# Synthesis and reactivity of 4-(trifluoromethyl)azetidin-2-ones

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**Abstract** Because of the beneficial effect of a trifluoromethyl group on the biological properties of bioactive compounds on the one hand and the versatile synthetic potential of β-lactams on the other hand, 4-$CF_3$-β-lactams comprises interesting entities for the preparation of a large variety of $CF_3$-substituted nitrogen-containing target structures with promising biological characteristics. In this review, we present an overview of different building block approach-based routes toward the synthesis of 4-(trifluoromethyl)azetidin-2-ones and the application of the "β-lactam synthon method" for the synthesis of a diverse set of (a)cyclic $CF_3$-substituted molecules by means of ring-opening and ring-transformation reactions.

**Keywords** Heterocycles • Strained molecules • Fluorine chemistry • Cyclizations • Ring opening

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## Introduction

The pivotal role of fluorine in medicinal chemistry is reflected by its presence in approximately 25% of the pharmaceuticals on the market and in the development pipeline. The increasing interest in fluorinated compounds is due to the favorable effect of fluorine on their pharmacological properties [1-3]. In particular, the use of fluorine-substituted molecules has been shown to increase the biological half-life by impeding the oxidative metabolism, and to increase bioabsorption by lipophilic effects [4-5]. Subsequently, synthetic chemistry focused on the incorporation of one or more fluorine atoms into organic molecules has resulted in many new approaches and strategies [1, 3, 6]. An important part of these endeavors has been devoted to the introduction of a trifluoromethyl group into constrained nitrogen-ring systems, such as β-lactams or azetidin-2-ones [7-10]. In addition to their well-known significance as antibacterial agents, β-lactams have been attracting considerable interest as building blocks and valuable intermediates from a synthetic point of view as well [11]. Because of the high ring strain associated with the four-membered ring system, β-lactams represent prominent substrates susceptible to ring-opening and ring-transformation reactions *en route* to a variety of nitrogen-containing acyclic and heterocyclic compounds [11-12]. Given the beneficial effect of fluorine introduction, β-lactams bearing a trifluoromethyl group can be considered as interesting entities for the construction of novel targets with a diverse set of potential applications.

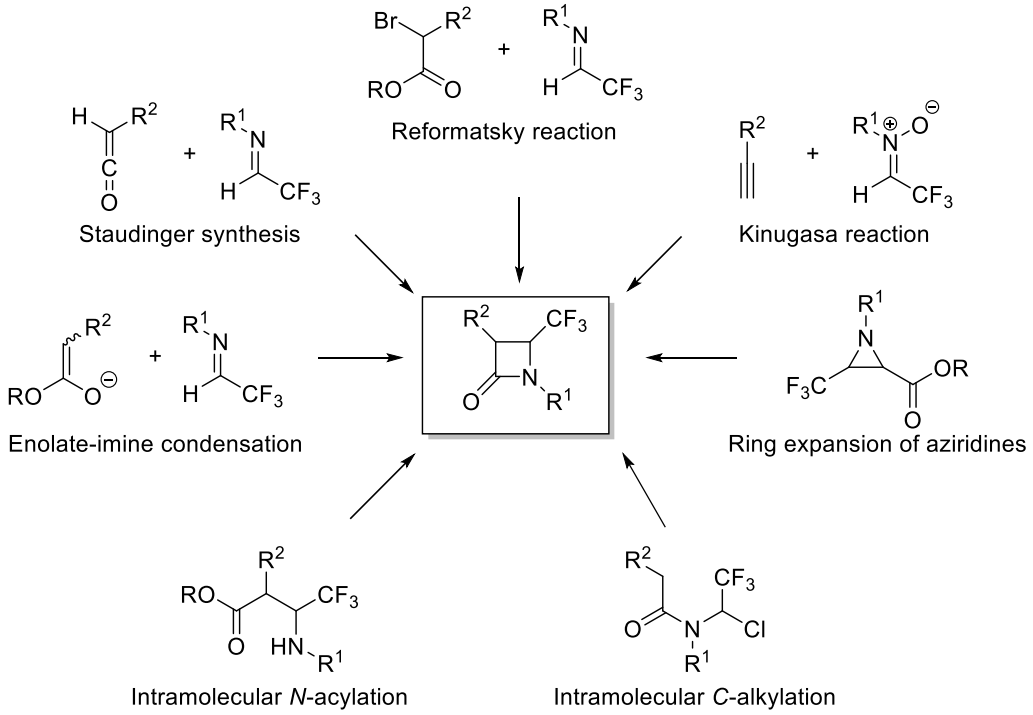
The synthesis of trifluoromethyl-containing structures can be accomplished by either a trifluoromethylation approach or by a building block strategy (fluorinated synthon approach). However, the preparation of sensitive $CF_3$-substituted structures is often hampered by difficulties associated with the late-stage introduction of the $CF_3$ group (safety implications, reagent reactivity, economics) [13-24]. As an alternative, the application of $CF_3$-containing building blocks can be pursued, thus avoiding the use of trifluoromethylating agents during the

synthesis. In that respect, the functionalization of β-lactams with a trifluoromethyl group comprises an interesting field of research and is increasingly applied to modify the biological and pharmacological properties of these compounds and their transformation products [5]. In this report, we present a short account of the main synthetic routes based on a building block approach as well as the reactivity profile of 4-$CF_3$-azetidin-2-ones toward $CF_3$-substituted amines and heterocyclic systems [25].

## Synthetic routes toward 4-(trifluoromethyl)azetidin-2-ones

A summary of the main synthetic routes to 4-trifluoromethyl-β-lactams is presented in Scheme 1.

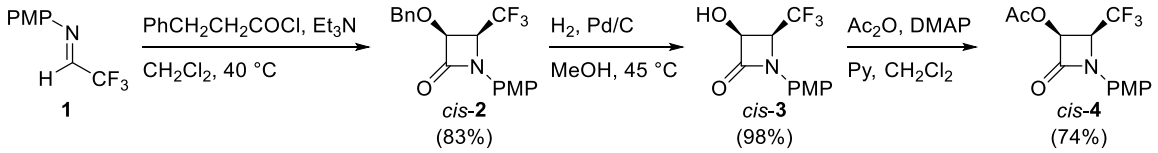
*Scheme 1*




## 1 Staudinger synthesis of 4-$CF_3$-azetidin-2-ones

The classical, well-known method for the construction of a β-lactam core concerns the Staudinger synthesis through a [2+2]-ketene-imine cyclocondensation [26-30]. For instance, this strategy has been employed by Kuznetsova et al. for the synthesis of *cis*-4-$CF_3$-β-lactam **4**. The direct use of acetoxyketene, generated *in situ* from acetoxyacetyl chloride and triethylamine, with $CF_3$-imine **1** [31] did not successfully furnish *cis*-4-$CF_3$-β-lactam **4**. In order to circumvent this unexpected obstacle, a short detour was proposed based on the cyclocondensation of benzyloxyketene with imine **1**, followed by hydrogenolysis and *O*-acetylation (Scheme 2). The reaction of benzyloxyketene with imine **1** was performed in dichloromethane at 40 °C, giving rise to racemic *cis*-4-$CF_3$-β-lactam **2** in high yield (83%). The *cis*-selectivity was determined based on the $^1$H NMR spectrum of β-lactam **2**, showing a coupling constant of 5-6 Hz ($CDCl_3$) between the two vicinal protons at the C3 and C4 position, as opposed to *trans*-β-lactams (1-2 Hz, $CDCl_3$) [26, 32]. Then, *cis*-β-lactam **2** was converted into *cis*-3-acetoxy-β-lactam **4** through hydrogenolysis with Pd/C as a catalyst, followed by acetylation in a yield of 74% [5, 32-34].

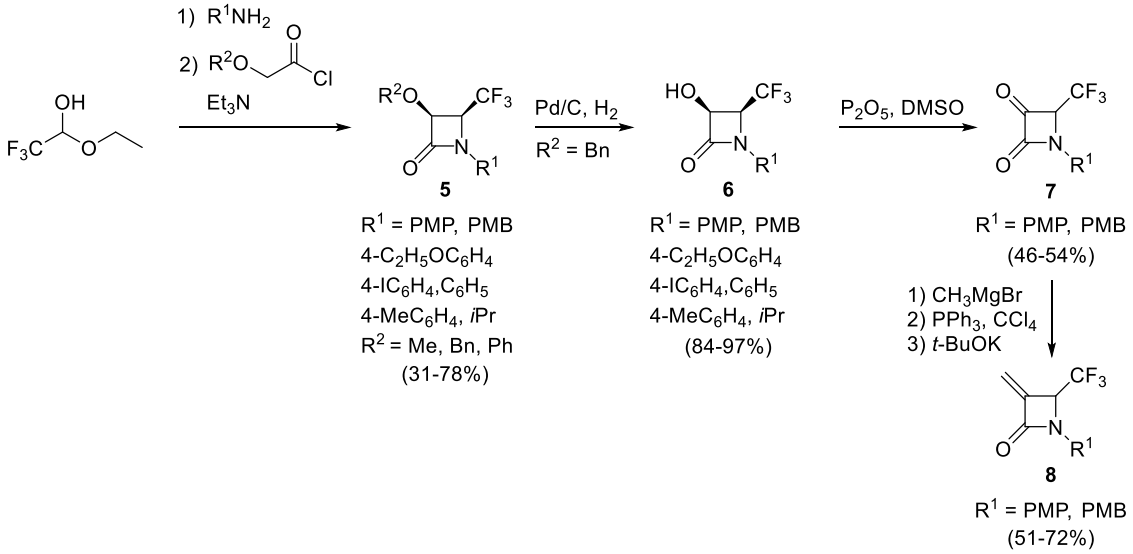
*Scheme 2*




Applying an identical procedure as reported for the synthesis of *cis*-alcohols **3**, a set of new 3-hydroxy-4-$CF_3$-β-lactams **6** has successfully been prepared from the corresponding 3-benzyloxy-4-$CF_3$-β-lactams **5** ($R^2$ = Bn) (Scheme 3). Besides 3-benzyloxy-4-$CF_3$-β-lactams, 3-methoxy/phenyloxy-4-$CF_3$-β-lactams **5** ($R^2$ = Me, Ph) were synthesized as well. The alcohols **6** were transformed into new 3-oxo-4-(trifluoromethyl)azetidin-2-ones **7** in acceptable yields (46-54%) through Albright-Onodera oxidation using $P_2O_5$/DMSO. Furthermore, 3-oxo-4-$CF_3$-β-lactams **7** were successfully converted into 3-methylene-4-$CF_3$-β-lactams **8** in 51-

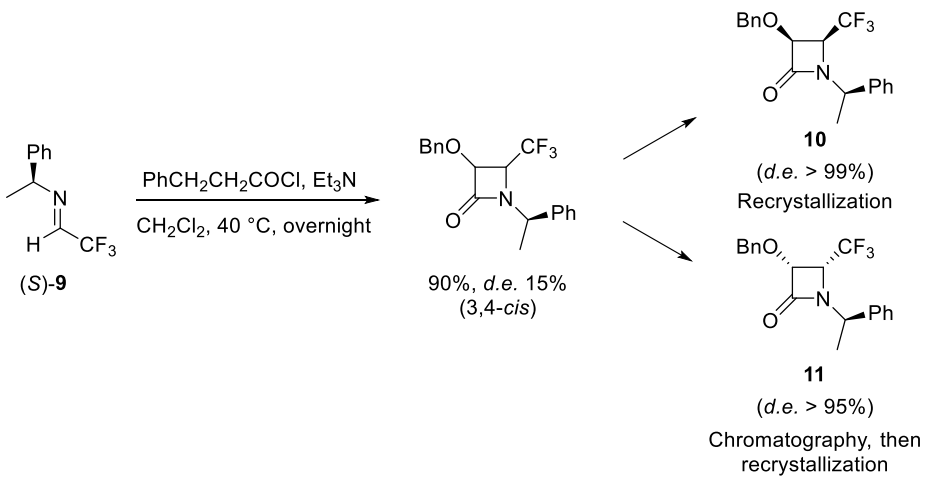
72% yield through the addition of methylmagnesium bromide across the cyclic ketone, followed by alcohol activation and elimination [35-38].

*Scheme 3*




[2+2]-Cyclocondensation of a chiral imine and achiral ketene comprises a useful route toward chiral azetidin-2-ones. The reaction of chiral imine **9**, prepared from trifluoroacetaldehyde hemiacetal and (*S*)-phenethylamine, with benzyloxyketene under classical Staudinger conditions has been reported to afford a crude mixture of *cis*-β-lactams **10** and **11** in 90% yield (Scheme 4), accompanied by minor amounts (5-8%) of *trans*-β-lactams. These *cis*-isomers were successfully separated by recrystalization of the crude mixture. Stereoisomer **10** was obtained in an excellent diastereomeric purity (> 99%) after recrystallization from ethanol, whereas stereoisomer **11** was isolated with a diastereomeric excess of 95% after $SiO_2$ chromatography and recrystallization from pentane [32].

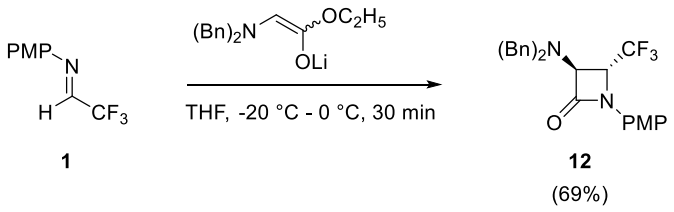
*Scheme 4*




## 2 Synthesis of 4-$CF_3$-azetidin-2-ones *via* enolate-imine condensation

The condensation of imine **1** with the lithium enolate of ethyl dibenzylaminoacetate, produced *in situ* from ethyl dibenzylaminoacetate and lithium diisopropylamide in dry THF, has been successfully performed leading to *trans*-4-$CF_3$-β-lactam **12** in 69% yield (Scheme 5) [31]. In related research, Clader et al. also applied an ester-imine condensation for the preparation of trifluoromethyl-substituted β-lactam derivatives in the course of their study on new cholesterol absorption inhibitors [39].

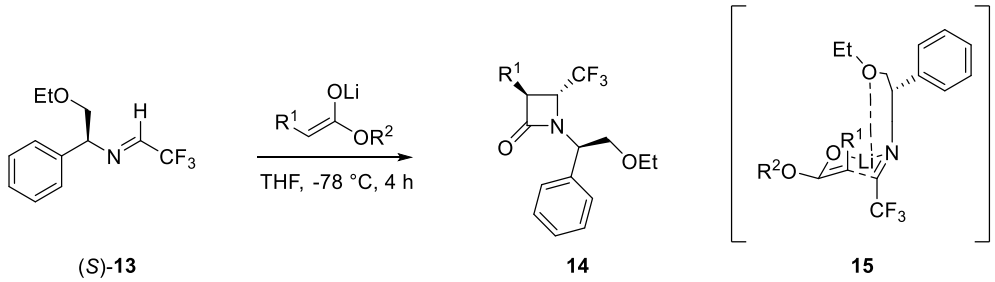
*Scheme 5*




Furthermore, chiral 4-trifluoromethyl-substituted azetidin-2-ones can also be prepared *via* the enolate-imine condensation strategy making use of imines containing a chiral fragment. The treatment of optically active trifluoromethylimine **13** with lithium enolates, derived from various ester derivatives, provided the *trans*-configuration at the C3- and C4-position of β-lactams **14** with rather high diastereoselectivity (95-99%). The high selectivity

was explained by a six-membered transition state **15** involving the imine and the enolate (Scheme 6) [40].

*Scheme 6*

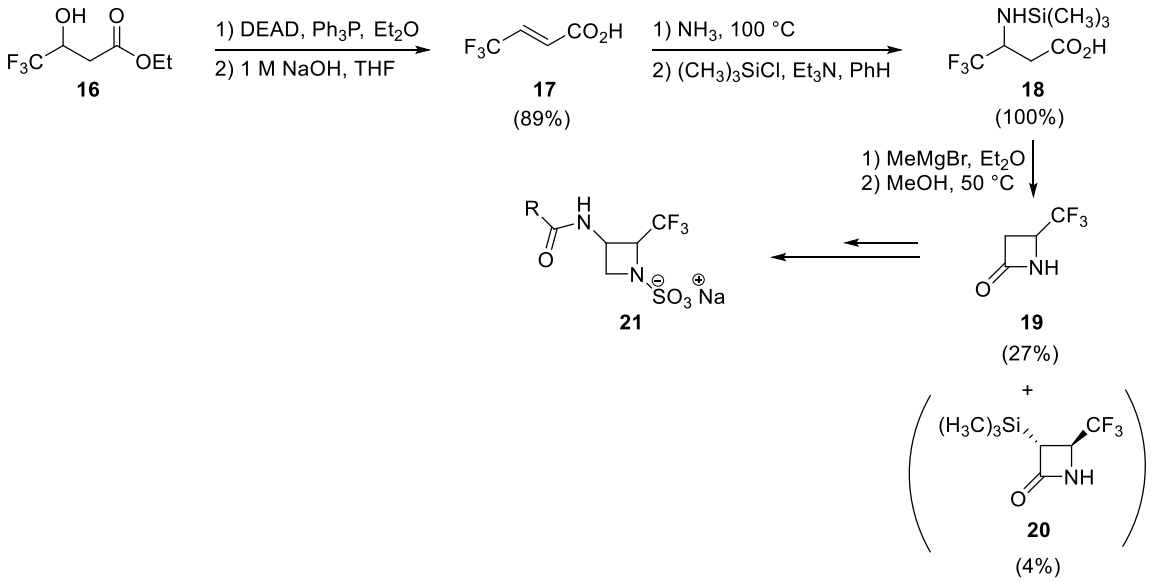



$R^1$ = H, $R^2$ = *i*Pr, 23%, *d.e.* > 99%
$R^1$ = H, $R^2$ = Me, 57%, *d.e.* 95%
$R^1$ = Me, $R^2$ = Me, 68%, *d.e.* > 99%
$R^1$ = PhO, $R^2$ = Et, 72%, *d.e.* > 99%

## 3 Synthesis of 4-$CF_3$-azetidin-2-ones *via* intramolecular *N*-acylation

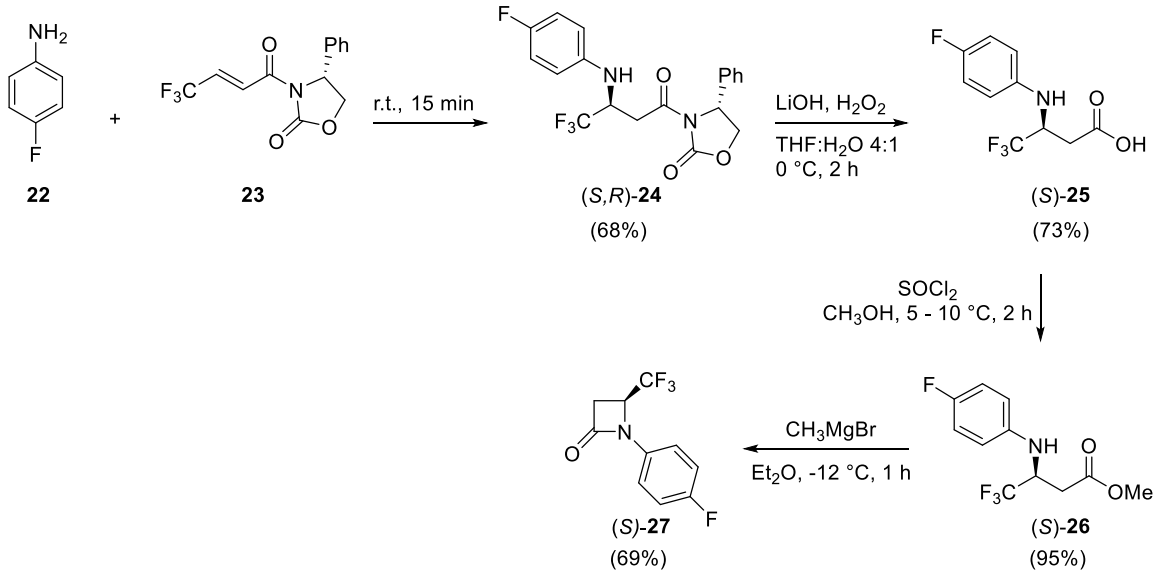
A convenient entry toward the construction of azetidin-2-ones comprises the cyclization of β-amino acid derivatives [12, 41]. In that respect, Robert and co-workers have reported the cyclization of trifluoromethylated amino acid derivative **18** with methylmagnesium bromide, giving rise to 4-trifluoromethyl-β-lactam **19** in a yield of 27% and C-silylated compound **20** as a side product (Scheme 7). Amino acid **18** was prepared in a quantitative yield by aminolysis and treatment of the corresponding unsaturated acid **17** with trimethylsilyl chloride, which had been effectively synthesized from alcohol **16** through elimination of water, followed by hydrolysis using sodium hydroxide in THF. With the desired 4-(trifluoromethyl)azetidin-2-one **19** in hand, the preparation of fluorine-containing sulfazecin analogs **21**, with interesting bactericidal properties, has been investigated [42].

*Scheme 7*



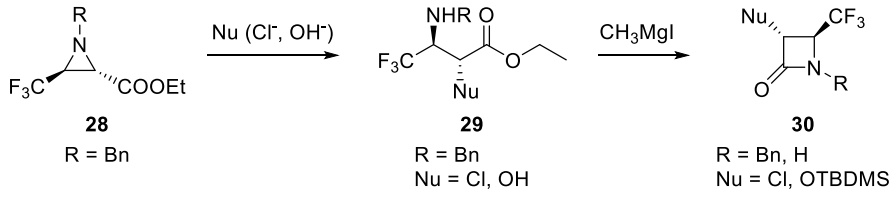

Yang and co-workers have devised a methodology to synthesize a $CF_3$-substituted β-amino acid using the aza-Michael reaction (Scheme 8). As such, the major diastereomer (*S,R*)-**24** was obtained in a yield of 68% upon treatment of chiral acrylamide **23** with aromatic amine **22**, without solvent and catalyst. Aza-Michael adduct **24** was hydrolyzed into amino acid **25** with LiOH-$H_2O_2$ in a good yield (73%). It should be noted that analogs of chiral α-trifluoromethyl amino acid **25** can also be prepared by reduction of the corresponding enamines or imines [43-45]. Furthermore, β-$CF_3$-β-amino ester **26**, derived from **25**, was cyclized in the presence of methylmagnesium bromide to construct enantioenriched 4-trifluoromethylated β-lactam **27** in 69% yield. The absolute stereochemistry of **27** was determined to be *S*, hence, the configuration of compound **25** was also assigned as *S* [43-46].

*Scheme 8*




Furthermore, chiral β-amino esters **29** have effectively been prepared by the regio- and stereoselective nucleophilic ring-opening reaction of 1-benzyl-3-trifluoromethyl-2-(ethoxycarbonyl)aziridine **28** (Scheme 9). *Via* Grignard-mediated intramolecular cyclization, *trans*-β-lactams **30** were produced from the corresponding β-amino esters **29**. The *trans*-configuration of β-lactams **30** was assigned by means of $^{1}$H NMR ($J_{H3,H4}$ = 1.8 Hz). The stereochemistry of *trans*-β-lactams **30** confirms the *anti*-relative configuration of β-amino esters **29** and underlines the stereoselectivity of the $S_N2$ ring-opening reaction of *trans*-benzyl-3-trifluoromethyl-2-(ethoxycarbonyl)aziridine **28** [47].

*Scheme 9*

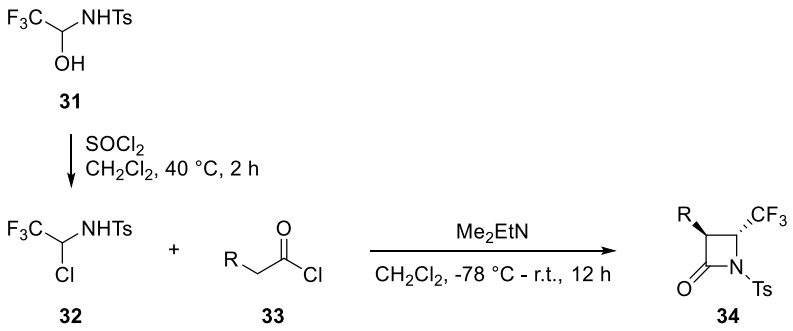



## 4 Synthesis of 4-$CF_3$-azetidin-2-ones *via* intramolecular *C*-alkylation

Petrick and co-workers have recently published a new methodology for the preparation of 4-trifluoromethylated *trans*-β-lactams **34** by reaction of *N*-(1-

chloro-2,2,2-trifluoroethyl)-4-methylbenzenesulfonamide **32** with various nonactivated aliphatic acid chlorides **33** in the presence of dimethylethylamine as a base and dichloromethane as a solvent (Scheme 10). Sulfonamide **32** was produced by the treatment of hemiaminal **31** with thionyl chloride in $CH_2Cl_2$ at 40 °C. The use of chloroamine **32** in the cyclization reaction can offer a convenient alternative for the construction of trifluoromethylated β-lactams from highly moisture-sensitive trifluoromethylated imines [48].

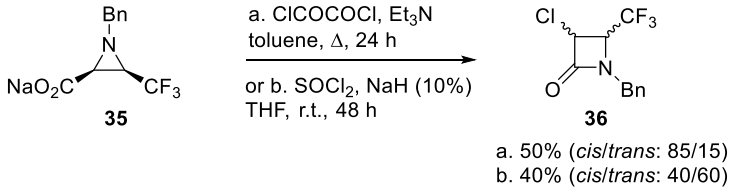
*Scheme 10*




## 5 Synthesis of 4-$CF_3$-azetidin-2-ones *via* direct ring expansion of 3-$CF_3$-aziridine-2-carboxylates

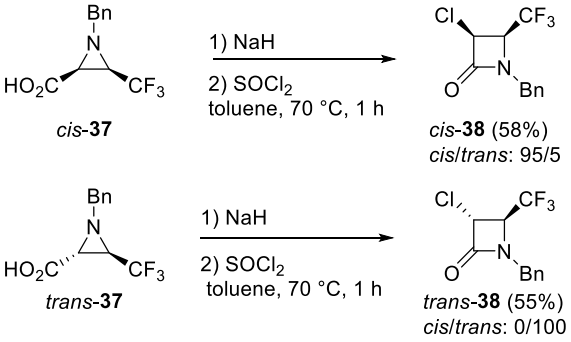
In analogy with the preparation of non-fluorinated azetidin-2-ones from the corresponding non-fluorinated aziridines [49-50], 3-chloro-4-$CF_3$-azetidin-2-one **36** was prepared through ring expansion of the corresponding fluorinated sodium aziridinyl carboxylate **35** with either oxalyl chloride or thionyl chloride (Scheme 11).

*Scheme 11*



The diastereoselectivities for this approach were significantly improved by considering the ring expansion of the carboxylic acid $CF_3$-aziridine analogs instead of the sodium salt (Scheme 12). Aziridines *cis*-**37** and *trans*-**37** were treated with NaH and then thionyl chloride in toluene at 70 °C, resulting in the corresponding *cis*- and *trans*-β-lactams **38** in relatively good yields and excellent stereoselectivities. The relative configurations of the products were confirmed by $^1$H NMR, pointing to coupling constants of 6 Hz (*cis*) and 3 Hz (*trans*). Continuing efforts have been devoted to synthesize a broad range of 4-$CF_3$-azetidin-2-ones using different halogenating reagents, bases and solvents [51].

*Scheme 12*

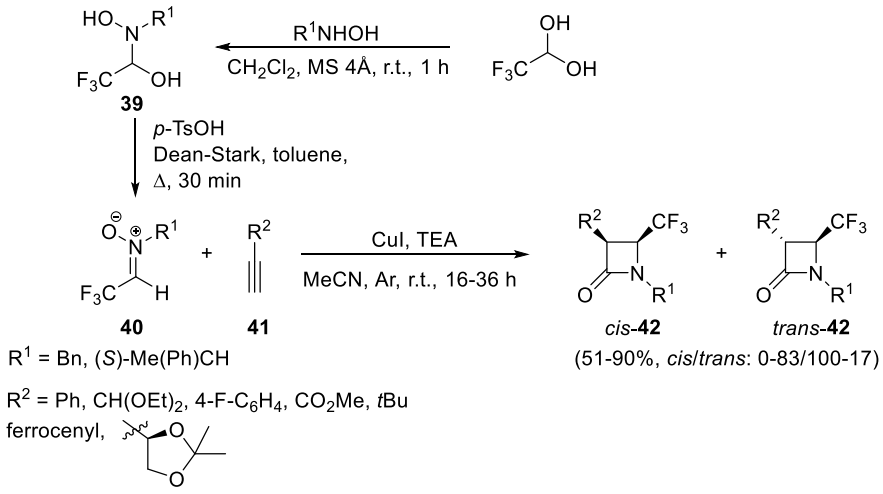



## 6 Synthesis of 4-$CF_3$-azetidin-2-ones *via* the Kinugasa reaction

The Kinugasa reaction offers a general access toward the synthesis of differently substituted β-lactams *via* initial [3+2]-cycloaddition of nitrones with terminal alkynes in the presence of a Cu(I) salt and a polar solvent (acetonitrile or pyridine) [52-54]. Grée and co-workers have applied this method for the preparation of 3-difluoroalkyl- and/or 3-(1-fluoroalkylidene)-β-lactams from propargylic *gem*-difluorides [55]. Very recently, Kowalski and co-workers have presented a new application of fluorinated nitrones for the preparation of fluoroalkylated β-lactams *via* the Kinugasa reaction. Trifluorinated nitrones **40** were prepared by treating the corresponding hemiaminals **39**, derived from fluoral, with para-

toluenesulfonic acid using a Dean–Stark apparatus (Scheme 13). The isolated and purified nitrones **40** were then treated with different monosubstituted acetylenes **41** under typical Kinugasa reaction conditions to form the expected 4-trifluoromethyl-β-lactams **42** in good to high yields. The *cis*- and *trans*-diastereoselectivity varied considerably depending on the type of substituent on the acetylene moiety ($R^2$) used in the reaction [25].

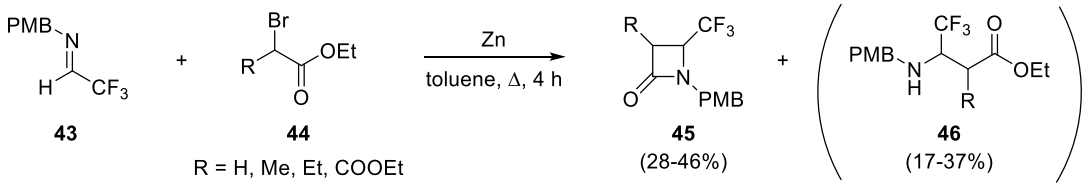
*Scheme 13*




## 7 Synthesis of 4-$CF_3$-azetidin-2-ones *via* the Reformatsky reaction

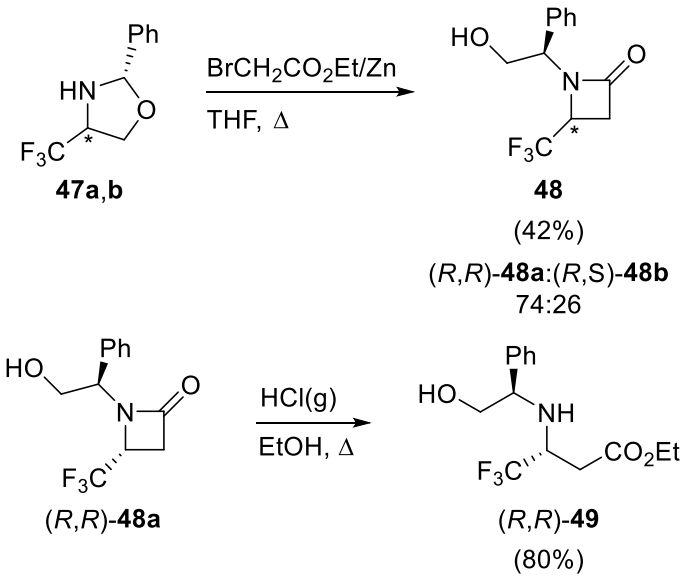
The Reformatsky reaction of imine **43** with *α*-bromocarboxylic esters **44** in the presence of activated zinc dust in anhydrous toluene has been reported to furnish β-lactams **45** as the main products, accompanied by β-amino esters **46** (Scheme 14) [56]. Information concerning the relative configuration of these products was not mentioned.

*Scheme 14*



This method has been further extended toward the use of chiral 1,3-oxazolidines. The reaction of 2-trifluoromethyl-1,3-oxazolidines **47a**,**b** and ethyl bromoacetate in the presence of zinc dust at reflux temperature in THF afforded 4-(trifluoromethyl)azetidin-2-ones **48a**,**b** in 42% yield as a 74:26 mixture of diastereoisomers (Scheme 15). This mixture was then purified by flash chromatography, giving pure (*R*,*R*)-**48a**. The lower stereoselectivity of this reaction as compared to results reported on nonfluorinated oxazolidines can be explained by inhibition of the oxazolidine ring opening toward imine formation as a result of the electron-withdrawing $CF_3$ group. The major diastereomer **48a** was easily converted into β-amino ester **49** by acidic ethanolysis in 80% yield [57].

*Scheme 15*




## The reactivity profile of 4-$CF_3$-azetidin-2-ones

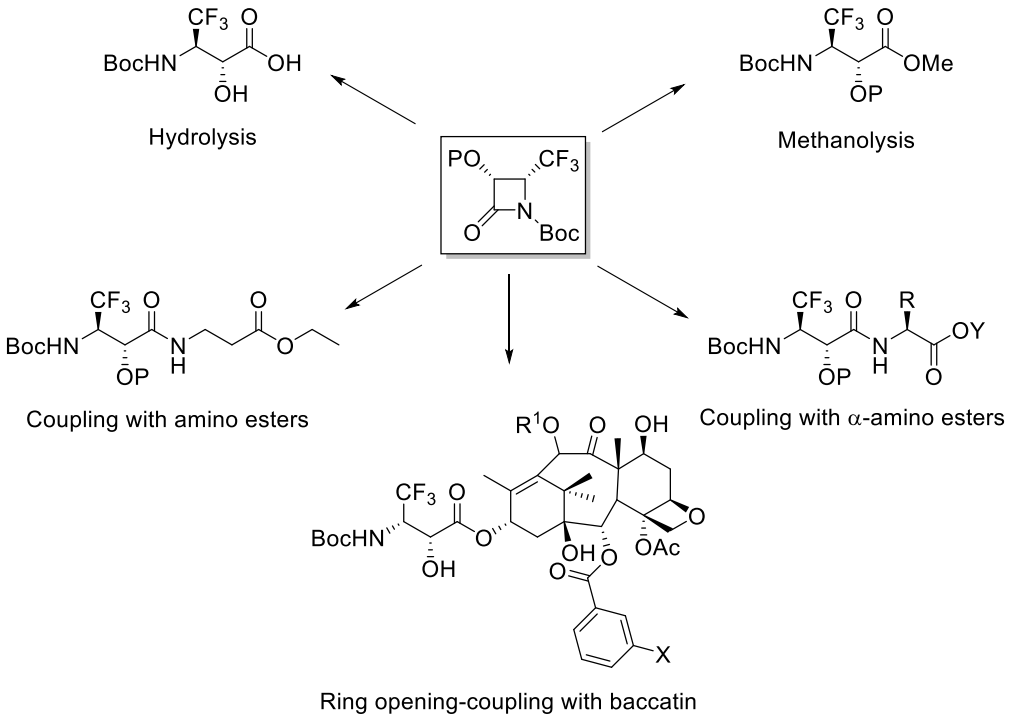
The study of 4-(trifluoromethyl)azetidin-2-ones comprises an appealing, yet rather scarcely explored research field to date. In general, 4-(trifluoromethyl)azetidin-2-ones represent useful building blocks (β-lactam synthon method) [34] for the preparation of a broad spectrum of

trifluoromethylated *N*-containing compounds. In this section, both ring-opening and ring-transformation reactions will be considered.

## 1 Ring-opening reactions of 4-$CF_3$-azetidin-2-ones

Because of the high ring strain of four-membered cyclic amides, 4-(trifluoromethyl)azetidin-2-ones can be deployed as excellent building blocks for the preparation of fluorinated amino acids, dipetides and taxoids through ring-opening reactions utilizing various nucleophiles (Scheme 16) [34].

*Scheme 16*

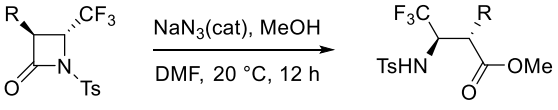



P = hydroxyl protecting group
R = (*S*)-phenylalanine, H
$R^1$ = MeCO, EtCO, $Me_2NCO$, MeOCO, H
X = MeO, F, Cl, $N_3$
Y = Me, Et

For example, the ring-opening methanolysis of 4-(trifluoromethyl)azetidin-2-ones **50**, catalyzed by sodium azide, has been performed in DMF at room temperature to generate the corresponding $CF_3$-containing β-amino esters **51** in good to almost quantitative yields as single diastereomers (Scheme 17) [32, 34,

48]. Besides, ring opening-coupling reactions of these 4-$CF_3$-β-lactams with amino esters or baccatines have been performed to afford the corresponding $CF_3$-containing dipeptides and taxoids, respectively. The synthesized fluoro-taxoids exhibited an excellent cytotoxicity against human breast cancer cell lines, especially against the drug-resistant cell line MCF7-R and LCC6-MDR [5, 33-34].

*Scheme 17*

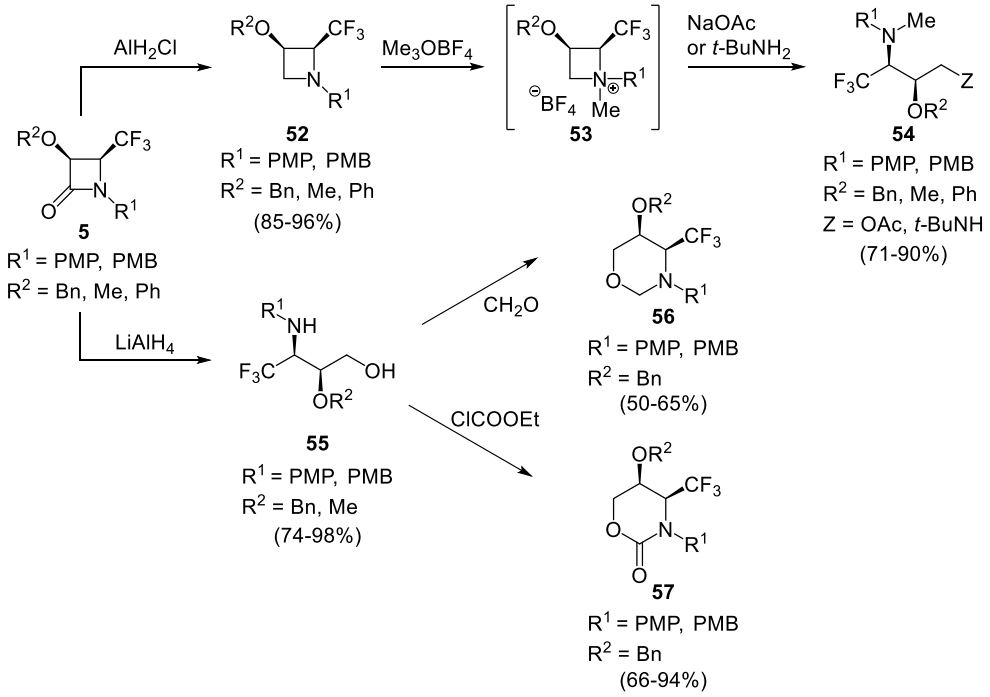



**50** **51**

R = Me, Et, Pr, *i*Pr, Bu, *t*Bu, $CH_2Ph$ (73-99%)

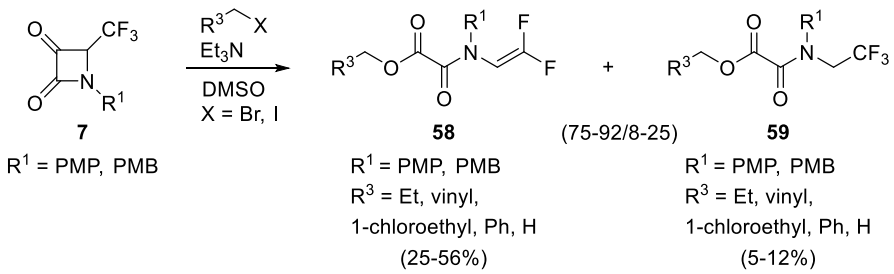
The reactivity of 4-$CF_3$-β-lactams **5** toward ring-opening reactions has been also performed based on an indirect or a direct approach. In the indirect approach, 4-$CF_3$-β-lactams **5** were subjected to initial carbonyl removal upon treatment with $AlH_2Cl$, providing azetidine intermediates **52**. Then, azetidinium salts **53**, derived from azetidines **52** through *N*-methylation, were subjected to ring opening by using different oxygen and nitrogen nucleophiles, furnishing a convenient entry toward a variety of α-(trifluoromethyl)amines **54** (Scheme 18). On the other hand, the direct reductive ring opening of 4-$CF_3$-β-lactams **5** was achieved upon treatment with $LiAlH_4$, yielding 3-aminopropan-1-ols **55**. Cyclization of the latter γ-amino alcohols **55** employing formaldehyde or ethyl chloroformate afforded new 1,3-oxazinanes **56** and 1,3-oxazinan-2-ones **57**, respectively [37].

*Scheme 18*




Ring opening of 3-oxo-β-lactams **7** through C3-C4 bond fission has unexpectedly been effected in attempts to form and trap the corresponding 2,3-dioxoazetidin-4-yl anions, resulting in 2-[(2,2-difluorovinyl)amino]-2-oxoacetates **58** as major products accompanied by minor amounts of 2-oxo-2-[(2,2,2-trifluoroethyl)amino]acetates **59** upon treatment with alkyl halides and triethylamine in DMSO (Scheme 19). This peculiar reactivity was investigated in-depth from both an experimental and a computational point of view in order to shed light on the underlying reaction mechanism [35]. This transformation was then proposed to proceed *via* initial alkyl halide to alcohol conversion, followed by alcohol addition across the oxo group of azetidine-2,3-diones **7** and subsequent C3-C4 bond cleavage.

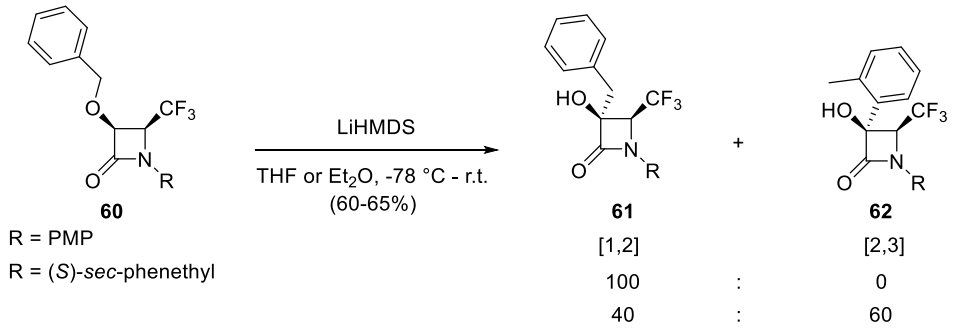
*Scheme 19*



## 2 Ring-transformation reactions of 4-$CF_3$-azetidin-2-ones

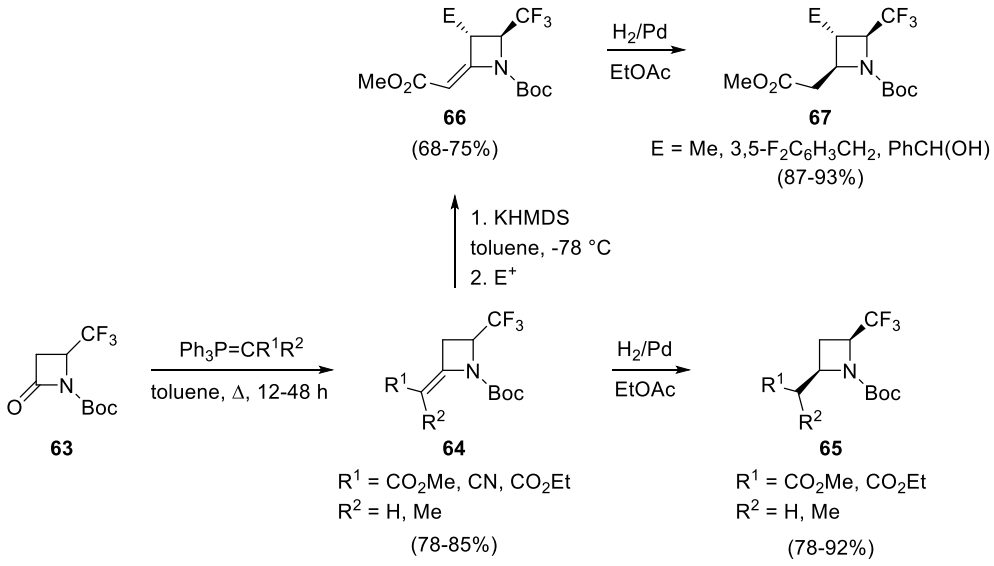
In addition to regioselective ring-opening reactions, 4-$CF_3$-β-lactams have also been shown to be useful building blocks for Wittig rearrangements and alkylation. The enolates of 3-benzyloxy-4-$CF_3$-β-lactams **60**, generated with LiHMDS in THF at -78 °C, were subjected to [1,2]- and *ortho*-[2,3]-Wittig rearrangements, producing 3-benzyl-3-hydroxy-β-lactams **61** and 3-(2-methylphenyl)-3-hydroxy-β-lactams **62**, respectively (Scheme 20), which are potential precursors for the synthesis of new trifluoromethyl-substituted isoserines. Besides, α-methyl-β-lactams were generated in excellent yields *via* quenching of the enolates of **60** with methyl iodide [58].

*Scheme 20*




Furthermore, 4-$CF_3$-β-lactams constitute convenient substrates for a classical Wittig reaction. For example, treatment of β-lactam **63** with stabilized ylides in toluene under reflux afforded alkylideneazetidines **64** in high yields (Scheme 21). Then, catalytic hydrogenation of **64** provided 4-trifluoromethylated 2-alkylazetidines **65** in 78-92% yield, in which the diastereoselectivity depended on the catalyst and the solvent used. Moreover, treatment of one derivative of **64** with potassium bis(trimethylsilyl)amide at -78 °C, followed by reaction with an alkyl halide or an aldehyde, furnished 3-alkyl-substituted derivatives **66** in 68-75% yield. Hydrogenation of compounds **66** with Pd/C in ethyl acetate gave *trans*-2,3-dialkylazetidines **67** in high yields as single isomers [59].

*Scheme 21*

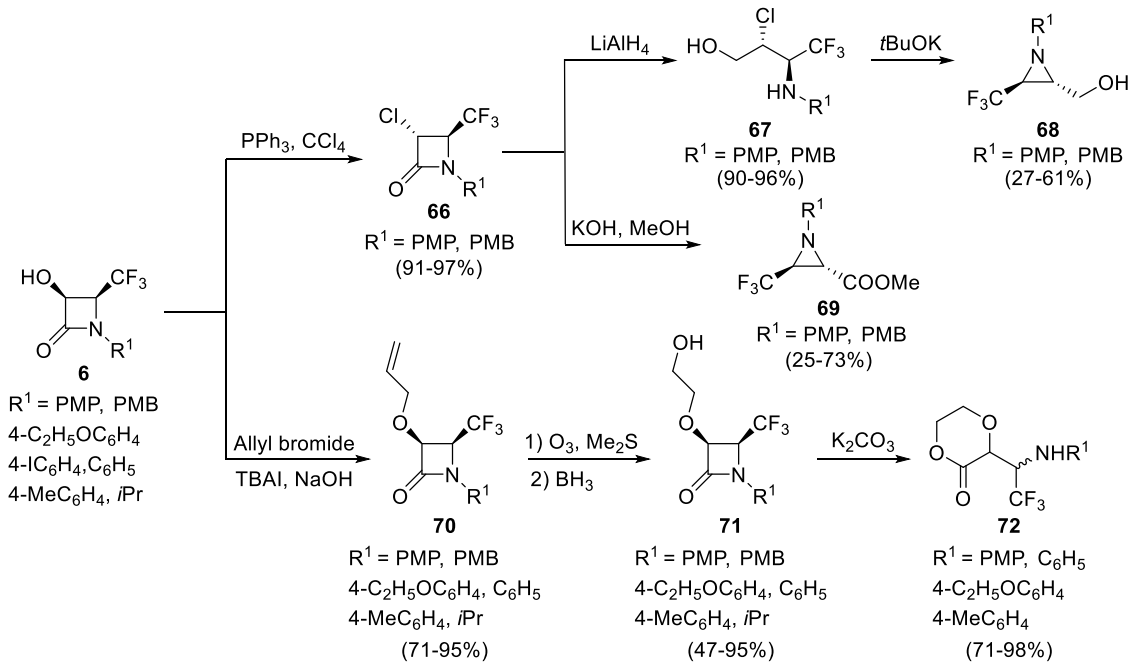



2-Hydroxy-4-$CF_3$-β-lactams **6** have been shown to be suitable substrates for ring contraction toward the synthesis of 2-substituted 3-(trifluoromethyl)aziridines *via* 3-chloro-4-$CF_3$-β-lactam intermediates. In that respect, treatment of *cis*-3-hydroxy-4-$CF_3$-β-lactams **6** with 2 equiv of $Ph_3P$ and a small amount of $NaHCO_3$ catalyst in $CCl_4$ afforded *trans*-3-chloro-4-$CF_3$-β-lactams **66** (Scheme 22). The ring closure of γ-amino alcohols **67**, derived from the $LiAlH_4$-mediated reductive ring opening of chlorides **66**, provided 3-trifluoromethylated aziridines **68** in 27-61% yield upon treatment with 0.8-1 equiv of *t*BuOK. On the other hand, treatment of chlorides **66** with 2 equiv of KOH in methanol under reflux for 20 min afforded the corresponding aziridine-2-carboxylates **69** in 25-73% yield. Besides, 3-chloro-β-lactams **66** have been shown to be versatile precursors for the construction a variety of novel chrorinated $CF_3$-containing aminopropane derivatives, 1,3-oxazinanes, 1,3-oxazinan-2-ones as well [36].

Furthermore, alcohols **6** proved to be suitable substrates for the synthesis of novel 3-[2,2,2-trifluoro-1-(arylamino)ethyl]-1,4-dioxan-2-ones **72** in high yields *via* intramolecular cyclization of 3-(2-hydroxyethoxy)-β-lactam intermediates **71** upon treatment with an excess of $K_2CO_3$ (Scheme 22). The 3-(2-hydroxyethoxy)-

β-lactams **71** were prepared from allyloxyderivatives **70** through an ozonolysis/reduction sequence [36].

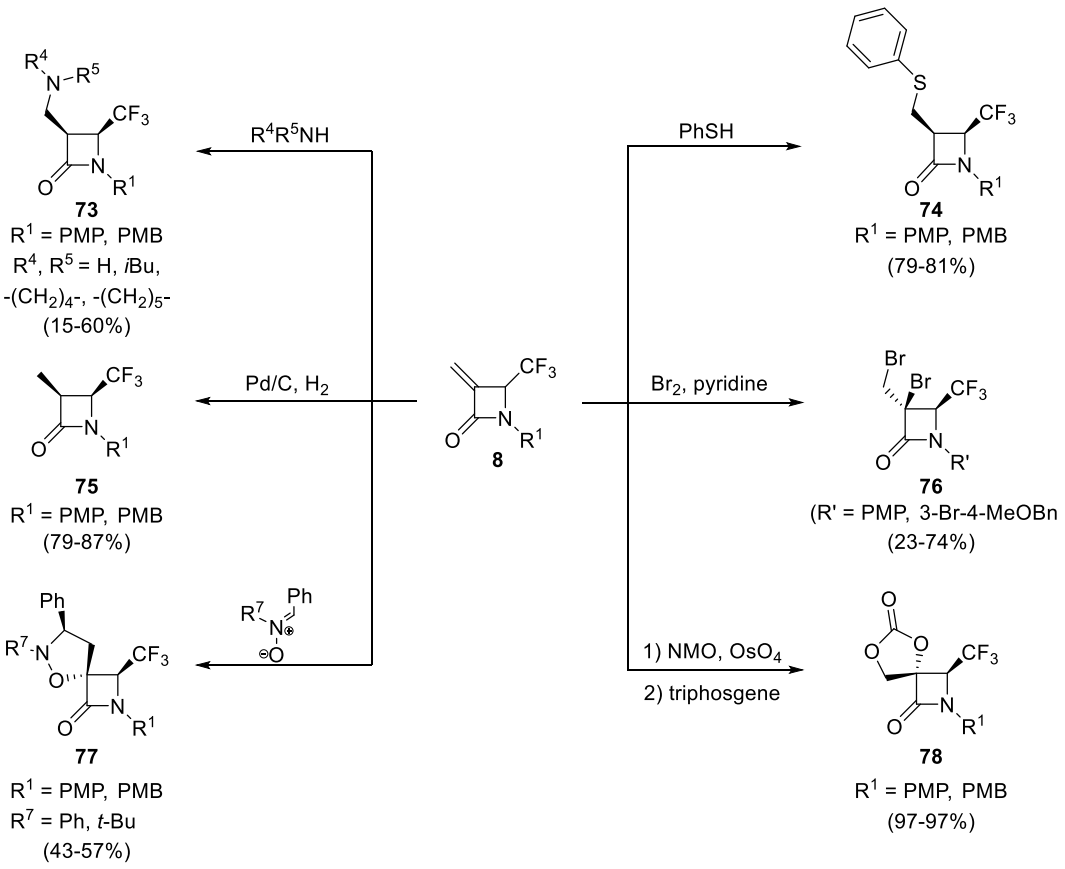
*Scheme 22*




The presence of an exocyclic carbon-carbon double bond as part of a constrained α,β-unsaturated amide fragment in 3-methylene-4-(trifluoromethyl)azetidin-2-ones **8** allows for a multilateral application. In particular, the Michael addition of nitrogen and sulfur nucleophiles onto 4-$CF_3$-β-lactams **8** furnished the corresponding 3-aminomethyl-4-(trifluoromethyl)azetidin-2-ones **73** and 3-phenylthiomethyl-4-(trifluoromethyl)azetidin-2-ones **74**, respectively (Scheme 23). The deployment of 4-$CF_3$-β-lactams **8** to undergo (electrophilic) additions led to 3-methyl-4-(trifluoromethyl)azetidin-2-ones **75** and 3-bromo-3-bromomethyl-4-(trifluoromethyl)azetidin-2-ones **76**. Furthermore, 4-$CF_3$-β-lactams **8** were shown to be susceptible to cycloaddition reactions. In particular, treatment of 3-methylene-β-lactams **8** with either *N*-phenyl- or *N*-*tert*-butyl-α-phenylnitrone afforded a convenient entry to 3-trifluoromethyl-5-oxa-2,6-diazaspiro[3.4]octan-1-ones **77**. 3-Trifluoromethyl-5,7-dioxa-2-azaspiro[3.4]octane-1,6-diones **78**

were prepared upon treatment of the corresponding diols, derived from the $OsO_4$-mediated oxidation of 3-methylene-β-lactams **8**, with triphosgene [38].

*Scheme 23*




## Conclusion

In conclusion, the study of 4-(trifluoromethyl)azetidin-2-ones comprises an interesting, yet hardly explored field in terms of both synthesis and reactivity. The most important synthetic routes toward these compounds are based on [2+2]-ketene-imine cyclocondensations (Staudinger synthesis), enolate-imine cyclocondensations, intramolecular *N*-acylations, intramolecular *C*-alkylations, ring expansions of aziridines, the Kinugasa reaction and the Reformatsky reaction. Moreover, the reactivity of 4-(trifluoromethyl)azetidin-2-ones has received little attention toward ring-opening reactions, although they provide an effective approach for the preparation of e.g. fluorinated amino acids, dipeptides,

taxoids and aminopropanes. In addition, these compounds have shown to be powerful substrates for a Wittig reaction, Wittig rearrangements, alkylation reactions, ring-rearrangement reactions, Michael additions, electrophilic additions and cycloadditions *en route* to a broad variety of $CF_3$-substituted aziridines, dioxan-2-ones as well as stereodefined mono- and spirocyclic β-lactams. In light of the increasing demand for new $CF_3$-substituted nitrogen compounds from a medicinal viewpoint, 4-$CF_3$-β-lactams can indeed be considered as very promising structures for further elaboration, and many more interesting new applications are to be expected in that respect in the near future.

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