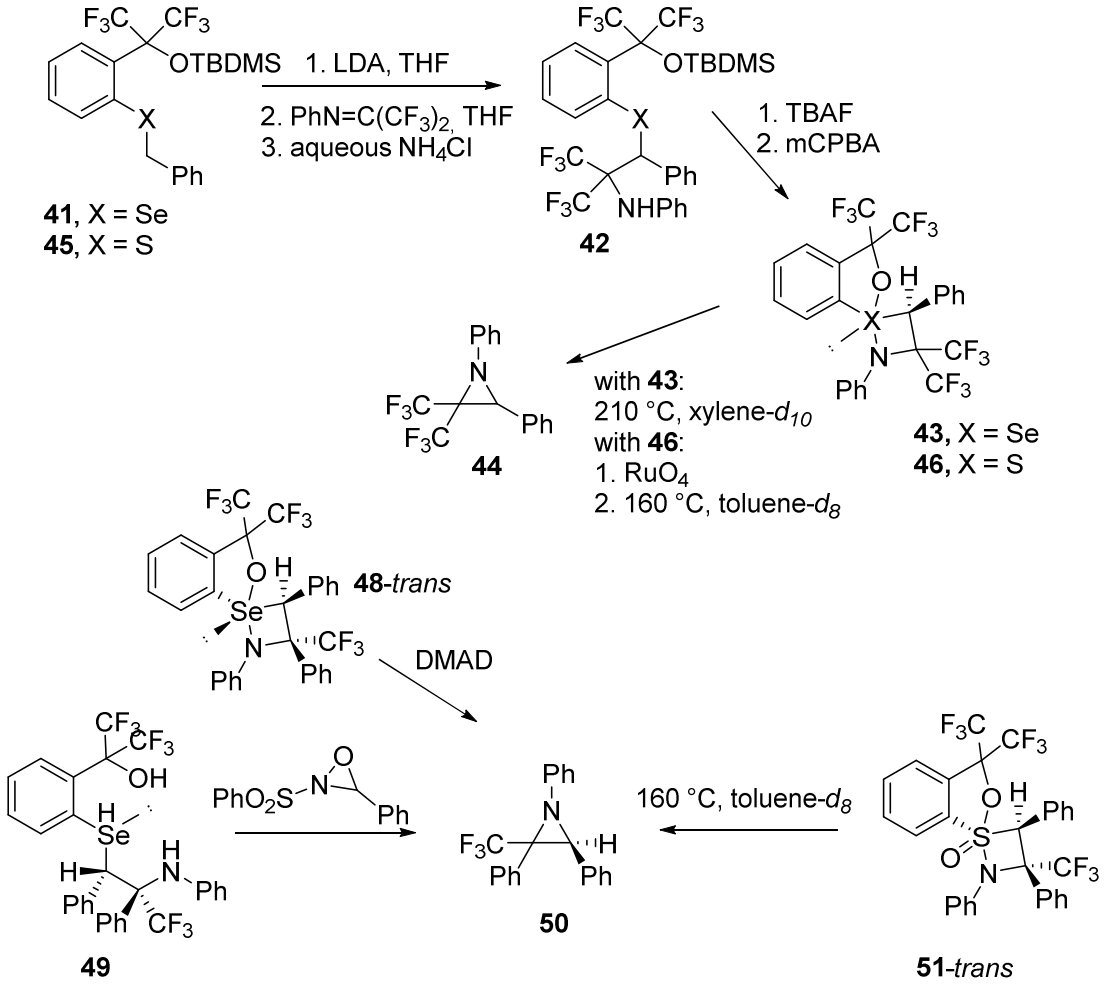


Figure 9. Synthesis of trifluoromethylaziridines **44** and **50** from heterocycles.

Surprisingly, oxidation of β-aminoalkyl selenide intermediate **49** with 2-benzenesulfonyl-3-phenyloxaziridine did not give the expected selenazetidine but a *cis*-aziridine **50** in 69% yield (Figure 9).

Cis- and *trans*-aziridines **50** were also obtained in very low yields through reaction of cycloadduct **48** (*trans*) with dimethyl acetylenedicarboxylate (DMAD).[46] Finally, the same *cis*- and *trans*-aziridines **50** were produced in 34 and 4% yields by thermal treatment of *trans*-thiazetidine **51** (preparation of *trans*-thiazetidine followed the same principle reported above).[47]

Another aziridination approach consisted in the thermal elimination of nitrogen from fluorinated triazoles. Purposely, a [2+3] cycloaddition reaction occurred between imines **52** derived from hexafluoroacetone and diazomethane or diazoethane. The corresponding 1,2,4-triazole derivatives **53** were isolated in high yields and regioselectively. The subsequent heating of compound in neat condition for 10 h at 150 °C afforded a ring contraction to give the aziridine **54** in 37% yield (Figure 10).[48] In 2013, a similar strategy has been reported using *N*-trifluoroacetylimines of trifluoropyruvate (**55**).

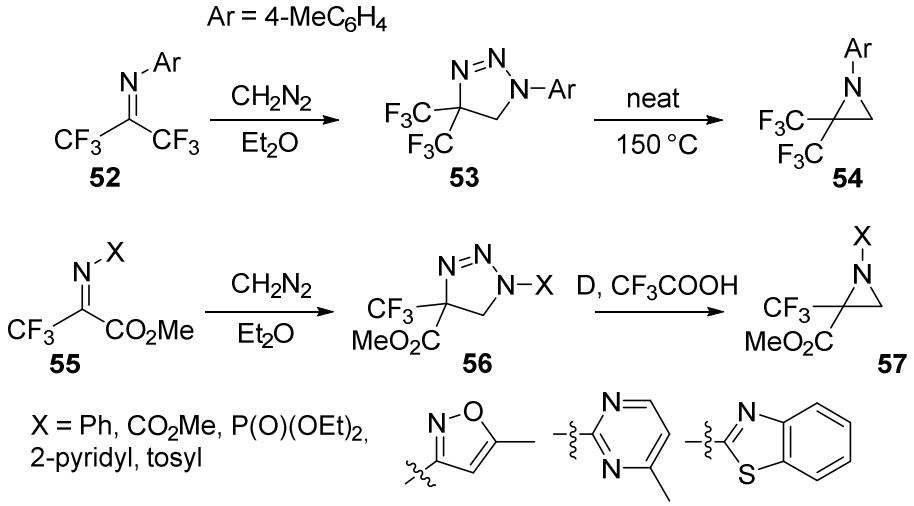


Figure 10. Synthesis of trifluoromethylaziridines **54** and**57** from heterocycles.

Cycloaddition reactions proceeded in the presence of diazomethane but a mixture of triazolines **56** and aziridines **57** was obtained (Figure 10). However, elimination of nitrogen from triazole ring occurred in high yields upon heating in the presence, in some cases, of an acid (CF_3COOH or HCl). Interestingly, the authors mentioned a spontaneous triazoline to aziridine transformation which was complete after several months at room temperature.[49] Isoxazoles belong to class of compounds capable of reacting under photo-irradiation. In general, these heterocycles are converted in oxazole isomers through photoconversion. However, when a CF_3 group is located at position 5, irradiation of **58** for 10 min in methanol produced a mixture of *cis*- and *trans*-isomers of aziridine **59** in very poor quantity (Figure 11).

The formation of such cycloadducts was more likely due to the reaction between an azirine intermediate and methanol.[50] Finally, the synthesis of fluorinated aziridine from heterocycles was carried out from a pre-formed CF_3-aziridine. Uneyama and coworkers demonstrated that *N*-protected aziridinyl anions can be considered as valuable building blocks.[23] The *N*-tosylaziridine **1b** appeared as the most efficient starting materials for further reactions toward various electrophiles. In these conditions, an aziridinyl anion was generated with BuLi as base.

The anion was able to react with aldehydes, ketones, acyl chloride, haloformate and bromoalkane to yield new CF_3-aziridines **1c** as potential precursors of α-trifluoromethyl-α,β-diamino acids or α-hydroxy-β-trifluoromethyl-β-amino acids (Figure 11).[51] In 2011, an improved methodology was presented regarding the

synthesis of *N*-tosyl-2-trifluoromethyl-2-alkyloxycarbonyl aziridine with *e.e.* higher than 98%. This compound was employed for the preparation of optically pure β-substituted-α-trifluoromethyl-α-amino acids.[52]

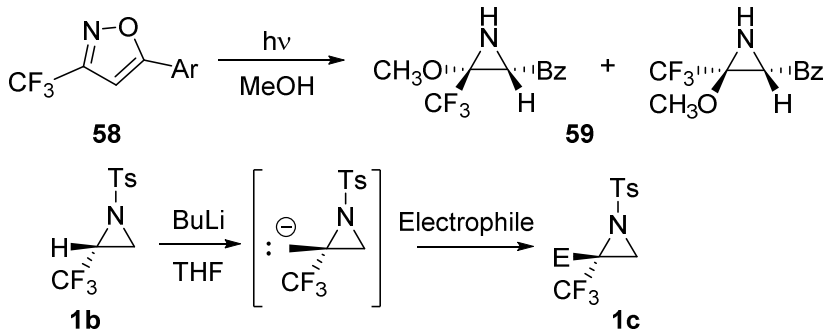


Figure 11. Synthesis of trifluoromethylaziridines **59** and **1c** from heterocycles.

2.4. Synthesis of trifluoromethylaziridines from olefins

In the course of preparation of CF_3-containing compounds, fluorinated olefins represent a class of commercially available synthons with a wide range of applications. In this respect, a three membered-ring formation was thereby elaborated from 4,4,4-trifluorocrotonate as starting building block. Here, the *trans*-3-trifluoromethyl-2-carbamoylaziridine **60a** was obtained after treatment with ammonia in 46% yield whereas cyclization with benzylamine led to *trans*-3-trifluoromethyl-2-methoxycarbonylaziridine **60b** in higher yield (70%) (Figure 12). NMR experiments confirmed the stereochemistry of the heterocycles. Further investigations aimed at creating F-N and Cl-N bonds by treatment of *N*-deprotected aziridines with fluorinating or chlorinating agents, *i.e.* F_2/NaF and *tert*-butyl-hypochlorite, respectively.[53] Taking advantage of previous results concerning the aziridination of olefins with ethyl nosyloxycarbamate as reagent, Tardella and coworkers prepared a set of fluorinated olefins possessing a geminal ester function. When ethyl nosyloxycarbamate was challenged with the olefin in the presence of NaH as base, an aza Michael reaction occurred, followed by the immediate ring closure into aziridines **61** in high yields (>86%) (Figure 12). These results were in contrast with reactions using CaO or LiOH as base which gave rise to α-trifluoromethyl β-amino esters. Other syntheses were achieved from chiral fluorinated olefins bearing the (-)-8-phenylmenthol or Helmchen's auxiliaries. In both cases, aziridines were isolated in high yields (>70%), however only the Helmchen's chiral group allowed a significant induction, the diastereoisomeric excess reaching 72% (Figure 12).[54] Additional investigations demonstrated that **62** precursors of trifluoromethyl olefins could react directly with nosyloxycarbamate derivatives to give the corresponding aziridines **61a**. Indeed, in the presence of a large amount of CaO (used as base), a cyclization reaction occurred between substituted 2,2,2-trifluoroethyl β-dicarbonyl compounds **62** and nosyloxycarbamate derivatives, aziridines **61a** being isolated in up to 78% yields (Figure 12).

Its conversion in methyl 2,3-dibromo-4,4,4-trifluorobutanoate with bromine produced an intermediate which was allowed to react with amines. The authors demonstrated that the ring closure did not involve an olefin formation but nitrene intermediates. Moreover, such a reaction requires the use of a trifluoro-methylated compound since the absence of reactivity was observed with non-fluorinated molecules.[55]

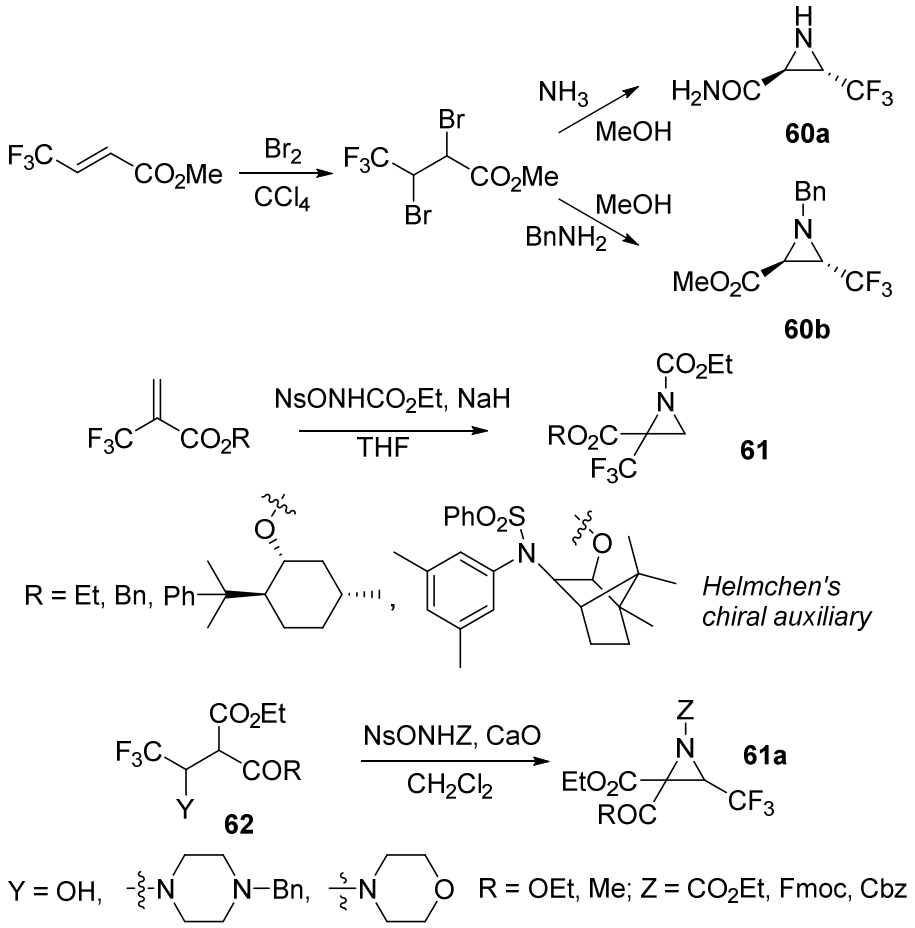
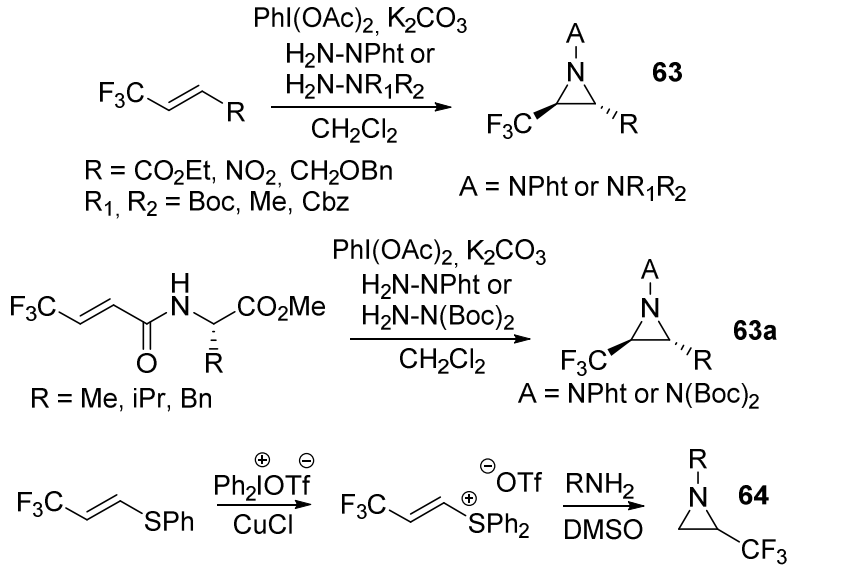


Figure 12. Synthesis of trifluoromethylaziridines **60a**, **60b**, **61** and **61a** from olefins.

An intermolecular aziridination was also evaluated using an oxidative reagent, namely iodobenzene diacetate ($PhI(OAc)_2$). Typically, the oxidative reaction condition involved a fluorinated olefin and carbazate or phtalimide reagents in the presence of an excess of potassium carbonate and $PhI(OAc)_2$ in dichloromethane. When simple olefins were used, (*E*) *N*-aminoaziridines **63** were obtained in 37 to 76% yields (Figure 13). In addition, other fluorinated olefins derived from amino acids allowed an *N*-aminoaziridination in yields higher than 64%. Some of these peptidomimetic diastereomers **63a** were further separated, providing thus a good entry to α-substituted β-CF_3-hydrazino acids through ring-opening reactions (Figure 13).[56]

Another strategy has consisted in the promotion of (β-trifluoromethyl)vinylsulfonium salts derived from fluorinated olefins. Consequently, preparation of sulfonium salts occurred from (β-trifluoromethyl)vinyl sulfides through quarternization with diphenyliodonium triflate, in the presence of CuCl(I) as catalyst. Its versatile reactivity was highlighted by reaction with a series of amines in DMSO at room temperature. The corresponding trifluoroaziridines **64** were generated in yields up to 94% (Figure 13). An asymmetric variation was investigated using (*S*)-1-phenethylamine as chiral component. The cycloadduct formation proceeded in good yield but with poor diastereoselectivity (54:46).[57]

Finally, we can mention the preparation of enantiomerically pure fluorinated aziridine through resolution processes. For instance, separation of enantiomers was achieved using chiral chromatography or lipase-catalyzed acetylation of aziridines.[58,59]



RNH_2 = benzylamine, 2-phenylethylamine, 3,5-dimethylbenzylamine, 3,5-bis(trifluoromethyl)benzylamine, 1-naphthylmethylamine, 2-diethyl-aminoethylamine, glycine ethyl ester hydrochloride, *p*-toluenesulfonamide

Figure 13. Synthesis of trifluoromethylaziridines **63**, **63a** and **64** from olefins.

3. Trifluoromethylazetidines

3.1. Synthesis of trifluoromethylazetidines from amines

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 the (*S*)-(α-benzyloxy)acetyl-2-oxazolidinone **65** and an imine derived from ethyl trifluoropyruvate. A stereoselective C-C bond formation occurred between the fluorinated imine and the chlorotitanium enolate of **65** in the presence of *i*-Pr_2NEt. The electrophilic addition yielded 88% of the "Evans" *anti*-adduct **66** as major isomer (91:9 ratio). Subsequently, removal of the chiral oxazolidinone group using a large excess of $NaBH_4$ in THF/H_2O provided the diastereomerically pure carbinol amino acid **67** in 87% yield. Finally, a tosylation step followed by intramolecular cyclization with BuLi led to azetidine **68** in 85% yield (Figure 14).[60] Following the same principle, trifluoromethylazetidines were elaborated in order to study their regioselective ring-opening. Typically, a set of fluorinated enamines **69** was obtained in good yields by condensation of ethyl 4,4,4-trifluoroacetoacetate with primary amines. Then, reduction of enamines with $NaBH_4$ and a chlorination step with thionyl chloride resulted in the corresponding *N*-alkyl-4-chloro-1,1,1-trifluorobutan-2-amines **70** in yields higher than 50%. Finally, the ring closure reaction required the treatment with LiHMDS as strong base to provide 1-alkyl-2-(trifluoromethyl)azetidines **71** in 59 to 90% yields (Figure 14).

Further investigations have shown a C_4 regiospecific ring-opening in the presence of nucleophiles through an azetidinium intermediate, in contrast with non-fluorinated azetidines.[61] In 2014, a straightforward synthesis of fluorinated azetidines was developed yielding both racemic and optically pure compounds. Reactions were initiated from trifluoroaldimines bearing either a benzyl group or (*R*)-phenylglycinol methyl ether as chiral auxiliary. Under Barbier condition, the allylation with allyl bromide and zinc in THF conducted to the formation of homoallylic amines **72** in good yields. Subsequently, the ring formation was studied through iodine-mediated cyclization in acetonitrile. As concerns the *N*-benzyl amine, the *cis*-

heterocycle **73** was obtained in 61% yield as major stereoisomer. When the ring closure was carried out with the chiral amine, the cyclization formed a mixture of diastereomers (*cis*/*trans* isomers, 81:19) in 71% yield (Figure 14). An additional purification step and X-ray diffraction analysis confirmed both the *cis*-stereoselectivity of the reaction and the absolute configuration of the chiral centres. The presence of the iodide atom at position 4 was found particularly useful for designing azetidine analogues by substitution or Huisgen 1,3-dipolar cycloaddition.[62] Finally, a four-membered ring was supposed to be formed in the frame of an aza Diels Alder reaction involving norbornadiene and a bis(trifluoromethyl) sulfonylimine, although identification resulted solely from LC-MS spectroscopic data.[63]

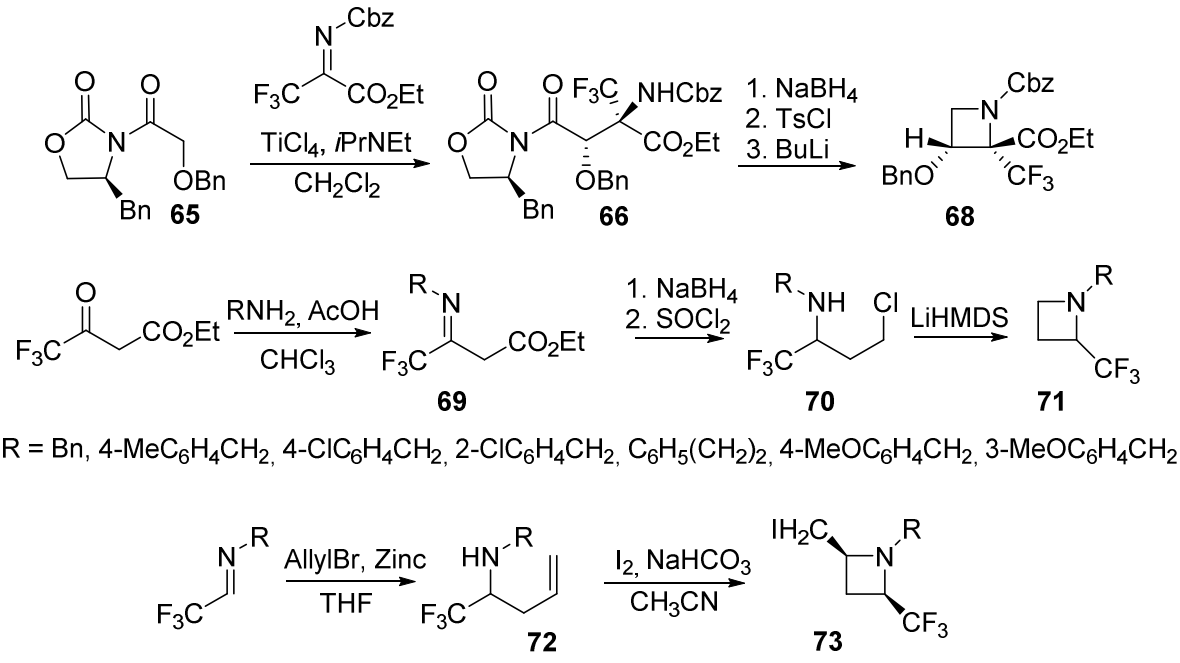


Figure 14. Synthesis of azetidines **68**, **71** and **73** from amines.

3.2. Synthesis of trifluoromethylazetidines from heterocycles

Similarly to aziridines, the transformation of heterocycles into azetidines was considered as a key strategy owing to the complexity of obtaining such small rings. Thus, De Vita and coworkers proposed the conversion of fluorinated lactam into its corresponding azetidine by means of a Wittig reaction. The synthetic procedure started from commercially available 3-amino-4,4,4-trifluorobutyric acid which was readily converted in 4-trifluoromethyl-β-lactam in 45% yield. After *N*-Boc protection, the resulting lactam **74** was reacted with various Wittig reagents, producing azetidines **75** bearing ester or nitrile functionalities in good yields (78-85%). These cycloadducts were also capable of undergoing other hydrogenation or alkylation reactions. It is worth to mention that an optically active version was investigated according to the same procedure using the optically pure 3-amino-4,4,4-trifluorobutyric acid. In this case, azetidines **75** were isolated as pure diastereomers (Figure 15).[64]

Another four-membered ring construction was presented by ring expansion starting from an epoxide. Hence, in the frame of the synthesis of new fluorinated protease inhibitors, a chemical sequence initiated from trifluoroaldimine **34** flanked with chiral (*R*)-phenylglycinol methyl ether group. Its alkylation by a Grignard reagent followed by acetylation with acetic anhydride conducted to the allylamine **76** in good

overall yields and high diastereoselectivity (>98%). Then, the targeted epoxide **77** was achieved by a two-step procedure, namely a bromhydrin formation by reaction with Br_2/H_2O, followed by ring closure in the presence of potassium *tert*-butoxide. Finally, when compound **77** was heated in refluxing isopropanol, the corresponding azetidinol **78** was isolated quantitatively as a single diastereomer (Figure 16). The subsequent crystallization of **78** allowed the determination of the *syn* configuration of asymmetric carbons C_2 and C_3 together with their absolute configuration.[65]

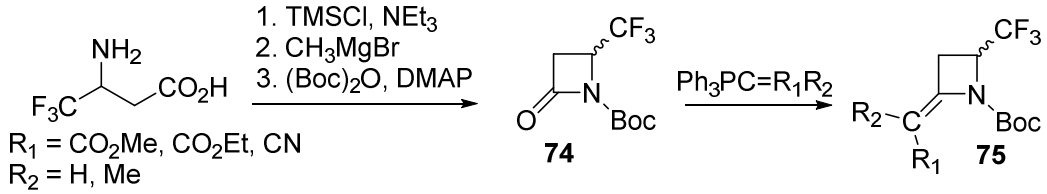


Figure 15. Synthesis of trifluoromethylazetidines **75** from heterocycles.

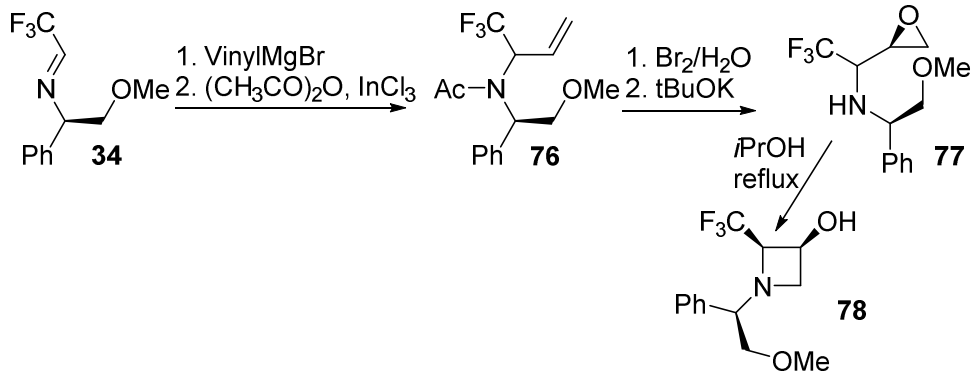


Figure 16. Synthesis of trifluoromethylazetidines **78** from heterocycles.

In 2013, De Kimpe and coworkers also reported a ring expansion of aziridine to azetidine according to an unexpected pathway. Whilst *cis*-*N*-tosyl aziridine **79** reacted with sulfur nucleophiles to give new aziridines by tosylate substitution, the attack of phenolate anions proceeded regiospecifically by tandem ring opening/ring closure through displacement of the OTs group. Thus, the intramolecular cyclization has given the resulting *cis*-azetidines **80** in 56-95% yields when the reaction was conducted in refluxing DMF (Figure 17).[37]

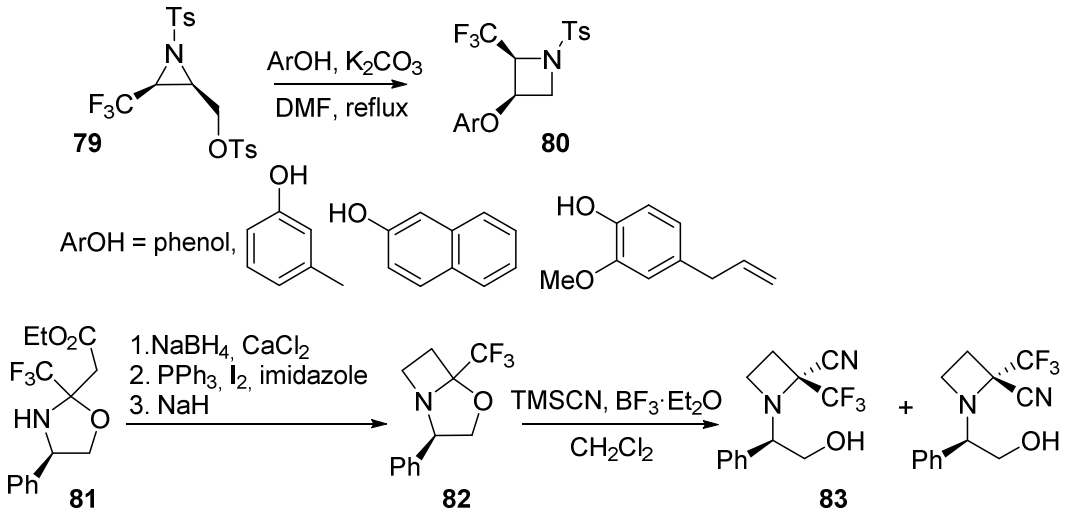


Figure 17. Synthesis of trifluoromethylazetidines **80** and **83** from heterocycles.

Finally, regarding the formation of constrained peptides incorporating novel α-trifluoromethylamino acids, the preparation of enantiopure trifluoromethylazetidines was carried out from diastereomerically pure oxazolidine **81**. First, the synthetic approach required the ester reduction with $NaBH_4$ in the presence of $CaCl_2$ in THF/MeOH (95% yield).

Then, bicyclic oxazolidine **82** was obtained as a single diastereomer according to a two-step procedure, *i.e.* conversion of the alcohol group into an iodo derivative using I_2/PPh_3/imidazole followed by a cyclization reaction with NaH in refluxing THF. When challenged with TMSCN and $BF_3{\cdot}Et_2O$ in dichloromethane, compound **82** underwent a Strecker-type reaction, giving rise to a 58:42 mixture of diastereomers of azetidine-2-carbonitriles **83** in 99% yield (Figure 17). After separation by chromatography on silica gel, both diastereomers allowed the formation of (*R*) and (*S*) α-trifluoromethyl homoserines by treatment with HCl.[66]

4. Conclusions

This brief overview regarding the preparation of fluorinated aziridines and azetidines has highlighted elegant synthetic strategies providing the expected heterocycles with potential high regio- and diastereoselectivities. Inspired by their hydrogenated counterparts, the formation of these fluorinated compounds have sometimes demonstrated a higher or unique reactivity regardless the chemical pathways. Interestingly, the aziridine formation has been the subject of numerous efforts which contributed to the development of varied chemical approaches, but much less strategies were developed for azetidines. However, such small heterocycles combined with the unique properties of fluorine should arise as key intermediates particularly in medicinal chemistry. This can be anticipated due to the potent biological activities of some non-fluorinated azetidine-containing compounds such as sphingosine-derived alkaloids possessing actomyosin ATPase-activating activity,[67] nanomolar selective CB2 receptor agonists,[68] or free fatty acid receptor 2 antagonists.[69] Since nitrogen heterocycles are of the highest relevance owing to their physico-chemical properties and their versatile application as building blocks, their trifluoromethylated congeners are expected to follow this trend and account for new challenges for chemists' imagination. Thus, some of these trifluoromethylated aziridines and azetidines were already used as precursors of novel fluorinated organophosphorus derivatives targeting pharmaceutical and agrochemical applications but also as intermediate for the formation of fluorinated amino acids.

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