“Two roads diverged in a wood, and I took the one less travelled by, that has made all the difference”

Robert Frost

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Synthesis of 4-(trifluoromethyl)azetidin-2-one building blocks and their transformation into novel CF_3-substituted amines and heterocyclic systems

M.Sc. Hang Dao Thi

Thesis submitted in fulfilment of the requirements for the degree of doctor (PhD)

of Applied Biological Sciences: Chemistry and Bioprocess Technology

Dutch translation of the title

Synthese van 4-(trifluormethyl)azetidin-2-onen en hun omzetting tot nieuwe CF_3-gesubstitueerde aminen en heterocyclische systemen

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LIST OF ABBREVIATIONS

Ac	acetyl
Ac_2O	acetic anhydride
$AlCl_3$	aluminium chloride
AlH_2Cl	monochloroalane
Ar	argon gas
ATR	attenuated total reflection
BH_3	trihydridoboron
Bn	benzyl
Br	bromide
Br_2	bromine
brs	broad singlet
Bu	butyl
cat	catalyst
CCl_4	carbon tetrachloride
$CDCl_3$	deuterated chloroform
CH_2Cl_2	dichloromethane
CH_2I_2	diiodomethane
CH_3MgBr	methylmagnesium bromide
$(CH_3)_3SiCl$	trimethylsilyl chloride
cm^{-1}	reciprocal centimeter
CuI	copper(I) iodide
d	doublet, day
d.e.	diastereomeric excess
d.r.	diastereomeric ratio
DEAD	diethyl azodicarboxylate
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide

equiv	equivalent
ESI	electrospray ionization
Et	ethyl
Et_2O	diethyl ether
EtOAc	ethyl acetate
Et_2Zn	diethylzinc
h	hour
H_2	hydrogen gas
H_2O	water
H_2O_2	hydrogen peroxide
HCl(g)	hydrogen chloride
Hex	hexane
HMPA	hexamethylphosphoramide
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry
Hz	hertz
I	iodide
*i*Pr	isopropyl
*i*PrOH	2-propanol
IR	infrared
J	coupling constant
K_2CO_3	potassium carbonate
KOH	potassium hydroxide
Li	lithium
$LiAlH_4$	lithium aluminium hydride
LiHMDS	lithium hexamethyldisilazide
LiOH	lithium hydroxide
m	multiplet
M	mother ion
m/z	mass number (m) over charge number (z)

Me	methyl
*m*CPBA	*meta*-chloroperoxybenzoic acid
Me_2S	dimethyl sulfide
Me_3SiOTf	trimethylsilyl trifluoromethanesulfonate
MeCN	acetonitrile
MeOH	methanol
$MgSO_4$	magnesium sulfate
MHz	megaHertz
min	minute
MS	molecular sieves
MW	microwave irradiation
N_2	nitrogen gas
NBS	*N*-bromosuccinimide
NaH	sodium hydride
$NaBH_4$	sodium borohydride
$NaHCO_3$	sodium hydrogen carbonate
NaN_3	sodium azide
NaOAc	sodium acetate
NaOH	sodium hydroxide
NH_3	ammonia
NH_4Cl	ammonium chloride
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
Nu	nucleophile
O_3	ozone
OsO_4	osmium tetroxide
P_2O_5	phosphorus pentoxide
Pd	palladium
PE	petroleum ether
Ph	phenyl

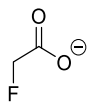
PhH	benzene
PMB	*para*-methoxybenzyl (4-methoxybenzyl)
PMP	*para*-methoxyphenyl (4-methoxyphenyl)
PPh_3	triphenylphosphine
p-TsOH	*para*-toluenesulfonic acid
Py	pyridine
r.t.	room temperature
R_f	retention factor
s	singlet
SiO_2	silicon dioxide (silica gel)
$SOCl_2$	thionyl chloride
t	triplet
TBAI	tetrabutylammonium iodide
*t*Bu	tertiary butyl
*t*BuOK	potassium *tert*-butoxide
THF	tetrahydrofuran
$TiCl_4$	titanium tetrachloride
TLC	thin layer chromatography
$ZnBr_2$	zinc bromide
Δ	reflux
δ	chemical shift
ΔG	Gibbs free energy

PhD ABSTRACT

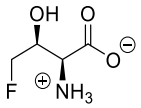
In light of the versatile synthetic potential of β-lactams on the one hand and the beneficial impact of fluorine on biological properties on the other hand, β-lactams bearing a trifluoromethyl group comprise interesting entities for the construction of novel targets with promising bioactivities. In this PhD thesis, the preparation and deployment of 4-trifluoromethyl-β-lactams as new building blocks toward a diverse set of functionalized CF_3-amines and CF_3-azaheterocycles was investigated. In particular, 3-benzyloxy-4-trifluoromethyl-β-lactams were conveniently synthesized as a first new class of building blocks. The aptitude of these systems with respect to ring-opening reactions was explored to enable an entry to functionalized aminopropane systems by either direct reductive β-lactam ring opening or initial carbonyl removal to azetidine intermediates, followed by ring opening. In addition, hydrogenolysis of the benzylether fragment in 3-benzyloxy-4-trifluoromethyl-β-lactams resulted in the formation of 3-hydroxy-4-trifluoromethyl-β-lactams as a second class of new building blocks. The latter alcohols enabled the construction of CF_3-containing ring-rearranged products, including aziridines through a ring-contraction protocol *via* 3-chloro-β-lactam intermediates and dioxan-2-ones *via* initial *O*-allylation. Furthermore, alcohol oxidation gave rise to 3-oxo-4-trifluoromethyl-β-lactams as a third class of new building blocks. Attempts to form and trap the corresponding 2,3-dioxoazetidin-4-yl anions unexpectedly resulted in ring opening through C3-C4 bond fission, culminating in 2-[(2,2-difluorovinyl)amino]-2-oxoacetate products. This peculiar mechanism was investigated in depth, both experimentally and computationally. Finally, an addition/elimination sequence applied to 3-oxo-4-trifluoromethyl-β-lactams afforded 3-methylene-4-trifluoromethyl-β-lactams as a fourth class of new building blocks, which were shown to be eligible substrates for Michael additions, electrophilic additions and cycloadditions *en route* to a variety of stereodefined mono- and spirocyclic 4-CF_3-β-lactams.

INTRODUCTION AND GOALS

Fluorine is the 13th most abundant element in the earth's crust, where it occurs predominantly in minerals as cryolite (Na_3AlF_6), fluorite (CaF_2) and fluorapatite ($Ca_5(PO_4)_3F$). However, only a few simple chemical entities in nature contain a carbon-fluorine bond, which is due to the insolubility of fluorine salts.[1] It is estimated that only five out of 130 000 unique natural products structurally characterized contain fluorine in their structures. Fluoroacetate **1** is the most common, and is found in many plants and in the *Streptomyces cattleya* bacterium.[2] Besides fluoroacetate, the amino acid 4-fluoro-L-threonine **2** is coproduced in the bacterium *S. cattleya* by an enzyme-catalyzed transfer of fluoroacetaldehyde onto L-threonine.[3]



1



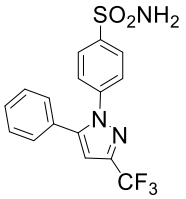
2

Although nature produces a limited number of fluorine-containing products, organofluorine compounds are emerging as crucial components in organic and medicinal chemistry. This is illustrated by their presence in approximately 25% of pharmaceuticals and in 30-40% of agrochemicals on the market.[4,1b] Fluorinated compounds have attracted tremendous attention because of the beneficial effects of fluorine on the physicochemical and pharmacokinetic properties of bioactive molecules, such as pKa, lipophilicity, metabolic stability and bioavailability.[5,4b] In fact, these pronounced impacts of fluorine are due to its atomic physical properties such as high electronegativity, relatively small size, very low polarizability, three tightly bonded electron lone pairs and an excellent overlap of the 2s and 2p orbitals with the corresponding orbitals of carbon.[6]

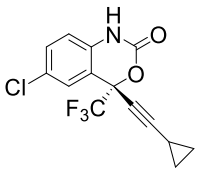
Because of the high electronegativity of fluorine ($\chi_{pauling} = 4$) the carbon-fluorine bond is highly polarized, very strong (C-F = 485 kJ/mol) and short. In addition, this bond has a low polarizability, which often leads to a higher lipophilicity of fluorinated compounds, especially in the case of aromatic fluorination and fluorination adjacent to atoms with π-bonds. The replacement of a single aromatic hydrogen by a fluorine atom results only in a modest increase in lipophilicity, whereas the replacement of substituents by a CF_3 group renders significant modulation of this property. Modulation of the lipophilicity of a compound has a profound effect on the absorption of pharmaceuticals in the body. Orally administered drugs can be commonly absorbed and distributed by passive transport processes, which depend on the permeability of the cell

membrane. An effective drug molecule requires a lipophilicity that allows it to penetrate the cell membrane without being trapped in it. Another effect of the strong electronegativity of fluorine comprises a significant influence on the pKa values of neighboring functional groups such as alcohols, carboxylic acids and amines.[7] Modulation of the pKa can be exploited to improve the solubility and bioavailability of orally administered drugs by affecting the absorption, distribution, metabolism and excretion processes (ADME).[4b,6b] However, the effect of fluorine substitution on the bioavailability of drugs can not be accurately predicted.[4b] In addition, the van der Waals radius of fluorine (1.47 Å) lies between oxygen (1.57 Å) and hydrogen (1.20 Å), thus the replacement of either oxygen or hydrogen with fluorine is commonly tolerated by biological targets.[1b] However, this is not the case for the trifluoromethyl group, which is actually closer in size to an isopropyl group rather than a methyl group.[7] Indeed, the CF_3 group can exert an effect comparable to a phenyl ring or *tert*-butyl group. The steric variation combined with the electron-withdrawing properties can lead to changes in the preferred molecular conformation upon a CF_3 group introduction.[4b]

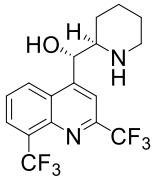
In light of the emerging interest in fluorinated compounds, many synthetic endeavors have been devoted to the construction of organic molecules bearing one or more fluorine atoms, for example a trifluoromethyl group, in their structures. Since H. L. Yale acknowledged the remarkable potential of a CF_3 group in medicinal chemistry in 1959,[8] a broad diversity of trifluoromethylated drugs has been designed and widely used such as celecoxib **3** (anti-inflammatory agent), efavirenz **4** (HIV-RT inhibitor) and mefloquine **5** (antimalarial).[9]



Celecoxib **3**
(Celebrex)



Efavirenz **4**
(Sustiva)



Mefloquine **5**
(Mefliam)

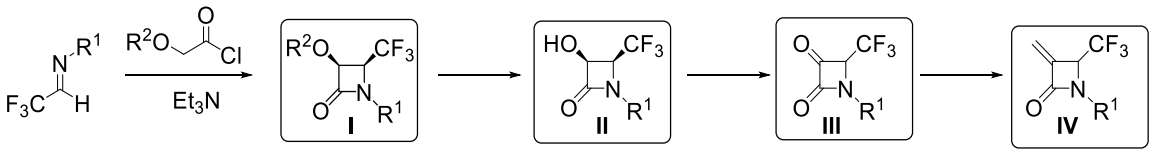
From a synthetic viewpoint, trifluoromethyl-containing molecules have been prepared based on two major strategies. The first one is the building-block approach (fluorinated synthon approach), which utilizes a trifluoromethylated starting material to assemble the target molecules. The other route concerns the late-stage trifluoromethylation strategy, which introduces a trifluoromethyl

group onto different types of organic substrates by means of either aromatic coupling reactions or radical/nucleophilic/electrophilic trifluoromethylation routes.[10] Because both strategies have advantages and disadvantages, they have been used complementary to each other. For example, the late-stage approach can enable the streamlined synthesis of the desired target compounds. However, expensive trifluoromethylation reagents and harsh reaction conditions are usually required. In addition, the reactive intermediates, which are generated during the trifluoromethylation reactions, are often unstable under the reaction conditions. In fact, only three of the fluorine-containing drugs introduced on the market in 2001-2011 were manufactured through this methodology. A complementary building block strategy can then be utilized to deal with the difficulties associated with the trifluoromethylation strategy. In fact 90% of the fluorinated pharmaceuticals prevalent over all therapeutic areas are prepared through the latter approach.[1b,11] Besides its pre-eminence, this methodology might appear to limit the position of fluorine in the target molecule. However, this obstacle is improved by the presence of many available fluorine-containing starting materials on the market.

The building block approach has been extensively exploited for the synthesis of small-ring molecules such as CF_3-substituted β-lactams or azetidine-2-ones, as the trifluoromethylation approach often compromises the structural integrity of these reactive and sensitive molecules.[12] In addition to their interesting pharmacological properties (antibacterial, antitumor and anti-inflammatory…), β-lactams have been known to be flexible synthons (β-lactam synthon method) for the preparation of a wide variety of nitrogen-containing acyclic and heterocyclic compounds.[13] In light of the interesting effects of fluorine introduction, β-lactams bearing a trifluoromethyl group can be considered as fascinating templates for the construction of novel targets with a diverse set of potential applications. For example, the transformation products of CF_3-substituted β-lactams have been applied to develop new taxoid anticancer drugs, which have been shown to be efficacious drugs with fewer side effects and superior pharmacological properties.[14]

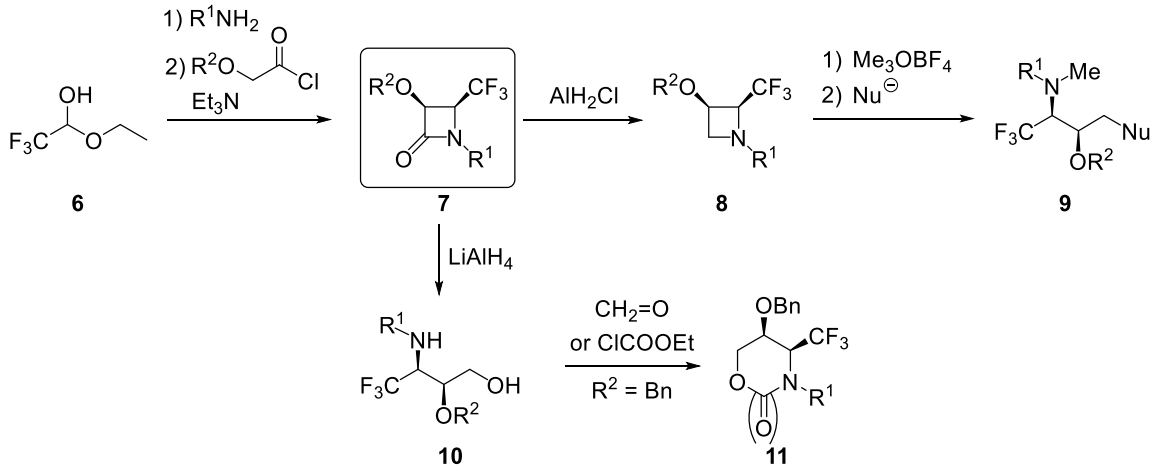
Intrigued by the tremendous synthetic potential of β-lactams in combination with the interesting effects of a trifluoromethyl group on biological properties, many efforts will be devoted in this PhD thesis to the synthesis and synthetic application of 4-trifluoromethyl-β-lactams. In that respect, 4-trifluoromethyl-β-lactams will be synthesized and deployed as building blocks (β-lactam synthon method) in the construction of novel nitrogen-containing acyclic and heterocyclic compounds through ring-opening and ring-transformation reactions. These objectives can be divided into four work packages based on the unexplored chemistry of 4-trifluoromethyl-β-lactam building blocks **I**,

II, **III**, **IV**, which can be synthesized in an interconnective way starting from CF_3-substituted imines *via* Staudinger β-lactam synthesis (Scheme 1).



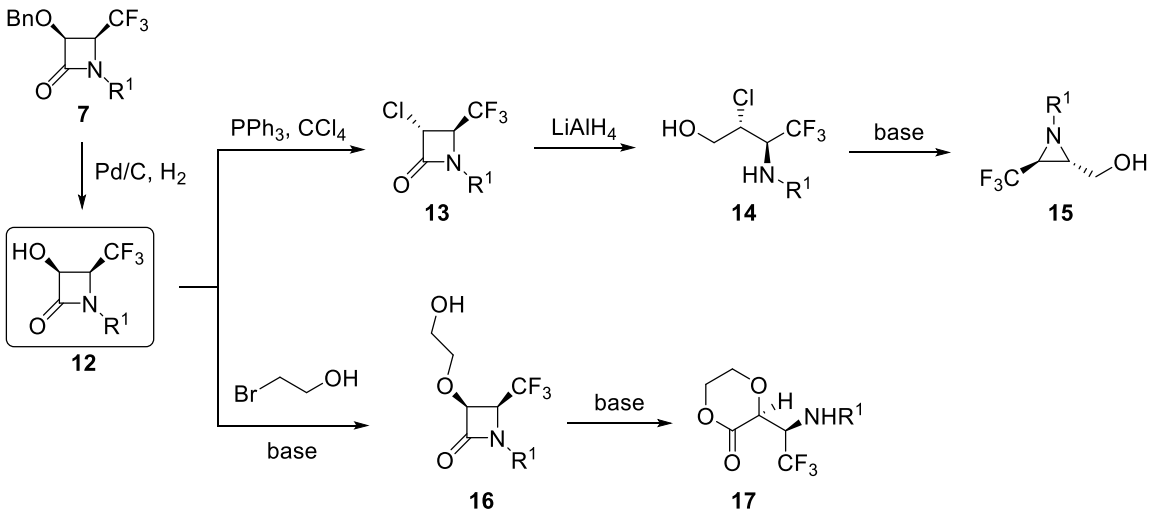
Scheme 1

In analogy with non-fluorinated β-lactams, CF_3-β-lactams have previously been shown to be suitable precursors for the preparation of aminopropane systems through ring-opening reactions.[15] However, ring opening of CF_3-substituted β-lactams has been mainly performed through a methanolysis approach.[16] In the first part of this thesis, the synthesis and reactivity of 3-alkoxy/aryloxy-4-trifluoromethyl-β-lactams **7**, as the first building blocks **I**, toward ring-opening reactions will be investigated utilizing various nucleophiles (Scheme 2). In that respect, the synthesis of 3-alkoxy/aryloxy-4-trifluoromethyl-β-lactams **7** starting from commercially available 1-ethoxy-2,2,2-trifluoroethanol **6** will be performed *via* imination and subsequent Staudinger β-lactam synthesis with alkyl/aryloxyacetyl chlorides. The ring-opening capability of 4-CF_3-β-lactams **7** will then be explored through an indirect or direct approach. In the indirect approach, initial AlH_2Cl-induced carbonyl reduction of 4-CF_3-β-lactams **7** will be performed to furnish 2-CF_3-azetidine intermediates **8**. Activation of the latter azetidines **8** utilizing trimethyloxonium tetrafluoroborate (Me_3OBF_4) and subsequent regiospecific ring opening with different nucleophiles (Nu^-) could lead to a diversity of functionalized trifluoromethyl-containing aminopropanes **9**. On the other hand, the direct ring opening of 4-CF_3-β-lactams **7** could be expected upon treatment with $LiAlH_4$, in line with the behavior of non-CF_3-substituted β-lactams, giving rise to CF_3-substituted γ-amino alcohols **10**.[17] Furthermore, the cyclization of γ-amino alcohols **10** with either formaldehyde or ethyl chloroformate will be exploited in order to afford trifluoromethylated 3-oxazinane and 1,3-oxazinan-2-one azaheterocycles **11**.[18]



Scheme 2

In the second part of this PhD thesis, 3-hydroxy-4-trifluoromethyl-β-lactams **12**, as a second class of building blocks **II**, will be synthesized through the hydrogenolysis of 3-benzyloxy-4-trifluoromethyl-β-lactams **7** (Scheme 3). It should be noted that the preparation of 3-hydroxy-β-lactam analogs has been documented,[16a] however, the reactivity of these alcohols has been hardly explored. The deployment of alcohols **12** as versatile substrates for the construction of a variety of CF_3-containing azaheterocyclic products will be pursued *via* ring-rearrangment reactions. As a first objective, ring contraction of alcohols **12** toward the synthesis of 2-substituted 3-(trifluoromethyl)aziridines **15** *via* new 3-chloro-β-lactam intermediates **13** will be considered. In analogy with non-CF_3-substituted 3-chloro-β-lactams,[15] the reductive ring opening of chlorides **13** by means of $LiAlH_4$ could lead to 3-amino-2-chloropropan-1-ols **14**, which could be prone to subsequent cyclization towards 2-substituted 3-(trifluoromethyl)aziridines **15** under basic conditions. This methodology might offer a new approach to the interesting class of trifluorinated aziridines, which have been mainly synthesized by using diazo compounds or by applying harsh reaction conditions.[19]

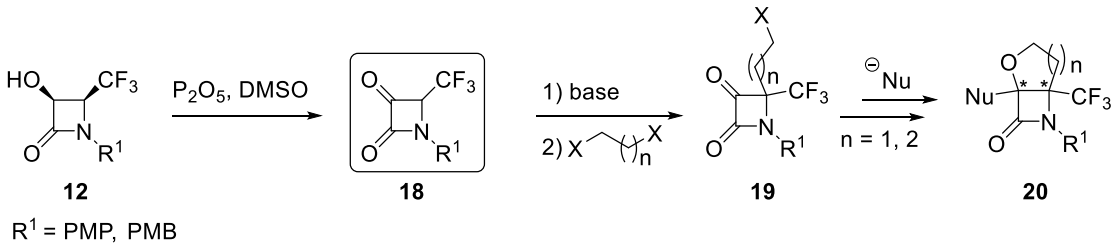


Scheme 3

In addition, the treatment of 3-hydroxy-β-lactams **12** with 2-bromoethan-1-ol in the presence of a base could afford 3-(2-hydroxyethoxy)-β-lactams **16**.[20] Due to the combination of the constrained β-lactam ring system and a nucleophilic alcohol group at a remote position, the resulting β-lactams **16** could undergo intramolecular cyclization toward six-membered azaheterocycles **17** upon treatment with a suitable base.[21] This transformation aptitude of 3-(2-hydroxyethoxy)-β-lactams **16** will be scrutinized to enable the synthesis of novel CF_3-containing 1,4-dioxan-2-ones **17**, which are known as important intermediates in the synthetic field of e.g. polymers, corrosion inhibitors and biomaterials.[22]

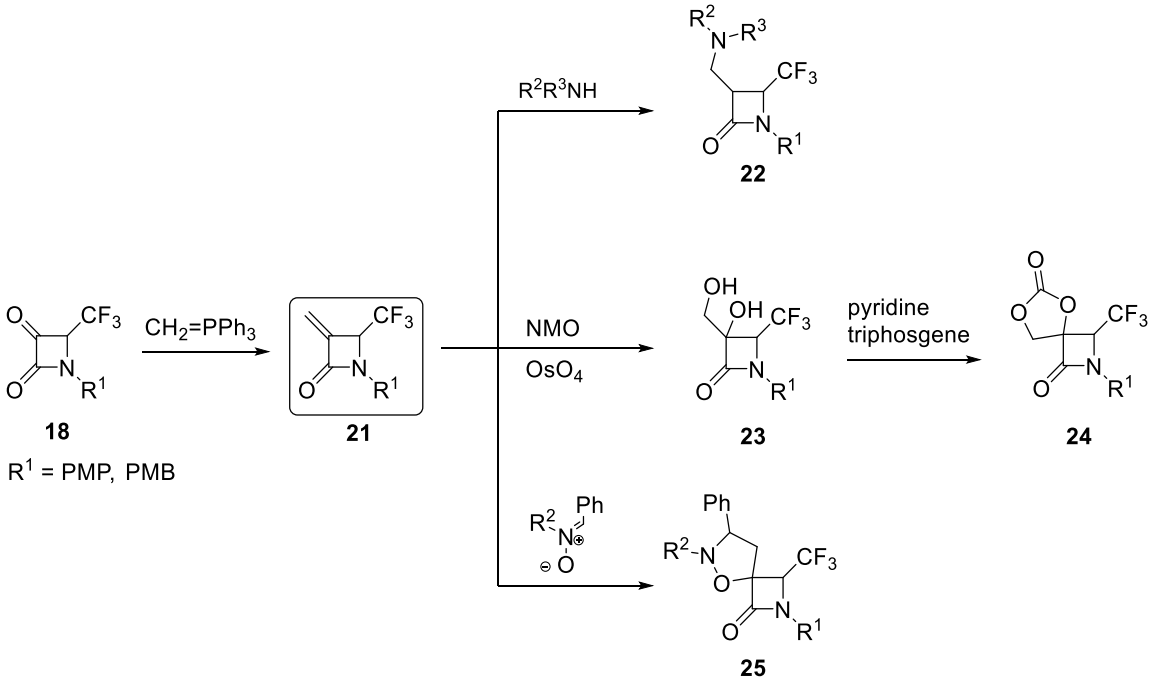
In the next part, 3-oxo-4-(trifluoromethyl)azetidin-2-ones **18**, as a third type of building blocks **III**, will be envisaged from the corresponding 3-hydroxy-4-trifluoromethyl-β-lactams **12** *via* Albright-Onodera oxidation using P_2O_5 in DMSO (Scheme 4). An important aspect of trifluoromethylated small-ring azaheterocycles, for example 2-CF_3-aziridines, comprises their suitability to undergo deprotonation in α-position with regard to the strong electron-withdrawing CF_3 group, resulting in the corresponding 2-(trifluoromethyl)aziridin-2-yl anions.[23] In analogy, the deployment of 4-trifluoromethyl-3-oxo-β-lactams might offer new opportunities for the introduction of an additional side chain through abstraction of the acidic C4-proton in α-position with respect to the oxo group and the CF_3 moiety. In that respect, treatment of 3-oxo-4-CF_3-β-lactams **18** with a suitable base could result in the corresponding 3,4-dioxo-2-(trifluoromethyl)azetidin-2-yl anions, followed by quenching with dihaloalkanes to afford the desired 3-oxo-4-haloalkyl-β-lactams **19**. Subsequently, cyclization of the resulting β-lactams **19**, which represent with electrophiles bearing an additional

leaving group, will be evaluated toward the synthesis of C-fuse bicyclic β-lactam **20** analogs, a promising class of compounds in medicine known as β-lactamase inhibitors.[24]



Scheme 4

In the final part, attempts will be made to synthesize 3-methylene-β-lactams **21** as a fourth class of new building blocks **IV** (Scheme 5). From a synthetic viewpoint, these β-lactams **21** can be prepared from 3-oxo-β-lactams **18** *via* a Wittig olefination upon treatment with methylenetriphenylphosphorane. The presence of an exocyclic carbon-carbon double bond coupled with the electron-withdrawing CF_3 group can allow 3-methylene-4-(trifluoromethyl)azetidin-2-ones **21** to be suitable synthons for Michael additions, addition reactions and cycloadditions *en route* to a variety of stereodefined mono- and spirocyclic 4-CF_3-β-lactams. More precisely, conjugate addition of nucleophiles (such as primary and secondary amines) across the electron-poor double bond in 3-methylene-β-lactams **21** could provide 3-functionalized 4-CF_3-azetidin-2-ones **22**. In addition, the suitability of 4-CF_3-β-lactams **21** for the preparation of CF_3-substituted spirocyclic structures *via* diol intermediates **23** will be investigated. As such, the synthesis of diols **23** is contemplated based on the OsO_4-mediated oxidation of 3-methylene-4-(trifluoromethyl)azetidin-2-ones **21** using *N*-methylmorpholine-*N*-oxide (NMO).[25] Subsequently, treatment of diols **23** with triphosgene in the presence of pyridine could afford 3-trifluoromethyl-5,7-dioxa-2-azaspiro[3.4]octane-1,6-diones **24**. Furthermore, the reactivity of 3-methylene-4-CF_3-β-lactams **21** will be scrutinized toward 1,3-dipolar nitrone-olefin cycloaddition to access novel spiro-fused β-lactam isoxazolidine systems. Thus, 3-methylene-β-lactams **21** will be treated with an α-phenylnitrone enabling a convenient entry to 7-phenyl-3-trifluoromethyl-5-oxa-2,6-diazaspiro[3.4]octan-1-ones **25**. It should be noted that the determination of the relative stereochemistry of all new compounds will be an important aspect of these studies in order to assign the correct structures.



Scheme 5

The overall objective of these four work packages is to provide fundamental insights into the unexplored chemistry of 4-trifluoromethyl-β-lactams in terms of both synthesis and reactivity. In light of the increasing demand for new fluorinated building blocks from a medicinal chemistry perspective, the deployment of these CF_3-β-lactam building blocks is expected to provide a broad range of CF_3-decorated nitrogen-containing acyclic and heterocyclic molecules, which can be used for a diverse set of new applications.

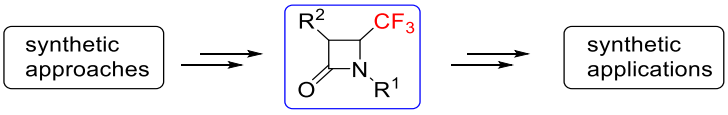
LITERATURE REVIEW

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

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.

Graphical abstract



Reference

Dao Thi, H., Van Nguyen, T., D'hooghe, M. "Synthesis and reactivity of 4-(trifluoromethyl)azetidin-2-ones". *Monatsh. Chem.* **2018**, *149*, 687-700. (I.F.1.28).

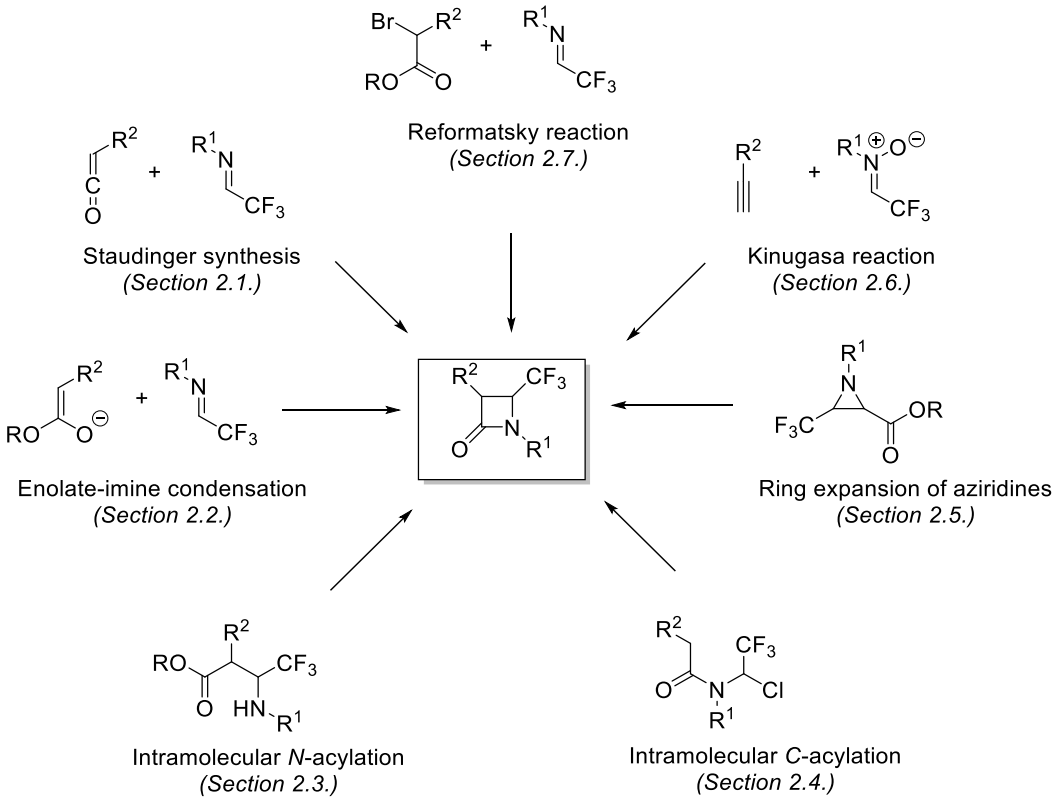
1. Introduction

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.[4a,26,1b] 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.[27,14a] Subsequently, synthetic chemistry focused on the incorporation of one or more fluorine atoms into organic molecules has resulted in many new approaches and strategies.[4a,1b,4b] 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.[28a,18,28b,23b] 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.[13a] 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.[13] 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).[10c,29a,23a,29b-29f,7,29g,9,29h] 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.[14a] The goal of this literature overview is to provide 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.[12]

2. 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.

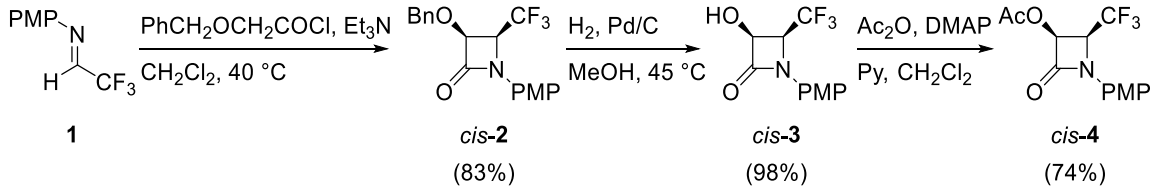


Scheme 1

2.1. 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.[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 smoothly performed in dichloromethane at 40 °C, giving racemic *cis*-4-CF_3-β-lactam

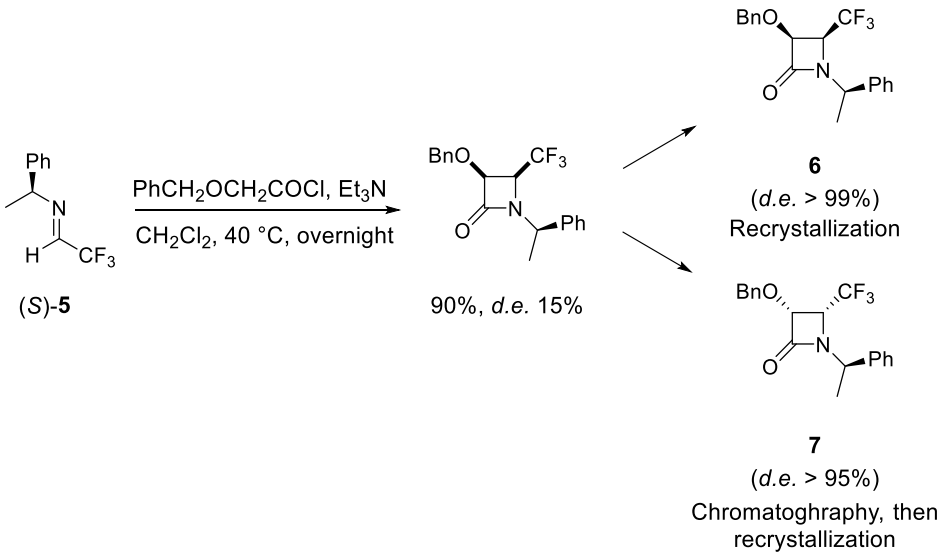
2 in high yield (83%). The *cis*-selectivity was determined based on the ^{1}H NMR spectrum of β-lactam **2**, showing a coupling constant between the two vicinal protons at the C3 and C4 position of 5-6 Hz ($CDCl_3$), as opposed to *trans*-β-lactams (1-2 Hz, $CDCl_3$).[16a,30a] Then, *cis*-β-lactam **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%.[16a,32,16b,14a]



1 *cis*-**2** (83%) *cis*-**3** (98%) *cis*-**4** (74%)

Scheme 2

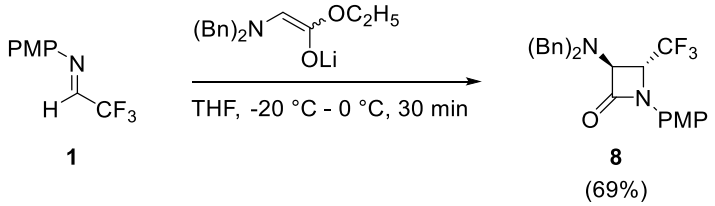
In addition, [2+2]-cyclocondensation of a chiral imine and achiral ketene comprises a useful route toward chiral azetidin-2-ones. The reaction of chiral imine **5**, prepared from trifluoroacetaldehyde hemiacetal and (*S*)-phenethylamine, with benzyloxyketene under classical Staudinger reaction conditions has been reported to afford a crude mixture of *cis*-β-lactams **6** and **7** in 90% yield (Scheme 3), accompanied by minor amounts (5-8%) of *trans*-β-lactams. These *cis*-isomers were successfully separated by recrystallization of the crude mixture. Stereoisomer **6** was obtained in an excellent diastereomeric purity (> 99%) after recrystallization from ethanol, whereas stereoisomer **7** was isolated with a diastereomeric excess of 95% after SiO_2 chromatography and recrystallization from pentane.[16a]



Scheme 3

2.2. Synthesis of 4-CF_3-azetidin-2-ones *via* enolate-imine condensation

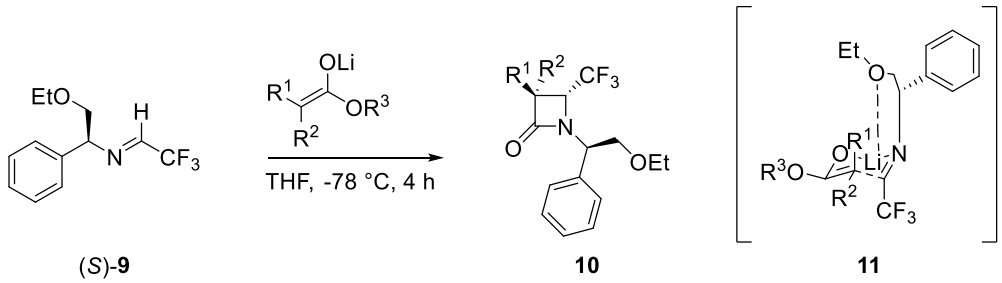
The condensation of imine **1** with the lithium enolate of ethyl dibenzylaminoacetate, produced *in situ* from ethyl dibenzylaminoacetate and lithium diisopropylamide in dry THF, has been successfully performed leading to *trans*-4-CF_3-β-lactam **8** in 69% yield (Scheme 4).[31] In related research, 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.[33]



Scheme 4

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 **9** with lithium enolates, derived from various ester

derivatives, provided the *trans*-configuration at the C3- and C4-position of β-lactams **10** (R^1 = Me, PhO) with rather high diastereoselectivity (95-99%). The high selectivity was explained by a six-membered transition state **11** involving the imine and the enolate (Scheme 5).[34]



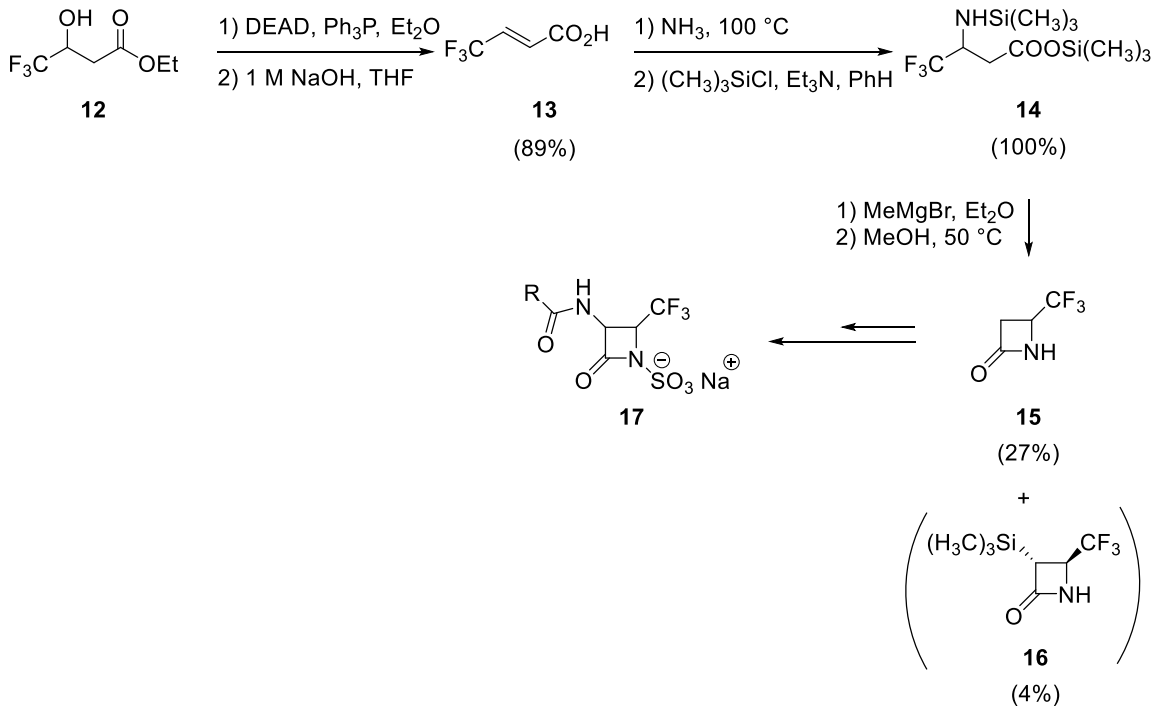
(*S*)-**9** **10** **11**

R^1 = H, R^2 = H, R^3 = *i*Pr, 23%, *d.e.* > 99%
R^1 = H, R^2 = H, R^3 = Me, 57%, *d.e.* 95%
R^1 = Me, R^2 = H, R^3 = Me, 68%, *d.e.* > 99%
R^1 = PhO, R^2 = H, R^3 = Et, 72%, *d.e.* > 99%

Scheme 5

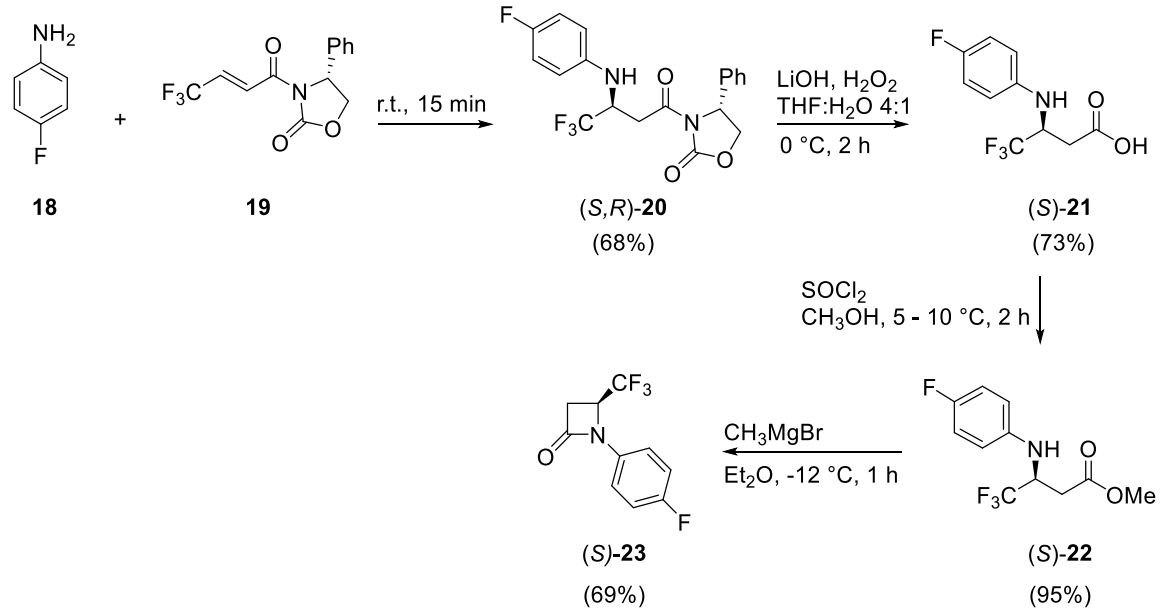
2.3. Synthesis of 4-CF_3-azetidin-2-ones *via* intramolecular *N*-acylation

A convenient entry toward the construction of azetidin-2-ones comprises the cyclization of β-amino acid derivatives.[35,13b] In that respect, Roberts and co-workers have reported the cyclization of trifluoromethylated amino acid derivative **14** with methylmagnesium bromide, giving rise to 4-trifluoromethyl-β-lactam **15** in a yield of 27% and *C*-silylated compound **16** as a side product (Scheme 6). Amino acid derivative **14** was prepared in a quantitative yield by aminolysis and treatment with trimethylsilyl chloride of the corresponding unsaturated acid **13**, which had been effectively synthesized from alcohol **12** by elimination of water, followed by hydrolysis using sodium hydroxide in THF. With the desired 4-(trifluoromethyl)azetidin-2-one **15** in hand, the preparation of fluorine-containing sulfazecin analogs **17**, with interesting bactericidal properties, has been investigated.[36]



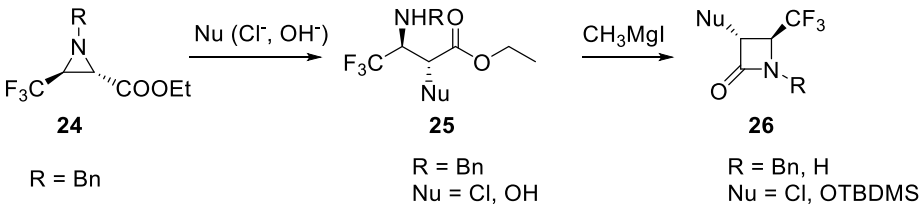
Scheme 6

Yang and co-workers have devised a methodology to synthesize a CF_3-substituted β-amino acid using the aza-Michael reaction (Scheme 7). As such, the major diastereomer (*S,R*)-**20** was obtained in a yield of 68% upon treatment of chiral acrylamide **19** with aromatic amine **18**, without solvent and catalyst. Aza-Michael adduct **20** was hydrolyzed into amino acid **21** with LiOH-H_2O_2 in a good yield (73%). It should be noted that analogs of chiral α-trifluoromethyl amino acid **21** can also be prepared by reduction of the corresponding enamines or imines.[37] Furthermore, β-CF_3-β-amino ester **22**, derived from **21**, was cyclized in the presence of methylmagnesium bromide to construct enantioenriched 4-trifluoromethylated β-lactam **23** in 69% yield. The absolute stereochemistry of **23** was determined to be *S*, hence, the configuration of compound **21** was assigned as *S*.[37-38]



Scheme 7

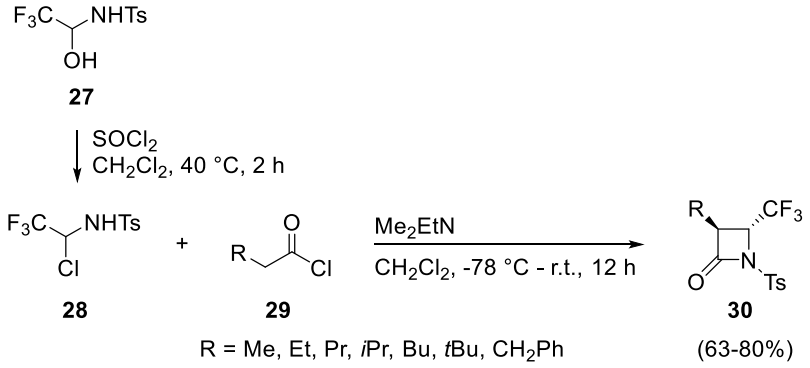
Furthermore, chiral β-amino esters **25** have effectively been prepared by the regio- and stereoselective nucleophilic ring-opening reaction of 1-benzyl-3-trifluoromethyl-2-(ethoxycarbonyl)aziridine **24** (Scheme 8). *Via* Grignard-mediated intramolecular cyclization, *trans*-β-lactams **26** were produced from the corresponding β-amino esters **25**. The *trans*-configuration of β-lactams **26** was assigned by means of ^{1}H NMR ($J_{H3,H4}$ = 1.8 Hz). The stereochemistry of *trans*-β-lactams **26** confirms the *anti* relative configuration of β-amino esters **25** and underlines the stereoselectivity of the ring-opening reaction of *trans*-benzyl-3-trifluoromethyl-2-(ethoxycarbonyl)aziridine **24**.[39]



Scheme 8

2.4. Synthesis of 4-CF_3-azetidin-2-ones *via* intramolecular *C*-alkylation

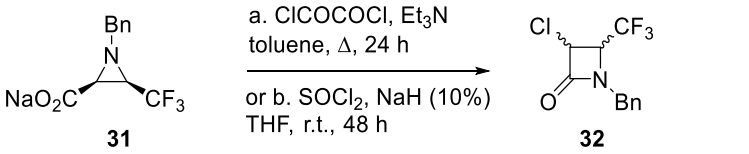
Petrik and co-workers have recently published a new methodology for the preparation of *trans*-4-trifluoromethylated β-lactams **30** by reaction of *N*-(1-chloro-2,2,2-trifluoroethyl)-4-methylbenzenesulfonamide **28** with various nonactivated aliphatic acid chlorides **29** in the presence of dimethylethylamine as a base and dichloromethane as a solvent (Scheme 9). Sulfonamide **28** was produced by the treatment of hemiaminal **27** with thionyl chloride in CH_2Cl_2 at 40 °C. The use of chloroamine **28** in the cyclization reaction can offer a convenient alternative for the construction of trifluoromethylated β-lactams based on the use of highly moisture-sensitive trifluoromethylated imines.[16c]



Scheme 9

2.5. Synthesis of 4-CF_3-azetidin-2-ones *via* direct ring expansion of 3-CF_3-aziridine-2-carboxylates

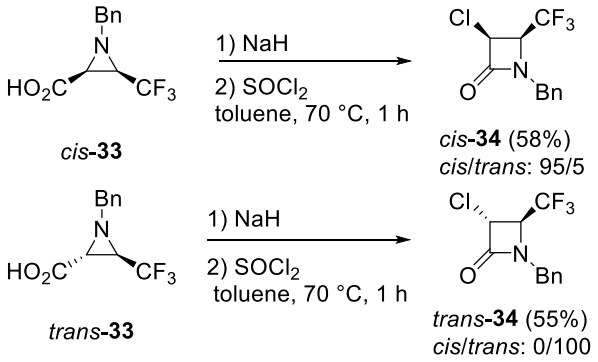
In analogy with the preparation of non-fluorinated azetidin-2-ones from the corresponding non-fluorinated aziridines,[40] 3-chloro-4-CF_3-azetidin-2-one **32** was prepared through ring expansion of the corresponding fluorinated sodium aziridinyl carboxylate **31** with either oxalyl chloride or thionyl chloride (Scheme 10).



a. 50% (*cis*/*trans*: 85/15)
b. 40% (*cis*/*trans*: 40/60)

Scheme 10

The diastereoselectivities were significantly improved by considering the ring expansion of the carboxylic acid CF_3-aziridine analogs instead of the sodium salts (Scheme 11). Aziridines ***cis*-33** and ***trans*-33** were treated with NaH and then thionyl chloride in toluene at 70 °C, resulting in the corresponding *cis*- and *trans*-β-lactams **34** 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.[41]

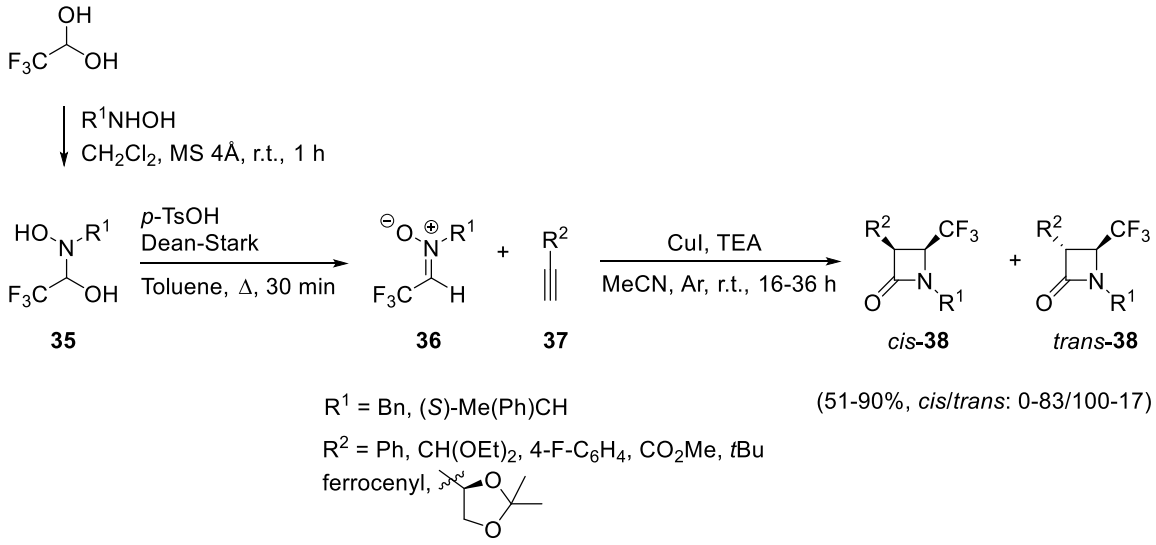


Scheme 11

2.6. 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).[42] El Dine and co-workers have applied this method for the preparation of 3-difluoroalkyl- and/or 3-(1-fluoroalkylidene)-β-lactams from

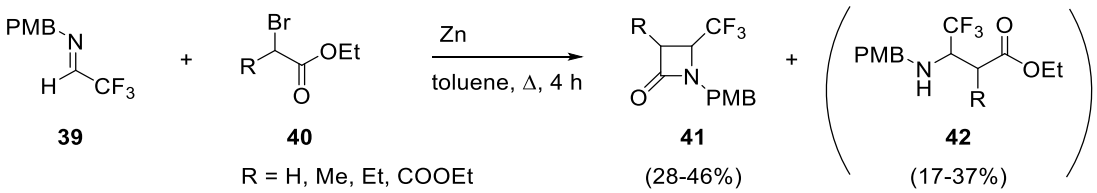
propargylic *gem*-difluorides.[43] Very recently, Kowalski and co-workers have presented a new application of fluorinated nitrones for the preparation of fluoroalkylated β-lactams *via* the Kinugasa reaction. Trifluorinated nitrones **36** were prepared by treating the corresponding hemiaminals **35**, derived from fluoral, with *para*-toluenesulfonic acid using a Dean-Stark apparatus (Scheme 12). The isolated and purified nitrones **36** were then treated with different mono-substituted acetylenes **37** under typical Kinugasa reaction conditions to form the expected 4-trifluoromethyl-β-lactams **38** 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.[12]



Scheme 12

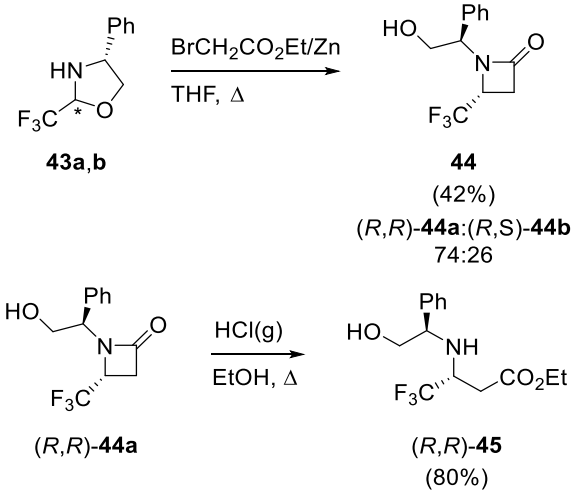
2.7. Synthesis of 4-CF_3-azetidin-2-ones *via* the Reformatsky reaction

The Reformatsky reaction of imine **39** with *α*-bromocarboxylic esters **40** in the presence of activated zinc dust in anhydrous toluene has been reported to furnish β-lactams **41** as the main products, accompanied by β-amino esters **42** (Scheme 13).[44] However, information concerning the relative configuration of these products was not mentioned.



Scheme 13

This method has been further extended toward the use of chiral 1,3-oxazolidines. The reaction of 2-trifluoromethyl-1,3-oxazolidines **43a**,**b** and ethyl bromoacetate in the presence of zinc dust at reflux temperature in THF afforded 4-(trifluoromethyl)azetidin-2-ones **44a**,**b** in 42% yield as a 74:26 mixture of diastereoisomers (Scheme 14). This mixture was then purified by flash chromatography, giving pure **44a**. 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 **44a** was easily converted into β-amino ester **45** by acidic ethanolysis in 80% yield.[45]



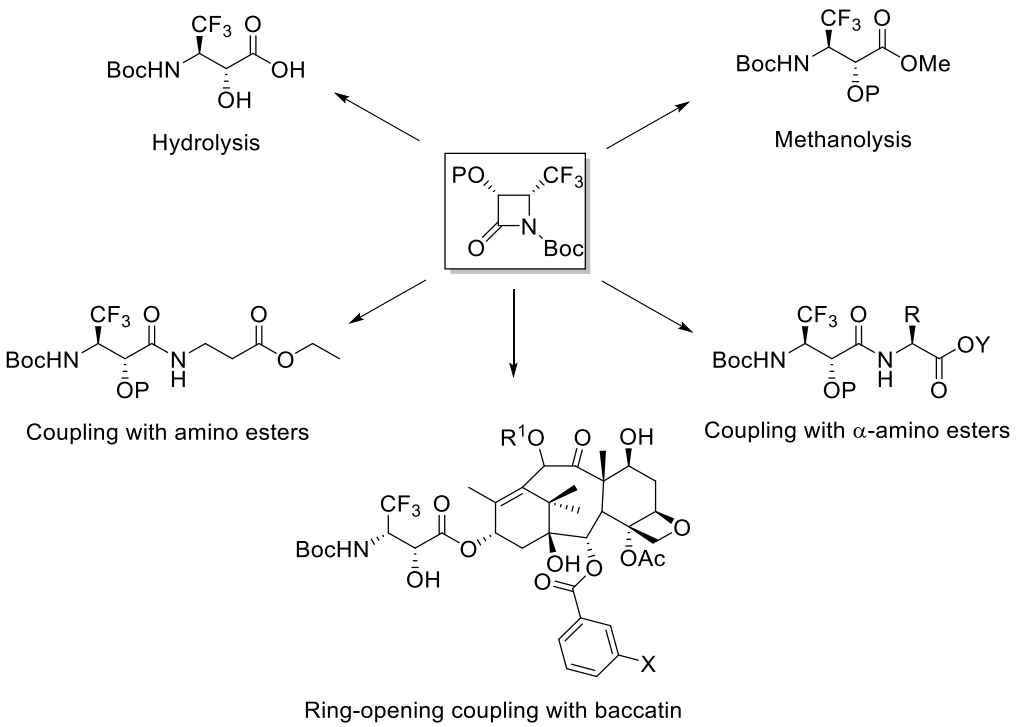
Scheme 14

3. 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)[16b] 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.

3.1. Ring-opening reactions of 4-CF_3-azetidin-2-ones

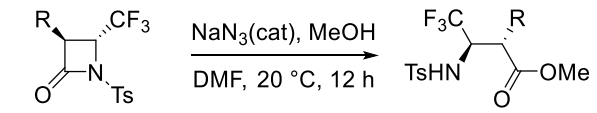
Because of the high ring strain of four-membered cyclic amides, 4-(trifluoromethyl)azetidin-2-ones can be deployed as excellent building blocks for the preparation of fluorinated amino acids, dipetides and taxoids through ring-opening reactions utilizing various nucleophiles (Scheme 15).[16b]



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

Scheme 15

For example, the ring-opening methanolysis of 4-(trifluoromethyl)azetidin-2-ones **46**, catalyzed by sodium azide, has been performed in DMF at room temperature to generate the corresponding CF_3-containing β-amino esters **47** in good to almost quantitative yields as single diastereomers (Scheme 16).[16] 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.[32,16b,14a]



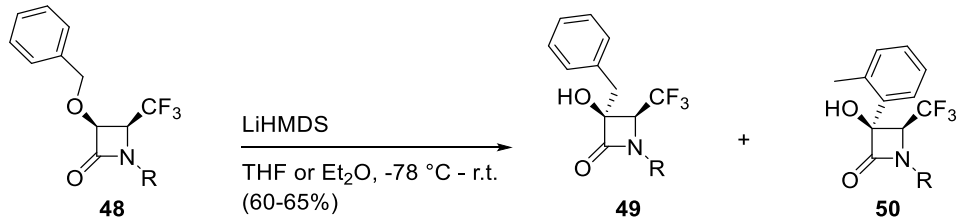
46 **47**

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

Scheme 16

3.2. 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 **48**, 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 **49** and 3-(2-methylphenyl)-3-hydroxy-β-lactams **50**, respectively (Scheme 17), which are potential precursors of new trifluoromethyl-substituted isoserines. Besides, α-methyl-β-lactams were generated in excellent yields *via* quenching of the enolates of **48** with methyl iodide.[46]



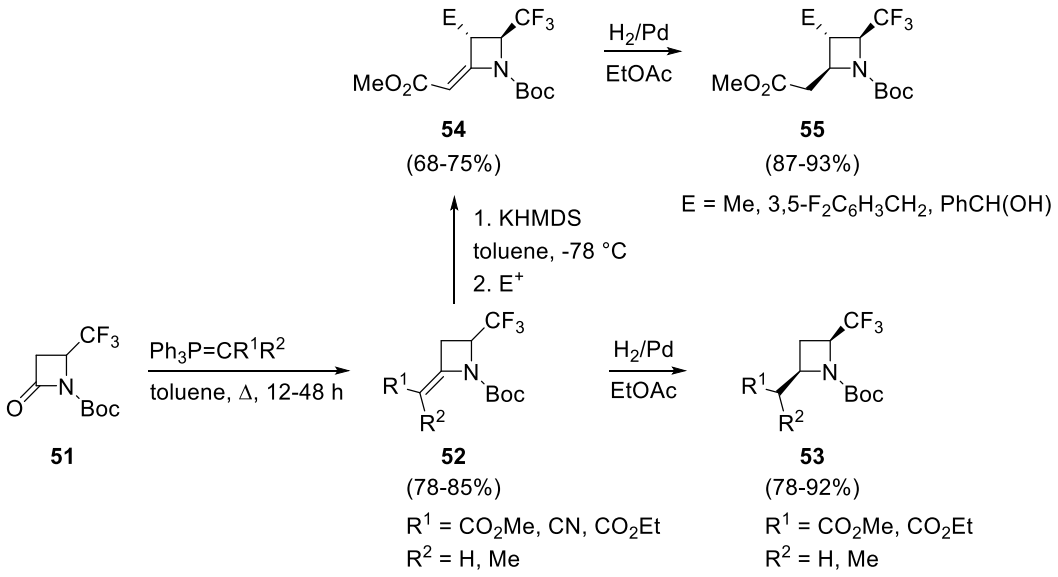
48 **49** **50**

	[1,2]		[2,3]
R = PMP	100	:	0
R = (*S*)-*sec*-phenethyl	40	:	60

Scheme 17

Furthermore, 4-CF_3-β-lactams constitute convenient substrates for a Wittig reaction. For example, treatment of β-lactam **51** with stabilized ylides in toluene under reflux afforded adducts **52** in high yield (Scheme 18). Then, catalytic hydrogenation of **52** provided 4-trifluoromethylated 2-alkylazetidines **53** in 78-92% yield, in which the diastereoselectivity depended on the catalyst and solvent used. Moreover, treatment of one derivative of **52** with potassium bis(trimethylsilyl)amide at -78 °C, followed by reaction with an alkyl halide or an aldehyde furnished 3-alkyl-substituted

derivatives **54** in 68-75% yield. Hydrogenation of compounds **54** with Pd/C in ethyl acetate gave *trans*-2,3-dialkylazetidines **55** in high yield as single isomers.[47]



Scheme 18

4. 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 and alkylation reactions. 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.

RESULTS AND DISCUSSION

This chapter is based on the following SCI-papers:

PART I

Dao Thi, H., Decuyper, L., Mollet, K., Kenis, S., De Kimpe, N., Van Nguyen, T., D'hooghe, M. "Synthesis of trifluoromethylated azetidines, aminopropanes, 1,3-oxazinanes, and 1,3-oxazinan-2-ones starting from 4-trifluoromethyl-β-lactam building blocks". *Synlett* **2016**, *27*, 1100-1105. (I.F. 2.42).

PART II

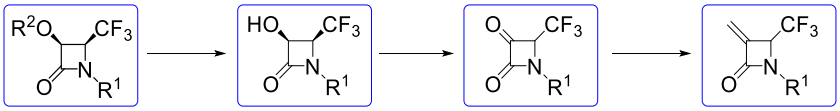
Dao Thi, H., Le Nhat Thuy, G., Catak, S., Van Speybroeck, V., Van Nguyen, T., D'hooghe, M. "Use of 3-hydroxy-4-(trifluoromethyl)azetidin-2-ones as building blocks for the preparation of trifluoromethyl-containing aminopropanes, 1,3-oxazinan(2-on)es, aziridines and 1,4-dioxan-2-ones". *Synthesis* **2018**, *50*, 1439-1456. (I.F. 2.65).

PART III

Dao Thi, H., Goossens, H., Hertsen, D., Otte, V., Van Nguyen, T., Van Speybroeck, V., D'hooghe, M. "Formation of fluorinated amido esters through unexpected C3-C4 bond fission in 4-trifluoromethyl-3-oxo-β-lactams". *Chem. Asian J.* **2018**, *13*, 421-431. (I.F. 4.08).

PART IV

Dao Thi, H., Danneels, B., Desmet, T., Van Hecke, K., Van Nguyen, T., D'hooghe, M. "Synthesis and applications of 3-methylene-4-(trifluoromethyl)azetidin-2-ones as building blocks for the preparation of mono- and spirocyclic 4-CF_3-β-lactams". *Asian J. Org. Chem.* **2016**, *5*, 1480-1491. (I.F. 2.79).



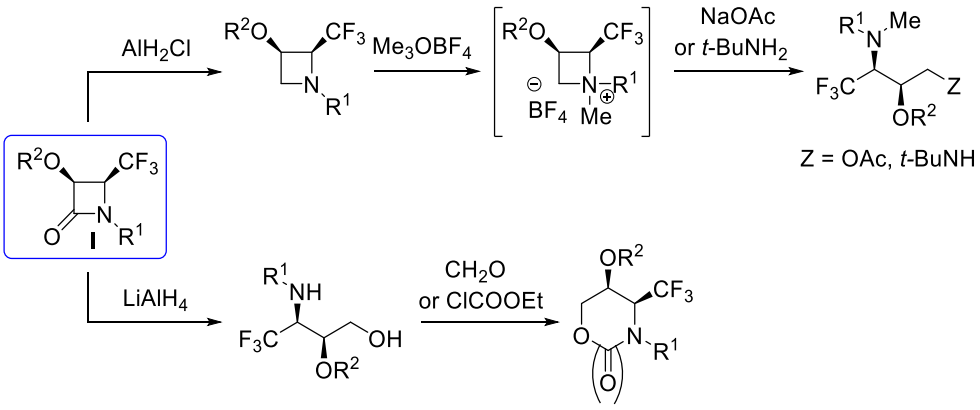
PART I

Synthesis of novel trifluoromethylated azetidines, aminopropanes, 1,3-oxazinanes and 1,3-oxazinan-2-ones starting from 4-trifluoromethyl-β-lactam building blocks

Abstract

This study reports on the preparation of 4-(trifluoromethyl)azetidin-2-ones and their synthetic potential as eligible new building blocks for the construction of CF_3-containing azetidines, diaminopropanes, aminopropanol derivatives, 1,3-oxazinanes and 1,3-oxazinan-2-ones. This β-lactam building block approach provides a convenient new entry into trifluoromethylated scaffolds as useful synthetic intermediates *en route* to a variety of CF_3-functionalized target structures.

Graphical abstract



Reference

Dao Thi, H., Decuyper, L., Mollet, K., Kenis, S., De Kimpe, N., Van Nguyen, T., D'hooghe, M. "Synthesis of trifluoromethylated azetidines, aminopropanes, 1,3-oxazinanes and 1,3-oxazinan-2-ones starting from 4-trifluoromethyl-β-lactam building blocks". *Synlett* **2016**, *27*, 1100-1105 (I.F. 2.42).

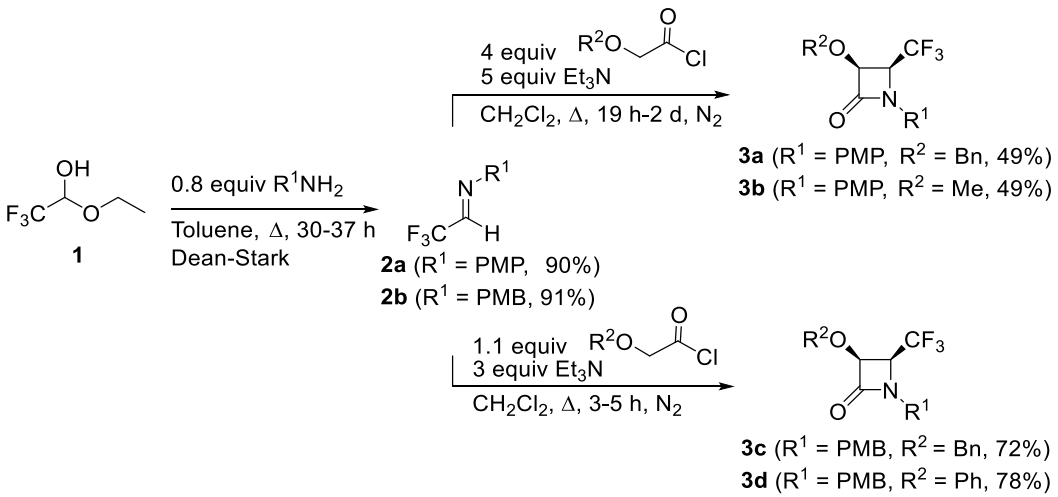
1. Introduction

Due to their inherent chemical and biological properties, β-lactams or azetidin-2-ones represent an important class of four-membered azaheterocycles. In addition to their celebrated antibacterial activities, β-lactams are for example known to inhibit HIV-1 protease[48] and to exhibit antitumor or antimalarial effects,[49] enabling their use in different therapeutic areas. Besides their pharmacological relevance, β-lactams are also considered as important building blocks in organic chemistry for the synthesis of a wide variety of acyclic and heterocyclic compounds, which in their turn can serve as synthons for the development of novel, biologically relevant target structures.[50] Because of the specific chemical and physical properties of fluorine, the introduction of a CF_3-moiety in pharmacologically active compounds is known to convey beneficial biological effects to the resulting molecules, hence the increasing interest from organic and medicinal chemists in polyfunctional CF_3-substituted scaffolds.[28a,18,51]

In this work, the synthesis of novel 3-alkoxy/aryloxy-4-(trifluoromethyl)azetidin-2-ones is aspired, and their synthetic elaboration into a variety of biologically relevant nitrogen compounds is evaluated to assess their versatility and applicability. A powerful method in organic synthesis involves the use of β-lactams for the preparation of functionalized azetidines by treatment with monochloroalane (AlH_2Cl), providing selective carbonyl removal without affecting the four-membered ring system. Although this approach has been widely applied on non-trifluoromethylated β-lactams,[52,17b] the selective reduction of 4-(trifluoromethyl)azetidin-2-ones to azetidines has not been reported in the literature to date. Therefore, the monochloroalane reduction of 4-CF_3-azetidin-2-ones as an entry into 2-(trifluoromethyl)azetidines will be evaluated in this study. Subsequently, activation of these novel CF_3-azetidines and regiospecific ring opening of the resulting azetidinium ions with different nucleophiles will be pursued *en route* to a diversity of functionalized trifluoromethyl-substituted aminopropanes as potential leads for the synthesis of biologically relevant compounds. In addition, the synthetic potential of 4-CF_3-β-lactams will be further investigated by converting them into amino alcohols upon a $LiAlH_4$-mediated reductive ring opening, analogous to the known reactivity of their non-fluorinated counterparts.[53] Furthermore, cyclization of the thus obtained CF_3-substituted γ-amino alcohols with formation of synthetically and biologically relevant 1,3-oxazinane and 1,3-oxazinan-2-one azaheterocycles is proposed.

2. Synthesis of *cis*-3-alkoxy/aryloxy-4-trifluoromethyl-β-lactam building blocks

In a first step of this study, the reaction of commercially available 1-ethoxy-2,2,2-trifluoroethanol **1** with 4-methoxyaniline or 4-methoxybenzylamine in toluene under Dean-Stark conditions gave rise to the desired trifluoroaldimines **2** in excellent yields.[54a,16a,54b] Subsequently, these imines were treated with 4 or 1.1 equiv of an (alkyl/aryl)oxyacetyl chloride in the presence of triethylamine, respectively, affording the corresponding *cis*-3-alkoxy/aryloxy-4-(trifluoromethyl)azetidin-2-ones **3** in 49-78% yield (Scheme 1).[54a,16a,54b,55a,30b,55b] Only for 3-methoxy-1-(4-methoxyphenyl)-β-lactam **3b**, a minor amount of the corresponding *trans* isomer was observed as well (*cis*/*trans*: 10/3). The *cis*-selectivity was determined based on the ^{1}H NMR spectra of β-lactams **3**, as the observed coupling constants between the two vicinal protons at C3 and C4 (J = 5-6 Hz, $CDCl_3$) corresponded well with those reported in the literature for *cis*-β-lactams.[16a,30b,55b] In this way, novel *cis*-CF_3-β-lactams **3a-d** were prepared *via* a diastereoselective cyclocondensation reaction between an imine **2**, prepared from 1-ethoxy-2,2,2-trifluoroethanol **1**, and an *in situ* generated ketene.



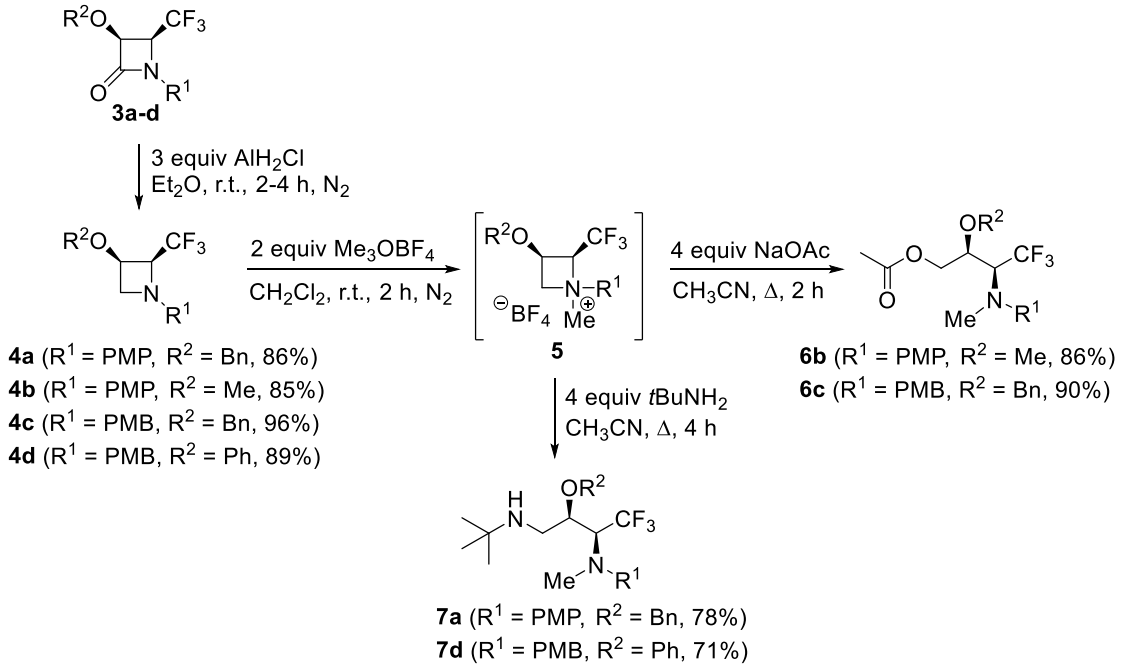
Scheme 1

3. Ring opening of *cis*-3-alkoxy/aryloxy-4-trifluoromethyl-β-lactams toward trifluoromethylated aminopropanes *via* azetidine intermediates

In the this part, the reduction of the synthesized 4-CF_3-azetidin-2-ones **3** by means of monochloroalane was evaluated to provide an entry into 2-(trifluoromethyl)azetidines **4**. Treatment of β-lactams **3** with three equiv of monochloroalane, *in situ* prepared from $LiAlH_4$ and $AlCl_3$, in

diethyl ether at room temperature for two to four hours furnished the desired azetidines **4** in excellent yields (85-96%, Scheme 2).[52,17b] It should be noted that little information on 2-CF_3-azetidines is available in the literature.[56a,47,56b,56c] The application of these novel *cis*-3-alkoxy/aryloxy-2-(trifluoromethyl)azetidines **4** as building blocks for the synthesis of a diversity of functionalized trifluoromethyl-substituted aminopropanes was evaluated next.[54b,52,17b] In that respect, alkylation of 2-(trifluoromethyl)azetidines **4** towards the corresponding azetidinium ions **5** utilizing two equiv of trimethyloxonium tetrafluoroborate (Me_3OBF_4) and subsequent ring opening by treatment with four equiv of sodium acetate or *tert*-butylamine, afforded the desired *syn*-2-alkoxy/aryloxy-3-amino-4,4,4-trifluorobutyl acetates **6b**,**c** and *syn*-2-alkoxy/aryloxy-4,4,4-trifluorobutan-1,3-diamines **7a**,**d**, respectively, in good to excellent yields (Scheme 2). It should be noted that, in line with our previous findings, ring opening of 2-CF_3-azetidinium salts **5** proceeded regiospecifically at C4, in contrast with the reactivity of azetidinium salts bearing other types of electron-withdrawing groups (e.g., acyl or cyano) at C2.[18]

In light of the known biological properties of compounds bearing a functionalized aminopropane skeleton,[57a-57d,53a,57e,53c-53e,57f] acetates **6b**,**c** and diamines **7a**,**d** might constitute valuable new chemical entities for further elaboration. For example, the class of diaminopropanols is known for its protease-inhibiting, antiarrhythmic and anesthetic activity.[57b,57c,57f] Moreover, due to the specific properties of fluorine, trifluoromethyl-containing functionalized aminopropanol derivatives could play an important role in the development of analogues of these bioactive compounds.[54b,58]



Scheme 2

4. Synthesis and transformation of *syn*-2-alkoxy/aryloxy-4,4,4-trifluorobutanols toward 1,3-oxazinanes, 1,3-oxazinan-2-ones and oxazepane analogs

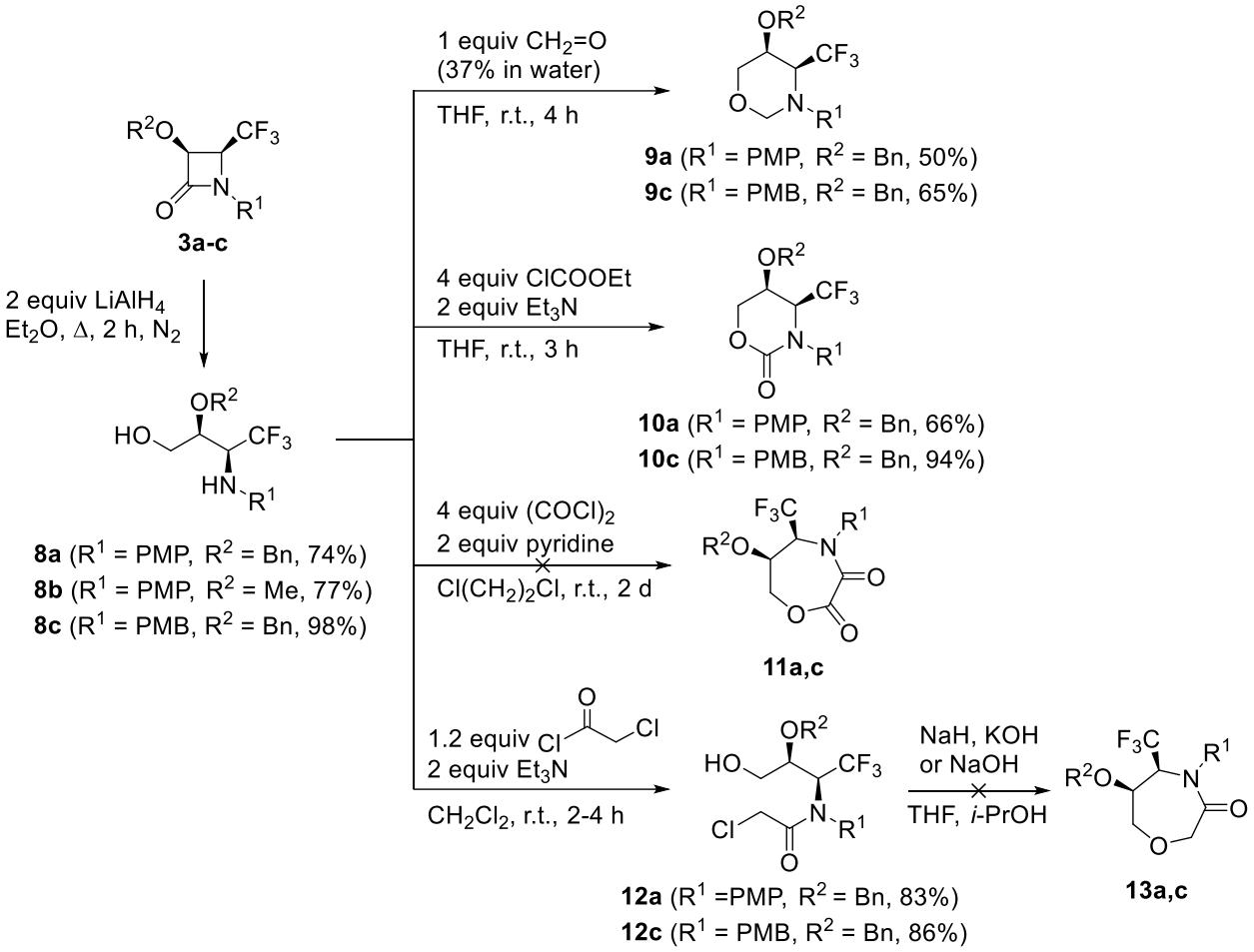
On the other hand, *cis*-azetidin-2-ones **3** were subjected to a reductive ring opening by means of lithium aluminium hydride, in analogy with the known chemical behavior of their non-fluorinated counterparts.[53a,53c-53e] As illustrated in Scheme 3, treatment of β-lactams **3a**-**c** with lithium aluminium hydride afforded the corresponding *syn*-2-alkoxy/aryloxy-4,4,4-trifluorobutanols **8a**-**c** in good yields.[52c] This *syn* relationship in amino alcohols **8** is a direct consequence of the selective Staudinger synthesis of stereodefined *cis*-β-lactams **3**, followed by transfer of the stereochemical information through the following $LiAlH_4$-mediated reduction step.

These γ-amino alcohols **8** bear significant biological potential because of their structural similarity to several classes of bioactive compounds. For example, the 1-alkylamino-3-aryloxypropan-2-ol family, including propranolol and timolol, provides β-adrenergic blocking agents (β-blockers) for the treatment of various vascular disorders.[57a,57d,57e] Moreover, 2-alkoxy-3-amino-3-arylpropan-1-ols have recently been shown to exhibit a promising antimalarial activity.[53e] The introduction of a trifluoromethyl substituent in these scaffolds could induce interesting beneficial changes in their biological properties.[59,4b] Therefore, CF_3-substituted γ-amino alcohols **8**, which have not been

described in the literature so far, are expected to serve as valuable templates for further development in the field of medicinal chemistry and chemical biology.

With the intention to introduce conformational constraint into the target compounds, *syn*-2-alkoxy/aryloxy-4,4,4-trifluorobutanols **8a**,**c** were subsequently converted into new trifluoromethylated oxazinanes **9** and oxazinan-2-ones **10**. Several literature reports describe the synthesis of non-fluorinated oxazinanes starting from amino alcohols, either as biologically relevant targets or as synthons for further elaboration.[57a,57d] 3-Aminopropan-1-ols **8a**,**c** were thus treated with formaldehyde (37% in water), resulting in new *cis*-5-benzyloxy-4-trifluoromethyl-1,3-oxazinanes **9a**,**c**. 3-Aminopropan-1-ols **8a**,**c** were also shown to be efficient precursors for the synthesis of a new class of CF_3-substituted oxazinan-2-ones **10**, of which non-fluorinated counterparts have been explored as inhibitors in the treatment of obesity and insulin resistance,[60] and fluorinated analogues have been applied in breast tumor imaging.[54a,16a,54b] For this purpose, 3-aminopropan-1-ols **8a**,**c** were treated with ethyl chloroformate and triethylamine, affording *cis*-5-benzyloxy-4-trifluoromethyl-1,3-oxazinan-2-ones **10a**,**c** in good yields (66-94%, Scheme 3). The 1,3-oxazinan-2-one motif has been encountered as a core structure in many natural products and pharmaceutical drugs, and these heterocycles have for example been explored as inhibitors of 11-β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) or as antibacterial agents.[60a,60c] Besides, compounds accommodating the 1,3-oxazinane system have also successfully been screened for their *in vitro* antiplasmodial activity and cytotoxicity.[57d]

In addition, the preparation of seven-membered oxazepane analogs **11a,c** as potential targets[60b,60c] was attempted by direct treatment of *syn*-2-benzyloxy-4,4,4-trifluorobutanols **8a**,**c** with oxalyl chloride in the presence of pyridine in 1,2-dichloroethane, in analogy with the synthesis of 1,3-oxazinane-2-ones **10**.[61] However, this cyclization reaction did not proceed as anticipated, resulting in complex mixtures. Other methods for constructing 1,4-oxazepanes were also tested, including the initial conversion of the amino group in butanols **8a,c** into the corresponding amides **12a**,**c** *via N*-acylation using 1.2 equiv of chloroacetyl chloride and two equiv of trimethylamine (Scheme 3), followed by treatment with different bases (KOH, NaOH or NaH) under different reaction conditions (solvent-time-temperature combinations) to effect cyclization toward 1,4-oxazepan-3-ones **13**. However, none of the conditions tested seemed appropriate to produce the desired seven-membered heterocycles.



Scheme 3

5. Conclusion

In conclusion, 4-trifluoromethyl-β-lactams were efficiently prepared and deployed as novel building blocks in the synthesis of CF_3-containing molecules with potential biological relevance. To that end, a suitable synthetic method was established for the conversion of these 4-CF_3-azetidin-2-ones into novel 3-alkoxy/aryloxy-2-(trifluoromethyl)azetidines by means of a selective monochloroalane reduction protocol. Furthermore, the synthetic potential of 2-CF_3-azetidines was demonstrated by their conversion into a variety of α-CF_3-substituted diaminopropanes and aminopropanol derivatives *via* transient azetidinium intermediates, which could serve as valuable precursors for the preparation of different target compounds. In addition, the conversion of 4-CF_3-β-lactams by means of reductive ring opening using lithium aluminium hydride furnished functionalized CF_3-containing γ-amino alcohols in a concise and efficient manner. Cyclization of

the latter γ-amino alcohols employing formaldehyde or ethyl chloroformate afforded a convenient entry into the corresponding new *cis*-5-benzyloxy-4-trifluoromethyl-1,3-oxazinanes and *cis*-5-benzyloxy-4-trifluoromethyl-1,3-oxazinan-2-ones, respectively.

6. Experimental details

General methods

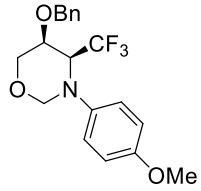
All reagents were purchased as commercially available sources without further purification. Diethyl ether, tetrahydrofuran and toluene were distilled from sodium benzophenone ketyl or sodium, while dichloromethane was distilled from calcium hydride prior to use. Solvents were removed under reduced pressure using a rotary evaporator. Silica gel (0.035 - 0.070 mm, pore diameter ca. 6 nm) was used for column chromatography. Solvent systems were determined *via* initial TLC analysis on glass-backed silica plates (Merck Kieselgel 60 with F254 indicator, precoated 0.25 mm). These plates were developed using standard visualization techniques or agents, UV fluorescence (254 and 366 nm) and/or coloring with a potassium permanganate solution. High resolution ^{1}H NMR (300 MHz, 400 MHz), ^{13}C NMR (75 MHz, 100.6 MHz) and ^{19}F NMR (282 MHz, 376 MHz) spectra were recorded with a Jeol Eclipse FT 300 or a Bruker Avance III Nanobay NMR spectrometer using deuterated solvents and tetramethylsilane (TMS) and trichlorofluoromethane ($CFCl_3$) as internal standards. Low resolution mass spectra were recorded *via* direct injection on an Agilent 1100 Series (ES, 4000 V) LC/MSD type SL mass spectrometer with Electron Spray Ionization Geometry (ESI 70 eV) and using a Mass Selective Detector (quadrupole). High resolution electron spray (ES) mass spectra were obtained with an Agilent Technologies 6210 Series Time-of-Flight. IR spectra were recorded on a Perkin-Elmer Spectrum BX FT-IR spectrometer (in neat form) with an ATR (Attenuated Total Reflectance) accessory. Melting points of crystalline compounds were measured using a Büchi B-540 apparatus or a Kofler bench, type WME Heizbank of Wagner & Munz.

The spectral data and procedures of compounds **1-8** have been reported in the literature.[62]

Synthesis of *cis*-5-benzyloxy-3-(4-methoxyaryl)-4-trifluoromethyl-1,3-oxazinanes 9

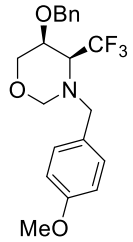
As a representative example, the synthesis of *cis*-5-benzyloxy-3-(4-methoxyphenyl)-4-trifluoromethyl-1,3-oxazinane **9a** is described. To a solution of *syn*-2-benzyloxy-4,4,4-trifluoro-3-(4-methoxyphenylamino)butan-1-ol **8a** (0.50 g, 1.41 mmol, 1 equiv) in THF (20 mL) was added formaldehyde (0.11 g, 1.41 mmol, 1 equiv, 37% solution in H_2O). The resulting mixture was stirred for four hours at room temperature, after which the solvent was removed *in vacuo*. Water (100 mL) was added to the mixture. Extraction with ethyl acetate (3 x 70 mL), drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded *cis*-5-benzyloxy-3-(4-methoxyphenyl)-4-trifluoromethyl-1,3-oxazinane **9a** in 50% yield, which was purified by means of recrystallization (Hex/EtOAc, 8/1) in order to obtain an analytically pure sample.

Cis-5-benzyloxy-3-(4-methoxyphenyl)-4-trifluoromethyl-1,3-oxazinane 9a



White crystals. Mp 58.5 °C. Recrystallization from Hex/EtOAc, 8/1. Yield 50%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.78 (3H, s, OCH_3), 3.85-3.92 (1H, m, CH(HCH)O), 3.96-4.03 (2H, m, CH(HCH)O and CHO), 4.08-4.17 (1H, m, $CHCF_3$), 4.48 and 4.65 (2 × 1H, 2 × d, J = 11.6 Hz, O(HCH)Ph), 4.80 and 4.85 (2 × 1H, 2 × d, J = 11.7 Hz, O(HCH)N), 6.82 and 7.09 (2 × 2H, 2 × d, J = 9.0 Hz, $N(CH_{arom})_{ortho}$ and $O(CH_{arom})_{ortho}$), 7.28-7.35 (5H, m, CH_{arom}). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 55.6 (OCH_3), 62.1 (q, J = 27.6 Hz, $CHCF_3$), 65.8 ($CHCH_2O$), 68.1 (CHO), 71.9 (OCH_2Ph), 77.6 (OCH_2N), 114.5 (2 × $O(HC_{arom})_{ortho}$), 121.7 (2 × $N(CH_{arom})_{ortho}$), 125.8 (q, J = 285.0 Hz, CF_3), 127.6, 128.0, 128.5 (5 x HC_{arom}), 137.3 ($C_{arom,quat}CH_2O$), 144.0 ($C_{arom,quat}N$), 155.5 ($C_{arom,quat}O$). ^{19}F NMR (376 MHz, $CDCl_3$): δ -64.87 (3F, d, J = 9.2 Hz, CF_3). IR (ATR, cm^{-1}): ν_{max} = 1510, 1360, 1252, 1240, 1171, 1154, 1094, 1029, 983, 909, 810, 737, 696. MS: *m/z* (%) 368 (M^+ + 1, 100). HRMS (ESI): calc. for $C_{19}H_{21}F_3NO_3^+$: 368.1468 $[M + H]^+$. Found: 368.1480.

Cis-5-benzyloxy-3-(4-methoxybenzyl)-4-trifluoromethyl-1,3-oxazinane 9c



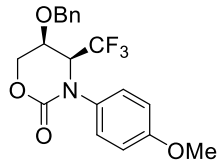
White crystals. Mp 40 °C. Recrystallization from Hexane. Yield 65%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.54 (1H, q × d, J = 9.3, 5.4 Hz, $CHCF_3$), 3.81 (3H, s, OCH_3), 3.84-3.97 (3H, m, $OCHCH_2O$), 3.97 and 4.03 (2 × 1H, 2 × d, J = 13.4 Hz, N(HCH)Ar), 4.23 (1H, d, J = 11.1 Hz, O(HCH)N), 4.52 (1H, d, J = 11.9 Hz, O(HCH)Ph), 4.55 (1H, d, J = 11.1 Hz, O(HCH)N), 4.61 (1H, d, J = 11.9 Hz, O(HCH)Ph), 6.86 and 7.22 (2 × 2H, 2 × d, J = 9.1 Hz, $NCH_2(CH_{arom})_{ortho}$ and $O(CH_{arom})_{ortho}$), 7.30-7.37 (5H, m, CH_{arom}). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 55.3 (OCH_3), 56.8 (NCH_2Ar), 58.0 (q, J = 27.3 Hz, $CHCF_3$), 66.6 (OCH_2CHO),

67.0 (OCH_2CHO), 71.6 (OCH_2Ph), 79.7 (OCH_2N), 113.9 (2 × $O(CH_{arom})_{ortho}$), 125.6 (q, J = 284.1 Hz, $CHCF_3$), 127.7, 128.0, 128.5 (5 × HC_{arom}), 129.8 ($OCH_2C_{arom,quat}$), 130.0 (2 × HC_{arom}), 137.4 $NCH_2C_{arom,quat}$), 159.1 ($OC_{arom,quat}$). ^{19}F NMR (376 MHz, $CDCl_3$): δ -64.60 (3F, d, J = 9.3 Hz, CF_3). IR (ATR, cm^{-1}): ν_{max} = 1610, 1509, 1247, 1150, 1103, 1032, 932, 731. MS (70 eV): *m/z* (%): 382 (M^+ + 1, 100). HRMS (ESI): calc. for $C_{20}H_{23}F_3NO_3^+$: 382.1525 $[M + H]^+$. Found: 382.1624.

Synthesis of *cis*-5-benzyloxy-3-(4-methoxyaryl)-4-trifluoromethyl-1,3-oxazinan-2-ones 10

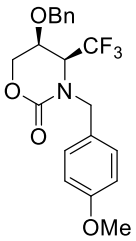
As a representative example, the synthesis of *cis*-5-benzyloxy-3-(4-methoxyphenyl)-4-trifluoromethyl-1,3-oxazinan-2-one **10a** is described. To a solution of *syn*-2-benzyloxy-4,4,4-trifluoro-3-(4-methoxyphenylamino)butan-1-ol **8a** (0.10 g, 0.28 mmol, 1 equiv.) in dry THF (20 mL) was added triethylamine (0.06 g, 0.56 mmol, 2 equiv) at 0 °C. Ethyl chloroformate (0.12 g, 1.13 mmol, 4 equiv) was added dropwise to the solution. The mixture was stirred at room temperature for four hours, the solvent was removed *in vacuo*, and the residue was redissolved in ethyl acetate (20 mL) and washed with water (2 x 20 mL). The aqueous phase was extracted with ethyl acetate (2 x 20 mL). Drying ($MgSO_4$), filtration of the drying agent, and removal of the solvent *in vacuo* afforded *cis*-5-benzyloxy-3-(4-methoxyphenyl)-4-trifluoromethyl-1,3-oxazinan-2-one **10a** in 66% yield, which was further purified by means of recrystallization from ethanol to obtain a pure sample.

***Cis*-5-benzyloxy-3-(4-methoxyphenyl)-4-trifluoromethyl-1,3-oxazinan-2-one 10a**



White crystals. Mp 141 °C. Recrystallization from EtOH. Yield 66%. ^1H NMR (400 MHz, $CDCl_3$): δ 3.81 (3H, s, OCH_3), 4.32-4.43 (3H, m, $CHCF_3$, $CHO(HCH)O$), 4.47-4.52 (1H, m, $CHO(HCH)O$), 4.67 and 4.75 (2 × 1H, 2 × d, J = 11.6 Hz, $O(HCH)Ph$), 6.90 and 7.14 (2 × 2H, 2 × d, J = 8.9 Hz, $N(CH_{arom})_{ortho}$ and $O(CH_{arom})_{ortho}$), 7.35-7.43 (5H, m, CH_{arom}). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 55.5 (OCH_3), 60.9 (q, J = 28.0 Hz, $CHCF_3$), 65.8 ($CHOCH_2O$), 68.0 ($CHOCH_2O$), 72.5 (OCH_2Ph), 114.6 (2 × $O(CH_{arom})_{ortho}$), 124.0 (q, J = 285.8 Hz, CF_3), 128.0, 128.5, 128.7, 128.8 (7 × HC_{arom}), 134.3, 136.1 1 ($CH_2C_{arom,quat}$ and $NC_{arom,quat}$), 151.3 ($OC_{arom,quat}$), 159.0 (C=O). ^{19}F NMR (376 MHz, $CDCl_3$): δ -66.96 (3F, d, J = 7.7 Hz, CF_3). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1700, ν_{max} = 1514, 1415, 1261, 1238, 1136, 1167, 1036, 827, 747. MS: *m/z* (%) 382 (M^+ + 1, 100). HRMS (ESI): calc. for $C_{19}H_{19}F_3NO_4^+$: 382.1261 $[M + H]^+$. Found: 382.1261.

Cis-5-benzyloxy-3-(4-methoxybenzyl)-4-trifluoromethyl-1,3-oxazinan-2-one 10c

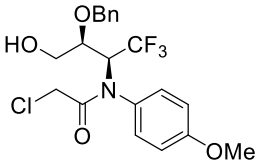


Brownish oil. R_f = 0.10 (Hex/EtOAc, 6/1). Yield 94%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.71-3.82 (2H, m, $CHCF_3$ and CHO), 3.85 (3H, s, OCH_3), 3.89 (1H, d, J = 14.9 Hz, (HCH)N), 4.20-4.25 and 4.31-4.37 (2 × 1H, 2 × m, (HCH)OC=O), 4.36 and 4.54 (2 × 1H, 2 × d, J = 11.9 Hz, O(HCH)Ph), 5.39 (1H, d, J = 14.9 Hz, (HCH)N), 6.89 (2H, d, J = 8.6 Hz, $O(CH_{arom})_{ortho}$), 7.09-7.12 (2H, m, CH_{arom}), 7.14 (2H, d, J = 8.6 Hz, $NCH_2(CH_{arom})_{ortho}$), 7.28-7.30 (3H, m, CH_{arom}). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 51.9 ($ArCH_2N$), 53.4 (q, J = 28.3 Hz, $CHCF_3$), 55.3 (OCH_3), 65.7 (CH_2OC=O), 67.2 (CHO), 72.2 (OCH_2Ph), 114.5 (2 × $O(HC_{arom})_{ortho}$), 124.8 (q, J = 286.2 Hz, CF_3), 127.0 ($NCH_2C_{arom,quat}$), 128.0, 128.6, 128.7, 129.9 (7 × HC_{arom}), 135.8 ($OCH_2C_{arom,quat}$), 151.8 ($OC_{arom,quat}$), 159.7 (C=O). ^{19}F NMR (376 MHz, $CDCl_3$): δ -67.23 (3F, d, J = 7.3 Hz, CF_3). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1704, ν_{max} = 1513, 1454, 1247, 1207, 1164, 1095, 1030, 817, 747, 699. MS (70 eV): *m/z* (%) 396 (M^+ + 1, 100). HRMS (ESI): calc. for $C_{20}H_{21}F_3NO_4^+$: 396.1417 $[M + H]^+$. Found: 396.1412.

Synthesis of s*yn-N*-(3-benzyloxy-1,1,1-trifluoro-4-hydroxybut-2-yl)-2-chloro-*N*-(4-methoxyaryl)acetamides 12

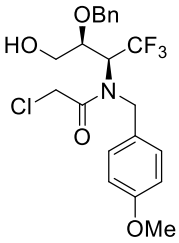
As a representative example, the synthesis of s*yn-N*-(3-benzyloxy-1,1,1-trifluoro-4-hydroxybut-2-yl)-2-chloro-*N*-(4-methoxyphenyl)acetamide **12a** is described. To a solution of *syn*-2-benzyloxy-4,4,4-trifluoro-3-(4-methoxyphenylamino)butan-1-ol **8a** (80 mg, 0.23 mmol, 1 equiv) in dry CH_2Cl_2 (20 mL) was added triethylamine (0.06 mL, 0.46 mmol, 2 equiv) at 0 °C. Chloroacetyl chloride (0,02 mL, 0.26 mmol, 1.2 equiv) was added dropwise to the solution. The mixture was stirred at room temperature for four hours, after which water (20 mL) was added, followed by extraction with CH_2Cl_2 (3 x 10 mL) and washing of the combined organic phases with brine (2 x 10 mL). Drying ($MgSO_4$), filtration of drying agent, and removal of the solvent *in vacuo* afforded s*yn-N*-(3-benzyloxy-1,1,1-trifluoro-4-hydroxybut-2-yl)-2-chloro-*N*-(4-methoxyphenyl)acetamide **12a** in 86% yield, which was further purified by means of column chromatography (Hex/EtOAc, 8/1) in order to obtain an analytically pure sample.

Syn-N-(3-benzyloxy-1,1,1-trifluoro-4-hydroxybut-2-yl)-2-chloro-*N*-(4-methoxyphenyl)acetamide 12a



Yellow oil. R_f = 0.23 (Hex/EtOAc, 8/1). Yield 86%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.74 (3H, s, OCH_3), 3.89-3.97 (3H, m, CH_2Cl and $CHCF_3$), 4.10-4.16 (3H, m, (HC<u>H</u>)O<u>H</u> and CHO), 4.36 (1H, d × d × d, J = 9.3, 9.3, 6.5 Hz, (HC<u>H</u>)OH), 4.66 and 4.70 (2 × 1H, 2 × d, J = 11.1 Hz, O(<u>H</u>C<u>H</u>)Ph), 6.64 and 6.77 (2 × 2H, 2 × d, J = 8.9 Hz, $N(CH_{arom})_{ortho}$ and $O(CH_{arom})_{ortho}$), 7.34-7.39 (5H, m, CH_{arom}). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 40.4 (CH_2Cl), 55.7 (OCH_3), 56.9 (q, J = 28.8 Hz, <u>C</u>HCF_3), 64.0 (CH_2OH), 73.6 (CHO), 73.8 (O<u>C</u>H_2Ph), 115.0, 115.1 (4 × $HC_{arom,ortho}$), 125.5 (q, J = 284.9 Hz, CF_3), 128.3, 128.4, 128.6 (5 × HC_{arom}), 136.9 (CH_2<u>C</u>$_{arom,quat}$), 140.1 ($NC_{arom,quat}$), 153.1 ($OC_{arom,quat}$), 166.7 (C=O). ^{19}F NMR (376 MHz, $CDCl_3$): δ -72.93 (3F, d, J = 7.8 Hz, CF_3). IR (ATR, cm^{-1}): ν_{OH} = 3396, ν_{CO} = 1759, ν_{max} = 1514, 1234, 1168, 1130, 1026, 820, 698. MS (70 eV): *m/z* (%) 432 (M^+ + 1, 100). HRMS (ESI): calc. for $C_{20}H_{21}ClF_3NO_4^+$: 432.1111 $[M + H]^+$. Found: 432.1202.

Syn-N-(3-benzyloxy-1,1,1-trifluoro-4-hydroxybut-2-yl)-2-chloro-*N*-(4-methoxybenzyl)acetamide 12c



Yellow oil. R_f = 0.26 (Hex/EtOAc, 8/1). Yield 83%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.11 (1H, s (broad), OH), 3.12 (1H, q × d, J = 7.5, 1.7 Hz, $CHCF_3$), 3.81 (1H, d, J = 12.8 Hz, (<u>H</u>CH)N), 3.82 (3H, s, OCH_3), 3.86 and 3.92 (2 × 1H, 2 × d, J = 15.0 Hz, (<u>H</u>C<u>H</u>)Cl), 3.98 (1H, t × d, J = 6.4, 1.7 Hz, CHO), 4.03 (1H, d, J = 12.8 Hz, (HC<u>H</u>)N), 4.28 and 4.31 (2 × 1H, 2 × (d × d), J = 10.9, 10.9, 6.4 Hz, (<u>H</u>C<u>H</u>)OH), 4.62 (2H, s, O<u>C</u>H_2Ph), 6.88 and 7.25 (2 × 2H, 2 × d, J = 8.6 Hz, NCH_2(C<u>H</u>$_{arom})_{ortho}$ and $O(CH_{arom})_{ortho}$), 7.32-7.39 (5H, m, CH_{arom}). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 40.5 (CH_2Cl), 50.7 (N<u>C</u>H_2Ar), 55.3 (OCH_3), 57.2 (q, J = 26.2 Hz, <u>C</u>HCF_3), 64.5 (CH_2OH), 73.6 (O<u>C</u>H_2Ph), 74.3 (q, J = 2.5 Hz, CHO), 113.8 (2 × $O(HC_{arom})_{ortho}$), 126.5 (q, J = 287.7 Hz, CF_3), 128.08, 128.10, 128.5, 129.9 (7 x HC_{arom}), 131.2 ($C_{arom,quat}$N), 137.3 (<u>C</u>$_{arom,quat}CH_2O$), 158.9 ($C_{arom,quat}$O), 166.7 (C=O). ^{19}F NMR (376 MHz, $CDCl_3$): δ -69.91 (3F, d, J = 7.5 Hz, CF_3). IR (ATR, cm^{-1}): ν_{OH} = 3371, ν_{CO} = 1762, ν_{max} = 1512, 1246, 1130, 1027, 830, 736, 697. MS (70 eV): *m/z* (%) 446 (M^+ + 1, 100). HRMS (ESI): calc. for $C_{21}H_{23}ClF_3NO_4^+$: 446.1268 $[M + H]^+$. Found: 446.1355.

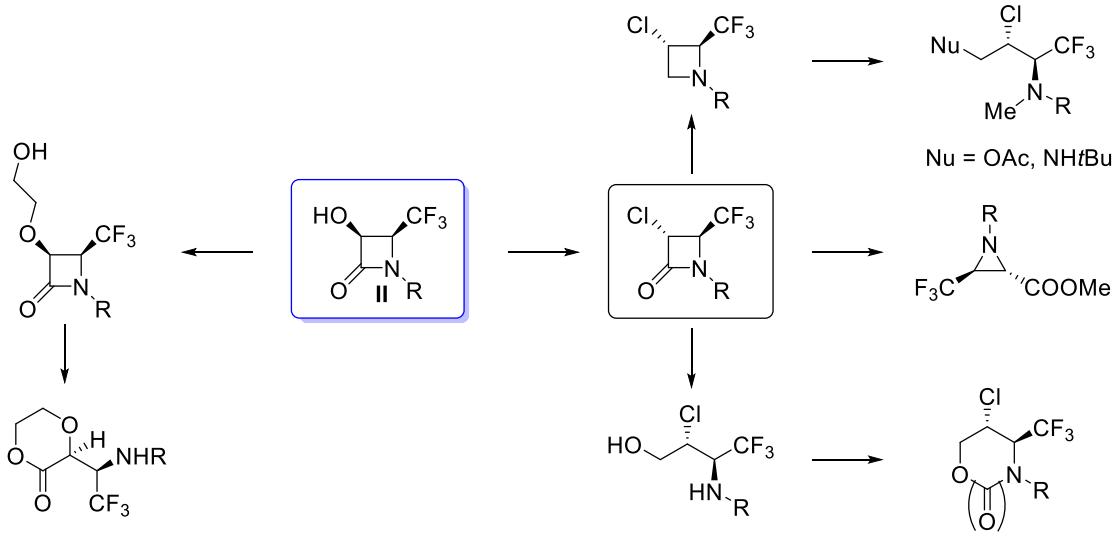
PART II

Use of 3-hydroxy-4-(trifluoromethyl)azetidin-2-ones as versatile building blocks for the preparation of trifluoromethyl-containing aminopropanes, 1,3-oxazinan(-2-on)es, aziridines and 1,4-dioxan-2-ones

Abstract

3-Hydroxy-4-(trifluoromethyl)azetidin-2-ones were synthesized from the corresponding 3-benzyloxy-β-lactams and successfully transformed into new 3-chloro-4-(trifluoromethyl)azetidin-2-one building blocks. The latter chlorides were shown to be eligible precursors for the construction of CF_3-containing aminopropanes, 1,3-oxazinanes, 1,3-oxazinan-2-ones and aziridines. In addition, 3-hydroxy-4-(trifluoromethyl)azetidin-2-ones proved to be interesting substrates for the synthesis of novel 3-[2,2,2-trifluoro-1-(arylamino)ethyl]-1,4-dioxan-2-ones *via* intramolecular cyclization of 3-(2-hydroxyethoxy)-β-lactam intermediates.

Graphical abstract



Reference

Dao Thi, H., Le Nhat Thuy, G., Catak, S.; Van Speybroeck, V., Van Nguyen, T., D'hooghe, M. "Use of 3-hydroxy-4-(trifluoromethyl)azetidin-2-ones as building blocks for the preparation of trifluoromethyl-containing aminopropanes, 1,3-oxazinan(-2-on)es, aziridines and 1,4-dioxan-2-ones". *Synthesis* **2018**, *50*, 1439-1456. (I.F. 2.65).

1. Introduction

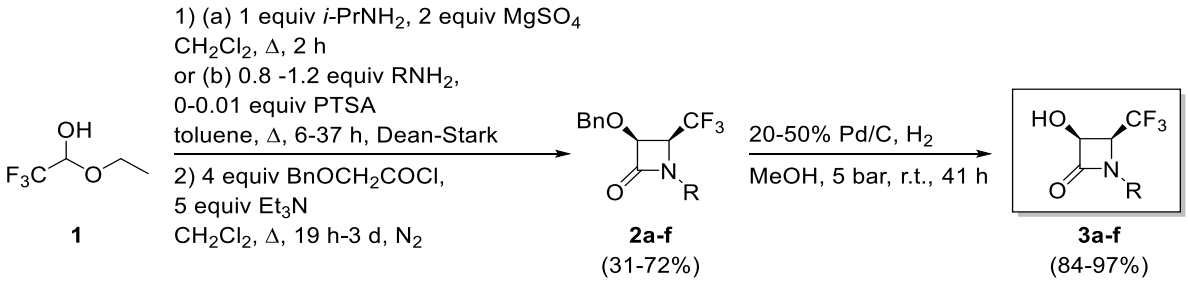
In light of the favorable effects of fluorine introduction, β-lactams bearing a trifluoromethyl group comprise interesting entities for the construction of novel targets with promising bioactivities. The most important synthetic routes toward 4-(trifluoromethyl)azetidin-2-ones using the building block strategy 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.[12] However, the reactivity study of 4-(trifluoromethyl)azetidin-2-ones toward both ring opening and ring transformation for the preparation of trifluoromethylated amines and heterocyclic compounds has received very little attention up to now, in sharp contrast to their non-fluorinated analogs.[14a,32,46,16b]

In continuation of our studies on the deployment of 4-trifluoromethyl-β-lactams as new building blocks in organic chemistry, we recently embarked on the synthesis and synthetic application of 3-hydroxy-4-trifluoromethyl-β-lactams. Within that framework, [2+2]-cyclocondensation between 2,2,2-trifluoroethan-1-imines and 2,2,2-trifluoro-1-(amino)ethan-1-ols, prepared from the commercially available 1-ethoxy-2,2,2-trifluoroethanol under Dean-Stark conditions, and the ketene derived from benzyloxyacetyl chloride furnished 3-benzyl-4-trifluoromethyl-β-lactams. The latter β-lactams were subjected to hydrogenolysis (Pd/C) to provide a convenient access to 3-hydroxy-4-CF_3-β-lactams. The aptitude of these systems with respect to ring-opening and ring-contraction reactions *via* 3-chloro-β-lactam intermediates was explored to enable an entry to functionalized CF_3-containing aminopropane and aziridine systems. In addition, manipulation of the alcohol group of 3-hydroxy-4-CF_3-β-lactams enabling the construction of CF_3-containing dioxan-2-ones *via* initial *O*-allylation was investigated.

2. Synthesis of 3-hydroxy-4-CF_3-β-lactam building blocks

In addition to the preparation of 3-benzyloxy-4-CF_3-β-lactams **2a-b** as described in our previous part, a set of four new 3-benzyloxy-4-CF_3-β-lactams **2c-f** was successfully synthesized, with slight modifications in the procedure. In the first step, 1-ethoxy-2,2,2-trifluoroethanol **1** was condensed with (a) isopropylamine in dichloromethane in the presence of $MgSO_4$ as drying agent or with (b) different arylamines (*p*-phenetidine, *p*-toluidine, 4-iodoaniline) in toluene in the presence of a catalytic amount of *p*-toluenesulfonic acid under Dean-Stark conditions. The resulting mixtures of

imines and their hemiaminal precursors were immediately used for the Staudinger synthesis, yielding *cis*-3-benzyloxy-β-lactams **2c-f** in acceptable yields (Scheme 1, Table 1). Besides the expected *cis*-β-lactams **2**, minor to rather significant amounts of *trans*-isomers of **2** were also detected (2-46%). The formation of these *trans*-β-lactams was confirmed based on ^{1}H NMR analysis, showing a coupling constant of 1-2 Hz ($CDCl_3$) between the two vicinal protons at the C3 and C4 position, as opposed to *cis*-β-lactams (5-6 Hz, $CDCl_3$).[39] The previously reported synthesis of β-lactams **2a-b** was achieved through a [2+2]-ketene-imine cyclocondensation between a trifluoromethylaldimine and benzyloxyacetyl chloride in the presence of Et_3N. Under these conditions, the *cis*-β-lactams **2a-b** were obtained in a relatively high stereoselectivity (*cis*/*trans* 95-98/5-2). However, the relative amount of *trans*-β-lactams in the **2c-f** cases was higher compared to those of **2a-b** (*cis*/*trans* 54-78/46-22, Table 1). This stereoselectivity issue might be due to the outcome of the cyclocondensation reaction between either a hemiaminal or a mixture of hemiaminal and imine, with benzyloxyacetyl chloride in the presence of Et_3N in the synthetic procedure toward β-lactams **2c-f**. It should indeed be noted that the treatment of 1-ethoxy-2,2,2-trifluoroethan-1-ol **1** with isopropylamine (a) led to 2,2,2-trifluoro-1-(isopropylamino)ethan-1-ol, whereas the use of arylamines (b) afforded a mixture of hemiaminals and imines. The *cis*-β-lactams **2a-f** were easily isolated through chromatography and subjected to hydrogenolysis (Pd/C) to produce the corresponding *cis*-alcohols **3a-f** in excellent yields (Scheme 1, Table 1). In the case of *cis*-3-benzyloxy-1-(4-iodophenyl)-4-(trifluoromethyl)azetidin-2-one **2d**, the hydrogenolysis furnished *cis*-3-benzyloxy-1-phenyl-4-(trifluoromethyl)azetidin-2-one instead of the expected *cis*-3-hydroxy-1-(4-iodophenyl)-4-(trifluoromethyl)azetidin-2-one, probably due to hydrogenolytic scission of the C_{arene}-I bond over the Pd/C catalyst.[63] Because the high adsorption of the *in situ* produced iodide anion led to a decrease in the catalytic activity of Pd/C, the resulting *cis*-3-benzyloxy-1-phenyl-4-(trifluoromethyl)azetidin-2-one was filtered through Celite® prior to debenzylation.[63] The latter was finally transformed into the corresponding *cis*-3-hydroxy-1-phenyl-4-(trifluoromethyl)azetidin-2-one **3d**, in an overall yield of 84%.



Scheme 1

Table 1: Isolated yields of compounds **2**, **3** and *cis*:*trans* ratios of compounds **2**

Entry	R	Compound **2**	*cis*:*trans*[a] **2**	Compound **3**
1	4-$MeOC_6H_4$	**2a** (49%)	98:2	**3a** (87%)
2	4-$MeOC_6H_4CH_2$	**2b** (72%)	95:5	**3b** (93%)
3	4-$C_2H_5OC_6H_4$	**2c** (47%)	78:22	**3c** (94%)
4	4-IC_6H_4/C_6H_5	**2d** (35%)[b]	54:46	**3d** (84%)[c]
6	4-MeC_6H_4	**2e** (31%)	67:33	**3e** (87%)
7	*i*Pr	**2f** (59%)	75:25	**3f** (97%)

[a]Determined by ^{19}F NMR spectroscopy ($CDCl_3$) of the crude reaction mixture **2**

[b]R = 4-IC_6H_4

[c]R = C_6H_5

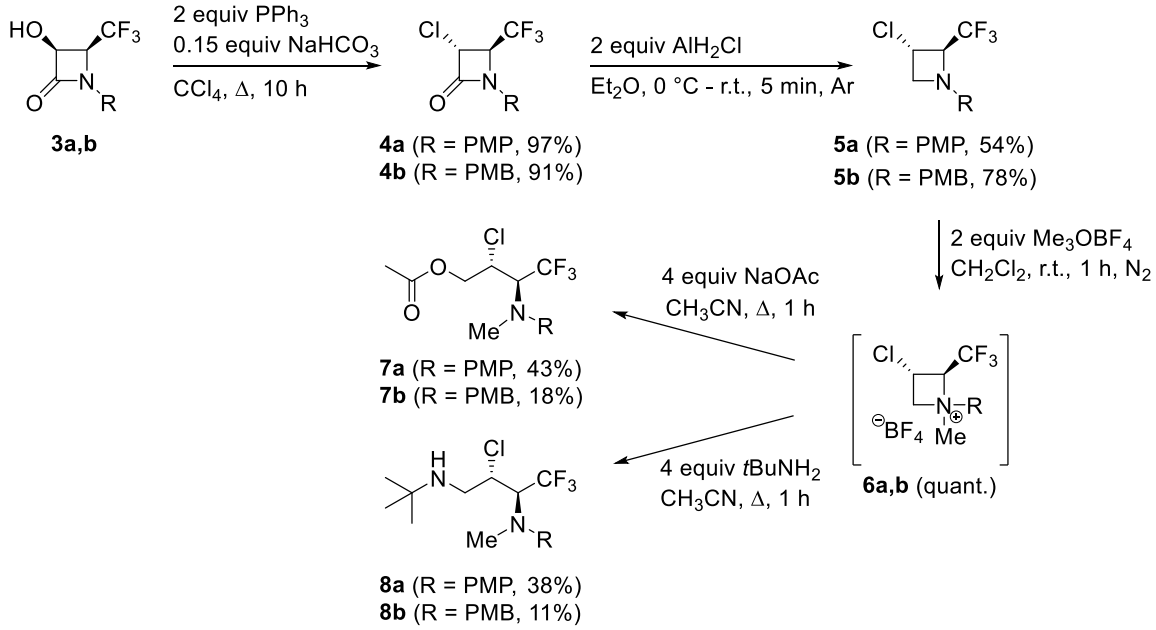
3. Reactivity profile of 3-hydroxy-4-CF_3-β-lactams

3.1. Ring opening and ring transformation of 3-hydroxy-4-CF_3-β-lactams *via* 3-chloro-β-lactams

In the next part, the eligibility of these 3-hydroxy-4-CF_3-β-lactams **3** as building blocks for the synthesis of functionalized trifluoromethyl-substituted compounds was assessed. In that respect, representative *cis*-3-hydroxy-4-(trifluoromethyl)azetidin-2-ones **3a,b** were transformed into *trans*-3-chloro-β-lactams **4a,b** in excellent yields (91-97%, Scheme 2) upon treatment with 2 equiv of Ph_3P and a small amount of $NaHCO_3$ catalyst in CCl_4 under reflux for 10 hours.[64] The *trans* configuration of β-lactams **4a,b** was confirmed based on the ^1H NMR spectrum ($J_{H3,H4}$ = 1-2 Hz,

$CDCl_3$), implying a clean S_N2 process. In order to simplify the synthetic procedure, the preparation of β-lactams **4** was attempted directly through the Staudinger synthesis using the same imines combined with chloroacetyl chloride and a variety of bases (2,6-lutidine, Et_3N, pyridine, proton sponge), in analogy with the synthesis of their non-fluorinated β-lactam counterparts.[65] However, this direct approach appeared to be unsuccessful for the preparation of trifluoromethylated β-lactams **4**. Therefore, a short detour was necessary, utilizing alcohols **3a,b** as valuable synthons to obtain the desired β-lactams **4a,b**. Besides this method, two complementary approaches have been reported to furnish 3-chloro-4-CF_3-β-lactam analogs, either by intramolecular cyclization of the corresponding β-amino esters[39] or by ring expansion of the corresponding aziridines.[41] The reactivity of 3-chloro-4-CF_3-β-lactams is virtually unexplored in the literature to date, in contrast to 3-chloro-β-lactams having no trifluoromethyl group at the C4 position. In that respect, the selective reduction of *trans*-3-chloro-4-CF_3-β-lactams **4a,b** by means of monochloroalane was evaluated to provide an entry into *trans*-3-chloro-2-(trifluoromethyl)azetidines **5a,b**. Treatment of β-lactams **4a,b** with two equiv of monochloroalane, in diethyl ether at room temperature for five minutes, produced the desired azetidines **5a,b** in good yields (54-78%, Scheme 2). In contrast to the reduction of 3-non-chlorinated 4-CF_3-β-lactams, the use of monochloroalane for the reduction of 3-chloro-2-(trifluoromethyl)azetidin-2-ones **4** required precise and optimized reaction conditions (time, temperature and molar equivalents of the reductant) to limit the formation of side products due to ring opening. Having these azetidines **5** in hand, their eligibility for the synthesis of a diversity of functionalized trifluoromethyl-substituted aminopropanes was evaluated. *N*-Alkylation of 3-chloro-2-(trifluoromethyl)azetidines **5** was performed prior to ring opening, upon treatment with trimethyloxonium tetrafluoroborate, furnishing the corresponding azetidinium salts **6a,b** in a quantitative way (Scheme 2). Subsequently, these salts were subjected to ring opening by using an oxygen and nitrogen nucleophile, providing a convenient entry toward a variety of α-(trifluoromethyl)amines. In particular, azetidinium salts **6** were treated with four equiv of sodium acetate or *tert*-butylamine, affording *anti*-2-chloro-3-amino-4,4,4-trifluorobutyl acetates **7a,b** and *anti*-2-chloro-4,4,4-trifluorobutane-1,3-diamines **8a,b**, respectively (Scheme 2), accompanied by a certain amount of azetidines **5** (20-47%). These results can be rationalized by considering competition between a ring-opening reaction at the C4 position and a *N*-demethylation reaction of azetidinium salts **6a,b** by the deployed nucleophiles.[66] Sodium acetate and *tert*-butylamine were selected as nucleophiles in analogy with previous investigations on the ring opening of *cis*-3-alkoxy-2-(trifluoromethyl)azetidines. In line with our previous findings on the chemistry of 2-CF_3-azetidinium ions,[18] ring opening of *trans*-3-chloro-2-(trifluoromethyl)azetidinium salts **6** proceeded regiospecifically at the non-substituted C4 position, in contrast with the reactivity of azetidinium

salts bearing other types of electron-withdrawing groups (acyl, cyano). It is also noteworthy that the treatment of non-chlorinated 2-CF_3-azetidinium salts with nucleophiles exclusively led to a regiospecific ring opening at the C4 position, without an accompanying *N*-demethylation pathway.[66,18]

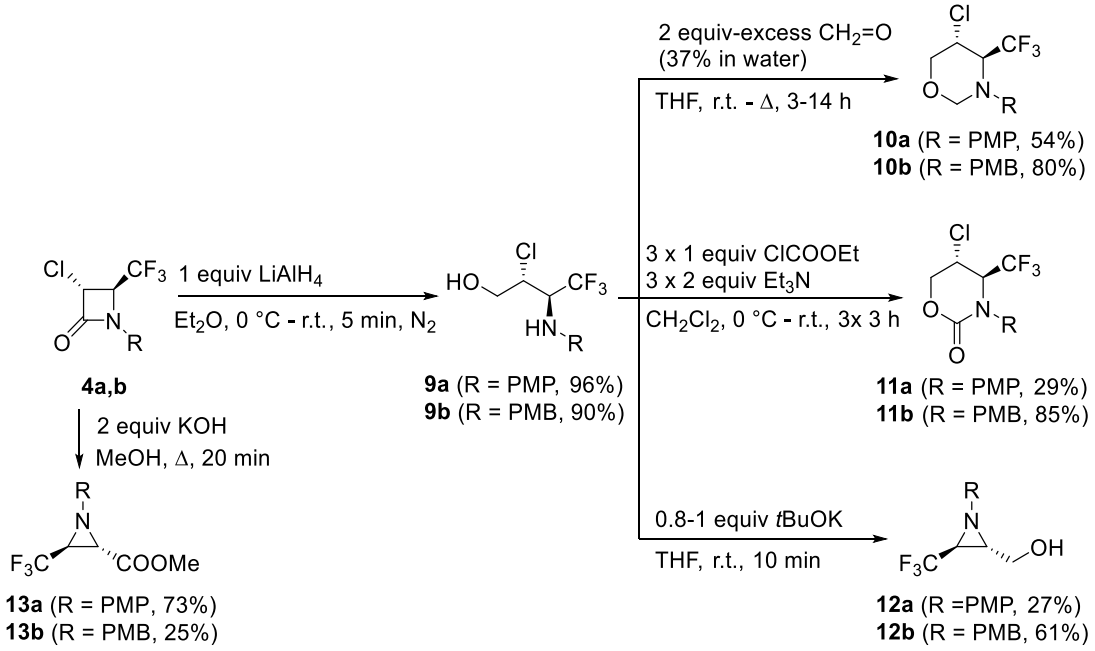


Scheme 2

In analogy with 3-non-chlorinated 4-(trifluoromethyl)azetidin-2-ones, 3-chloro-β-lactams **4a,b** might be valuable precursors for the stereoselective synthesis of fluorinated β-amino alcohols. In that respect, *trans*-3-chloro-4-(trifluoromethyl)azetidin-2-ones **4a,b** were subjected to a $LiAlH_4$-mediated reductive ring opening, using 1 equiv of $LiAlH_4$ in Et_2O at room temperature for five minutes, furnishing the corresponding *anti*-3-amino-2-chloro-4,4,4-trifluorobutanols **9a,b** in excellent yields (90-96%, Scheme 3). It should be noted that utilizing a stoichiometric amount of $LiAlH_4$ and a precise timing is required to avoid the generation of undesired side products. The use of 2 equiv of $LiAlH_4$ in different solvents (Et_2O, THF) at room temperature or under reflux only led to decomposition of the starting material **4**, as opposed to the results obtained upon treatment of non-CF_3-substituted 2-chloro-β-lactams with $LiAlH_4$.[17] CF_3-Substituted 1,3-aminoalcohols have been recognized as potential substrates for the preparation of a wide range of interesting trifluoromethyl-containing azaheterocyclic compounds.[67] For that purpose, the cyclization of *anti*-3-amino-2-chloro-4,4,4-trifluorobutanols **9a,b** was pursued to generate novel trifluoromethylated

oxazinanes and oxazinan-2-ones. As such, the treatment of 3-aminopropan-1-ols **9a,b** with formaldehyde (37% in water) in THF resulted in the corresponding new *trans*-5-chloro-4-trifluoromethyl-1,3-oxazinanes **10a,b** in 54-80% yield (Scheme 3). 1,3-Oxazinane scaffolds have been encountered as a core structure in many natural products and pharmaceuticals, because they possess a wide spectrum of biological activities such as anti-HIV, antibacterial, antitumor, antituberculosis and fungicidal properties.[68] Hence, a number of methods has been developed to enable their synthesis. However, reports on the synthesis of 1,3-oxazinanes with new functional groups remain rather scarce in the literature.[67b,18] In that respect, the deployment of β-aminoalcohols bearing a trifluoromethyl group might provide interesting trifluorinated 1,3-oxazinanes with promising biological properties.

In addition, the cyclization of 3-aminopropan-1-ols **9a,b** was performed utilizing three times one equiv of ethyl chloroformate and two equiv of triethylamine in CH_2Cl_2 at room temperature for three hours, furnishing the corresponding *trans*-5-chloro-4-trifluoromethyl-1,3-oxazinan-2-ones **11a,b** in 29-85% yield (Scheme 3).[69] 1,3-Oxazinan-2-ones are of interest due to their valuable biological activities as well. For example, they have been employed in the treatment of Alzheimer's disease, in herbicides with excellent crop-weed selectivity, in the treatment of diseases related to kinase activity, and in the regulation of cholesterol.[70,69] Therefore, new *trans*-5-chloro-4-trifluoromethyl-1,3-oxazinan-2-ones **11a,b** might possess interesting properties for further applications.



Scheme 3

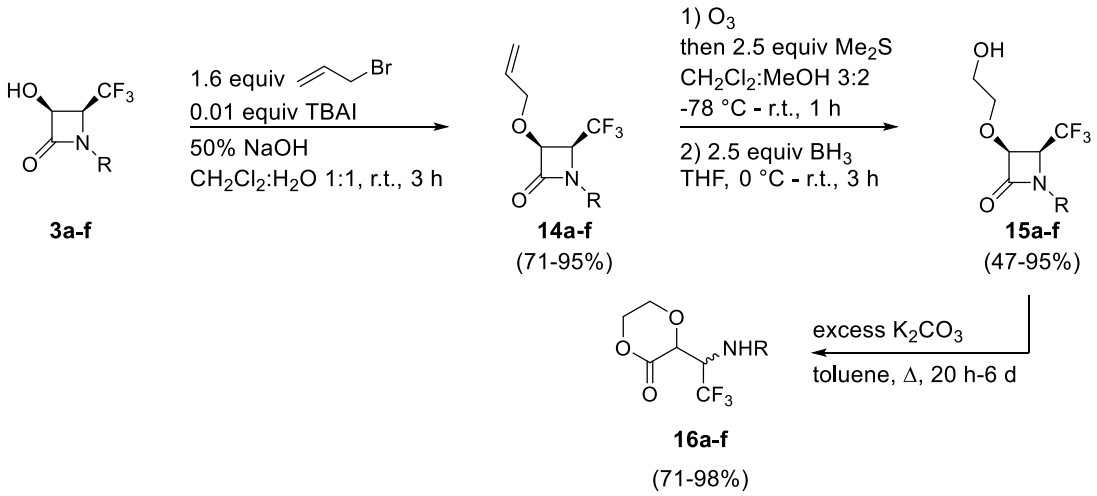
In addition, the reactivity of *trans*-3-chloro-4-CF_3-β-lactams **4a,b** was explored to effect ring contraction toward the synthesis of 2-substituted 3-(trifluoromethyl)aziridines. According to a previous study from our group, reductive ring contraction of *trans*-4-aryl-3-chloroazetidin-2-ones toward aziridines was directly achieved utilizing $LiAlH_4$ in THF or Et_2O.[17a,65b] However, the analogous reduction of *trans*-3-chloro-4-CF_3-β-lactams **4** with 1-2 equiv of $LiAlH_4$ in Et_2O at room temperature or under reflux for two hours did not furnish the desired aziridines **12**. This could be due to the strong inductive effect of the trifluoromethyl group, rendering the nitrogen atom less basic, thus prohibiting the cyclization. To provide access to the aziridines **12a,b**, a base-induced ring closure of amino alcohols **9a,b** upon treatment with 0.8-1 equiv of *t*BuOK in THF was explored successfully (Scheme 3).[71] On the other hand, treatment of *trans*-3-chloro-4-CF_3-azetidine-2-ones **4a,b** with 2 equiv of KOH in methanol under reflux for 20 min afforded the corresponding aziridine-2-carboxylates **13a,b** in 25-73% yield. Although 2-substituted 3-(trifluoromethyl)aziridines constitute eligible substrates for the synthesis of valuable fluorinated compounds, synthetic pathways toward these structures remain scarce, and most of these methods use diazo compounds or require harsh reaction conditions. For instance, Akiyama *et al*. have reported the preparation of *cis*-2-hydroxymethyl-3-(trifluoromethyl)aziridine **12a** from the corresponding CF_3-substituted aziridine carboxylate, which was also derived from a diazoacetate.[72] In recent research of our group, a novel stereoselective approach toward the synthesis of *trans*-2-substituted 3-(trifluoromethyl)aziridines starting from the commercially available trifluoromethyl ketones has been developed.[19] The use of *trans*-3-chloro-4-CF_3-β-lactams as versatile substrates for the synthesis of trifluoromethylated aziridines offers a new approach to this interesting aziridine subclass.

3.2. Ring-transformation study of 3-hydroxy-4-CF_3-β-lactams toward 3-[2,2,2-trifluoro-1-(arylamino)ethyl]-1,4-dioxan-2-ones

In the final part of this study, alcohols **3a**-**f** were evaluated as building blocks toward the synthesis of novel CF_3-containing 1,4-dioxan-2-ones. In that respect, *cis*-alcohols **3a**-**f** were subjected to initial *O*-allylation, yielding the corresponding *cis*-3-allyloxy-4-(trifluoromethyl)azetidin-2-ones **14a-f** in high yields (71-95%, Table 2) upon treatment with 1.6 equiv of allyl bromide in the presence of TBAI as a catalyst, under basic conditions (Scheme 4).[73] The direct preparation of β-lactams **14** was attempted using the Staudinger synthesis between the corresponding imine and allyloxyacetyl chloride, in accordance with the preparation of their non-fluorinated β-lactam counterparts.[21] However, this approach only resulted in a complex mixture instead of the desired

products **14**. In the following step, *cis*-3-allyloxy-4-(trifluoromethyl)azetidin-2-ones **14a-f** were subjected to an ozonolysis reaction followed by a reductive workup with 2.5 equiv of Me_2S, providing the corresponding aldehyde intermediates. These aldehydes were immediately reduced with 2.5 equiv of BH_3 (1M in Et_2O) in THF at room temperature for three hours, furnishing the corresponding *cis*-3-(2-hydroxyethoxy)-4-(trifluoromethyl)azetidin-2-ones **15a-f** in yields of 47-95% (Table 2).[21] It should be noted that the use of BH_3 (1M in Et_2O) was observed to be superior to the use of $NaBH_4$ or $LiBH_4$ in this reductive reaction, because attempts with the latter agents were always accompanied by a reductive β-lactam ring opening.

Due to the combination of the constrained β-lactam ring system and a nucleophilic alcohol group at a remote position, 3-(2-hydroxyethoxy)- and 3-(2-hydroxyethyl)-β-lactams have been documented to undergo ring rearrangement to generate five- and six-membered azaheterocycles.[21,74] Hence, the potency of *cis*-3-(2-hydroxyethoxy)-4-(trifluoromethyl)azetidin-2-ones **15a-f** with respect to ring transformation toward 1,4-dioxan-2-ones **16** was evaluated in the next step. In order to transform β-lactams **15a-f** into ring-rearranged products **16**, a set of different reaction conditions was assessed. In particular, treatment of β-lactams **15** with a variety of bases (NaH, pyridine, Et_3N, LiOH) in different solvents (THF, toluene, DMF, CH_2Cl_2) under different temperatures (0 °C, r.t., reflux) led to either complex mixtures or recuperation of the substrates. Fortunately, treatment of *cis*-3-(2-hydroxyethoxy)-4-(trifluoromethyl)azetidin-2-ones **15** with an excess of K_2CO_3 in toluene under reflux proved to be optimal to enable the desired intramolecular ring-opening reaction, furnishing an inseparable diastereomeric mixture of 3-[2,2,2-trifluoro-1-(arylamino)ethyl]-1,4-dioxan-2-ones **16** in excellent yields (71-98%, Scheme 4, Table 2).[21,74a] Only in the case of β-lactams **15b,f**, no ring transformation products **16b,f** were observed. These results show that the presence of electron-withdrawing substituents at the N1 position might accelerate the intramolecular ring opening of β-lactams to give trifluoromethylated 1,4-dioxan-2-ones **16**. Indeed, the stabilizing effect of an aromatic ring at nitrogen in **15a,c-e** promotes the formation of the corresponding nitrogen anion after ring opening, whereas the presence of an electron-donating alkyl group in **15b,f** impedes this process.

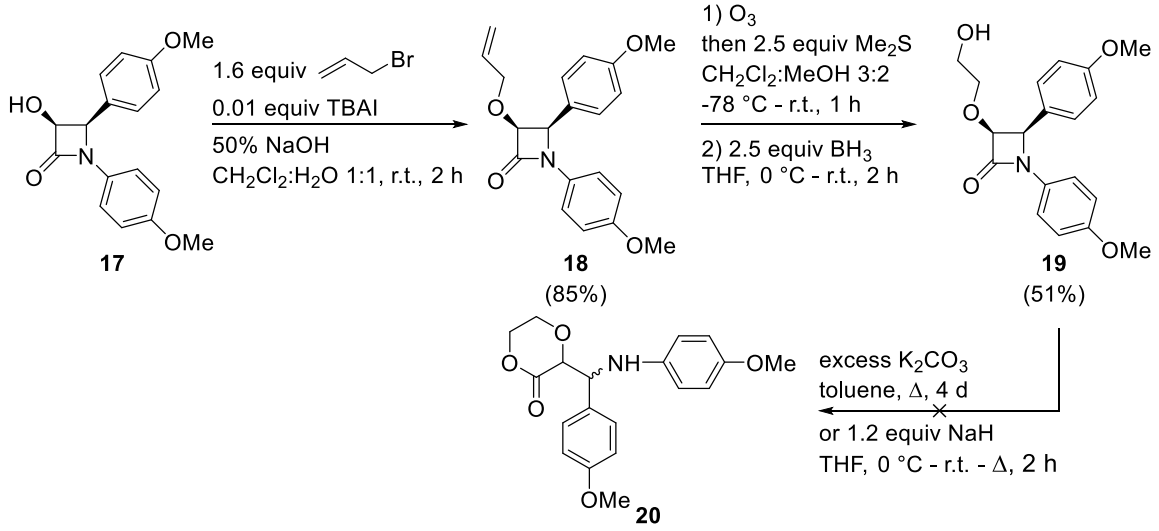


Scheme 4

Table 2: Isolated yields of compounds **14, 15, 16** and *syn*:*anti* ratios of compounds **16**					
Entry	R	Compound **14**	Compound **15**	Compound **16**	*d.r.* (**16**)
1	4-$MeOC_6H_4$	**14a** (94%)	**15a** (72%)	**16a** (81%)	78:22
2	4-$MeOC_6H_4CH_2$	**14b** (95%)	**15b** (77%)	**16b** (0%)	-
3	4-$C_2H_5OC_6H_4$	**14c** (84%)	**15c** (72%)	**16c** (86%)	72:28
4	C_6H_5	**14d** (77%)	**15d** (95%)	**16d** (71%)	69:31
5	4-MeC_6H_4	**14e** (71%)	**15e** (63%)	**16e** (98%)	75:25
6	*i*Pr	**14f** (79%)	**15f** (47%)	**16f** (0%)	-

In the course of our study on CF_3-substituted β-lactams, we realized that a CF_3-group does significantly affect the behavior of these molecules. Therefore, in order to gain insight into the influence of the trifluoromethyl group with respect to intramolecular cyclization, *cis*-3-(2-hydroxyethoxy)-1,4-bis(4-methoxyphenyl)azetidin-2-one **19** was synthesized (Scheme 5), which bears a 4-methoxyphenyl group at the C4 position (instead of the trifluoromethyl group). This compound **19** was prepared from the corresponding *cis*-3-allyloxy-1,4-bis(4-methoxyphenyl)azetidin-2-one **18**, derived from alcohol **17**,[75] using the above-described procedure (Scheme 5). The preparation of β-lactam **18** has also been reported by Zarei upon the treatment of allyloxyacetic acid with Schiff base and phosphonitrilic chloride (hexachlorotriphosphazene) in the presence of triethylamine.[76] Surprisingly, the treatment of *cis*-3-(2-hydroxyethoxy)-1,4-bis(4-methoxyphenyl)azetidin-2-one **19** with an excess of K_2CO_3 in

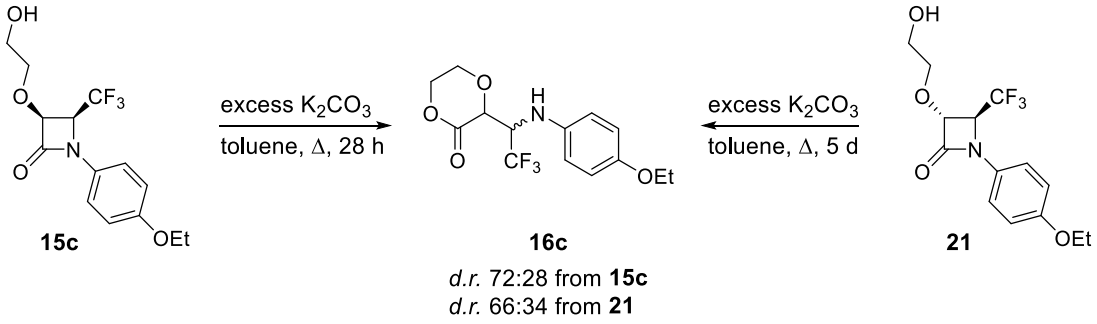
toluene under reflux for four days solely led to recuperation of the starting material **19**. As K_2CO_3 might not be strong enough as a base to realize nucleophilic ring opening in this case, a more potent base (NaH) was used. However, the intramolecular cyclization toward 1,4-dioxan-2-one **20** was never observed, and this approach resulted in either the recovery of starting material **19** or a complex mixture (Scheme 5). This observation indicates that the specific combination of the aromatic group at N1 and the CF_3 group at C4, as in *cis*-3-(2-hydroxyethoxy)-4-(trifluoromethyl)azetidin-2-ones **15**, is important for the base-induced transformation into CF_3-substituted 1,4-dioxan-2-ones **16**. It should be stressed that the synthetic chemistry concerning 1,4-dioxan-2-one scaffolds, starting from monocyclic β-lactams, has been sporadically documented in the literature (as side products).[21] These 1,4-dioxan-2-one derivatives have been mainly synthesized from 1,2-diol,[77] glycolic acid[78] and glycerol derivatives.[79] In addition, 1,4-dioxan-2-one derivatives play an important role as intermediates in the synthetic field of polymers, corrosion inhibitors and biomaterials.[22] In that respect, the convenient approach toward CF_3-substituted 1,4-dioxan-2-ones **16** using CF_3-substituted β-lactam alcohols **15** as building blocks provided new insights and opportunities from both a fundamental and applied point of view.



Scheme 5

Because the resulting diastereoisomers **16** could not be separated by means of column chromatography on silica gel, preparative HPLC (Supelco Ascentis C18; H_2O/CH_3CN) and recrystallization (CH_2Cl_2/Et_2O 1/1 or Et_2O), other attempts were made to determine the relative

stereochemistry of 3-[2,2,2-trifluoro-1-(arylamino)ethyl]-1,4-dioxan-2-ones **16**. For that reason, three additional experiments were performed to examine the behavior of *cis*-β-lactams **15** toward intramolecular cyclization under basic conditions. In a first experiment, the intramolecular cyclization of *trans*-1-(4-ethoxyphenyl)-3-(2-hydroxyethoxy)-4-(trifluoromethyl)azetidin-2-one **21** (the *trans* counterpart of *cis*-β-lactam **15c**, derived from the corresponding *trans*-1-(4-ethoxyphenyl)-3-allyloxy-4-(trifluoromethyl)azetidin-2-one in an overall yield of 11%) as a model compound toward 3-{1-[(4-ethoxyphenyl)amino]-2,2,2-trifluoroethyl}-1,4-dioxan-2-one **16c** was tested. Remarkably, the use of identical reactions conditions (excess of K_2CO_3 in toluene under reflux for five days) applied to *trans*-1-(4-ethoxyphenyl)-3-(2-hydroxyethoxy)-4-(trifluoromethyl)azetidin-2-one **21** also led to a mixture of two isomers **16c** in a ratio of 66:34, similar to the 72:28 mixture obtained from **15c** (Scheme 6).



Scheme 6

In a second experiment, the pure diastereoisomer *cis*-3-allyloxy-1-(4-ethoxyphenyl)-4-(trifluoromethyl)azetidin-2-one **14c** was treated with an excess of K_2CO_3 in toluene under reflux for five days, resulting in a *cis*/*trans* mixture of 3-allyloxy-1-(4-ethoxyphenyl)-4-(trifluoromethyl)azetidin-2-one in a ratio of 40:60 (*cis*:*trans*). In the last experiment, the diastereomeric mixture of 3-{1-[(4-ethoxyphenyl)amino]-2,2,2-trifluoroethyl}-1,4-dioxan-2-one **16c** (*d.r.* 72:28) was treated with an excess of K_2CO_3 in toluene under reflux for one day, which did not affect the diastereomeric ratio.

Based on these experimental results, we propose that a dynamic equilibrium between intramolecular ring opening and epimerization of *cis*-alcohols **15** occurred in the presence of K_2CO_3, which led to the corresponding (3*S*,1'*R*;3*R*,1'*S*)-3-[2,2,2-trifluoro-1-(arylamino)ethyl]-1,4-dioxan-2-ones **16** (as major products) and *trans*-alcohols **15**. Then, *trans*-alcohols **15** were in turn

subjected to intramolecular ring opening, leading to the corresponding (3*R*,1'*R*;3*S*,1'*S*)-3-[2,2,2-trifluoro-1-(arylamino)ethyl]-1,4-dioxan-2-ones **16** (as minor isomers). In addition to the experiments, DFT calculations were performed to assess the stability of the diastereomeric pairs. Relative Gibbs free energies indicate that (3*S*,1'*R*;3*R*,1'*S*)-**16** is more stable than (3*R*,1'*R*;3*S*,1'*S*)-**16** if the mixture of the two diastereoisomers is considered (see SI). Hence, 3-(2,2,2-trifluoro-1-aminoethyl-1,4-dioxan-2-ones (3*S*,1'*R*)- and (3*R*,1'*S*)-**16** are proposed to be the major products in the inseparable mixture of diastereoisomers (Fig. 1).

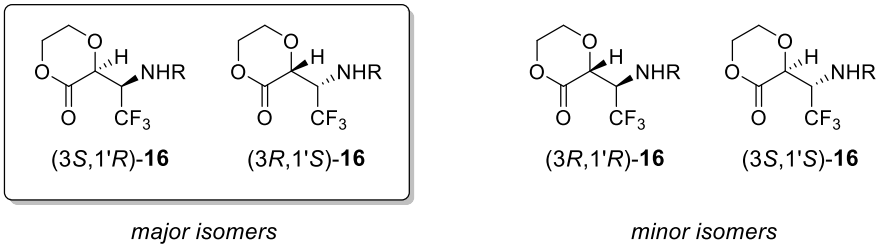


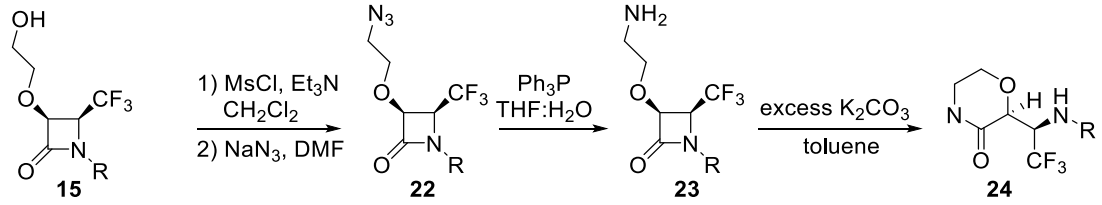
Fig. 1. Overview of possible isomers for structures **16**

4. Conclusion

In conclusion, a set of *cis*-3-hydroxy-4-(trifluoromethyl)azetidin-2-ones was effectively synthesized and successfully deployed as versatile new building blocks for the construction of a variety of CF_3-containing amines and heterocyclic molecules. To that end, *cis*-3-hydroxy-4-CF_3-β-lactams were transformed into *trans*-3-chloro-4-CF_3-β-lactams, which served as eligible substrates for the preparation of α-CF_3-substituted aminopropane derivatives through a regiospecific ring opening of intermediate azetidinium salts. Besides, new *trans*-5-chloro-4-trifluoromethyl-1,3-oxazinanes and *trans*-5-chloro-4-trifluoromethyl-1,3-oxazinan-2-ones were produced through cyclization of trifluoromethylated γ-amino alcohols, with formaldehyde or ethyl chloroformate, respectively. Moreover, 2-substituted 3-trifluoromethylated aziridines were synthesized, either by base-induced ring closure of γ-amino alcohols or upon direct treatment of 3-chloro-β-lactams with KOH. In addition, 3-hydroxy-4-(trifluoromethyl)azetidin-2-ones proved to be suitable substrates for the synthesis of novel 3-[2,2,2-trifluoro-1-(arylamino)ethyl]-1,4-dioxan-2-ones in high yields through ring rearrangement.

5. Perspectives

To gain an insight into the scope of the intramolecular ring rearrangement of monocyclic β-lactams bearing a nucleophilic moiety at the remote C3 position, *cis*-3-(2-hydroxyethoxy)-4-(trifluoromethyl)azetidin-2-ones **15** could be converted into *cis*-3-(2-aminoethoxy)-4-(trifluoromethyl)azetidin-2-ones **23** (Scheme 7).[21] In that respect, the azides **22** could be synthesized upon treatment of alcohols **15** with MsCl in the presence of Et_3N, followed by substitution of the resulting mesylates with NaN_3. Then, Staudinger reduction of latter azides with triphenylphosphane could result in the free amines **23**, which might be suitable for a base-induced rearrangement toward trifluoromethylated morpholin-3-one derivatives **24**. Morpholin-3-one chemistry is of significant importance due to their broad range of pharmacological activities including analgesic, anti-inflammatory, anticancer, antidepressant and HIV-protease inhibitor activity.[80] The search for new, functionalized morpholin-2-one derivatives remains a relevant issue in medicinal chemistry, thus CF_3-substituted morpholin-3-ones **24** attained in this way could present new compounds with promising biological properties.



Scheme 7

6. Experimental details

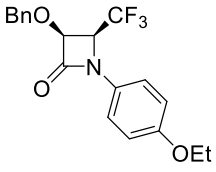
General methods

The ozonolysis reaction was performed with an Ozonia Triogen Model LAB2B laboratory ozone generator, connected to a Bronkhorst Flow-Bus E-7000 type mass flow meter to control the dry air inflow and an Anseros Ozomat Model GM Non-Dispersive UV-analyzer to measure the ozone concentration.

Synthesis of 3-benzyloxy-4-(trifluoromethyl)azetidin-2-ones 2

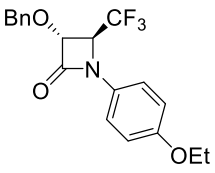
To a solution of 1-ethoxy-2,2,2-trifluoroethanol (1.00 g, 0.82 mL, 6,94 mmol, 1 equiv) in toluene (30 mL) was added *p*-phenetidine (0.76 g, 0.71 mL, 5.55 mmol, 0.8 equiv) and an amount of *p*-toluenesulfonic acid catalyst (13.2 mg, 0.07 mmol, 0.01 equiv). The resulting mixture was heated at reflux temperature for three hours under Dean-Stark conditions, affording *N*-(4-ethoxyphenyl)-2,2,2-trifluoroethan-1-imine in high purity (> 90 % based on NMR). Due to its hydrolytic instability, after evaporation of the crude mixture, the resulting product (1.23 g, 5.67 mmol, 1equiv) was immediately dissolved in in dry CH_2Cl_2 (50 mL) at 0 °C under argon atmosphere and triethylamine (2.87 g, 3.95 mL, 28.4 mmol, 5 equiv) was added to the solution. Benzyloxyacetyl chloride (4.17 g, 3.57 mL, 22.68 mmol, 4 equiv) was then added dropwise to the reaction mixture. After stirring the reaction mixture for three days under reflux, water (20 mL) was added to the mixture. Extraction with CH_2Cl_2 (3 × 20 mL), washing with brine (3 × 20 mL), drying ($MgSO_4$), filtration of the drying agent and evaporation of solvent afforded a mixture of two isomers *cis*:*trans* in a ratio of 78:22. The two isomers were separated by means of column chromatography on silica gel (PE/EtOAc, 9/1), then recrystallization from EtOH was performed to obtain analytically pure *cis*-3-benzyloxy-1-(4-ethoxyphenyl)-4-(trifluoromethyl)azetidin-2-one **2c** (47%) and *trans*-3-benzyloxy-1-(4-ethoxyphenyl)-4-(trifluoromethyl)azetidin-2-one **2c** (10%).

Cis-3-benzyloxy-1-(4-ethoxyphenyl)-4-(trifluoromethyl)azetidin-2-one 2c



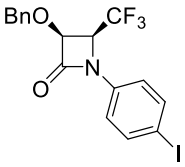
White crystals. Mp 83 °C. R_f = 0.23 (PE/EtOAc, 9/1). Then, recrystallization from EtOH. *Cis*:*trans* 78:22. Yield 47%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.40 (3H, t, J = 7.0 Hz, $OCH_2C\underline{H}_3$), 4.01 (2H, q, J = 7.0 Hz, $OC\underline{H}_2CH_3$), 4.61 (1H, quintet, J = 5.4 Hz, $CHCF_3$), 4.80 and 4.85 (2H, 2 × d, J = 11.8 Hz, $OC\underline{H}_2Ph$), 4.98 (1H, d, J = 5.4 Hz, $OC\underline{H}CHCF_3$), 6.87 (2H, d, J = 9.0 Hz, $O(CH_{arom})_{ortho}$), 7.32-7.41 (7H, m, $N(CH_{arom})_{ortho}$ and CH_{arom}). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 14.8 ($OCH_2\underline{C}H_3$), 57.7 (q, J = 33.1 Hz, $\underline{C}HCF_3$), 63.7 ($O\underline{C}H_2CH_3$), 73.8 ($\underline{C}H_2Ph$), 80.2 ($O\underline{C}HCHCF_3$), 115.0 (2 × $O(CH_{arom})_{ortho}$), 119.4 (2 × $N(CH_{arom})_{ortho}$), 123.8 (q, J = 284.4 Hz, $CH\underline{C}F_3$), 127.9, 128.3, 128.6, 129.3 (6 × CH_{arom}), 136.1 ($CH_2\underline{C}_{arom,quat}$), 156.6 ($OC_{arom,quat}$), 163.8 (C=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -68.37 (3F, d, J = 5.4 Hz, CF_3). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1749, ν_{max} = 1514, 1364, 1267, 1163, 1136, 1022, 922, 825, 735, 505. MS (70eV): 366 (M^+ + 1, 100).

Trans-3-benzyloxy-1-(4-ethoxyphenyl)-4-(trifluoromethyl)azetidin-2-one



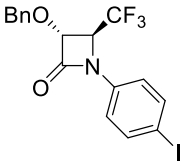
White crystals. Mp 71 °C. R_f = 0.49 (PE/EtOAc, 9/1). Yield 10%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.40 (3H, t, J = 7.0 Hz, $OCH_2\underline{C}H_3$), 4.01 (2H, q, J = 7.0 Hz, $OC\underline{H}_2CH_3$), 4.41 (1H, q × d, J = 5.6, 1.1 Hz, $CHCF_3$), 4.76 and 4.82 (2H, 2 × d, J = 11.5 Hz, $OC\underline{H}_2Ph$), 4.88 (1H, d, J = 1.1 Hz, $OC\underline{H}CHCF_3$), 6.88 and 7.32 (2 × 2H, 2 × d, J = 8.9 Hz, $N(CH_{arom})_{ortho}$ and $O(CH_{arom})_{ortho}$), 7.33-7.39 (5H, m, CH_{arom}). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 14.8 ($OCH_2\underline{C}H_3$), 59.8 (q, J = 34.2 Hz, $\underline{C}HCF_3$), 63.7 ($O\underline{C}H_2CH_3$), 73.2 ($\underline{C}H_2Ph$), 82.0 ($O\underline{C}HCHCF_3$), 115.0 (2 × $O(CH_{arom})_{ortho}$), 120.1 (2 × $N(CH_{arom})_{ortho}$), 123.6 (q, J = 280.5 Hz, $CH\underline{C}F_3$), 128.2, 128.5, 128.7 (5 × CH_{arom}), 128.9 ($NC_{arom,quat}$), 135.9 ($CH_2\underline{C}_{arom,quat}$), 156.8 ($OC_{arom,quat}$), 162.5 (C=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -71.38 (3F, d, J = 5.6 Hz, CF_3). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1763, ν_{max} = 1514, 1398, 1281, 1244, 1148, 1113, 1045, 843, 735, 694. MS (70eV): 366 (M^+ + 1, 100).

Cis-3-benzyloxy-1-(4-iodophenyl)-4-(trifluoromethyl)azetidin-2-one 2d



White crystals. Mp 125 °C. R_f = 0.15 (PE/EtOAc, 12/1). Then, recrystallization from EtOH. Yield 35%. *Cis*:*trans*, 54:46. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.64 (1H, quintet, J = 5.4 Hz, $CHCF_3$), 4.79 and 4.85 (2H, 2 × d, J = 11.8 Hz, $OC\underline{H}_2Ph$), 4.99 (1H, d, J = 5.4 Hz, $OC\underline{H}CHCF_3$), 7.23 (2H, d, J = 8.7 Hz, $N(CH_{arom})_{ortho}$), 7.32-7.39 (5H, m, CH_{arom}), 7.67 (2H, d, J = 8.7 Hz, $I(CH_{arom})_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 57.4 (q, J = 33.4 Hz, $\underline{C}HCF_3$), 73.9 ($\underline{C}H_2Ph$), 80.2 ($O\underline{C}HCHCF_3$), 89.0 ($IC_{arom,quat}$), 119.4 (2 × $N(CH_{arom})_{ortho}$), 123.6 (q, J = 280.1 Hz, $CH\underline{C}F_3$), 128.0, 128.4, 128.7 (5 × CH_{arom}), 135.8 ($NC_{arom,quat}$), 135.9 ($CH_2\underline{C}_{arom,quat}$), 138.2 (2 × $I(CH_{arom})_{ortho}$), 164.1 (C=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -68.21 (3F, d, J = 5.4 Hz, CF_3). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1761, ν_{max} = 1489, 1364, 1267, 1238, 1165, 1128, 816, 737, 694, 498. MS (70eV): 465 (M^+ + 18, 100), 448 (M^+ + 1, 55).

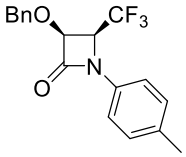
Trans-3-benzyloxy-1-(4-iodophenyl)-4-(trifluoromethyl)azetidin-2-one



White crystals. Mp 78 °C. R_f = 0.52 (PE/EtOAc, 9/1). Then, recrystallization from EtOH. Yield 27%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.36 (1H, q × d, J = 5.6, 1.3 Hz, $CHCF_3$), 4.69 and 4.76 (2H, 2 × d, J = 11.6 Hz, $OC\underline{H}_2Ph$), 4.82 (1H, d, J = 1.3 Hz, $OC\underline{H}CHCF_3$), 7.11 (2H, d, J = 8.7 Hz, $N(CH_{arom})_{ortho}$), 7.28-7.34 (5H, m, CH_{arom}), 7.61 (2H, d, J = 8.7 Hz, $I(CH_{arom})_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 59.6 (q, J = 34.5 Hz, $\underline{C}HCF_3$), 73.3 ($\underline{C}H_2Ph$), 82.2 (q, J = 1.5 Hz, $O\underline{C}HCHCF_3$), 89.4 ($IC_{arom,quat}$), 119.8 (2 × $N(CH_{arom})_{ortho}$), 123.4 (q, J = 280.2 Hz, $CH\underline{C}F_3$), 128.2, 128.65, 128.74 (5 × CH_{arom}), 135.6 ($CH_2\underline{C}_{arom,quat}$), 138.3 (2 × $I(CH_{arom})_{ortho}$), 162.6 (C=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -71.12 (3F,

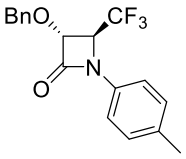
d, J = 5.6 Hz, CF_3). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1757, ν_{max} = 1587, 1489, 1393, 1364, 1111, 1001, 696, 498. MS (70eV): 448 (M^+ + 1, 50).

Cis-3-benzyloxy-1-(4-methylphenyl)-4-(trifluoromethyl)azetidin-2-one 2e



White crystals. Mp 113 °C. R_f = 0.25 (PE/EtOAc, 9/1). Then, recrystallization from EtOH. Yield 35%. *Cis*:*trans*, 67:33. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.31 (3H, s, CH_3), 4.63 (1H, quintet, J = 5.3 Hz, $CHCF_3$), 4.78 and 4.84 (2H, 2 × d, J = 11.8 Hz, OCH_2Ph), 4.96 (1H, d, J = 5.3 Hz, $OCHCHCF_3$), 7.14 (2H, d, J = 8.3 Hz, $N(CH_{arom})_{ortho}$), 7.33-7.40 (7H, m, $CH_3(CH_{arom})_{ortho}$ and CH_{arom}). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 20.9 (CH_3), 57.4 (q, J = 33.2 Hz, $CHCF_3$), 73.8 (CH_2Ph), 80.2 ($OCHCHCF_3$), 117.7 (2 × $CH_3(CH_{arom})_{ortho}$), 123.8 (q, J = 280.4 Hz, $CHCF_3$), 127.9, 128.3, 128.6 (5 × CH_{arom}), 129.8 (2 × $N(CH_{arom})_{ortho}$), 133.7, 135.3, 136.1 (3 × $C_{arom,quat}$), 164.0 (C=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -68.29 (3F, d, J = 5.3 Hz, CF_3). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1769, ν_{max} = 1514, 1360, 1265, 1167, 1130, 812, 760, 694, 494. MS (70eV): 336 (M^+ + 1, 100).

Trans-3-benzyloxy-1-(4-methylphenyl)-4-(trifluoromethyl)azetidin-2-one

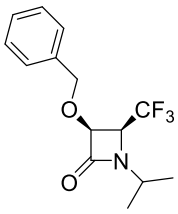


White crystals. Mp 62 °C. R_f = 0.52 (PE/EtOAc, 9/1). Then, recrystallization from EtOH. Yield 14%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.24 (3H, s, CH_3), 4.35 (1H, q × d, J = 5.6, 1.2 Hz, $CHCF_3$), 4.67 and 4.74 (2H, 2 × d, J = 11.6 Hz, OCH_2Ph), 4.80 (1H, d, J = 1.2 Hz, $OCHCHCF_3$), 7.08 and 7.22 (2 × 2H, 2 × d, J = 8.3 Hz, $N(CH_{arom})_{ortho}$, $CH_3(CH_{arom})_{ortho}$), 7.25-7.30 (5H, m, CH_{arom}). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 21.0 (CH_3), 59.6 (q, J = 34.4 Hz, $CHCF_3$), 73.2 (CH_2Ph), 82.0 (q, J = 2.0 Hz, $OCHCHCF_3$), 118.2 (2 × $CH_3(CH_{arom})_{ortho}$), 123.6 (q, J = 280.4 Hz, $CHCF_3$), 128.2, 128.5, 128.7 (5 × CH_{arom}), 129.8 (2 × $N(CH_{arom})_{ortho}$), 133.4 ($NC_{arom,quat}$), 135.6 ($CH_3C_{arom,quat}$), 135.9 ($CH_2C_{arom,quat}$), 162.6 (C=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -71.22 (3F, d, J = 5.6 Hz, CF_3). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1759, ν_{max} = 1512, 1391, 1348, 1277, 1163, 1138, 1109, 810, 739, 698, 509, 436. MS (70eV): 336 (M^+ + 1, 100).

Cis-3-benzyloxy-1-isopropyl-4-(trifluoromethyl)azetidin-2-one 2f

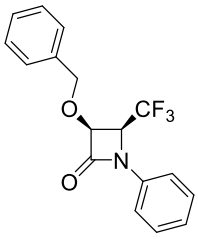
To a solution of 1-ethoxy-2,2,2-trifluoroethanol (1.00 g, 0.82 mL, 6,94 mmol, 1 equiv) in anhydrous CH_2Cl_2 (20 mL) was added isopropylamine (0.41 g, 0.60 mL, 6.94 mmol, 1 equiv) and $MgSO_4$ (1.67 g, 13.88 mmol, 2 equiv). After stirring for two hours under reflux, $MgSO_4$ was removed by filtration. Evaporation of the solvent *in vacuo* gave 2,2,2-trifluoro-1-(isopropylamino)ethan-1-ol (0.76 g, 4.84 mmol, 70%) as white crystals. Benzyloxyacetyl chloride (3.56 g, 3.04 mL, 19.36 mmol, 4 equiv) was added dropwise to an ice-cooled solution of the latter *N*-isopropyl hemiaminal

(0.76 g, 4.84 mmol, 1 equiv) and triethylamine (2.44 g, 3.37 mL, 24.2 mmol, 5 equiv) in anhydrous CH_2Cl_2 (30 mL). After stirring for 19 hours under reflux, water (30 mL) was poured into the reaction mixture and extracted with CH_2Cl_2 (2 × 25 mL). Drying ($MgSO_4$), filtration of the drying agent and removal of the solvent afforded a mixture of two isomers *cis*:*trans* in a ratio of 75:25. Pure *cis*-3-benzyloxy-1-isopropyl-4-(trifluoromethyl)azetidin-2-one **2f** (59%) was obtained by means of column chromatography on silica gel (PE/EtOAc, 9/1).



Yellowish solid. Mp 45 °C. R_f = 0.11 (PE/EtOAc, 9/1). Yield 59%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 and 1.29 (2 × 3H, 2 × d, J = 6.8 Hz, $(C\underline{H}_3)_2CHN$), 3.88 (1H, septet, J = 6.8 Hz, $(CH_3)_2C\underline{H}$), 4.11 (1H, q × d, J = 6.1, 5.2 Hz, $CHCF_3$), 4.73 (1H, 2 × d, J = 11.8 Hz, O($\underline{H}$CH)Ph), 4.75 (1H, d, J = 5.2 Hz, $C\underline{H}CHCF_3$), 4.77 (1H, 2 × d, J = 11.8 Hz, O(HC$\underline{H}$)Ph), 7.28-7.36 (5H, m, CH_{arom}). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 19.4 and 21.1 ($(\underline{C}H_3)_2CH$), 45.1 ($(CH_3)_2\underline{C}H$), 56.5 (q, J = 33.1 Hz, $\underline{C}HCF_3$), 73.4 (O$\underline{C}H_2$Ph), 80.0 ($\underline{C}HCHCF_3$), 123.9 (q, J = 279.8 Hz, CF_3), 127.9, 128.2, 128.5 (5 × CH_{arom}), 136.3 ($C_{arom,quat}$), 166.1 (C=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -69.33 (3F, d, J = 6.1 Hz, CF_3). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1763, ν_{max} = 1393, 1354, 1277, 1161, 1138, 1113, 735, 696. MS (70eV): 288 (M^+ + 1, 100).

Cis-3-benzyloxy-1-phenyl-4-(trifluoromethyl)azetidin-2-one



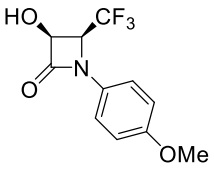
White crystals. Mp 95 °C. R_f = 0.24 (PE/EtOAc, 9/1). Yield 86%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.67 (1H, quintet, J = 5.4 Hz, $CHCF_3$), 4.80 and 4.85 (2H, 2 × d, J = 11.8 Hz, OC$\underline{H}_2$Ph), 4.98 (1H, d, J = 5.4 Hz, OC$\underline{H}CHCF_3$), 7.17 (1H, t, J = 7.4 Hz, CH_{arom}), 7.31-7.41 (7H, m, CH_{arom}), 7.46 (2H, d, J = 8.1 Hz, CH_{arom}). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 57.4 (q, J = 33.3 Hz, $\underline{C}HCF_3$), 73.8 ($\underline{C}H_2$Ph), 80.1 (O$\underline{C}HCHCF_3$), 117.6 (2 × CH_{arom}), 123.7 (q, J = 281.0 Hz, CF_3), 125.5, 128.0, 128.4, 128.6, 129.3 (8 × CH_{arom}), 136.1, 136.2 (2 × $C_{arom,quat}$), 164.2 (C=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -68.26 (3F, d, J = 5.4 Hz, CF_3). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1757, ν_{max} = 1499, 1366, 1167, 1138, 739, 752, 669, 490. MS (70eV): 322 (M^+ + 1, 100).

Synthesis of 3-hydroxy-4-(trifluoromethyl)azetidin-2-ones 3

As a representative example, the synthesis of *cis*-3-hydroxy-1-(4-methoxyphenyl)-4-(trifluoromethyl)azetidin-2-one **3a** is described. Palladium on activated carbon (20% w/w) was added to a solution of *cis*-3-benzyloxy-1-(4-methoxyphenyl)-4-(trifluoromethyl)azetidin-2-one **2a** (6.00 g, 17.09 mmol, 1 equiv) in methanol (15 mL) and the resulting mixture was placed in a Parr apparatus. The inside of the Parr apparatus was then degassed and filled with hydrogen gas, after

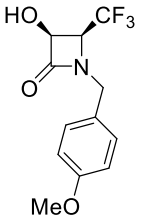
which the mixture was stirred at room temperature for 41 hours while applying 5 bar of hydrogen gas. Filtration of the heterogenous mixture through Celite® and evaporation of the solvent *in vacuo* afforded *cis*-3-hydroxy-1-(4-methoxyphenyl)-4-(trifluoromethyl)azetidin-2-one **2a**, which was purified by recystallization from Hex/EtOAc, 30/1 in a yield of 87%.

***Cis*-3-hydroxy-1-(4-methoxyphenyl)-4-(trifluoromethyl)azetidin-2-one 3a**



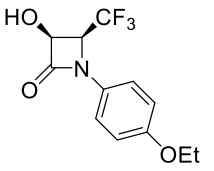
White crystals. Mp 160 °C. Recrystallization from Hex/EtOAc, 30/1. Yield 87%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.25 (1H, s, OH), 3.80 (3H, s, OCH_3), 4.62 (1H, quintet, J = 5.6 Hz, $CHCF_3$), 5.28 (1H, d, J = 5.6 Hz, C<u>H</u>OH), 6.90 and 7.40 (2 × 2H, 2 × d, J = 9.1 Hz, $N(CH_{arom})_{ortho}$) and $O(CH_{arom})_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 55.5 (OCH_3), 58.1 (q, J = 32.1, <u>C</u>HCF$_3$), 75.5 (CHOH), 114.5 (2 × $O(CH_{arom})_{ortho}$), 119.4 (2 × $N(CH_{arom})_{ortho}$), 123.7 (q, J = 282.4 Hz, CF_3), 129.3 ($C_{arom,quat}N$), 157.4 ($C_{arom,quat}O$), 164.8 (C=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -68.47 (3F, d, J = 5.6 Hz, CF_3). IR (ATR, cm^{-1}): ν_{OH} = 3320, $\nu_{C=O}$ = 1729, ν_{max} = 1515, 1248, 1169, 1141, 1021, 821, 645. MS (70eV): m/z (%): 262 (M^+ + 1, 100). HRMS (ESI) calcd for $C_{11}H_{11}F_3NO_3^+$: 262.06861 $[M + H]^+$. Found: 262.0682.

***Cis*-3-hydroxy-1-(4-methoxybenzyl)-4-(trifluoromethyl)azetidin-2-one 3b**



White crystals. Mp 114 °C. Recrystallization from Hex/EtOAc, 30/1. Yield 93%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.80 (3H, s, OCH_3), 3.89 (1H, q × d, J = 5.1, 6.2 Hz, $CHCF_3$), 3.97 (1H, d, J = 14.8 Hz, N(<u>H</u>CH)), 4.70 (1H, d, J = 6.8 Hz, OH), 4.78 (1H, d, J = 14.8 Hz, N(HC<u>H</u>)), 5.06 (1H, d × d, J = 6.8, 5.1 Hz, C<u>H</u>OH), 6.88 and 7.15 (2 × 2H, 2 × d, J = 8.6 Hz, $O(CH_{arom})_{ortho}$ and $O(CH_{arom})_{meta}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 44.8 (NCH_2), 55.3 (OCH_3), 57.1 (q, J = 31.8, <u>C</u>HCF$_3$), 75.7 (CHOH), 114.4 (2 × $O(CH_{arom})_{ortho}$), 123.9 (q, J = 280.2 Hz, CF_3), 125.8 ($NCH_2\underline{C}_{arom,quat}$), 129.9 (2 × $O(CH_{arom})_{meta}$), 159.6 ($C_{arom,quat}O$), 168.7 (C=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -69.33 (3F, d, J = 6.2 Hz, CF_3). IR (ATR, cm^{-1}): ν_{OH} = 3296, $\nu_{C=O}$ = 1733, ν_{max} = 1513, 1409, 1247, 1158, 1126, 1033, 919, 840, 814, 655. MS (70eV): m/z (%): 276 (M^+ + 1, 100). HRMS (ESI) calcd for $C_{12}H_{13}F_3NO_3^+$: 276.0842 $[M + H]^+$. Found: 276.0844.

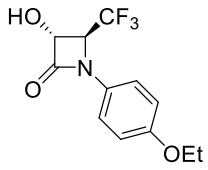
***Cis*-1-(4-ethoxyphenyl)-3-hydroxy-4-(trifluoromethyl)azetidin-2-one 3c**



White crystals. Mp 144 °C. Recrystallization from Hex/EtOAc, 30/1. Yield 94%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.40 (3H, t, J = 7.0 Hz, $OCH_2C\underline{H}_3$), 4.01 (2H, q, J = 7.0 Hz, $OC\underline{H}_2CH_3$), 4.20 (1H, s, OH), 4.63 (1H, quintet, J = 5.5 Hz, $CHCF_3$), 5.31 (1H, d, J = 5.5 Hz, OC<u>H</u>CHCF$_3$), 6.87 and 7.37 (2 × 2H, 2 × d, J = 9.0 Hz, $N(CH_{arom})_{ortho}$ and $O(CH_{arom})_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 14.8 ($OCH_2\underline{C}H_3$), 58.2 (q, J =

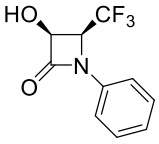
32.0 Hz, $\underline{C}HCF_3$), 63.8 ($O\underline{C}H_2CH_3$), 75.2 ($O\underline{C}HCHCF_3$), 115.0 (2 × $O(CH_{arom})_{ortho}$), 119.5 (2 × $N(CH_{arom})_{ortho}$), 123.7 (q, J = 281.6 Hz, CF_3), 129.1 ($NC_{arom,quat}$), 156.8 ($OC_{arom,quat}$), 165.6 (C=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -68.48 (3F, d, J = 5.5 Hz, CF_3). IR (ATR, cm^{-1}): ν_{OH} = 3306, $\nu_{C=O}$ = 1728, ν_{max} = 1514, 1296, 1250, 1167, 1136, 1038, 860, 822, 652, 522. MS (70eV): 276 (M^+ + 1, 70).

Trans-1-(4-ethoxyphenyl)-3-hydroxy-4-(trifluoromethyl)azetidin-2-one



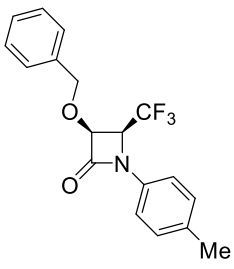
White crystals. Mp 102 °C. Recrystallization from Hex/EtOAc, 30/1. Yield 84%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.41 (3H, t, J = 7.0 Hz, $OCH_2C\underline{H}_3$), 4.00 (2H, q, J = 7.0 Hz, $OC\underline{H}_2CH_3$), 4.42 (1H, q × d, J = 5.7, 1.1 Hz, $CHCF_3$), 4.93 (1H, s, OH), 5.03 (1H, ~s, $OC\underline{H}CHCF_3$), 6.85 and 7.26 (2 × 2H, 2 × d, J = 9.0 Hz, $N(CH_{arom})_{ortho}$ and $O(CH_{arom})_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 14.7 ($OCH_2\underline{C}H_3$), 61.4 (q, J = 34.2 Hz, $\underline{C}HCF_3$), 63.8 ($O\underline{C}H_2CH_3$), 76.2 (q, J = 2.2 Hz, $O\underline{C}HCHCF_3$), 115.0 (2 × $O(CH_{arom})_{ortho}$), 120.4 (2 × $N(CH_{arom})_{ortho}$), 123.5 (q, J = 280.3 Hz, CF_3), 128.3 ($NC_{arom,quat}$), 157.1 ($OC_{arom,quat}$), 166.0 (C=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -71.72 (3F, d, J = 5.7 Hz, CF_3). IR (ATR, cm^{-1}): ν_{OH} = 3237, $\nu_{C=O}$ = 1736, ν_{max} = 1512, 1479, 1400, 1283, 1250, 1144, 1103, 1049, 876, 822, 696. MS (70eV): 276 (M^+ + 1, 100).

Cis-3-hydroxy-1-phenyl-4-(trifluoromethyl)azetidin-2-one 3d



White crystals. Mp 164 °C. Recrystallization from Hex/EtOAc, 30/1. Yield 84%. ^{1}H NMR (400 MHz, CD_3OD): δ 4.98 (1H, quintet, J = 5.7 Hz, $CHCF_3$), 5.29 (1H, d, J = 5.7 Hz, $C\underline{H}CHCF_3$), 7.19 (1H, t, J = 7.7 Hz, $N(CH_{arom})_{para}$), 7.39 (2H, t, J = 7.8 Hz, $N(CH_{arom})_{meta}$), 7.51 (2H, d, J = 7.8 Hz, $N(CH_{arom})_{ortho}$). ^{13}C NMR (100.6 MHz, CD_3OD): δ 57.8 (q, J = 31.5 Hz, $\underline{C}HCF_3$), 74.9 ($\underline{C}HCHCF_3$), 117.4 (2 × $N(CH_{arom})_{ortho}$), 124.3 (q, J = 279.7 Hz, $CH\underline{C}F_3$), 124.9 ($N(CH_{arom})_{para}$), 128.8 (2 × $N(CH_{arom})_{meta}$), 136.7 ($NC_{arom,quat}$), 167.0 (C=O). ^{19}F NMR (376.5 MHz, CD_3OD): δ -70.18 (3F, d, J = 5.7 Hz, CF_3). IR (ATR, cm^{-1}): ν_{OH} = 2448, $\nu_{C=O}$ = 1724, ν_{max} = 1499, 1393, 1281, 1252, 1142, 758, 691, 664. MS (70eV): 249 (M^+ + 18, 100).

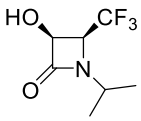
Cis-3-hydroxy-1-(4-methylphenyl)-4-(trifluoromethyl)azetidin-2-one 3e



White crystals. Mp 176 °C. Recrystallization from Hex/EtOAc, 30/1. Yield 87%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.33 (3H, s, CH_3), 3.22 (1H, brs, OH), 4.66 (1H, quintet, J = 5.5 Hz, $CHCF_3$), 5.28 (1H, d × d, J = 8.2, 5.5 Hz, $OC\underline{H}CHCF_3$), 7.17 and 7.36 (2 × 2H, 2 × d, J = 8.3 Hz, $N(CH_{arom})_{ortho}$ and $CH_3(C\underline{H}_{arom})_{ortho}$). ^{13}C NMR (100.6 MHz, CD_3OD): δ 19.5 (CH_3), 57.8 (q, J = 31.5 Hz, $\underline{C}HCF_3$), 74.9 (OCH), 117.5 (2 × $CH_3(\underline{C}H_{arom})_{ortho}$), 124.3 (q, J = 279.9 Hz, $CH\underline{C}F_3$),

129.2 (2 × N(CH_{arom})$_{ortho}$), 134.1 (N$C_{arom,quat}$), 134.9 ($CH_3\underline{C}_{arom,quat}$), 166.8 (C=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -68.41 (3F, d, J = 5.5 Hz, CF_3). IR (ATR, cm^{-1}): ν_{OH} = 2455, $\nu_{C=O}$ = 1732, ν_{max} = 1512, 1389, 1281, 1248, 1167, 1082, 860, 810, 646, 471. MS (70eV): 263 (M^+ + 18, 100), 246 (M^+ + 1, 40).

Cis-3-hydroxy-1-isopropyl-4-(trifluoromethyl)azetidin-2-one 3f

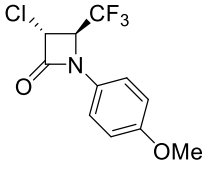


White crystals. Mp 85 °C. Recrystallization from Hex/EtOAc, 30/1. Yield 97%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26 and 1.30 (2 × 3H, 2 × d, J = 6.8 Hz, ($C\underline{H}_3$)$_2$CHN), 3.87 (1H, septet, J = 6.8 Hz, (CH_3)$_2$C$\underline{H}$N), 4.12 (1H, q × d, J = 6.3, 5.1 Hz, $CHCF_3$), 4.61 (1H, d, J = 5.9 Hz, OH), 5.07 (1H, d × d, J = 5.9, 5.1 Hz, C$\underline{H}$CHCF$_3$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 19.3 and 21.0 (($\underline{C}H_3$)$_2$CH), 45.4 ((CH_3)$_2\underline{C}$H), 57.2 (q, J = 32.1 Hz, $\underline{C}HCF_3$), 74.7 (OCH), 123.8 (q, J = 279.7 Hz, CF_3), 168.6 (C=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -69.44 (3F, d, J = 6.3 Hz, CF_3). IR (ATR, cm^{-1}): ν_{OH} = 3240, $\nu_{C=O}$ = 1719, ν_{max} = 1580, 1385, 1371, 1217, 1153, 1119, 1053, 932, 854, 810, 646. MS (70eV): 198 (M^+ + 1, 70).

Synthesis of *trans*-3-chloro-4-(trifluoromethyl)azetidin-2-ones 4

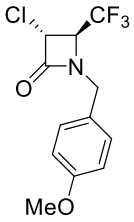
To a solution of *cis*-3-hydroxy-1-(4-methoxyphenyl)-4-(trifluoromethyl)azetidin-2-one **3a** (1.49 g, 5.71 mmol, 1 equiv) in CCl_4 (10 mL) at room temperature was added triphenylphosphine (2.99 g, 11.42 mmol, 2 equiv) and $NaHCO_3$ as a catalyst (0.07 g, 0.86 mmol, 0.15 equiv). The mixture was heated under reflux for 10 hours. Filtration of the heterogenous mixture through Celite® and evaporation of the solvent *in vacuo* afforded *trans*-3-chloro-1-(4-methoxyphenyl)-4-(trifluoromethyl)azetidin-2-one **4a** (1.54 g, 5.52 mmol, 97%), which was purified by means of column chromatography on silica gel (PE/EtOAc, 8/1).

Trans-3-chloro-1-(4-methoxyphenyl)-4-(trifluoromethyl)azetidin-2-one 4a



Colorless solid. Mp 52 °C. R_f = 0.32 (PE/EtOAc, 8/1). Yield 97%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.80 (3H, s, OCH_3), 4.55 (1H, q × d, J = 5.3, 1.8 Hz, $CHCF_3$), 4.93 (1H, d, J = 1.8 Hz, CHCl), 6.91 and 7.35 (2 × 2H, 2 × d, J = 9.1 Hz, N(CH_{arom})$_{ortho}$) and O(CH_{arom})$_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 55.5 (OCH_3), 55.8 (q, J = 2.0 Hz, CHCl), 61.8 (q, J = 34.9 Hz, $\underline{C}HCF_3$), 114.6 (2 × O(CH_{arom})$_{ortho}$), 120.1 (2 × N(CH_{arom})$_{ortho}$), 123.1 (q, J = 281.1 Hz, CF_3), 128.7 ($C_{arom,quat}$N), 157.8 ($C_{arom,quat}$O), 159.0 (C=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -72.36 (3F, d, J = 5.3 Hz, CF_3). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1771, ν_{max} = 1510, 1269, 1256, 1173, 1159, 1132, 1113, 1090, 1038, 878, 820, 800, 689, 588, 511, 424. MS (70eV): m/z (%): 297 (M^+ + 18, 100).

Trans-3-chloro-1-(4-methoxybenzyl)-4-(trifluoromethyl)azetidin-2-one 4b

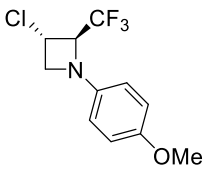


Yellowish oil. R_f = 0.40 (PE/EtOAc, 8)/1). Yield 91%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.808 (1H, q × d, J = 5.7, 1.4 Hz, $CHCF_3$), 3.811 (3H, s, OCH_3), 3.96 (1H, d, J = 15.0 Hz, N(HC<u>H</u>)Ar), 4.81 (1H, d, J = 1.4 Hz, CHCl), 4.86 (1H, d, J = 15.0 Hz, N(<u>H</u>CH)Ar), 6.91 and 7.19 (2 × 2H, 2 × d, J = 8.6 Hz, $NCH_2(C\underline{H}_{arom})_{ortho}$ and $O(CH_{arom})_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 45.6 ($N\underline{C}H_2Ar$), 55.3 (OCH_3), 55.9 (q, J = 2.4 Hz, CHCl), 60.1 (q, J = 34.7 Hz, $\underline{C}HCF_3$), 114.5 (2 × $O(CH_{arom})_{ortho}$), 123.1 (q, J = 280.2 Hz, CF_3), 125.3 ($C_{arom,quat}N$), 129.9 (2 × $NCH_2(\underline{C}H_{arom})_{ortho}$), 159.8 ($C_{arom,quat}O$), 161.9 (C=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -73.72 (3F, d, J = 5.7 Hz, CF_3). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1786, ν_{max} = 1514, 1275, 1246, 1190, 1161, 1132, 1107, 1032, 835, 687, 621. MS (70eV): m/z (%): 294 (M^+ + 1, 10), 311 (M^+ + 18, 100).

The synthesis of *trans*-3-chloro-2-(trifluoromethyl)azetidines 5

To an ice-cooled solution of $AlCl_3$ (0.38 g, 2.86 mmol, 2 equiv) in dry Et_2O (10 mL), $LiAlH_4$ (1M in THF, 0.11 g, 2.86 mL, 2.86 mmol, 2 equiv) was carefully added dropwise. The reaction mixture was allowed to reach room temperature, and then was heated for 30 minutes at reflux temperature. Afterwards, the reaction mixture was cooled to 0 °C and *trans*-3-chloro-1-(4-methoxyphenyl)-4-(trifluoromethyl)azetidin-2-one **4a** (0.40 g, 1.43 mmol, 1 equiv) was added. After stirring for five minutes at room temperature, the reaction was quenched with water (10 mL) and filtered through a short pad of Celite®. Extraction with Et_2O (3 × 10 mL), drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded a crude mixture. The ^{1}H NMR and ^{19}F NMR of this mixture showed it to consist of *trans*-3-chloro-1-(4-methoxyphenyl)-2-(trifluoromethyl)azetidine **5a** and a ring-opening product *anti*-2-chloro-4,4,4-trifluoro-3-[(4-methoxyphenyl)amino]butan-1-ol in a ratio of 66:34. The mixture was separated by flash column chromatography (PE/EtOAc, 12/1) to give pure *trans*-3-chloro-1-(4-methoxyphenyl)-2-(trifluoromethyl)azetidine **5a** (54%).

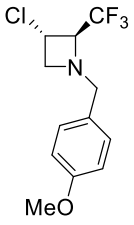
Trans-3-chloro-1-(4-methoxyphenyl)-2-(trifluoromethyl)azetidine 5a



Yellow solid. Mp 50 °C. R_f = 0.55 (PE/EtOAc, 12/1). Yield 54%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.76 (3H, s, OCH_3), 3.78 (1H, d × d, J = 7.9, 6.7 Hz, (<u>H</u>CH)CHCl), 4.38 (1H, q, J = 5.5 Hz, $CHCF_3$), 4.49 (1H, d × d, J = 7.9, 6.7 Hz, (HC<u>H</u>)CHCl), 4.69 (1H, d × d × d, J = 6.7, 6.7, 5.5 Hz, CHCl), 6.61 and 6.85 (2 × 2H, 2 × d, J = 9.0 Hz, $N(CH_{arom})_{ortho}$) and $O(CH_{arom})_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 44.2 (q, J = 3.4 Hz, CHCl), 55.7 (OCH_3), 61.3 ($\underline{C}H_2CHCl$), 73.0 (q, J = 33.4 Hz, $\underline{C}HCF_3$), 114.0 (q, J =

1.2 Hz, 2 × N(CH_{arom})$_{ortho}$), 114.8 (2 × O(CH_{arom})$_{ortho}$), 123.9 (q, J = 279.6 Hz, CF_3), 143.6 ($C_{arom,quat}$N), 154.1 ($C_{arom,quat}$O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -75.70 (3F, d, J = 5.5 Hz, CF_3). IR (ATR, cm^{-1}): ν_{max} = 1508, 1273, 1263, 1242, 1157, 1126, 1034, 824, 795, 692, 529. MS (70eV): m/z (%): 266 (M^+ + 1, 100).

Trans-3-chloro-1-(4-methoxybenzyl)-2-(trifluoromethyl)azetidine 5b

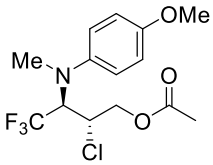


Yellowish solid. Mp 56 °C. R_f = 0.78 (PE/EtOAc, 12/1). Yield 78%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.05 (1H, t, J = 7.4 Hz, (HCH)CHCl), 3.54 (1H, d, J = 12.7 Hz, N(HCH)Ar), 3.69-3.75 (2H, m, $CHCF_3$, (HCH)CHCl), 3.80 (3H, s, OCH_3), 3.93 (1H, d, J = 12.7 Hz, N(HCH)Ar), 4.39 (1H, q, J = 6.7 Hz, CHCl), 6.87 and 7.18 (2 × 2H, 2 × d, J = 8.6 Hz, NCH_2(CH_{arom})$_{ortho}$) and O(CH_{arom})$_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 43.6 (q, J = 3.5 Hz, CHCl), 55.3 (OCH_3), 60.2 (CH_2CHCl), 61.1 (NCH_2Ar), 72.7 (q, J = 32.3 Hz, $CHCF_3$), 113.9 (2 × O(CH_{arom})$_{ortho}$), 123.9 (q, J = 278.6 Hz, CF_3), 127.8 ($C_{arom,quat}$N), 130.1 (2 × NCH_2(CH_{arom})$_{ortho}$), 159.2 ($C_{arom,quat}$O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -75.98 (3F, d, J = 6.7 Hz, CF_3). IR (ATR, cm^{-1}): ν_{max} = 1514, 1283, 1250, 1236, 1161, 1142, 1123, 1082, 1032, 827, 781, 762, 696. MS (70eV): m/z (%): 280 (M^+ + 1, 13).

Synthesis of *anti*-2-chloro-4,4,4-trifluoro-3-[*N*-(4-methoxybenzyl/phenyl)-*N*-methylamino]butyl acetates 7

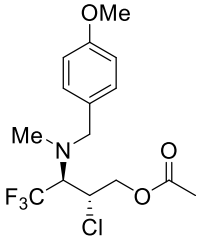
In a flame-dried flask under nitrogen atmosphere, Me_3OBF_4 (0.11 g, 0.74 mmol, 2 equiv) was added to an ice-cooled solution of *trans*-3-chloro-1-(4-methoxyphenyl)-2-(trifluoromethyl)azetidine **5a** (0.10 g, 0.37 mmol, 1 equiv) in dry CH_2Cl_2 (5 mL). After stirring for one hour at room temperature, the solvent was evaporated and the resulting residue was redissolved in CH_3CN (5 mL), after which NaOAc (0.12 g, 1.48 mmol, 4 equiv) was added. After stirring at reflux temperature for one hour, the reaction mixture was extracted with CH_2Cl_2 (3 × 5 mL) and washed with brine (3 × 5 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded a crude mixture of *anti*-2-chloro-4,4,4-trifluoro-3-[*N*-(4-methoxyphenyl)-*N*-methylamino]butyl acetate **7a** (43%) and the recovery of *trans*-3-chloro-1-(4-methoxyphenyl)-2-(trifluoromethyl)azetidine **5a** (0.02 g, 0.08 mmol) in a ratio of 53:47, which were separated by means of preparative TLC (Hex/EtOAc, 9/1) to obtain analytically pure compounds.

Anti-2-chloro-4,4,4-trifluoro-3-[*N*-(4-methoxyphenyl)-*N*-methylamino]butyl acetate 7a



Yellowish solid. Mp 48 °C. R_f = 0.30 (Hex/EtOAc, 9/1). Yield 43%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.93 (3H, s, $COOCH_3$), 2.79 (3H, q, J = 1.3 Hz, NCH_3), 3.70 (3H, s, OCH_3), 4.20-4.25 (1H, m, $CHCF_3$), 4.33-4.43 (3H, m, CHCl, $OC\underline{H}_2CHCl$), 6.73-6.78 (4H, m, $N(CH_{arom})_{ortho}$ and $O(CH_{arom})_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 20.5 ($COO\underline{C}H_3$), 33.2 (NCH_3), 52.5 (CHCl), 55.6 (OCH_3), 64.7 (q, J = 27.2 Hz, $\underline{C}HCF_3$), 65.2 ($O\underline{C}H_2CHCl$), 114.7 (2 × $O(CH_{arom})_{ortho}$), 116.5 (2 × $N(CH_{arom})_{ortho}$), 125.5 (q, J = 289.4 Hz, $CH\underline{C}F_3$), 143.5 ($NC_{arom,quat}$), 153.6 ($OC_{arom,quat}$), 170.3 (C=O). ^{19}F NMR (376 MHz, $CDCl_3$): δ -64.59 (3F, d, J = 6.1 Hz, CF_3). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1734, ν_{max} = 1514, 1252, 1227, 1163, 1140, 1107, 1045, 1034, 826. MS (70 eV): m/z (%): 340 (M^+ + 1, 100).

Anti-2-chloro-4,4,4-trifluoro-3-[*N*-(4-methoxybenzyl)-*N*-methylamino]butyl acetate 7b



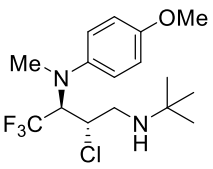
Yellowish solid. Mp 47 °C. R_f = 0.23 (Hex/EtOAc,10/1). Yield 18%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.05 (3H, s, $COOCH_3$), 2.38 (3H, q, J = 1.8 Hz, NCH_3), 3.49 (1H, d × q, J = 9.1, 7.7 Hz, $CHCF_3$), 3.77 (1H, 2 × d, J = 12.8 Hz, ($\underline{H}$CH)N), 3.80 (3H, s, OCH_3), 3.82 (1H, 2 × d, J = 12.8 Hz, (HC$\underline{H}$)N), 4.25-4.35 (2H, m, CHCl, O($\underline{H}$CH)CHCl), 4.55 (1H, d × d, J = 11.8, 2.7 Hz, O(HC$\underline{H}$)CHCl), 6.86 and 7.15 (2 × 2H, 2 × d, J = 8.6 Hz, $NCH_2(C\underline{H}_{arom})_{ortho}$ and $O(CH_{arom})_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 20.7 ($COO\underline{C}H_3$), 36.5 (NCH_3), 53.1 (CHCl), 55.3 (OCH_3), 60.0 ($N\underline{C}H_2Ar$), 65.0 (q, J = 24.9 Hz, $\underline{C}HCF_3$), 65.6 ($O\underline{C}H_2CHCl$), 113.9 (2 × $O(CH_{arom})_{ortho}$), 126.6 (q, J = 293.4 Hz, $CH\underline{C}F_3$), 129.7 ($NCH_2\underline{C}_{arom,quat}$), 130.1 (2 × $NCH_2(C\underline{H}_{arom})_{ortho}$), 159.1 ($OC_{arom,quat}$), 170.6 (C=O). ^{19}F NMR (376 MHz, $CDCl_3$): δ -62.33 (3F, d, J = 7.7 Hz, CF_3). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1744, ν_{max} = 1512, 1233, 1169, 1119, 1107, 1061, 1034. MS (70 eV): m/z (%): 371 (M^+ + 18, 40).

Synthesis of *anti*-N^1-(*tert*-butyl)-2-chloro-4,4,4-trifluoro-N^3-(4-methoxybenzyl/phenyl)-N^3-methylbutane-1,3-diamines 8

In a flame-dried flask under nitrogen atmosphere, Me_3OBF_4 (0.11 g, 0.74 mmol, 2 equiv) was added to an ice-cooled solution of *trans*-3-chloro-1-(4-methoxyphenyl)-2-(trifluoromethyl)azetidine **5a** (0.10 g, 0.37 mmol, 1 equiv) in dry CH_2Cl_2 (5 mL). After stirring for one hour at room temperature, the solvent was evaporated and the resulting residue was redissolved in CH_3CN (5 mL), followed by the addition of *tert*-butylamine (0.11 g, 0.16 mL, 1.48 mmol, 4 equiv). After stirring at reflux temperature for one hour, the reaction mixture was extracted with CH_2Cl_2 (3 × 5 mL) and washed with brine (3 × 5 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the

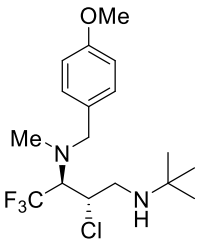
solvent afforded a crude mixture of *anti*-N^1-(*tert*-butyl)-2-chloro-4,4,4-trifluoro-N^3-(4-methoxyphenyl)-N^3-methylbutane-1,3-diamine **8a** (38%) and the recuperation of *trans*-3-chloro-1-(4-methoxyphenyl)-2-(trifluoromethyl)azetidine **5a** (0.005 g, 0.02 mmol) in a ratio of 80:20, which were separated by means of preparative TLC (Hex/EtOAc, 10/1) to obtain analytically pure samples.

Anti-N^1-(*tert*-butyl)-2-chloro-4,4,4-trifluoro-N^3-(4-methoxyphenyl)-N^3-methylbutane-1,3-diamine 8a



Yellow oil. Solidified in fridge. R_f = 0.14 (Hex/EtOAc,10/1). Yield 38%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.94 (9H, s, $C_{quat}(CH_3)_3$), 2.76 (3H, q, J = 1.4 Hz, NCH_3), 2.83 (1H, d × d, J = 12.3, 5.6 Hz, (HCH)NH), 2.94 (1H, d × d, J = 12.3, 3.2 Hz, (HCH)NH)), 3.70 (3H, s, OCH_3), 4.32 (1H, d × d × d, J = 9.6, 5.6, 3.2 Hz, CHCl), 4.53 (1H, d × q, J = 9.6, 7.5 Hz, $CHCF_3$), 6.76 and 6.85 (2 × 2H, 2 × d, J = 9.3 Hz, $N(CH_{arom})_{ortho}$ and $O(CH_{arom})_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 29.0 ($C_{quat}(\underline{C}H_3)_3$), 32.9 ($NCH_3$), 45.5 ($ClCH\underline{C}H_2$), 50.1 ($\underline{C}_{quat}(CH_3)_3$), 55.6 ($OCH_3$), 57.1 (CHCl), 64.7 (q, J = 26.5 Hz, $\underline{C}HCF_3$), 114.5 (2 × $O(CH_{arom})_{ortho}$), 116.5 (2 × $N(CH_{arom})_{ortho}$), 125.9 (q, J = 290.0 Hz, $CH\underline{C}F_3$), 144.0 ($NC_{arom,quat}$), 153.2 ($OC_{arom,quat}$). ^{19}F NMR (376 MHz, $CDCl_3$): δ -64.15 (3F, d, J = 7.5 Hz, CF_3). IR (ATR, cm^{-1}): ν_{NH} = 2959, ν_{max} = 1512, 1246, 1225, 1165, 1132, 1101, 1038, 818, 698. MS (70 eV): m/z (%): 353 (M^+ + 1, 100).

Anti-N^1-(*tert*-butyl)-2-chloro-4,4,4-trifluoro-N^3-(4-methoxybenzyl)-N^3-methylbutane-1,3-diamine 8b

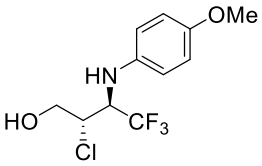


Yellowish oil. R_f = 0.25 (PE/EtOAc,12/1). Yield 11%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.98 (9H, s, $C_{quat}(CH_3)_3$), 1.49 (1H, d, J = 3.1 Hz, (HCH)NH), 1.63 (1H, d, J = 6.5 Hz, (HCH)NH)), 2.02 (1H, d × d × d, J = 8.3, 6.5, 3.1 Hz, CHCl), 2.44 (3H, q, J = 1.2 Hz, NCH_3), 2.70 (1H, quintet, J = 8.3 Hz, $CHCF_3$), 3.73 and 3.79 (2 × 1H, 2 × d, J = 13.3 Hz, N(HCH) Ar), 3.80 (3H, s, OCH_3), 6.84 and 7.21 (2 × 2H, 2 × d, J = 8.6 Hz, $NCH_2(C\underline{H}_{arom})_{ortho}$ and $O(CH_{arom})_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 24.5 ($ClCH\underline{C}H_2$), 26.4 ($C_{quat}(\underline{C}H_3)_3$), 29.4 (CHCl), 38.2 ($NCH_3$), 53.2 ($\underline{C}_{quat}(CH_3)_3$), 55.3 ($OCH_3$), 58.9 ($N\underline{C}H_2Ar$), 66.8 (q, J = 24.6 Hz, $\underline{C}HCF_3$), 113.8 (2 × $O(CH_{arom})_{ortho}$), 127.2 (q, J = 290.9 Hz, $CH\underline{C}F_3$), 129.6 (2 × $NCH_2(\underline{C}H_{arom})_{ortho}$), 131.0 ($NCH_2\underline{C}_{arom,quat}$), 158.8 ($OC_{arom,quat}$). ^{19}F NMR (376 MHz, $CDCl_3$): δ -67.19 (3F, d, J = 8.3 Hz, CF_3). IR (ATR, cm^{-1}): ν_{NH} = 2967, 2928, ν_{max} = 1512, 1244, 1169, 1103, 1034, 829, 814. MS (70 eV): m/z (%): 331 (M^+ - 35, 100).

Synthesis of *anti*-2-chloro-4,4,4-trifluoro-3-[(4-methoxybenzyl/phenyl)amino]butan-1-ols 9

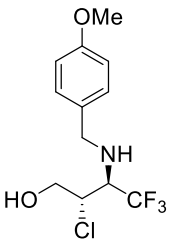
To an ice-cooled solution of *trans*-3-chloro-1-(4-methoxyphenyl)-4-(trifluoromethyl)azetidin-2-one **4a** (0.50 g, 1.79 mmol, 1 equiv) in Et_2O (10 mL) was added $LiAlH_4$ (1M in THF, 0.07 g, 1.79 mL, 1.79 mmol, 1 equiv) in small portions whilst stirring. After stirring for five minutes at room temperature, the reaction mixture was cooled to 0 °C, quenched with water (5 mL) and filtered through a short pad of Celite®. Extraction with Et_2O (3 × 5 mL), drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded *anti*-2-chloro-4,4,4-trifluoro-3-[(4-methoxyphenyl)amino]butan-1-ol **9a**, which was purified by means of column chromatography on silica gel (Hex/EtOAc, 3/1) to obtain an analytically pure sample (0.49 g, 1.73 mmol, 96%).

Anti-2-chloro-4,4,4-trifluoro-3-[(4-methoxyphenyl)amino]butan-1-ol 9a



Yellowish oil. R_f = 0.32 (Hex/EtOAc, 3/1). Yield 96%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.43 (1H, t, J = 6.4 Hz, OH), 3.74 (3H, s, OCH_3), 3.92-4.29 (5H, m, C$\underline{H}_2$CHCl, CHCl, NH, $CHCF_3$), 6.70 and 6.80 (2 × 2H, 2 × d, J = 8.9 Hz, $O(CH_{arom})_{ortho}$ and $N(CH_{arom})_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 55.7 (OCH_3), 59.0 (CHCl), 60.8 (q, J = 28.5 Hz, $\underline{C}HCF_3$), 64.1 (q, J = 2.0 Hz, $\underline{C}H_2CHCl$), 115.0 (2 × $N(HC_{arom})_{ortho}$), 115.9 (2 × $O(HC_{arom})_{ortho}$), 125.1 (q, J = 284.8 Hz, CF_3), 139.9 ($NC_{arom,quat}$), 153.6 ($OC_{arom,quat}$). ^{19}F NMR (376 MHz, $CDCl_3$): δ -71.30 (3F, d, J = 6.6 Hz, CF_3). IR (ATR, cm^{-1}): $\nu_{NH,OH}$ = 3387, ν_{max} = 1510, 1233, 1171, 1125, 1032, 820. MS (70 eV): *m/z* (%) 284 (M^+ + 1, 100).

Anti-2-chloro-4,4,4-trifluoro-3-[(4-methoxybenzyl)amino]butan-1-ol 9b

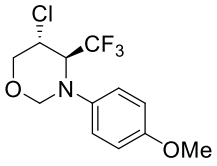


Yellowish oil. R_f = 0.43 (Hex/EtOAc, 3/1). Yield 90%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.54 (1H, q × d, J = 7.4, 5.6 Hz, $CHCF_3$), 3.83 (3H, s, OCH_3), 3.876 (1H, d, J = 12.7 Hz, (HC$\underline{H}$)N), 3.877 (1H, d × d, J = 12.3, 4.5 Hz, ($\underline{H}$CH)CHCl), 3.99 (1H, d × d, J = 12.3, 5.0 Hz, (HC$\underline{H}$)CHCl), 4.02 (1H, d, J = 12.7 Hz, ($\underline{H}$CH)N), 4.17 (1H, q, J = 5.6 Hz, CHCl), 6.91 and 7.28 (2 × 2H, 2 × d, J = 8.6 Hz, $O(CH_{arom})_{ortho}$ and $NCH_2(C\underline{H}_{arom})_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 52.4 (Ar$\underline{C}H_2$N), 55.3 (OCH_3), 58.6 (CHCl), 62.3 (q, J = 27.1 Hz, $\underline{C}HCF_3$), 64.8 (q, J = 1.2 Hz, $\underline{C}H_2CHCl$), 114.0 (2 × $O(HC_{arom})_{ortho}$), 125.6 (q, J = 285.6 Hz, CF_3), 129.8 (2 × $N(HC_{arom})_{ortho}$), 130.4 ($NC_{arom,quat}$), 159.2 ($OC_{arom,quat}$). ^{19}F NMR (376 MHz, $CDCl_3$): δ -70.36 (3F, d, J = 7.4 Hz, CF_3). IR (ATR, cm^{-1}): $\nu_{NH,OH}$ = 3356, ν_{max} = 1512, 1244, 1163, 1126, 1032, 831, 816. GC-MS: *m/z* (%) = 297 (M^+, 2), 174 (6), 136 (11), 121 (100), 78 (8).

Synthesis of *trans*-5-chloro-3-(4-methoxybenzyl/phenyl)-4-trifluoromethyl-1,3-oxazinanes 10

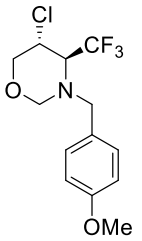
To a solution of *anti*-2-chloro-4,4,4-trifluoro-3-[(4-methoxyphenyl)amino]butan-1-ol **9a** (0.10 g, 0.35 mmol, 1 equiv) in THF (5 mL) in a pressure vial was added an excess of formaldehyde (37% solution in H_2O,1 mL) at room temperature. The resulting mixture was stirred for three hours under reflux, after which water (5 mL) was added to the mixture. Extraction with ethyl acetate (3 x 7 mL), drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded *trans*-5-chloro-3-(4-methoxyphenyl)-4-trifluoromethyl-1,3-oxazinane **10a**, which was purified by means of preparative TLC (Hex/EtOAc, 10/1) to provide an analytically pure sample in a yield of 54% (0.06 g, 0.20 mmol).

Trans-5-chloro-3-(4-methoxyphenyl)-4-trifluoromethyl-1,3-oxazinane 10a



Yellowish solid. Mp 64 °C. R_f = 0.53 (Hex/EtOAc, 10/1). Yield 54%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.81 (3H, s, OCH_3), 4.11-4.20 (2H, m, $CHCF_3$, O(HCH)CHCl), 4.26-4.33 (2H, m, O(HCH)CHCl, CHCl), 4.98 (1H, d × q, J = 11.7, 1.4 Hz, O(HCH)N), 5.04 (1H, d, J = 11.7 Hz, O(HCH)N), 6.86 and 7.22 (2 × 2H, 2 × d, J = 9.0 Hz, $N(CH_{arom})_{ortho}$ and $O(CH_{arom})_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 49.9 (CHCl), 55.5 (OCH_3), 66.5 (q, J = 29.6 Hz, $CHCF_3$), 69.4 (OCH_2CHCl), 78.7 (q, J = 1.7 Hz, OCH_2N), 114.4 (2 × $O(CH_{arom})_{ortho}$), 122.0 (2 × $N(CH_{arom})_{ortho}$), 124.8 (q, J = 284.8 Hz, $CHCF_3$), 145.0 ($NC_{arom,quat}$), 155.7 ($OC_{arom,quat}$). ^{19}F NMR (376 MHz, $CDCl_3$): δ -70.96 (3F, d, J = 9.0 Hz, CF_3). IR (ATR, cm^{-1}): ν_{max} = 1508, 1238, 1223, 1182, 1167, 1136, 1109, 1074, 1051, 1034, 999, 972, 851, 833, 824, 785, 665, 530. MS (70 eV): *m/z* (%): 296 (M^+ + 1, 100).

Trans-5-chloro-3-(4-methoxybenzyl)-4-trifluoromethyl-1,3-oxazinane 10b



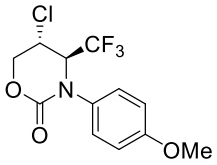
White yellowish solid. Mp 89 °C. R_f = 0.41 (Hex/EtOAc, 10/1). Yield 80%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.65 (1H, q × d, J = 9.2, 2.3 Hz, $CHCF_3$), 3.81 (3H, s, OCH_3), 4.06 (1H, d × d, J = 14.2, 3.4 Hz, O(HCH)CHCl), 4.20-4.25 (3H, m, O(HCH)CHCl, CHCl, N(HCH)Ar), 4.30 (1H, d, J = 13.3 Hz, N(HCH)Ar), 4.38 (1H, d, J = 11.5 Hz, O(HCH)N), 4.59 (1H, d × q, J = 11.5, 1.1 Hz, O(HCH)N), 6.87 and 7.28 (2 × 2H, 2 × d, J = 8.7 Hz, $NCH_2(CH_{arom})_{ortho}$ and $O(CH_{arom})_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 49.2 (CHCl), 55.3 (OCH_3), 57.8 (NCH_2Ar), 62.6 (q, J = 29.0 Hz, $CHCF_3$), 70.8 (OCH_2CHCl), 80.2 (q, J = 1.2 Hz, OCH_2N), 113.8 (2 × $O(CH_{arom})_{ortho}$), 124.5 (q, J = 283.9 Hz, $CHCF_3$), 129.5 ($NCH_2C_{arom,quat}$), 130.4 (2 × $NCH_2(CH_{arom})_{ortho}$), 159.2 ($OC_{arom,quat}$). ^{19}F NMR (376 MHz, $CDCl_3$): δ -69.60 (3F, d, J = 9.2

Hz, CF_3). IR (ATR, cm^{-1}): ν_{max} = 1510, 1246, 1182, 1167, 1109, 1090, 1053, 1034, 999, 970, 837, 665, 515. GC-MS: *m/z* (%) = 309 (M^+, 8), 121 (100), 78 (8).

Synthesis of *trans*-5-chloro-3-(4-methoxybenzyl/phenyl)-4-trifluoromethyl-1,3-oxazinan-2-ones 11

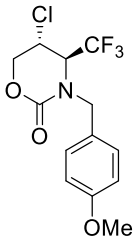
To a solution of *anti*-2-chloro-4,4,4-trifluoro-3-[(4-methoxyphenyl)amino]butan-1-ol **9a** (0.10 g, 0.35 mmol, 1 equiv) in dry CH_2Cl_2 (8 mL) was added triethylamine (0.07 g, 0.1 mL, 0.70 mmol, 2 equiv) at 0 °C. Ethyl chloroformate (0.04 g, 0.04 mL, 0.35 mmol, 1 equiv) was added dropwise to the solution. The mixture was stirred at room temperature for three hours, after which the reaction mixture was extracted with CH_2Cl_2 (3 × 5 mL) and washed with brine (3 × 5 mL). Drying ($MgSO_4$), filtration of the drying agent, and removal of the solvent *in vacuo* afforded a mixture of *anti*-2-chloro-4,4,4-trifluoro-3-[(4-methoxyphenyl)amino]butan-1-ol **9a** and *trans*-5-chloro-3-(4-methoxyphenyl)-4-trifluoromethyl-1,3-oxazinan-2-one **11a** in a ratio of 66:34. The mixture was redissolved in dry CH_2Cl_2 (5 mL) and an analogous procedure was repeated two more times. In this way, the starting material **9a** was completely converted into *trans*-5-chloro-3-(4-methoxyphenyl)-4-trifluoromethyl-1,3-oxazinan-2-one **11a** (29%), which was purified by means of preparative TLC (Hex/EtOAc, 4/1) to obtain an analytically pure sample.

***Trans*-5-chloro-3-(4-methoxyphenyl)-4-trifluoromethyl-1,3-oxazinan-2-one 11a**



White yellowish solid. Mp 100 °C. R_f = 0.12 (Hex/EtOAc, 4/1). Yield 29%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.82 (3H, s, OCH_3), 4.43 (1H, q × t, *J* = 6.5, 2.3 Hz, $CHCF_3$), 4.51 (1H, d, *J* = 13.3 Hz, O(HCH)CHCl), 4.68 (1H, q, *J* = 2.3 Hz, CHCl), 4.83 (1H, d × d, *J* = 13.3, 2.3 Hz, O(HCH)CHCl), 6.94 and 7.25 (2 × 2H, 2 × d, *J* = 8.9 Hz, $N(CH_{arom})_{ortho}$ and $O(CH_{arom})_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 46.8 (q, *J* = 1.2 Hz, CHCl), 55.5 (OCH_3), 67.0 (q, *J* = 29.9 Hz, $\underline{C}HCF_3$), 69.0 (q, *J* = 2.2 Hz, $O\underline{C}H_2CHCl$), 114.8 (2 × $O(CH_{arom})_{ortho}$), 123.1 (q, *J* = 285.7 Hz, $CH\underline{C}F_3$), 128.7 (2 × $N(CH_{arom})_{ortho}$), 134.2 ($NC_{arom,quat}$), 150.2 ($OC_{arom,quat}$), 159.3 (C=O). ^{19}F NMR (376 MHz, $CDCl_3$): δ -71.67 (3F, d, *J* = 6.5 Hz, CF_3). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1705, ν_{max} = 1514, 1429, 1319, 1184, 1167, 1134, 1115, 1026, 827, 748, 665, 581. MS (70 eV): *m/z* (%): 310 (M^+ + 1, 100).

Trans-5-chloro-3-(4-methoxybenzyl)-4-trifluoromethyl-1,3-oxazinan-2-one 11b

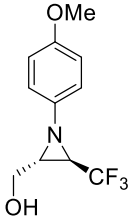


Yellow solid. Mp 68 °C. R_f = 0.21 (Hex/EtOAc, 4/1). Yield 85%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.81 (3H, s, OCH_3), 3.91 (1H, q × t, J = 6.5, 2.4 Hz, $CHCF_3$), 3.96 (1H, d, J = 14.8 Hz, N(HC<u>H</u>)Ar), 4.31 (1H, d × q, J = 13.1, 1.1 Hz, O(<u>H</u>CH)CHCl), 4.45 (1H, q, J = 2.4 Hz, CHCl), 4.68 (1H, d × d, J = 13.1, 2.4 Hz, O(HC<u>H</u>)CHCl), 5.54 (1H, d, J = 14.8 Hz, N(<u>H</u>CH)Ar), 6.89 and 7.26 (2 × 2H, 2 × d, J = 8.5 Hz, $NCH_2(C\underline{H}_{arom})_{ortho}$ and $O(CH_{arom})_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 46.3 (q, J = 1.2 Hz, CHCl), 51.0 (q, J = 1.2 Hz, $N\underline{C}H_2Ar$), 55.3 (OCH_3), 59.8 (q, J = 30.0 Hz, $\underline{C}HCF_3$), 68.3 (q, J = 2.0 Hz, $O\underline{C}H_2CHCl$), 114.2 (2 × $O(CH_{arom})_{ortho}$), 123.6 (q, J = 286.1 Hz, $CH\underline{C}F_3$), 125.9 ($NCH_2\underline{C}_{arom,quat}$), 130.8 (2 × $NCH_2(\underline{C}H_{arom})_{ortho}$), 151.0 ($OC_{arom,quat}$), 159.8 (C=O). ^{19}F NMR (376 MHz, $CDCl_3$): δ -71.03 (3F, d, J = 6.5 Hz, CF_3). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1697, ν_{max} = 1512, 1435, 1250, 1231, 1209, 1165, 1148, 1111, 1092, 1032, 1011, 750, 669, 588. MS (70 eV): *m/z* (%): 324 (M^+ + 1, 60).

Synthesis of *trans*-2-hydroxymethyl-1-(4-methoxybenzyl/phenyl)-3-(trifluoromethyl)aziridines 12

t-BuOK (1M in THF, 0.03 g, 0.28 mL, 0.28 mmol, 0.8 equiv) was added dropwise to a stirred solution of *anti*-2-chloro-4,4,4-trifluoro-3-[(4-methoxyphenyl)amino]butan-1-ol **9a** (0.10 g, 0.35 mmol, 1 equiv) in dry THF (5 mL), and the resulting suspension was stirred at room temperature under argon for 10 minutes. The reaction mixture was extracted with EtOAc (3 × 5 mL) and washed with brine (3 × 5 mL). Drying ($MgSO_4$), filtration of the drying agent, and removal of the solvent *in vacuo* afforded *trans*-2-hydroxymethyl-1-(4-methoxyphenyl)-3-(trifluoromethyl)aziridine **12a** (0.02 g, 0.08 mmol, 27%), which was purified by means of preparative TLC (Hex/EtOAc, 5/1) to obtain an analytically pure sample.

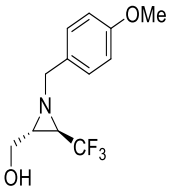
Trans-2-hydroxymethyl-1-(4-methoxyphenyl)-3-(trifluoromethyl)aziridine 12a



Orange solid. Mp 53 °C. R_f = 0.38 (Hex/EtOAc, 5/1). Yield 27%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.68 (1H, d × d, J = 4.8, 2.6 Hz, (<u>H</u>CH)OH), 2.79 (1H, d × d, J = 4.8, 4.2 Hz, (HC<u>H</u>)OH), 3.37-3.39 (1H, m, C<u>H</u>CHCF$_3$), 3.65 (1H, d, J = 9.4 Hz, OH), 3.74 (3H, s, OCH_3), 4.03-4.11 (1H, m, $CHCF_3$), 6.62 and 6.78 (2 × 2H, 2 × d, J = 8.9 Hz, $O(CH_{arom})_{ortho}$ and $N(CH_{arom})_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 42.3 (CH_2OH), 48.1 (q, J = 2.7 Hz, $\underline{C}HCHCF_3$), 55.6 (q, J = 29.3 Hz, $\underline{C}HCF_3$), 55.7 (OCH_3), 115.0 (2 × $N(HC_{arom})_{ortho}$), 115.1 (2 × $O(HC_{arom})_{ortho}$), 125.4 (q, J = 284.0 Hz, CF_3), 139.9 ($NC_{arom,quat}$), 153.3 ($OC_{arom,quat}$). ^{19}F

NMR (376 MHz, $CDCl_3$): δ -74.78 (3F, d, J = 7.9 Hz, CF_3). IR (ATR, cm^{-1}): ν_{OH} = 3374, ν_{max} = 1514, 1258, 1231, 1165, 1148, 1125, 1111, 1034, 824, 764, 525. MS (70 eV): *m/z* (%) 248 (M^+ + 1, 100).

Trans-2-hydroxymethyl-1-(4-methoxybenzyl)-3-(trifluoromethyl)aziridine 12b

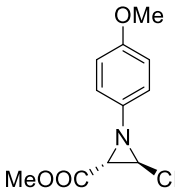


Light yellow oil. R_f = 0.46 (Hex/EtOAc, 4/1). Yield 61%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.78 (1H, d × d, J = 5.1, 2.6 Hz, (HCH)OH), 2.82 (1H, d × d, J = 5.1, 4.3 Hz, (HCH)OH), 3.05 (1H, q × d, J = 7.3, 4.3 Hz, $CHCF_3$), 3.17 (1H, t × d, J = 4.3, 2.6 Hz, CHCHCF$_3$), 3.83 (3H, s, OCH_3), 3.90 and 3.98 (2 × 1H, 2 × d, J = 13.1 Hz, NCH_2Ar), 6.89 and 7.28 (2 × 2H, 2 × d, J = 8.7 Hz, $O(CH_{arom})_{ortho}$ and $NCH_2(CH_{arom})_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 43.6 (CH_2OH), 49.7 (q, J = 2.9 Hz, CHCHCF$_3$), 51.0 (ArCH_2N), 55.3 (OCH_3), 59.1 (q, J = 27.5 Hz, $CHCF_3$), 113.9 (2 × $O(HC_{arom})_{ortho}$), 125.8 (q, J = 284.3 Hz, CF_3), 129.5 (2 × $NCH_2(CH_{arom})_{ortho}$), 131.2 ($NCH_2C_{arom,quat}$), 158.9 ($OC_{arom,quat}$). ^{19}F NMR (376 MHz, $CDCl_3$): δ -73.15 (3F, d, J = 7.3 Hz, CF_3). IR (ATR, cm^{-1}): ν_{OH} = 3350, ν_{max} = 1512, 1246, 1150, 1123, 1105, 1034, 831, 816. GC-MS: *m/z* (%) = 261 (M^+, 17), 136 (19), 121 (100), 78 (9).

Synthesis of *trans*-2-methoxycarbonyl-1-(4-methoxybenzyl/phenyl)-3-(trifluoromethyl)aziridines 13

KOH (0.02 g, 0.36 mmol, 2 equiv) was added to an solution of *trans*-3-chloro-1-(4-methoxyphenyl)-4-(trifluoromethyl)azetidin-2-one **4a** (0.05 g, 0.18 mmol, 1 equiv) in MeOH (6 mL). After stirring for 20 minutes under reflux, the reaction mixture was cooled to 0 °C, and quenched with water (5 mL). Extraction with EtOAc (3 × 5 mL), drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded *trans*-2-methoxycarbonyl-1-(4-methoxyphenyl)-3-(trifluoromethyl)aziridine **13a**, which was purified by means of preparative TLC (Hex/EtOAc, 5/1) to provide white yellowish solid in a yield of 73% (0.04 g, 0.14 mmol).

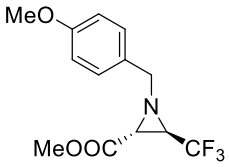
Trans-2-methoxycarbonyl-1-(4-methoxyphenyl)-3-(trifluoromethyl)aziridine 13a



White yellowish solid. Mp 74 °C. R_f = 0.40 (Hex/EtOAc, 5/1). Yield 73%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.30-3.33 (2H, m, CHCHCF$_3$, CHCHCF$_3$), 3.57 (3H, s, COOMe), 3.68 (3H, s, OCH_3), 6.71-6.76 (4H, m, $O(CH_{arom})_{ortho}$ and $N(CH_{arom})_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 39.2 (q, J = 1.9 Hz, CHCHCF$_3$), 42.1 (q, J = 40.7 Hz, $CHCF_3$), 52.8 ($COOCH_3$), 55.4 (OCH_3), 114.5 (2 × $O(HC_{arom})_{ortho}$), 120.3 (2 × $N(HC_{arom})_{ortho}$), 122.9 (q, J = 273.9 Hz, CF_3), 139.3 ($NC_{arom,quat}$), 156.2 ($OC_{arom,quat}$), 165.7 (C=O).

^{19}F NMR (376 MHz, $CDCl_3$): δ -71.08 (3F, ~s, CF_3). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1730, ν_{max} = 1508, 1265, 1246, 1148, 1080, 1030, 1013, 872, 833, 696. MS (70 eV): *m/z* (%) 276 (M^+ + 1, 100).

Trans-1-(4-methoxybenzyl)-2-methoxycarbonyl-3-(trifluoromethyl)aziridine 13b

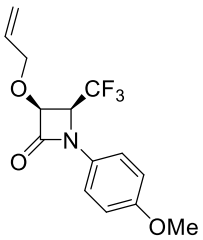


Light yellow oil. R_f = 0.21 (Hex/EtOAc, 5/1). Yield 25%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.86-2.91 (2H, m, CHC<u>H</u>CF_3, C<u>H</u>CHCF_3), 3.66 (3H, s, COOMe), 3.73 (3H, s, OCH_3), 3.80 and 3.94 (2 × 1H, 2 × d, *J* = 13.0 Hz, NC<u>H</u>$_2$Ar), 6.79 and 7.17 (2 × 2H, 2 × d, *J* = 8.6 Hz, O(CH_{arom})$_{ortho}$ and NCH_2(C<u>H</u>$_{arom}$)$_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 37.3 (<u>C</u>HCHCF_3), 43.7 (q, *J* =39.7 Hz, <u>C</u>HCF_3), 52.2 (COO<u>C</u>H_3), 53.8 (N<u>C</u>H_2Ar), 55.2 (OCH_3), 113.8 (2 × O(HC_{arom})$_{ortho}$), 123.0 (q, *J* = 273.9 Hz, CF_3), 129.49 ($NC_{arom,quat}$), 129.53 (2 × NCH_2(<u>C</u>H$_{arom}$)$_{ortho}$), 159.0 ($OC_{arom,quat}$), 167.3 (C=O). ^{19}F NMR (376 MHz, $CDCl_3$): δ -71.28 (3F, ~s, CF_3). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1736, ν_{max} = 1514, 1344, 1246, 1207, 1175, 1144, 1032, 804. GC-MS: *m/z* (%) = 290 (M^+, 4), 274 (10), 258 (8), 220 (17), 188 (16), 136 (16), 121 (100), 78 (7).

Synthesis of *cis*-3-allyloxy-4-(trifluoromethyl)azetidin-2-ones 14

To a solution of *cis*-3-hydroxy-1-(4-methoxybenzyl)-4-(trifluoromethyl)azetidin-2-one **3b** (0.30 g, 1.09 mmol, 1 equiv), tetrabutylammonium iodide (0.003 g, 0.01 mmol, 0.01 equiv) and allyl bromide (0.21 g, 0.15 mL, 1.74 mmol, 1.6 equiv) in CH_2Cl_2 (10 mL) was added aqueous sodium hydroxide (50%, 5 g, 10 mL). After stirring for three hours at room temperature, the reaction mixture was extracted with CH_2Cl_2 (3 × 5 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent *in vacuo* afforded *cis*-3-allyloxy-1-(4-methoxybenzyl)-4-(trifluoromethyl)azetidin-2-one **14b**, which was purified by means of column chromatography (Hex/EtOAc, 5/1) to obtain an analytically pure sample (0.33 g, 1.04 mmol, 95%).

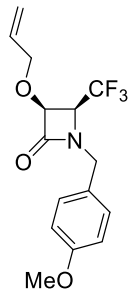
Cis-3-allyloxy-1-(4-methoxyphenyl)-4-(trifluoromethyl)azetidin-2-one 14a



White crystals. Mp 81 °C. R_f = 0.61 (Hex/EtOAc, 2/1) or recrystallization (CH_2Cl_2/Et_2O, 1/3). Yield 94%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.80 (3H, s, OCH_3), 4.22-4.32 (2H, m, OC<u>H</u>$_2$CHCH_2), 4.61 (1H, quintet, *J* = 5.4 Hz, CHCF_3), 4.96 (1H, d, *J* = 5.4 Hz, OC<u>H</u>CHCF_3), 5.30 (1H, d × q, *J* = 10.6, 1.3 Hz, OCH_2CH(HC<u>H</u>)), 5.39 (1H, d × q, *J* = 17.2, 1.6 Hz, OCH_2CH(<u>H</u>CH)), 5.94 (1H, d × d × t, *J* = 17.2, 10.6, 5.4 Hz, OCH_2C<u>H</u>CH_2), 6.89 and 7.40 (2 × 2H, 2 × d, *J* = 9.0 Hz, N(CH_{arom})$_{ortho}$ and O(CH_{arom})$_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 55.5 (OCH_3), 57.8 (q, *J* = 33.0 Hz, <u>C</u>HCF_3), 73.1 (O<u>C</u>H_2CHCH_2), 80.4 (O<u>C</u>HCHCF_3), 114.4 (2 × O(CH_{arom})$_{ortho}$), 118.9 (COCH_2CH<u>C</u>H_2), 119.4

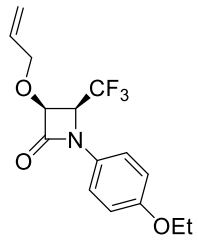
(2 × N(CH_{arom})$_{ortho}$), 123.7 (q, J = 280.7 Hz, CF_3), 129.4 ($NC_{arom,quat}$), 132.8 ($OCH_2\underline{C}HCH_2$), 157.2 ($OC_{arom,quat}$), 163.9 (C=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -68.52 (3F, d, J = 5.4 Hz, CF_3). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1759, ν_{max} = 1516, 1389, 1273, 1134, 982, 837, 808, 642, 505. MS (70eV): 302 (M^+ + 1, 100).

Cis-3-allyloxy-1-(4-methoxybenzyl)-4-(trifluoromethyl)azetidin-2-one 14b



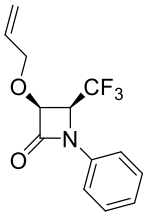
White crystals. Mp 67 °C. R_f = 0.27 (Hex/EtOAc, 5/1). Yield 95%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.80 (3H, s, OCH_3), 3.87 (1H, quintet, J = 5.6 Hz, $CHCF_3$), 3.95 (1H, d, J = 14.8 Hz, N(HC$\underline{H}$), 4.18 (2H, d, J = 5.5 Hz, OC$\underline{H}_2$CHCH_2), 4.74 (1H, d, J = 5.6 Hz, OCH), 4.81 (1H, d, J = 14.8 Hz, N($\underline{H}$CH), 5.25 (1H, d, J = 10.6 Hz, OCH_2CH(HC$\underline{H}$)), 5.33 (1H, d × q, J = 17.2, 1.5 Hz, OCH_2CH($\underline{H}$CH)), 5.88 (1H, d × d × t, J = 17.2, 10.6, 5.5 Hz, $OCH_2\underline{C}HCH_2$), 6.87 and 7.16 (2 × 2H, 2 × d, J = 8.5 Hz, NCH_2(C$\underline{H}_{arom}$)$_{ortho}$ and O(CH_{arom})$_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 44.5 (NCH_2), 55.3 (OCH_3), 56.4 (q, J = 32.7 Hz, $\underline{C}HCF_3$), 72.8 ($O\underline{C}H_2CHCH_2$), 81.1 ($O\underline{C}HCHCF_3$), 114.4 (2 × O(CH_{arom})$_{ortho}$), 118.7 ($OCH_2CH\underline{C}H_2$), 123.9 (q, J = 280.2 Hz, $CH\underline{C}F_3$), 126.1 ($NCH_2\underline{C}_{arom,quat}$), 129.9 (2 × NCH_2($\underline{C}H_{arom}$)$_{ortho}$), 132.9 ($COCH_2\underline{C}HCH_2$), 159.6 ($OC_{arom,quat}$), 166.4 (C=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -69.33 (3F, d, J = 5.6 Hz, CF_3). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1759, ν_{max} = 1514, 1352, 1279, 1244, 1152, 1126, 1113, 1032, 920, 837, 669, 635, 590, 519. MS (70eV): 316 (M^+ + 1, 100).

Cis-3-allyloxy-1-(4-ethoxyphenyl)-4-(trifluoromethyl)azetidin-2-one 14c



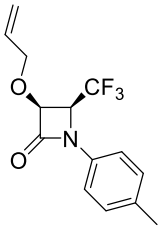
White crystals. Mp 83 °C. Recrystallization (CH_2Cl_2/Et_2O, 1/3). Yield 84%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.39 (3H, t, J = 7.0 Hz, $OCH_2C\underline{H}_3$), 4.00 (2H, q, J = 7.0 Hz, $OC\underline{H}_2CH_3$), 4.21-4.30 (2H, m, $OC\underline{H}_2CHCH_2$), 4.61 (1H, quintet, J = 5.4 Hz, $CHCF_3$), 4.95 (1H, d, J = 5.4 Hz, $OC\underline{H}CHCF_3$), 5.29 (1H, d × q, J = 10.7, 1.4 Hz, OCH_2CH(HC$\underline{H}$)), 5.38 (1H, d × q, J = 17.2, 1.6 Hz, OCH_2CH($\underline{H}$CH)), 5.93 (1H, d × d × t, J = 17.2, 10.7, 5.4 Hz, $OCH_2\underline{C}HCH_2$), 6.86 and 7.37 (2 × 2H, 2 × d, J = 9.0 Hz, N(CH_{arom})$_{ortho}$ and O(CH_{arom})$_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 14.8 ($OCH_2\underline{C}H_3$), 57.8 (q, J = 33.0 Hz, $\underline{C}HCF_3$), 63.7 ($O\underline{C}H_2CH_3$), 73.0 ($O\underline{C}H_2CHCH_2$), 80.5 ($O\underline{C}HCHCF_3$), 115.0 (2 × O(CH_{arom})$_{ortho}$), 118.8 ($OCH_2CH\underline{C}H_2$), 119.4 (2 × N(CH_{arom})$_{ortho}$), 123.7 (q, J = 280.8 Hz, CF_3), 129.3 ($NC_{arom,quat}$), 132.8 ($OCH_2\underline{C}HCH_2$), 156.6 ($OC_{arom,quat}$), 164.0 (C=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -68.54 (3F, d, J = 5.4 Hz, CF_3). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1757, ν_{max} = 1518, 1391, 1258, 1136, 1111, 980, 922, 824, 650, 525. MS (70eV): 316 (M^+ + 1, 100).

Cis-3-allyloxy-1-phenyl-4-(trifluoromethyl)azetidin-2-one 14d



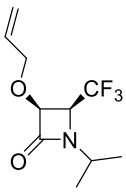
White yellowish solid. Mp <45 °C. R_f = 0.36 (PE/EtOAc, 4/1). Yield 77%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.24-4.32 (2H, m, OC<u>H</u>$_2$CHCH$_2$), 4.67 (1H, quintet, J = 5.4 Hz, C<u>H</u>CF$_3$), 4.98 (1H, d, J = 5.4 Hz, OC<u>H</u>CHCF$_3$), 5.31 (1H, d × q, J = 10.6, 1.3 Hz, OCH$_2$CH(HC<u>H</u>)), 5.40 (1H, d × q, J = 17.3, 1.5 Hz, OCH$_2$CH(<u>H</u>CH)), 5.94 (1H, d × d × t, J = 17.3, 10.6, 5.4 Hz, OCH$_2$C<u>H</u>CH$_2$), 7.18 (1H, t, J = 7.7 Hz, N(CH$_{arom}$)$_{para}$), 7.36 (2H, t, J = 7.7 Hz, N(CH$_{arom}$)$_{meta}$), 7.47 (2H, d, J = 7.7 Hz, N(CH$_{arom}$)$_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 57.5 (q, J = 33.2 Hz, <u>C</u>HCF$_3$), 73.1 (O<u>C</u>H$_2$CHCH$_2$), 80.3 (O<u>C</u>HCHCF$_3$), 117.6 (2 × N(CH$_{arom}$)$_{ortho}$), 119.0 (OCH$_2$CH<u>C</u>H$_2$), 123.7 (q, J = 280.8 Hz, CF$_3$), 125.5 (N(CH$_{arom}$)$_{para}$), 129.3 (2 × N(CH$_{arom}$)$_{meta}$), 132.8 (OCH$_2$<u>C</u>HCH$_2$), 136.2 (N<u>C</u>$_{arom,quat}$), 164.3 (C=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -68.41 (3F, d, J = 5.4 Hz, CF$_3$). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1767, ν_{max} = 1599, 1499, 1360, 1279, 1134, 989, 930, 752, 689, 490. MS (70eV): 272 (M^+ + 1, 100).

Cis-3-allyloxy-1-(4-methylphenyl)-4-(trifluoromethyl)azetidin-2-one 14e



White crystals. Mp 78 °C. Recrystallization (CH_2Cl_2/Et_2O, 1/3). Yield 71%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.25 (3H, s, CH$_3$), 4.15-4.24 (2H, m, OC<u>H</u>$_2$CHCH$_2$), 4.57 (1H, quintet, J = 5.4 Hz, C<u>H</u>CF$_3$), 4.89 (1H, d, J = 5.4 Hz, OC<u>H</u>CHCF$_3$), 5.23 (1H, d, J = 10.7 Hz, OCH$_2$CH(HC<u>H</u>)), 5.32 (1H, d, J = 17.2 Hz, OCH$_2$CH(<u>H</u>CH)), 5.87 (1H, d × d × t, J = 17.2, 10.7, 5.5 Hz, OCH$_2$C<u>H</u>CH$_2$), 7.09 and 7.28 (2 × 2H, 2 × d, J = 8.2 Hz, N(CH$_{arom}$)$_{ortho}$ and CH$_3$(C<u>H</u>$_{arom}$)$_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 20.9 (CH$_3$), 57.5 (q, J = 33.2 Hz, <u>C</u>HCF$_3$), 73.1 (O<u>C</u>H$_2$CHCH$_2$), 80.3 (O<u>C</u>HCHCF$_3$), 117.7 (2 × CH$_3$(<u>C</u>H$_{arom}$)$_{ortho}$), 118.9 (OCH$_2$CH<u>C</u>H$_2$), 123.7 (q, J = 280.9 Hz, CF$_3$), 129.7 (2 × N(CH$_{arom}$)$_{ortho}$), 132.8 (OCH$_2$<u>C</u>HCH$_2$), 133.7 (N<u>C</u>$_{arom,quat}$), 135.3 (CH$_3$<u>C</u>$_{arom,quat}$), 164.1 (C=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -68.46 (3F, d, J = 5.4 Hz, CF$_3$). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1748, ν_{max} = 1516, 1396, 1364, 1275, 1246, 1167, 1134, 1005, 816, 646, 482. MS (70eV): 286 (M^+ + 1, 100).

Cis-3-allyloxy-1-isopropyl-4-(trifluoromethyl)azetidin-2-one 14f



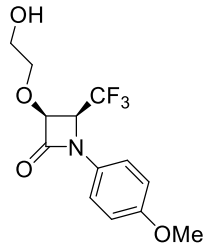
White yellowish oil. Solidified in fridge. R_f = 0.42 (PE/EtOAc, 4/1). Yield 79%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26 and 1.29 (2 × 3H, 2 × d, J = 6.8 Hz, (C<u>H</u>$_3$)$_2$CH), 3.88 (1H, septet, J = 6.8 Hz, (CH$_3$)$_2$C<u>H</u>), 4.11 (1H, q × d, J = 6.0, 4.8 Hz, C<u>H</u>CF$_3$), 4.15-4.24 (2H, m, OC<u>H</u>$_2$CHCH$_2$), 4.74 (1H, d, J = 4.8 Hz, OC<u>H</u>CHCF$_3$), 5.26 (1H, d × q, J = 10.6, 1.4 Hz, OCH$_2$CH(<u>H</u>CH), 5.35 (1H, d × q, J = 17.2, 1.6 Hz, OCH$_2$CH(HC<u>H</u>), 5.90 (1H, d × q × t, J = 17.2, 10.6, 5.4 Hz, OCH$_2$C<u>H</u>CH$_2$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 19.3 and 21.1 ((<u>C</u>H$_3$)$_2$CH), 45.1 ((CH$_3$)$_2$<u>C</u>H), 56.6 (q, J = 33.0 Hz, <u>C</u>HCF$_3$), 72.7 (O<u>C</u>H$_2$CHCH$_2$), 80.2 (OC<u>H</u>CHCF$_3$), 118.5

($OCH_2CH\underline{C}H_2$), 123.9 (q, J = 279.8 Hz, CF_3), 133.0 ($OCH_2\underline{C}HCH_2$), 166.2 (C=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -69.49 (3F, d, J = 6.0 Hz, CF_3). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1761, ν_{max} = 1281, 1213, 1148, 1123, 1009, 928, 660. MS (70eV): 238 (M^+ + 1, 100).

Synthesis of 3-(2-hydroxyethoxy)-4-(trifluoromethyl)azetidin-2-ones 15

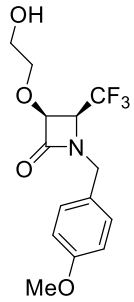
In a 250 mL flame-dried flask, *cis*-3-allyloxy-1-(4-methoxyphenyl)-4-(trifluoromethyl)azetidin-2-one **14a** (0.12 g, 0.40 mmol, 1 equiv) was dissolved in a mixture of dry CH_2Cl_2 (15 mL) and dry MeOH (10 mL). A small pinch of Sudan III indicator was added to the reaction mixture. The reaction mixture was sparged with ozone at -78 °C until the red color of the reaction mixture dissipated. The mixture was stirred for one hour at room temperature in the presence of dimethyl sulfide (0.06 g, 0.07 mL, 1 mmol, 2.5 equiv), after which the reaction mixture was extracted with water (10 mL). The water phase was then extracted three times with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were washed three times with brine (3 × 5 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure, affording a crude mixture. To the crude mixture in dry THF (6 mL) at 0 °C was added gradually BH_3 (1M in Et_2O, 1 mL, 1 mmol, 2.5 equiv). The temperature was allowed to rise to room temperature and the reaction was stirred for three hours at this temperature. The mixture was extracted with EtOAc (3 × 8 mL) and washed with brine (3 × 5 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent *in vacuo* afforded *cis*-3-(2-hydroxyethoxy)-1-(4-methoxyphenyl)-4-(trifluoromethyl)azetidin-2-one **15a** (0.09 g, 0.30 mmol, 72%), which was purified by means of column chromatography (Hex/EtOAc, 3/1) to obtain an analytically pure sample.

***Cis*-3-(2-hydroxyethoxy)-1-(4-methoxyphenyl)-4-(trifluoromethyl)azetidin-2-one 15a**



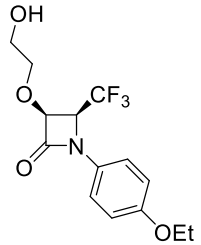
Yellow oil. R_f = 0.14 (Hex/EtOAc, 3/1). Yield 72%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.67 (1H, t, J = 5.7 Hz, OH), 3.73 (3H, s, OCH_3), 3.75-3.80 (3H, m, $O(\underline{H}CH)CH_2$ and $C\underline{H}_2OH$), 3.85-3.91 (1H, m, $O(HC\underline{H})CH_2$), 4.60 (1H, quintet, J = 5.4 Hz, $CHCF_3$), 4.95 (1H, d, J = 5.4 Hz, $OC\underline{H}CHCF_3$), 6.83 and 7.32 (2 × 2H, 2 × d, J = 9.0 Hz, $N(CH_{arom})_{ortho}$ and $O(CH_{arom})_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 55.5 (OCH_3), 58.0 (q, J = 33.1 Hz, $\underline{C}HCF_3$), 62.2 (CH_2OH), 74.9 ($\underline{C}H_2CH_2OH$), 82.2 ($O\underline{C}HCHCF_3$), 114.5 (2 × $O(CH_{arom})_{ortho}$), 119.6 (2 × $N(CH_{arom})_{ortho}$), 123.6 (q, J = 281.0 Hz, $CH\underline{C}F_3$), 129.1 ($NC_{arom,quat}$), 157.4 ($OC_{arom,quat}$), 164.6 (C=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -68.42 (3F, d, J = 5.4 Hz, CF_3). IR (ATR, cm^{-1}): ν_{OH} = 3393; $\nu_{C=O}$ = 1744, ν_{max} =1512, 1233, 1128, 1032, 822, 681. MS (70eV): 306 (M^+ + 1, 100).

Cis-3-(2-hydroxyethoxy)-1-(4-methoxybenzyl)-4-(trifluoromethyl)azetidin-2-one 15b



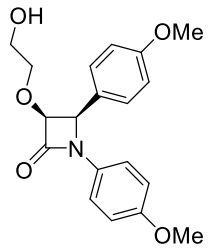
Yellowish oil. R_f = 0.15 (Hex/EtOAc, 1/1). Yield 77%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.89 (1H, t, J = 6.6 Hz, OH), 3.71-3.79 (3H, m, O(HCH)CH_2 and CH_2OH), 3.81 (3H, s, OCH_3), 3.82-3.88 (1H, m, O(HCH)CH_2), 3.94 (1H, q × d, J = 6.1, 4.9 Hz, $CHCF_3$), 3.97 (1H, d, J = 14.5 Hz, N(HCH)), 4.80 (1H, d, J = 4.9 Hz, OCHCHCF_3), 4.81 (1H, d, J = 14.5 Hz, N(HCH)), 6.88 and 7.16 (2 × 2H, 2 × d, J = 8.6 Hz, $NCH_2(CH_{arom})_{ortho}$ and $O(CH_{arom})_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 44.6 (NCH_2), 55.3 (OCH_3), 56.7 (q, J = 32.9 Hz, $CHCF_3$), 62.2 (CH_2OH), 74.8 (CH_2CH_2OH), 82.7 (OCHCHCF_3), 114.4 (2 × $O(CH_{arom})_{ortho}$), 123.8 (q, J = 280.2 Hz, $CHCF_3$), 125.8 ($NC_{arom,quat}$), 129.9 (2 × $NCH_2(CH_{arom})_{ortho}$), 159.6 ($OC_{arom,quat}$), 167.2 (C=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -69.26 (3F, d, J = 6.1 Hz, CF_3). IR (ATR, cm^{-1}): ν_{OH} = 3431; $\nu_{C=O}$ = 1759, ν_{max} = 1514, 1279, 1246, 1159, 1130, 1030, 800, 664, 513. MS (70eV): 320 (M^+ + 1, 100).

Cis-1-(4-ethoxyphenyl)-3-(2-hydroxyethoxy)-4-(trifluoromethyl)azetidin-2-one 15c



White solid. Mp 81 °C. R_f = 0.10 (PE/EtOAc, 2/1). Yield 72%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.40 (3H, t, J = 7.0 Hz, OCH_2CH_3), 2.93 (1H, t, J = 6.2 Hz, CH_2OH), 3.77-3.89 (3H, m, O(HCH)CH_2 and CH_2OH), 3.91-395 (1H, m, O(HCH)CH_2), 4.01 (2H, q, J = 7.0 Hz, OCH_2CH_3), 4.67 (1H, quintet, J = 5.4 Hz, $CHCF_3$), 5.02 (1H, d, J = 5.4 Hz, OCHCHCF_3), 6.88 and 7.37 (2 × 2H, 2 × d, J = 9.0 Hz, $N(CH_{arom})_{ortho}$ and $O(CH_{arom})_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 14.8 (OCH_2CH_3), 58.0 (q, J = 33.1 Hz, $CHCF_3$), 62.1 (CH_2OH), 63.8 (OCH_2CH_3), 74.9 (CH_2CH_2OH), 82.1 (OCHCHCF_3), 115.0 (2 × $O(CH_{arom})_{ortho}$), 119.5 (2 × $N(CH_{arom})_{ortho}$), 123.6 (q, J = 280.9 Hz, $CHCF_3$), 129.0 ($NC_{arom,quat}$), 156.8 ($OC_{arom,quat}$), 164.6 (C=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -68.44 (3F, d, J = 5.4 Hz, CF_3). IR (ATR, cm^{-1}): ν_{OH} = 3399; $\nu_{C=O}$ = 1759, ν_{max} = 1510, 1391, 1250, 1169, 1146, 1121, 1043, 841, 824, 656. MS (70eV): 320 (M^+ + 1, 100).

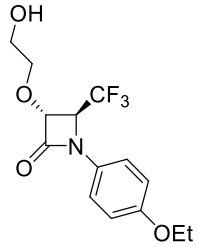
Cis-3-(2-hydroxyethoxy)-1,4-bis(4-methoxyphenyl)azetidin-2-one 19



White crystals. Mp 105 °C. R_f = 0.10 (PE/EtOAc, 1/1). Yield 51%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.32 (1H, t, J = 6.7 Hz, OH), 3.30-3.55 (4H, m, OCH_2CH_2OH), 3.66 and 3.72 (2 × 3H, 2 × s, OCH_3), 4.85 (1H, d, J = 4.8 Hz, OCHCH), 5.11 (1H, d, J = 4.8 Hz, OCHCH), 6.71 (2H, d, J = 9.0 Hz, $N(CH_{arom})_{meta}$), 6.84 (2H, d, J = 8.6 Hz, $CH(CH_{arom})_{meta}$), 7.19 (2H, d, J = 9.0 Hz, $N(CH_{arom})_{ortho}$), 7.24 (2H, d, J = 8.6 Hz, $CH(CH_{arom})_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 55.3 and 55.4 (2 × OCH_3), 61.9 (CH_2OH), 62.0 (OCHCH), 73.4 (CH_2CH_2OH), 83.9 (OCHCH), 114.1 (2 × $CH(CH_{arom})_{meta}$), 114.3 (2 ×

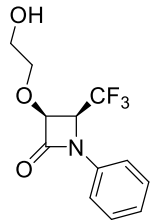
$N(CH_{arom})_{meta}$), 118.9 (2 × $N(CH_{arom})_{ortho}$), 125.1 ($NC_{arom,quat}$), 129.3 (2 × $CH(\underline{C}H_{arom})_{ortho}$), 130.4 ($CH\underline{C}_{arom,quat}$), 156.5 and 160.0 (2 × $OC_{arom,quat}$), 164.5 (C=O). IR (ATR, cm^{-1}): ν_{OH} = 3273, $\nu_{C=O}$ = 1736, ν_{max} = 1510, 1396, 1298, 1236, 1175, 1132, 1028, 835, 800, 540. MS (70eV): 344 (M^+ + 1, 100).

Trans-1-(4-ethoxyphenyl)-3-(2-hydroxyethoxy)-4-(trifluoromethyl)azetidin-2-one 21



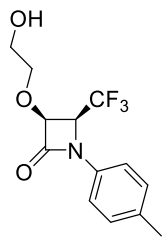
Colorless oil. R_f = 0.42 (PE/EtOAc, 1/1). Yield 60%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.41 (3H, t, J = 7.0 Hz, $OCH_2C\underline{H}_3$), 2.77 (1H, t, J = 5.5 Hz, OH), 3.78-3.93 (4H, m, $OC\underline{H}_2C\underline{H}_2OH$), 4.02 (2H, q, J = 7.0 Hz, $OC\underline{H}_2CH_3$), 4.45 (1H, q × d, J = 5.6, 1.3 Hz, $CHCF_3$), 4.87 (1H, d, J = 1.3 Hz, $OC\underline{H}CHCF_3$), 6.89 and 7.33 (2 × 2H, 2 × d, J = 8.9 Hz, $N(CH_{arom})_{ortho}$ and $O(CH_{arom})_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 14.8 ($OCH_2\underline{C}H_3$), 60.1 (q, J = 34.3 Hz, $\underline{C}HCF_3$), 61.9 (CH_2OH), 63.8 ($O\underline{C}H_2CH_3$), 73.6 ($\underline{C}H_2CH_2OH$), 83.3 (q, J = 1.5 Hz, $O\underline{C}HCHCF_3$), 115.1 (2 × $O(CH_{arom})_{ortho}$), 120.2 (2 × $N(CH_{arom})_{ortho}$), 123.5 (q, J = 280.3 Hz, $CH\underline{C}F_3$), 128.6 ($NC_{arom,quat}$), 157.0 ($OC_{arom,quat}$), 163.2 (C=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -71.48 (3F, d, J = 5.6 Hz, CF_3). IR (ATR, cm^{-1}): ν_{OH} = 3447, $\nu_{C=O}$ = 1755, ν_{max} =1512, 1395, 1246, 1159, 1115, 1045, 829, 700, 515. MS (70eV): 320 (M^+ + 1, 100).

Cis-3-(2-hydroxyethoxy)-1-phenyl-4-(trifluoromethyl)azetidin-2-one 15d



Yellowish oil. R_f = 0.31 (PE/EtOAc, 1/1). Yield 95%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.55 (1H, t, J = 5.6 Hz, OH), 3.72-3.92 (4H, m, $OC\underline{H}_2C\underline{H}_2OH$), 4.67 (1H, quintet, J = 5.4 Hz, $CHCF_3$), 4.97 (1H, d, J = 5.4 Hz, $OC\underline{H}CHCF_3$), 7.13 (1H, t, J = 7.8 Hz, $N(CH_{arom})_{para}$), 7.31 (2H, t, J = 7.8 Hz, $N(CH_{arom})_{meta}$), 7.40 (2H, d, J = 7.8 Hz, $N(CH_{arom})_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 57.7 (q, J = 33.3 Hz, $\underline{C}HCF_3$), 62.2 (CH_2OH), 74.9 ($O\underline{C}H_2CH_2$), 82.1 ($O\underline{C}HCHCF_3$), 117.7 (2 × $N(CH_{arom})_{ortho}$), 123.6 (q, J = 280.2 Hz, CF_3), 125.7 ($N(CH_{arom})_{para}$), 129.3 (2 × $N(CH_{arom})_{meta}$), 136.0 ($NC_{arom,quat}$), 164.9 (C=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -68.31 (3F, d, J = 5.4 Hz, CF_3). IR (ATR, cm^{-1}): ν_{OH} = 3428, $\nu_{C=O}$ = 1761, ν_{max} = 1599, 1499, 1360, 1277, 1136, 752, 689, 486. MS (70eV): 276 (M^+ + 1, 100).

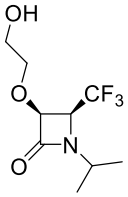
Cis-3-(2-hydroxyethoxy)-1-(4-methylphenyl)-4-(trifluoromethyl)azetidin-2-one 15e



White crystals. Mp 79 °C. R_f = 0.14 (PE/EtOAc, 2/1). Yield 63%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.26 (3H, s, CH_3), 2.65 (1H, brs, OH), 3.73-3.91(4H, m, $OC\underline{H}_2C\underline{H}_2OH$), 4.63 (1H, quintet, J = 5.4 Hz, $CHCF_3$), 4.95 (1H, d, J = 5.4 Hz, $OC\underline{H}CHCF_3$), 7.10 and 7.28 (2 × 2H, 2 × d, J = 8.3 Hz, $N(CH_{arom})_{ortho}$ and $CH_3(C\underline{H}_{arom})_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 21.0 (CH_3), 57.8 (q, J = 33.1 Hz, $\underline{C}HCF_3$), 62.2 (CH_2OH), 74.9 ($\underline{C}H_2CH_2OH$), 82.1 ($O\underline{C}HCHCF_3$), 117.8 (2 × $CH_3(\underline{C}H_{arom})_{ortho}$), 123.6 (q, J = 281.0 Hz, CF_3),

129.8 (2 × N(CH_{arom})$_{ortho}$), 133.5 (N$C_{arom,quat}$), 135.6 ($CH_3$$\underline{C}_{arom,quat}$), 164.8 (C=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -68.36 (3F, d, J = 5.4 Hz, CF_3). IR (ATR, cm^{-1}): ν_{OH} = 3358, $\nu_{C=O}$ = 1753, ν_{max} = 1514, 1398, 1366, 1275, 1244, 1140, 1028, 814, 646, 494. MS (70eV): 290 (M^+ + 1, 100).

Cis-3-(2-hydroxyethoxy)-1-isopropyl-4-(trifluoromethyl)azetidin-2-one 15f



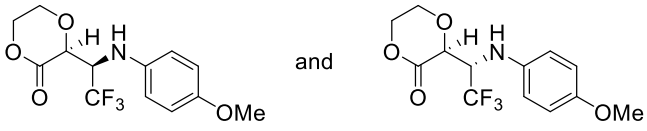
Yellow oil. R_f = 0.15 (PE/EtOAc, 1/1). Yield 47%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.27 and 1.31 (2 × 3H, 2 × d, J = 6.8 Hz, ($C\underline{H}_3$)$_2$CH), 3.12 (1H, t, J = 6.4 Hz, OH), 3.71-3.91 (5H, m, (CH_3)$_2$C$\underline{H}$, OC$\underline{H}_2$C$\underline{H}_2$OH), 4.17 (1H, q × d, J = 6.1, 4.9 Hz, $CHCF_3$), 4.79 (1H, d, J = 4.9 Hz, OC$\underline{H}$C$\underline{H}$$CF_3$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 19.4 and 21.0 (($\underline{C}H_3$)$_2$CH), 45.4 ((CH_3)$_2$$\underline{C}$H), 56.9 (q, J = 33.1 Hz, $\underline{C}$HCF_3), 62.2 (CH_2OH), 74.8 ($\underline{C}H_2CH_2$OH), 81.8 (O$\underline{C}$HCHCF_3), 123.7 (q, J = 279.8 Hz, CF_3), 167.2 (C=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -69.40 (3F, d, J = 6.1 Hz, CF_3). IR (ATR, cm^{-1}): ν_{OH} = 3428, $\nu_{C=O}$ = 1755, ν_{max} = 1281, 1217, 1148, 1042, 849, 660. MS (70eV): 242 (M^+ + 1, 100).

Synthesis of 3-[2,2,2-trifluoro-1-(arylamino)ethyl]-1,4-dioxan-2-ones 16

A solution of *cis*-1-(4-ethoxyphenyl)-3-(2-hydroxyethoxy)-4-(trifluoromethyl)azetidin-2-one **15c** (0.05 g, 0.16 mmol, 1 equiv) and an excess of K_2CO_3 in toluene was heated at reflux temperature for 28 hours. The reaction mixture was then filtered through a small pad of Celite® and concentrated under reduced pressure, resulting in a crude mixture. The ^{19}F NMR of this mixture showed it to consist of *syn*-3-{1-[(4-ethoxyphenyl)amino]-2,2,2-trifluoroethyl}-1,4-dioxan-2-one and *anti*-3-{1-[(4-ethoxyphenyl)amino]-2,2,2-trifluoroethyl}-1,4-dioxan-2-one **16c** in a ratio of 72:28. The mixture was purified by means of preparative TLC (PE/EtOAc, 6/1), providing an pure but inseparable mixture of *syn*-3-{1-[(4-ethoxyphenyl)amino]-2,2,2-trifluoroethyl}-1,4-dioxan-2-one and *anti*-3-{1-[(4-ethoxyphenyl)amino]-2,2,2-trifluoroethyl}-1,4-dioxan-2-one **16c** (86%).

3-{2,2,2-Trifluoro-1-[(4-methoxyphenyl)amino]ethyl}-1,4-dioxan-2-one 16a

Spectral data derived from the mixture of diastereomers

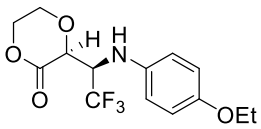
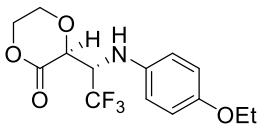


Yellow oil. R_f = 0.18 (PE/EtOAc, 3/1). Yield 81%. *Syn*:*anti* 78:22. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.68 and 3.69 (3H, s, OMe), 3.73-4.05 (3H, m, OC$\underline{H}_2$C$\underline{H}_2$OCO, NH), 4.32-4.36 (1H, m, ($\underline{H}$CH)OCO), 4.47-4.67 (3H, m, (HC$\underline{H}$)OCO, $CHCF_3$ and OC$\underline{H}$CHCF_3), 6.65-6.77 (4H, m, N(CH_{arom})$_{ortho}$ and O(CH_{arom})$_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 55.6 and 55.7 (OCH_3), 59.0 (q, J = 28.8 Hz, $\underline{C}$HCF_3), 62.7 and 62.8 (O$\underline{C}$H$_2$CH$_2$OCO), 68.53 and 68.55 ($\underline{C}H_2$OCO), 74.1 and 75.4 (q, J = 1.5 and 1.9 Hz, O$\underline{C}$HCO),

114.8 and 115.1 (2 × O(CH_{arom})$_{ortho}$), 116.5 and 116.8 (2 × N(CH_{arom})$_{ortho}$), 124.9 (q, J = 285.9 Hz, CH<u>C</u>F_3), 138.0 and 138.9 (N$C_{arom,quat}$), 154.0 (O$C_{arom,quat}$), 165.9 and 166.2 (C=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -72.22 and -69.98 (3F, d, J = 7.5 and 6.9 Hz, CF_3). IR (ATR, cm^{-1}): ν_{NH} = 3393, 2922, $\nu_{C=O}$ = 1721, ν_{max} = 1520, 1458, 1244, 1233, 1140, 1123, 1074, 826, 694, 519. MS (70eV): 306 (M^+ + 1, 100). HRMS (ESI) for $C_{13}H_{15}F_3NO_4^+$: 306.0948 [M + H]$^+$. Found: 306.0935.

3-{1-[(4-Ethoxyphenyl)amino]-2,2,2-trifluoroethyl}-1,4-dioxan-2-one 16c

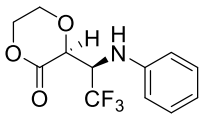
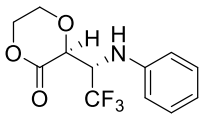
Spectral data derived from the mixture of diastereomers


and


Yellow crystals. Mp 108 °C. R_f = 0.08 (PE/EtOAc, 6/1). Yield 86%. *Syn*:*anti* 72:28. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 and 1.38 (3H, t, J = 6.9 and 7.1 Hz, $CH_2C\underline{H}_3$), 3.80-4.11 (5H, m, $OC\underline{H}_2CH_2OCO$, NH and $C\underline{H}_2CH_3$), 4.39-4.42 (1H, m, (<u>H</u>CH)OCO), 4.54-4.74 (3H, m, (HC<u>H</u>)OCO, C<u>H</u>CF_3 and OC<u>H</u>CHCF_3), 6.71-6.83 (4H, m, N(CH_{arom})$_{ortho}$ and O(CH_{arom})$_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 14.9 ($CH_2\underline{C}H_3$), 59.0 and 59.2 (q, J = 29.0 and 28.3 Hz, <u>C</u>HCF_3), 62.7 and 62.8 ($O\underline{C}H_2CH_2OCO$), 63.86 and 63.95 ($\underline{C}H_2CH_3$), 68.5 ($\underline{C}H_2OCO$), 74.1 and 75.4 (q, J = 1.5 and 1.9 Hz, O<u>C</u>HCO), 115.6 and 115.9 (2 × O(CH_{arom})$_{ortho}$), 116.5 and 116.8 (2 × N(CH_{arom})$_{ortho}$), 124.5 and 124.9 (q, J = 283.5 and 285.9 Hz, CH<u>C</u>F_3), 137.9 and 138.8 (N$C_{arom,quat}$), 153.3 (O$C_{arom,quat}$), 165.9 and 166.2 (C=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -72.21 and -70.00 (3F, d, J = 7.7 and 6.9 Hz, CF_3). IR (ATR, cm^{-1}): ν_{NH} = 3374, 3352; $\nu_{C=O}$ = 1721, ν_{max} = 1520, 1231, 1105, 1049, 949, 926, 808, 694, 521. MS (70eV): 320 (M^+ + 1, 100). HRMS (ESI) for $C_{14}H_{17}F_3NO_4^+$: 320.1104 [M + H]$^+$. Found: 320.1094.

3-[2,2,2-Trifluoro-1-(phenylamino)ethyl]-1,4-dioxan-2-one 16d

Spectral data derived from the mixture of diastereomers

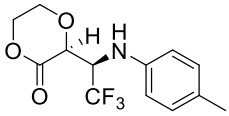

and


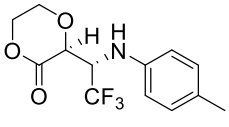
Yellowish solid. Mp 85 °C. R_f = 0.38 (PE/EtOAc, 2/1). Yield 71%. *Syn*:*anti* 69:31. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.75-4.29 (3H, m, $OC\underline{H}_2CH_2OCO$, NH), 4.41-4.44 (1H, m, (<u>H</u>CH)OCO), 4.56-4.89 (3H, m, (HC<u>H</u>)OCO, C<u>H</u>CF_3 and OC<u>H</u>CHCF_3), 6.71-6.89 and 7.19-7.27 (5H, m, CH_{arom}). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 57.1 and 57.6 (q, J = 29.5 and 28.8 Hz, <u>C</u>HCF_3), 62.8 and 62.9 ($O\underline{C}H_2CH_2OCO$), 68.5 and 68.6 ($OCH_2\underline{C}H_2OCO$), 74.4 and 75.3 (q, J = 1.5 and 1.9 Hz, O<u>C</u>HCO), 114.4 and 114.6 (2 × N(CH_{arom})$_{ortho}$), 120.10 and 120.11 (N(CH_{arom})$_{para}$), 124.4 and 124.8 (q, J = 282.2 and 285.7 Hz, CH<u>C</u>F_3), 129.4 and 129.7 (2 × N(CH_{arom})$_{meta}$), 144.2 and 145.0 (N$C_{arom,quat}$), 165.7 and 166.0 (C=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ - 72.51 and -70.00 (3F, d, J = 7.2 and 6.8 Hz, CF_3). IR (ATR, cm^{-1}): ν_{NH} = 3385; $\nu_{C=O}$ =

1722, ν_{max} = 1603, 1254, 1167, 1140, 1111, 1074, 930, 750, 691, 505. MS (70eV): 276 (M^+ + 1, 100). HRMS (ESI) for $C_{12}H_{13}F_3NO_3^+$: 276.0842 $[M + H]^+$. Found: 276.0846.

3-{2,2,2-Trifluoro-[1-(4-methylphenyl)amino]ethyl}-1,4-dioxan-2-one 16e

Spectral data derived from the mixture of diastereomers



and


White solid. Mp 109 °C. R_f = 0.38 (PE/EtOAc, 2/1). Yield 98%. *Syn*:*anti* 75:25. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.24 and 2.26 (3H, s, CH_3), 3.79-4.16 (3H, m, $OC\underline{H}_2CH_2OCO$, NH), 4.39-4.43 (1H, m, ($\underline{H}$CH)OCO), 4.54-4.61 and 4.70-4.83 (3H, m, (HC$\underline{H}$)OCO, $CHCF_3$ and $OC\underline{H}CHCF_3$), 6.68 and 7.01; 6.69 and 7.05 (2 × 2H, 2 × d, J = 8.3 and 8.4 Hz, $N(CH_{arom})_{ortho}$ and $CH_3(C\underline{H}_{arom})_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 20.43 and 20.45 (CH_3), 57.8 and 58.2 (q, J = 29.3 and 28.8 Hz, $\underline{C}HCF_3$), 62.7 and 62.8 ($O\underline{C}H_2CH_2OCO$), 68.5 ($OCH_2\underline{C}H_2OCO$), 74.2 and 75.3 (q, J = 1.2 and 1.8 Hz, $O\underline{C}HCO$), 114.8 and 115.0 (2 × $N(CH_{arom})_{ortho}$), 124.5 and 124.9 (q, J = 283.6 and 285.8 Hz, $CH\underline{C}F_3$), 129.5 and 129.6 ($CH_3\underline{C}_{arom,quat}$), 129.9 and 130.2 (2 × $CH_3(\underline{C}H_{arom})_{ortho}$), 141.8 and 142.7 ($NC_{arom,quat}$), 165.8 and 166.1 (C=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -72.41 and -70.00 (3F, d, J = 7.0 and 6.9 Hz, CF_3). IR (ATR, cm^{-1}): ν_{NH} = 3383, 3360, $\nu_{C=O}$ = 1721, ν_{max} = 1526, 1252, 1159, 1125, 1105, 1070, 1047, 930, 812, 692, 519. MS (70eV): 290 (M^+ + 1, 100). HRMS (ESI) for $C_{13}H_{15}F_3NO_3^+$: 290.0999 $[M + H]^+$. Found: 290.0985.

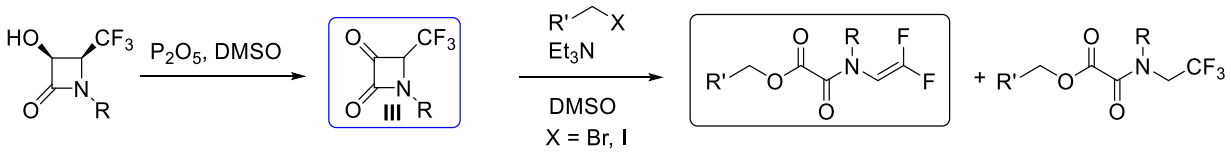
PART III

Formation of fluorinated amido esters through unexpected C3-C4 bond fission in 4-trifluoromethyl-3-oxo-β-lactams

Abstract

4-Trifluoromethyl-3-oxo-β-lactams were unexpectedly transformed into 2-[(2,2-difluorovinyl)amino]-2-oxoacetates as major products, accompanied by minor amounts of 2-oxo-2-[(2,2,2-trifluoroethyl)amino]acetates, upon treatment with alkyl halides and triethylamine in DMSO. This peculiar C3-C4 bond fission reactivity was investigated in-depth, from both an experimental and a computational point of view, in order to shed light on the underlying reation mechanism.

Graphical abstract



Reference

Dao Thi, H., Goossens, H., Hertsen, D., Otte, V., Van Nguyen, T., Van Speybroeck, V., D'hooghe, M. "Formation of fluorinated amido esters through unexpected C3-C4 bond fission in 4-trifluoromethyl-3-oxo-β-lactams". *Chem. Asian J.* **2018**, *13*, 421-431. (I.F. 4.08).

1. Introduction

In general, 3-oxo-β-lactams (or azetidine-2,3-diones) can be recognized as versatile precursors for the synthesis of a broad variety of β-lactam and non-β-lactam products. For example, deployment of 3-oxo-β-lactams has been reported to afford a variety of 3-amino-β-lactams, 3-hydroxy-β-lactams and amino acid derivatives.[81] As can be seen from published reactivity studies on trifluoromethylated small-ring heterocycles, the presence of a CF_3-group has a pronounced effect on their overall behavior in terms of synthetic elaboration. In a previous communications on the chemistry of 2-CF_3-aziridines and -azetidines revealed an unexpected and even opposite reactivity as compared to their 2-alkyl-substituted counterparts.[39,82a,82b,28a,82c,28b,82d,23b,82e,19,82f,82g] Another important feature of trifluoromethylated azaheterocycles comprises their suitability to undergo deprotonation in α-position with respect to the strong electron-withdrawing CF_3 group, as exemplified by the generation of the 2-(trifluoromethyl)aziridin-2-yl anion and its subsequent neutralization by means of different types of electrophiles.[23] In that respect, the deployment of 4-trifluoromethyl-3-oxo-β-lactams might offer new opportunities for the installation of an additional side chain through abstraction of the acidic C4-proton in α-position with respect to the oxo group and the CF_3 moiety. Consequently, attempts were made in the present work to address this synthetic challenge, and the results of this study are described below.

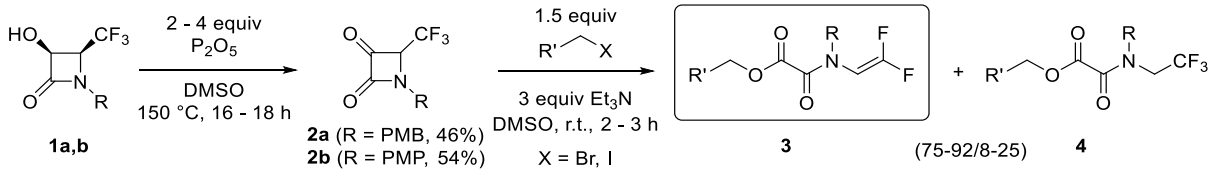
2. Synthesis of 4-trifluoromethyl-3-oxo-β-lactam building blocks and their transformation into amido esters

4-Trifluoromethyl-3-oxo-β-lactams are rather unstable upon prolonged preservation and should therefore be freshly prepared and used immediately for further elaboration. To that end, 3-hydroxy-4-trifluoromethyl-β-lactams **1** were synthesized through hydrogenolysis of the corresponding 3-benzyloxy-β-lactams, which are easily accessible *via* [2+2]-cyclocondensation between trifluoroaldimines, prepared from the commercially available 1-ethoxy-2,2,2-trifluoroethanol using 4-methoxyaniline or 4-methoxybenzylamine in toluene under Dean-Stark conditions, and the ketene derived from benzyloxyacetyl chloride. A subsequent Albright-Onodera oxidation using P_2O_5 in DMSO afforded the contemplated 3-oxo-4-(trifluoromethyl)azetidin-2-ones **2** in acceptable yields (Scheme 1). Having these 3-oxo-β-lactams **2** in hand, their eligibility as substrates for α-alkylation through the intermediacy of a 3,4-dioxo-2-(trifluoromethyl)azetidin-2-yl anion was assessed next. However, treatment of these ketones **2** with a variety of bases (LDA, LiHMDS, *n*-

BuLi, NaH, Et_3N, NaOH) under different reaction conditions, including variation of the temperature (0 °C, -78 °C, -100 °C), solvent (THF, CH_2Cl_2), and additive (HMPA, $TiCl_4$, Me_3SiOTf, $ZnBr_2$), in the presence of 1-iodopropane as an electrophile always led to the formation of rather complex mixtures. These observations at least confirmed the intrinsic reactivity/instability of 4-trifluoromethyl-3-oxo-β-lactams.

Remarkably, in one of these many attempts, the combination of 1.5 equiv of 1-iodopropane and 3 equiv of Et_3N in DMSO at room temperature resulted in a clean and full conversion of the starting material **2a**. More precisely, this approach provided a mixture of two reaction products in a 87/13 ratio, from which the major product was identified as propyl 2-[(2,2-difluorovinyl)(4-methoxybenzyl)amino]-2-oxoacetate **3a** and the minor product as propyl 2-oxo-2-[(4-methoxybenzyl)(2,2,2-trifluoroethyl)amino]acetate **4a** upon careful spectroscopic analysis.

This unexpected and unprecedented reactivity urged us to explore the scope of this new transformation in detail. At first, methodology validation was pursued by varying the electrophile and, besides 1-iodopropane, also allyl bromide, 1-chloro-3-iodopropane, benzyl bromide and iodomethane were thus deployed. In all cases, 4-trifluoromethyl-3-oxo-β-lactams **2** were successfully converted into mixtures of *N*-(2,2-difluorovinyl) amido esters **3** as major products and *N*-(2,2,2-trifluoroethyl) amido esters **4** as minor constituents in a 75-92/8-25 ratio (Table 1), which could be easily separated. Instead of DMSO, also DMF was shown to be a suitable solvent to induce these reactions, albeit resulting in a lower selectivity (~1/1 mixtures of compounds **3** and **4**). Acetonitrile and dichloromethane appeared to be unfit as solvents and only produced complex reaction mixtures.



Scheme 1. Synthesis of 4-trifluoromethyl-3-oxo-β-lactams **2** and their transformation into amido esters **3** and **4**

Table 1. Transformation of 4-trifluoromethyl-3-oxo-β-lactams **2** into 2-[(2,2-difluorovinyl)amino]-2-oxoacetates **3** and 2-oxo-2-[(2,2,2-trifluoroethyl)amino]acetates **4**

Entry	R	R'	**3** (yield[a])	**4** (yield[a])	Ratio **3**/**4**[b]
1	PMB	Et	**3a** (56)	**4a** (12)	87/13
2	PMB	vinyl	**3b** (25)	**4b** (5)	87/13
3	PMB	1-chloroethyl	**3c** (42)	**4c** (10)	80/20
4	PMB	Ph	**3d** (50)	**4d** (11)	75/25
5	PMB	H	**3e** (33)	**4e** (7)	80/20
6	PMP	Et	**3f** (30)	**4f** (9)	79/21
7	PMP	vinyl	**3g** (35)	**4g** (-)[c]	86/14
8	PMP	1-chloroethyl	**3h** (38)	**4h** (-)[c]	90/10
9	PMP	Ph	**3i** (50)	**4i** (-)[c]	92/8
10	PMP	H	**3j** (42)	**4j** (5)	88/12

[a] isolated yield after HPLC purification

[b] determined by means of ^{1}H NMR analysis ($CDCl_3$) of the reaction mixture

[c] not isolated

3. Proposal mechanisms of the C3-C4 bond fission in 3-oxo-β-lactams toward amido esters

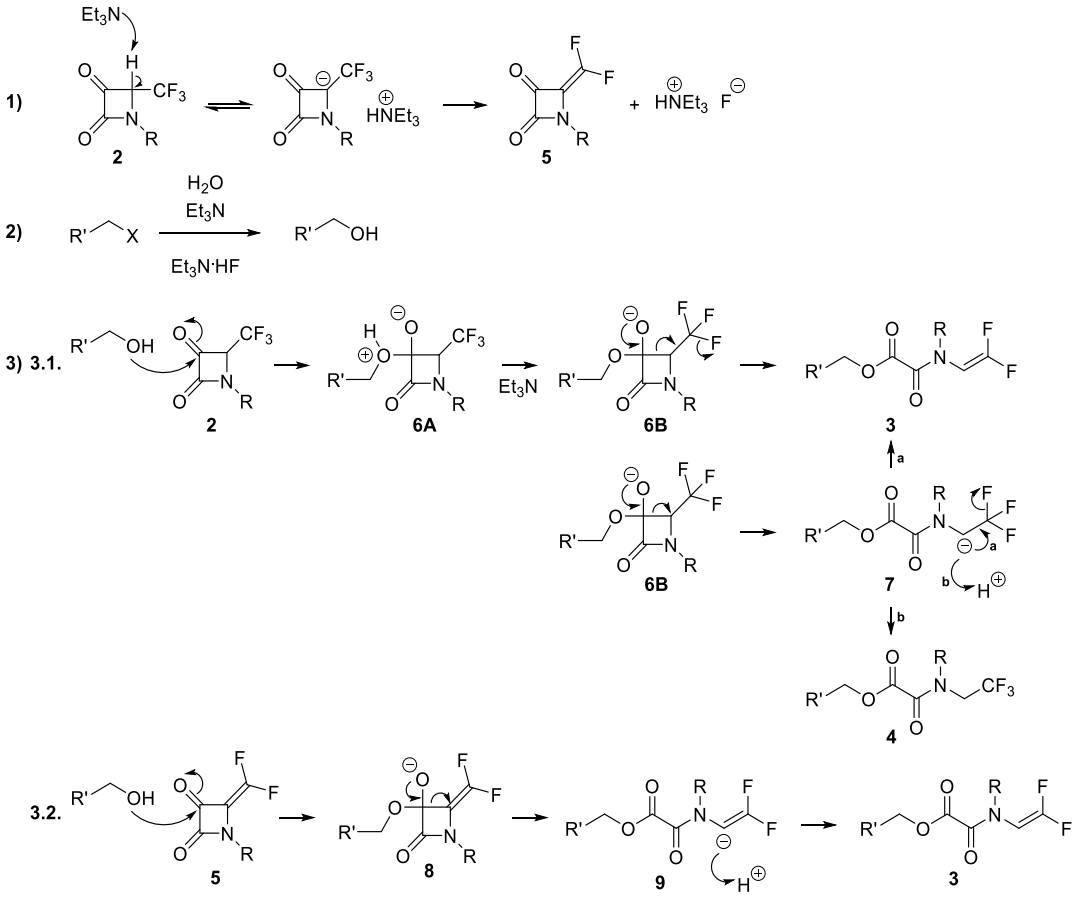
In the next part, efforts were devoted to clarify the peculiar reactivity associated with this unexpected transformation.[81k] To that end, each of the reaction parameters was changed in turn in order to see the effect on the outcome. First, the alkyl halide was omitted, affording only a complex reaction mixture. Apparently, treatment with Et_3N in DMSO does affect the 3-oxo-β-lactam substrate **2**, pointing to a probable deprotonation followed by rapid degradation. Next, the base (Et_3N) was left out, resulting in mainly recuperation of the starting material. These observations underline the importance of combining 1-iodopropane and Et_3N to evoke the desired reactivity. As the combination of an alkyl halide and Et_3N in DMSO is known to be characteristic for the Kornblum oxidation,[83] the possible intermediacy of an aldehyde in this reaction was investigated as well. However, replacement of 1-iodopropane with propanal (the Kornblum oxidation product of 1-iodopropane) did not result in conversion of the substrate **2**.

Based on the ester portion present in the obtained products **3**/**4**, it is clear that an oxygen atom (probably resulting from water) is introduced during this transformation. In order to verify whether

an alcohol could trigger the same reactivity, 3-oxo-β-lactams **2** were treated with propan-1-ol (instead of 1-iodopropane) in DMSO in the presence of Et_3N. Interestingly, this test reaction indeed furnished the same amido esters **3** and **4** in a 98/2 ratio, pointing to a possible formation and participation of propanol in the initial 1-iodopropane/Et_3N approach to a certain extent. The presence of Et_3N seemed to be inevitable, as treatment with propanol without this base resulted in recuperation of the substrate only. In order to check this rather curious iodopropane-to-propanol conversion hypothesis, benzoyl chloride and a fluoride source (TBAF) was added to a solution of 1-iodopropane and Et_3N in DMF, after which formation of a small amount of the corresponding propyl benzoate (the reaction product of the *in situ* formed propanol and benzoyl chloride) at r.t. was acknowledged by means of GC-MS. Based on the above-described results, the mechanism behind this peculiar transformation might (partly) rely on an initial conversion of the alkyl halide into the corresponding alcohol by residual water, which subsequently induced β-lactam ring cleavage. Given the fact that Et_3N was shown to affect the 3-oxo-β-lactam substrate **2**, the formation of triethylamine hydrofluoride seems reasonable, and this salt might even act as a catalyst to facilitate the alkyl halide-to-alcohol interconversion according to literature information.[84] To acknowledge the potential role of fluoride as a catalyst, Et_3N was replaced with TBAF, also resulting in the formation of amido esters **3** and **4** in a 97/3 ratio. Possibly, Et_3N is necessary to provide a catalytic amount of $Et_3N{\cdot}HF$ as a fluoride source in this reaction (through dehydrofluorination of substrates **2**). It should also be noted that the alkyl halide/TBAF combination offers a convenient protocol for the almost exclusive formation of 2-[(2,2-difluorovinyl)amino]-2-oxoacetates **3** (**3**/**4**: 97/3).

To summarize, careful variation of the reaction parameters allowed us to suggest the following unexpected reaction mechanism to partly account for the formation of 2-[(2,2-difluorovinyl)amino]-2-oxoacetates **3** and 2-oxo-2-[(2,2,2-trifluoroethyl)amino]acetates **4** upon treatment of 4-trifluoromethyl-3-oxo-β-lactams **2** with an alkyl halide in the presence of Et_3N in DMSO or DMF (Scheme 2): step 1) (partial) dehydrofluorination of substrates **2** through the action of Et_3N, leading to the formation of $Et_3N{\cdot}HF$ and 4-(difluoromethylene)azetidine-2,3-dione **5**; step 2) ($Et_3N{\cdot}HF$-assisted) transformation of the alkyl halide into the corresponding alcohol due to residual water present in the solvent and/or reagents; step 3) addition of this alcohol across the ketone carbonyl group in 3-oxo-β-lactams followed by subsequent C3-C4 bond fission. Alcohol addition onto 4-trifluoromethyl-3-oxo-β-lactams **2** provides access to both end products **3** and **4** *via* the common intermediate **7** (route 3.1), whereas reaction with the *in situ* formed 4-difluoromethylene-β-lactam **5** only results in production of the main compound **3** (route 3.2). Direct fluoride expulsion from **6B** to **3** can also be considered. Pathways 3.1 and 3.2 might be competitive, but only route 3.1 can

account for the presence of the minor product **4**. As an experiment in which a 3-oxo-β-lactam **2** was treated with propan-1-ol in DMSO showed Et_3N to be necessary to provoke reaction, a fast proton transfer from **6A** to Et_3N and subsequent ring opening of anionic intermediate **6B** could further support the observed reactivity (as the more stable corresponding neutral hemiacetal would probably not suffer from ring cleavage).



Scheme 2. Possible mechanistic rationalization of the observed reactivity to (partly) explain the formation of compounds **3** and **4**

The peculiar role of the CF_3 group in this story was further acknowledged upon treatment of a 4-phenyl- and a 4-isopropyl-3-oxo-β-lactam with propanol in DMSO in the presence or absence of Et_3N, leading to complex mixtures or no conversion of the substrate. Apparently, the strong electron-withdrawing properties of the CF_3 group are required to induce C3-C4 ring fission.

The proposed route, based on an initial alkyl halide-to-alcohol interconversion, should most probably be considered as a minor option in the overall mechanism. Nonetheless, as the formation of a small amount of propanol (trapped as propyl benzoate) from iodopropane could be demonstrated, this unexpected pathway should not be ruled out and probably accounts for part of the final product formation. In order to provide additional support for this peculiar mechanistic proposal, theoretical calculations were performed to obtain more insight into the preference for the various proposed reaction pathways. Particular attention was devoted to the dehydrofluorination reaction, necessary to account for the formation of major compounds **3**, as this step could theoretically occur at different stages throughout the proposed overall mechanism. The main objective of this computational study was merely to verify if this proposal is realistic, not to claim that this is the only right one.

The M06-2X/6-31++G(d,p) level of theory was used for geometry optimizations, since this level of theory was proven to yield reliable results for reactions involving small *N*-heterocycles.[85,81k] Furthermore, M06-2X accounts for dispersion effects to some extent.[86] However, a benchmarking study on dispersion-inclusive DFT methods showed that M06-2X is one of the preferable functionals for hydrogen-bonded systems while it is less preferred for dispersion-dominated systems.[87] Although Hydrogen bonds play an important role in some pathways under study, most pathways are dispersion-dominated. Therefore, the electronic energies were determined at the B3LYP-D3/6-311++G(d,p) level of theory with inclusion of dispersion corrections using the D3 dispersion correction scheme.[88] These corrections, proposed by Grimme et al., account for dispersion effects in complex systems and at long range.[89] This methodology has been applied successfully to (ring-opening) reactions of 3-oxo-ß-lactams.[81k] Minima (ground states) and first-order saddle points (transition states) were characterized by normal mode analysis. The normal modes obtained at the M06-2X/6-31++G(d,p) were used as input for the thermal corrections at 1 atm and 298 K. A continuum model was used to account for the solvent environment.[90] Adding explicit solvent molecules on top of the reacting molecules, including EtOH, and the base Et_3N would make the system fairly complex to explore all pathways. All computations were carried out with the Gaussian 09 program package.[91]

For this theoretical study, R = R' = Me was chosen. On top of the evidences from the experimental study, the calculations clearly showed the necessity of Et_3N for the reaction to proceed. Whereas activation barriers of over 300 kJ/mol were found for the dehydrofluoration of 4-trifluoromethyl-3-oxo-β-lactam **2** to 4-(difluoromethylene)azetidine-2,3-dione **5** in preliminary calculations without

Et_3N, these barriers were lowered tremendously by assistance of Et_3N. The Gibbs free energy profile for the reaction of **2** to **5** (Scheme 2, step 1) with assistance of Et_3N is shown in Figure 1.

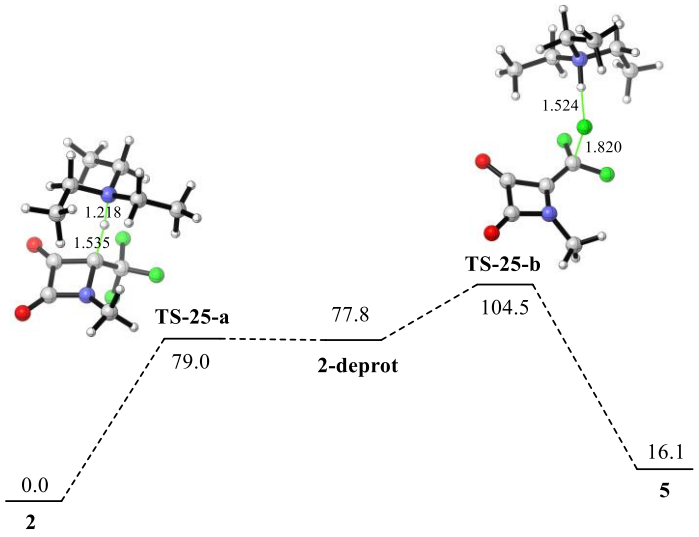


Figure 1. Gibbs free energy profile for the dehydrofluoration of 4-trifluoromethyl-3-oxo-β-lactam **2** to 4-(difluoromethylene)azetidine-2,3-dione **5** with assistance of Et_3N (PCM (ε = 46,83) B3LYP-D3/6-311+G(d,p)//PCM (ε = 46,83) M06-2X/6-31++G(d,p), kJ/mol). Energies relative to the separate reactants. Some critical distances are given in Å.

An activation barrier of 79.0 kJ/mol is found for the deprotonation step, whereas an energy barrier of 104.5 kJ/mol has to be overcome for defluorination by the protonated base Et_3NH^+. The latter barrier is relatively high and it may be assumed that the defluorination of the deprotonated 3-oxo-β-lactam **2** will thus not take place. On the other hand, the protonated base Et_3NH^+, resulting from deprotonation of **2**, can facilitate the transformation of e.g. ethyl halide to ethanol (Scheme 2, step 2).

The Gibbs free energy profile for the addition of ethanol across the ketone carbonyl group in 3-oxo-β-lactam **2** (Scheme 2, step 3.1, first part) is shown in Figure 2. An activation barrier of 74.7 kJ/mol is found for the reaction with assistance of Et_3N, which substracts the hydroxylic hydrogen atom from ethanol during the reaction, whereas a barrier of over 150 kJ/mol was found from preliminary calculations without Et_3N, showing the necessity of Et_3N for the addition of ethanol (which is also in agreement with the experimental observations).

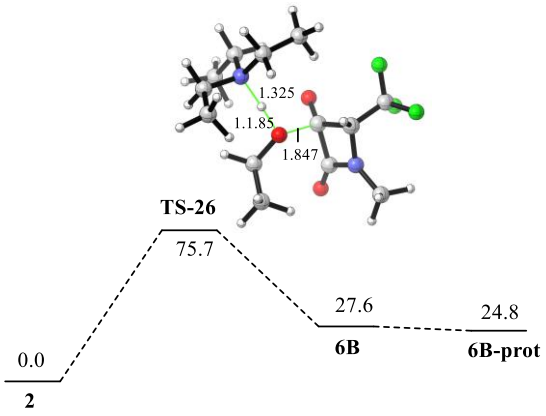


Figure 2. Gibbs free energy profile for the addition of ethanol to 3-oxo-β-lactam **2** with assistance of Et_3N (PCM (ε = 46,83) B3LYP-D3/6-311+G(d,p)//PCM (ε = 46,83) M06-2X/6-31++G(d,p), kJ/mol). Energies relative to the separate reactants. Some critical distances are given in Å.

Thus, the activation barrier for the addition of ethanol to **2** (Scheme 2, step 3.1, first part) is lower than the activation barrier for the conversion of **2** to **5**, further suggesting that the dehydrofluoration of 3-oxo-β-lactam **2** (step 1) will not take place. Additionally, assistance of ethanol in the defluorination of the deprotonated 3-oxo-β-lactam **2** (Scheme 2, step 1) was investigated. However, the assistance was found not to lower the activation barrier

Whereas hemiacetal **6** can easily be deprotonated at the hydroxyl group on the C3 position, deprotonation at the C4 carbon atom and dehydrofluoration with formation of **8** are very unlikely. On the other hand, ring opening of **6B** can lead to intermediate **7**, which will be readily protonated with formation of the minor product **4**, or direct ring opening of **6B** with simultaneous defluorination can lead to the major product **3** (Scheme 2, step 3.1, last part). Ring opening of **6** with simultaneous proton transfer and direct formation of the minor product **4** is less likely since protonated Et_3N cannot easily approach the carbon atom which has to be protonated. The Gibbs free energy profiles for the pathways for the formation of products **3** and **4** from **6B** are shown in Figure 3.

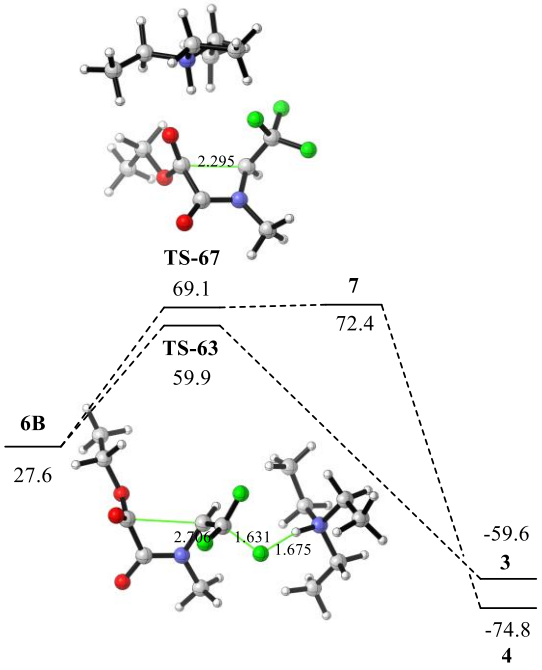
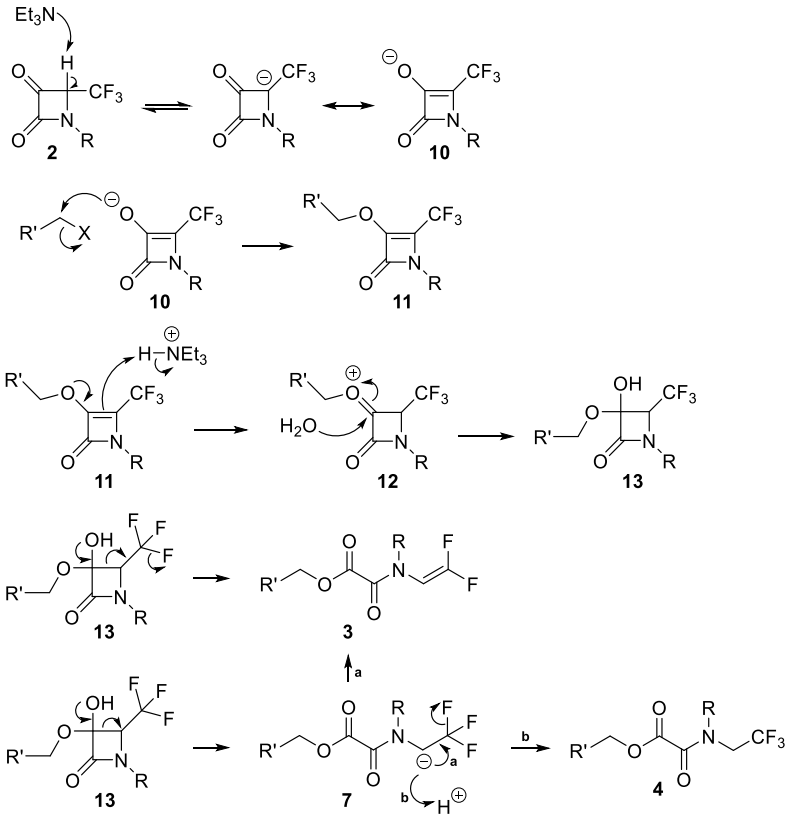


Figure 3. Gibbs free energy profiles for the conversion of intermediate **6B** to products **3** and **4** with assistance of Et_3N (PCM (ε = 46,83) B3LYP-D3/6-311+G(d,p)//PCM (ε = 46,83) M06-2X/6-31++G(d,p), kJ/mol). Energies relative to reactants **2** with ethanol and Et_3N. Some critical distances are given in Å.

A clearly lower activation barrier is found for the formation of the major product **3** if ring opening of **6B** occurs simultaneously with defluorination ($\Delta G^{\ddagger}$ = 59.9 kJ/mol versus 69.1 kJ/mol for the formation of the minor product **4**), explaining why **3** is the major product. On the other hand, the difference between the activation barriers of both pathways is less than 10 kJ/mol, explaining the possibility for the formation of **4** as a side product.

In summary, these calculations showed that deprotonation of 3-oxo-β-lactam **2** by Et_3N (Scheme 2, step 1) could result in formation of the protonated base Et_3NH^+, which facilitates the transformation of ethyl halide to ethanol (Scheme 2, step 2). Subsequently, ethanol can add across the ketone carbonyl group in 3-oxo-β-lactam **2** (Scheme 2, step 3.1) with formation of intermediate **6**, which is transferred to the major product **3** by ring opening with concomitant defluorination. Alternatively, ring opening can lead to intermediate **7**, which will be readily protonated with formation of the minor product **4**. In other words, although this mechanistic route probably only accounts for a minor fraction of the final products, the calculations show that it concerns a realistic pathway.

Nonetheless, it is clear that other mechanistic options to explain the observed reactivity cannot be ruled out based on the above-described findings. For example, an at first sight more reasonable approach is based on the *O*-alkylation of the enolate anion **10** formed after deprotonation by Et_3N, producing enol ether **11**. Re-protonation at C4 then affords an electrophilic oxonium ion **12**, which suffers from water addition to afford hemiacetal **13**. The latter intermediate finally undergoes a C3-C4 bond fission (with or without concomitant dehydrofluorination) to result in final structures **3** and **4** (Scheme 3). Unfortunately, attempts to provide evidence for the intermediacy of enol ethers **11** by means of NMR or MS were unsuccessful.



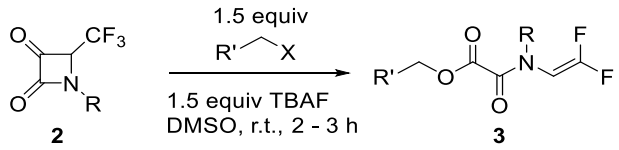
Scheme 3. Alternative mechanism for the formation of compounds **3** and **4** *via* an enol ether intermediate **11**

Although the participation of water seems to be necessary at some point to account for the presence of three oxygen atoms in the final products, the role of this adventitious water remains curious. In order to demonstrate the intervention of water during the process, a final experiment was performed involving treatment of 3-oxo-β-lactam **2b** with allyl bromide in dry DMSO in the

presence of 10 equiv of ^{18}O-labeled water. The detection of the corresponding molecular m/z ion 313 in MS for structure **3** (with a M+2 mass as compared to the O^{16}-containing counterpart) confirmed the incorporation of $H_2{}^{18}O$ during the reaction pathway, and only the expected m/z 311 ion was observed when no ^{18}O-labeled water was used. Based on NMR analysis before and after aqueous work-up, we suppose that water participation during work-up constitutes an important pathway in the overall mechanism, and that the role of adventitious water present in the solvent or reagents is probably minimal.

4. Conclusion

Treatment of 4-trifluoromethyl-3-oxo-β-lactams with an alkyl halide and triethylamine in DMSO unexpectedly resulted in the formation of 2-[(2,2-difluorovinyl)amino]-2-oxoacetates as major products, accompanied by minor amounts of 2-oxo-2-[(2,2,2-trifluoroethyl)amino]acetates, through an unprecedented C3-C4 β-lactam bond fission. This peculiar reactivity was investigated from both an experimental and a computational point of view in order to shed light on the underlying reaction mechanism. Furthermore, the alkyl halide/TBAF combination was shown to offer a convenient alternative protocol for the selective formation of 2-[(2,2-difluorovinyl)amino]-2-oxoacetates **3** from 4-CF_3-3-oxo-β-lactams **2**. Given the current pharmaceutical interest in fluorinated building blocks, these newly obtained fluorinated amido esters might be of importance for further studies as well.

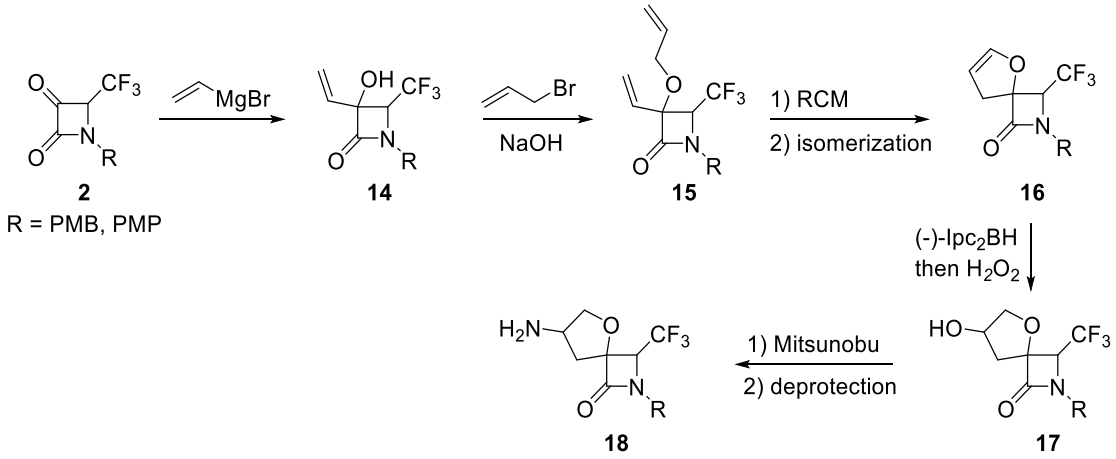


2 **3**

5. Perspectives

In addition, 4-trifluoromethyl-3-oxo-β-lactams **2** can be suitable substrates to provide novel CF_3-substituted 5-oxa-2-azaspiro[3.4]octan-1-ones **18** (Scheme 4). In that respect, 3-oxo-β-lactams **2** will be converted into alcohols **14** upon treatment with vinylmagnesium bromide. The resulting tertiary alcohol will be transformed into the corresponding allyl ethers **15**, which will then be

subjected to ring-closing metathesis (RCM) to afford spirodihydrofurans **16**. These cyclic enol ethers can be used as eligible substrates to access amines **18** through the use of Mitsunobu displacement of the secondary alcohol **17**, which can be prepared from enol ethers **16** upon treatment with (-)-Ipc_2BH.[92] Spiro-β-lactam compounds are of paramount value to medicinal chemistry because of their antiviral and antibacterial properties, as well as for cholesterol absorption.[93] Thus, spiro-β-lactams **18** bearing a CF_3 group might be valuable compounds with interesting biological properties.



Scheme 4

6. Experimental details

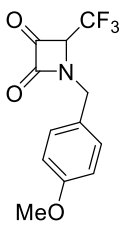
General methods

High Performance Liquid Chromatography (HPLC) was performed on an Agilent 1200 Series with UV/DAD detector, the column was of the type Eclipse Plus C18 (4,6 × 50 mm, particle size 3,5 µm), using solvent system ($MeCN/H_2O$, from 30% to 100% MeCN). Gas chromatography–mass spectrometry (GC-MS) were performed on an Agilent 6890 Series.

Synthesis of 4-trifluoromethyl-3-oxoazetidin-2-ones 2

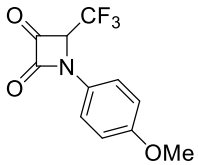
As a representative example, the synthesis of 1-(4-methoxybenzyl)-4-trifluoromethyl-3-oxoazetidin-2-one **2a** is described. Phosphorus pentoxide (0.52 g, 3.66 mmol, 2 equiv) was added slowly to 75 mL of dry DMSO at 0 °C and the resulting mixture was stirred at room temperature for 10 min. Then, the starting material *cis*-3-hydroxy-1-(4-methoxybenzyl)-4-(trifluoromethyl)azetidin-2-one **1a** (0.50 g, 1.82 mmol, 1 equiv), dissolved in 37.5 (mL) of dry DMSO, was added dropwise. The resulting mixture was stirred for 18 hours at 150 °C. The reaction was quenched with ice-cooled water (100 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed five times with brine (5 × 20 mL) to remove the excess of DMSO, then dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by recrystallization in diethyl ether to give 1-(4-methoxybenzyl)-4-trifluoromethyl-3-oxoazetidin-2-one **2a** in a yield of 46%.

1-(4-Methoxybenzyl)-4-trifluoromethyl-3-oxoazetidin-2-one 2a



White crystals. Mp 101 °C. Recrystallization in Et_2O. Yield 46%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.82 (3H, s, OCH_3), 4.27 (1H, q, J = 6.0 Hz, $CHCF_3$), 4.30 and 5.21 (2 × 1H, 2 × d, J = 14.8 Hz, N(HCH)Ar), 6.92 and 7.22 (2 × 2H, 2 × d, J = 8.6 Hz, $NCH_2(CH_{arom})_{ortho}$) and $O(CH_{arom})_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 46.4 (NCH_2Ar), 55.3 (OCH_3), 68.2 (q, J = 34.7 Hz, $CHCF_3$), 114.8 (2 × $O(CH_{arom})_{ortho}$), 122.2 (q, J = 280.1 Hz, CF_3), 124.2 (2 × $NCH_2(CH_{arom})_{ortho}$), 130.3 (2 × $OC_{arom,quat}$), 160.1 ($OC_{arom,quat}$), 162.6 (NC=O), 183.7 (CF_3CHC=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -70.37 (3F, d, J = 6.0 Hz, CF_3). IR (ATR, cm^{-1}): $\nu_{CHC=O}$ = 1838, $\nu_{NC=O}$ = 1766, ν_{max} = 1515, 1252, 1181, 1138, 1036, 884, 872, 700, 650. GC-MS: *m/z* (%) = 273 (M^+, 5), 121 (100), 78 (8).

1-(4-Methoxyphenyl)-4-trifluoromethyl-3-oxoazetidin-2-one 2b

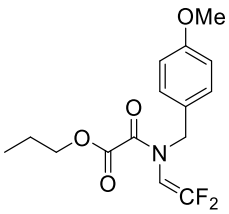


Yellow crystals. Mp 72 °C. in Et_2O/Hex, 3/1. Yield 54%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.85 (3H, s, OCH_3), 5.02 (1H, q, J = 5.2 Hz, $CHCF_3$), 6.99 and 7.57 (2 × 2H, 2 × d, J = 9.1 Hz, $N(CH_{arom})_{ortho}$) and $O(CH_{arom})_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 55.6 (OCH_3), 69.7 (q, J = 35.1 Hz, $CHCF_3$), 114.9 (2 × $O(HC_{arom})_{ortho}$), 119.7 (2 × $O(HC_{arom})_{meta}$), 122.2 (q, J = 281.5 Hz, CF_3), 129.0 ($NC_{arom,quat}$), 158.8 ($OC_{arom,quat}$), 159.2 (CF_3CHC=O), 181.8 (NC=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -68.71 (3F, d, J = 5.2 Hz, CF_3). IR (ATR, cm^{-1}): $\nu_{CHC=O}$ = 1820, $\nu_{NC=O}$ = 1760, ν_{max} = 1609, 1509, 1248, 1142, 1021, 980, 829. GC-MS: *m/z* (%) = 259 (M^+, 23), 188 (10), 203 (78), 134 (100), 107 (16), 92 (12), 77 (12).

Synthesis of propyl 2-[(2,2-difluorovinyl)(4-methoxybenzyl)amino]-2-oxoacetate 3a and propyl 2-[(4-methoxybenzyl)(2,2,2-trifluoroethyl)amino]-2-oxoacetate 4a

As a representative example, the synthesis of propyl 2-[(2,2-difluorovinyl)(4-methoxybenzyl)amino]-2-oxoacetate **3a** and propyl 2-oxo-2-[(4-methoxybenzyl)(2,2,2-trifluoroethyl)amino]acetate **4a** is described. To a solution of 1-(4-methoxybenzyl)-4-trifluoromethyl-3-oxoazetidin-2-one **2a** (0.10 g, 0.37 mmol, 1 equiv) in DMSO (10 mL) was added 1-iodopropane (0.05 mL, 0.55 mmol, 1.5 equiv) and triethylamine (0.15 mL, 1.11 mmol, 3 equiv) at room temperature. The resulting mixture was stirred for two hours at the same temperature. The reaction mixture was quenched with water (20 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic phases were washed with brine (5 x 10 mL). Drying ($MgSO_4$), filtration of the drying agent, and removal of the solvent *in vacuo* afforded a crude product. The ^{1}H NMR of the crude product showed it to be a mixture of propyl 2-[(2,2-difluorovinyl)(4-methoxybenzyl)amino]-2-oxoacetate **3a** and propyl 2-oxo-2-[(4-methoxybenzyl)(2,2,2-trifluoroethyl)amino]acetate **4a** in a ratio of 87:13, which was separated by means of preparative HPLC (Supelco Ascentis C18, H_2O-CH_3CN, 35:65) giving pure propyl 2-[(2,2-difluorovinyl)(4-methoxybenzyl)amino]-2-oxoacetate **3a** in a yield of 56% and propyl 2-oxo-2-[(4-methoxybenzyl)(2,2,2-trifluoroethyl)amino]acetate **4a** in a yield of 12%.

Propyl 2-[(2,2-difluorovinyl)(4-methoxybenzyl)amino]-2-oxoacetate 3a



Yellow oil. HPLC (Supelco Ascentis C18, H_2O/CH_3CN, 35/65, flow rate 6 mL min^{-1}, detection at 220 nm, t_R= 33.61-33.99 min). Yield 56%. 2 rotamers 81/19

Major rotamer

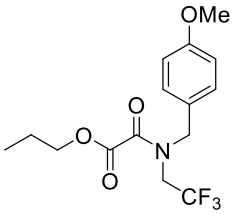
^{1}H NMR (400 MHz, $CDCl_3$): δ 0.97 (3H, t, J = 7.0 Hz, $OCH_2CH_2C\underline{H}_3$), 1.73 (2H, sextet, J = 7.0 Hz, $OCH_2C\underline{H}_2CH_3$), 3.80 (3H, s, OCH_3), 4.22 (2H, t, J = 7.0 Hz, $OC\underline{H}_2CH_2CH_3$), 4.62 (2H, s, NCH_2), 5.31 (1H, d × d, J = 18.0, 3.0 Hz, $CHCF_2$), 6.87 and 7.21 (2 × 2H, 2 × d, J = 8.6 Hz, $NCH_2(C\underline{H}_{arom})_{ortho}$ and $O(CH_{arom})_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 10.1 ($OCH_2CH_2\underline{C}H_3$), 21.7 ($OCH_2\underline{C}H_2CH_3$), 49.8 (t, J = 1.6 Hz, $N\underline{C}H_2Ar$), 55.27 (OCH_3), 67.8 ($O\underline{C}H_2CH_2CH_3$), 85.5 (d × d, J = 49.1, 15.1 Hz, $\underline{C}HCF_2$), 114.16 (2 × $O(CH_{arom})_{ortho}$), 126.8 ($NCH_2\underline{C}_{arom,quat}$), 130.1 (2 × $O(CH_{arom})_{meta}$), 158.5 (d × d, J = 298.1, 292.4 Hz, CF_2), 159.5 ($OC_{arom,quat}$), 161.8 (t, J = 2.2 Hz, NC=O), 162.2 (OC=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -93.21 (1F, d × d, J = 27.1, 3.0 Hz, $\underline{F}CF$), -83.54 (1F, d × d, J = 27.1, 18.0 Hz, $FC\underline{F}$).

Minor rotamer (detectable signals)

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.95 (3H, t, J = 7.1 Hz, $OCH_2CH_2C\underline{H}_3$), 1.73 (2H, sextet, J = 7.1 Hz, $OCH_2C\underline{H}_2CH_3$), 3.80 (3H, s, OCH_3), 4.25 (2H, t, J = 7.1 Hz, $OC\underline{H}_2CH_2CH_3$), 4.57 (2H, s, NCH_2), 5.52 (1H, d, J = 21.5 Hz, $CHCF_2$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 10.2 ($OCH_2CH_2\underline{C}H_3$), 21.7 ($OCH_2\underline{C}H_2CH_3$), 52.0 (d, J = 3.5 Hz, NCH_2), 55.30 (OCH_3), 68.1 ($O\underline{C}H_2CH_2CH_3$), 84.3 (d × d, J = 51.6, 12.8 Hz, $\underline{C}HCF_2$), 114.24 (2 × $O(CH_{arom})_{ortho}$), 126.4 ($NCH_2\underline{C}_{arom,quat}$), 129.0 (2 × $O(CH_{arom})_{meta}$), 156.9 (d, J = 294.7 Hz, CF_2), 159.7 ($OC_{arom,quat}$), 161.2 (NC=O), 162.3 (OC=O).^{19}F NMR (376.5 MHz, $CDCl_3$): δ -97.29 (1F, d, J = 42.1 Hz, $\underline{F}CF$), -82.73 (1F, d × d, J = 42.1, 21.5 Hz, $FC\underline{F}$).

IR (ATR, cm^{-1}): $\nu_{OC=O}$ = 1744, $\nu_{NC=O}$ = 1674, ν_{max} = 1513, 1416, 1243, 1174, 1032, 800. MS (70eV): m/z (%): 314 (M^+ + 1, 100). HRMS (ESI) calcd for $C_{15}H_{18}F_2NO_4^+$: 314.1198 $[M + H]^+$. Found: 314.1204.

Propyl 2-oxo-2-[(4-methoxybenzyl)(2,2,2-trifluoroethyl)amino]acetate 4a



Yellowish oil. HPLC (Supelco Ascentis C18, H_2O/CH_3CN, 35/65, flow rate 6 mL min^{-1}, detection at 220 nm, t_R = 40.11-40.25 min). Yield 12%. 2 rotamers 66/34

Major rotamer

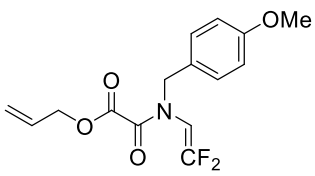
^{1}H NMR (400 MHz, $CDCl_3$): δ 0.95-1.01 (3H, m, $CH_2C\underline{H}_3$), 1.71-1.81 (2H, m, $CH_2C\underline{H}_2CH_3$), 3.82 (3H, s, OCH_3), 3.88 (2H, q, J = 8.9 Hz, CH_2CF_3), 4.27 (2H, t, J = 6.7 Hz, $C\underline{H}_2CH_2CH_3$), 4.53 (2H, s, NCH_2), 6.91 and 7.22 (2 × 2H, 2 × d, J = 8.6 Hz, $NCH_2(C\underline{H}_{arom})_{ortho}$ and $O(CH_{arom})_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 10.24 ($CH_2CH_2\underline{C}H_3$), 21.8 ($CH_2\underline{C}H_2CH_3$), 42.8 (q, J = 34.2 Hz, $\underline{C}HCF_3$), 51.3 ($N\underline{C}H_2Ar$), 55.4 (OCH_3), 68.1 ($\underline{C}H_2CH_2CH_3$), 114.53 (2 × $O(CH_{arom})_{ortho}$), 124.2 (q, J = 281.2 Hz, CF_3), 125.4 ($NCH_2C_{arom,quat}$), 129.6 (2 × $O(CH_{arom})_{meta}$), 160.0 ($OC_{arom,quat}$), 162.4 (NC=O), 162.6 (OC=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -68.44 (3F, t, J = 8.9 Hz, CF_3).

Minor rotanmer

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.95-1.01 (3H, m, $CH_2C\underline{H}_3$), 1.71-1.81 (2H, m, $CH_2C\underline{H}_2CH_3$), 3.81 (3H, s, OCH_3), 3.94 (2H, q, J = 8.9 Hz, $C\underline{H}_2CF_3$), 4.26 (2H, t, J = 6.7 Hz, $C\underline{H}_2CH_2CH_3$), 4.71 (2H, s, NCH_2), 6.90 and 7.20 (2 × 2H, 2 × d, J = 8.3 Hz, $NCH_2(C\underline{H}_{arom})_{ortho}$ and $O(CH_{arom})_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 10.15 ($CH_2CH_2\underline{C}H_3$), 21.7 ($CH_2\underline{C}H_2CH_3$), 46.6 (q, J = 28.9 Hz, $\underline{C}HCF_3$), 48.2 ($N\underline{C}H_2Ar$), 55.3 (OCH_3), 68.2 ($\underline{C}H_2CH_2CH_3$), 114.46 (2 × $O(CH_{arom})_{ortho}$), 123.9 (q, J = 282.9 Hz, CF_3), 126.4 ($NCH_2\underline{C}_{arom,quat}$), 130.0 ($NCH_2(\underline{C}H_{arom})_{ortho}$), 159.7 ($OC_{arom,quat}$), 161.7 (NC=O), 161.8 (OC=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -69.87 (3F, t, J = 8. 9 Hz, CF_3).

IR (ATR, cm^{-1}): $\nu_{OC=O}$ = 1737, $\nu_{NC=O}$ = 1673, ν_{max} = 1514, 1445, 1249, 1154, 1111, 1031, 831. MS (70eV): m/z (%): 356 (M^+ + 23, 5). HRMS (ESI) calcd for $C_{15}H_{19}F_3NO_4^+$: 334.1261 $[M + H]^+$. Found: 334.1268.

Allyl 2-[(2,2-difluorovinyl)(4-methoxybenzyl)amino]-2-oxoacetate 3b



Yellow oil. HPLC (Supelco Ascentis C18, H_2O/CH_3CN, 45/55, flow rate 6 mL min^{-1}, detection at 220 nm, t_R= 52.93-53.89 min). Yield 25%. 2 rotamers 83/17.

Major rotamer

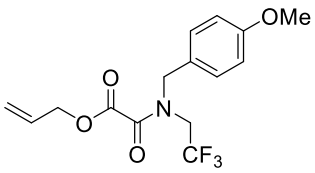
^{1}H NMR (400 MHz, $CDCl_3$): δ 3.80 (3H, s, OCH_3), 4.62 (2H, s, NCH_2), 4.74 (2H, d × t, J = 6.2, 1.2 Hz, $OC\underline{H}_2CHCH_2$), 5.30 (1H, d × d, J = 18.2, 3.1 Hz, $CHCF_2$), 5.32 (1H, d × q, J = 10.4, 1.2 Hz, $OCH_2CH(\underline{H}CH)$), 5.40 (1H, d × q, J = 16.9, 1.2 Hz, $OCH_2CH(HC\underline{H})$), 5.93 (1H, d × d × t, J = 16.9, 10.4, 6.2 Hz, $OCH_2C\underline{H}CH_2$), 6.87 and 7.21 (2 × 2H, 2 × d, J = 9.0 Hz, $NCH_2(C\underline{H}_{arom})_{ortho}$ and $O(CH_{arom})_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 49.8 (t, J = 2.2 Hz, NCH_2), 55.28 (OCH_3), 66.6 ($CO\underline{C}H_2CHCH_2$), 85.5 (d × d, J = 49.1, 15.1 Hz, $\underline{C}HCF_2$), 114.2 (2 × $O(CH_{arom})_{ortho}$), 120.3 ($COCH_2CH\underline{C}H_2$), 126.7 ($NCH_2\underline{C}_{arom,quat}$), 130.1 (2 × $O(CH_{arom})_{meta}$), 130.5 ($COCH_2\underline{C}HCH_2$), 158.4 (d × d, J = 298.9, 293.0 Hz, CF_2), 159.5 ($OC_{arom,quat}$), 161.5 (t, J = 2.2 Hz, NC=O), 161.7 (OC=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -93.00 (1F, d × d, J = 26.6, 3.1 Hz, $\underline{F}CF$), -83.26 (1F, d × d, J = 26.6, 18.2 Hz, $FC\underline{F}$).

Minor rotamer (detectable signals)

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.81 (3H, s, OCH_3), 4.56 (2H, s, NCH_2), 4.77 (2H, d × t, J = 6.1, 1.2 Hz, $OC\underline{H}_2CHCH_2$), 5.51 (1H, d × d, J = 21.3, 1.4 Hz, $CHCF_2$), 5.87-5.97 (1H, m, $OCH_2C\underline{H}CH_2$), 6.88 and 7.20 (2 × 2H, 2 × d, J = 8.8 Hz, $NCH_2(C\underline{H}_{arom})_{ortho}$ and $O(CH_{arom})_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 52.0 (d, J = 3.9 Hz, NCH_2), 55.30 (OCH_3), 66.9 ($CO\underline{C}H_2CHCH_2$), 84.3 (d × d, J = 51.5, 12.9 Hz, $\underline{C}HCF_2$), 114.3 (2 × $O(CH_{arom})_{ortho}$), 120.5 ($COCH_2CH\underline{C}H_2$), 126.3 ($NCH_2\underline{C}_{arom,quat}$), 129.1 (2 × $O(CH_{arom})_{meta}$), 130.4 ($COCH_2\underline{C}HCH_2$), 159.7 ($OC_{arom,quat}$), 160.8 (NC=O), 161.8 (OC=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -97.09 (1F, d, J = 41.6 Hz, $\underline{F}CF$), -82.55 (1F, d × d, J = 41.6, 21.3 Hz, $FC\underline{F}$).

IR (ATR, cm^{-1}): $\nu_{OC=O}$ = 1745, $\nu_{NC=O}$ = 1674, ν_{max} = 1514, 1414, 1243, 1172, 1032, 937, 800. MS (70eV): m/z (%): 312 (M^+ +1, 14). HRMS (ESI) calcd for $C_{15}H_{16}F_2NO_4^+$: 312.1042 $[M + H]^+$. Found: 312.1044.

Allyl 2-oxo-2-[(4-methoxybenzyl)(2,2,2-trifluoroethyl)amino]acetate 4b



Yellow oil. HPLC (Supelco Ascentis C18, H_2O/CH_3CN, 45/55, flow rate 6 mL min^{-1}, detection at 220 nm, t_R= 63.36-64.73min). Yield 5%. 2 rotamer 67/33

Major rotamer

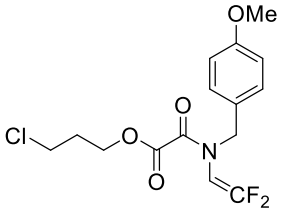
^{1}H NMR (400 MHz, $CDCl_3$): δ 3.82 (3H, s, OCH_3), 3.88 (2H, q, J = 8.9 Hz, CH_2CF_3), 4.53 (2H, s, NCH_2), 4.78-4.80 (2H, m, $OC\underline{H}_2CHCH_2$), 5.33 (1H, d × d, J = 10.4, 0.8 Hz, $OCH_2CH(\underline{H}CH)$), 5.42 (1H, d × q, J = 17.1, 1.4 Hz, $OCH_2CH(HC\underline{H})$), 5.90-6.01 (1H, m, $OCH_2C\underline{H}CH_2$), 6.91 and 7.22 (2 × 2H, 2 × d, J = 8.6 Hz, $NCH_2(C\underline{H}_{arom})_{ortho}$ and $O(CH_{arom})_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 42.8 (q, J = 34.5 Hz, $\underline{C}H_2CF_3$), 51.3 ($N\underline{C}H_2Ar$), 55.35 (OCH_3), 66.9 ($O\underline{C}H_2CHCH_2$), 114.52 (2 × $O(CH_{arom})_{ortho}$), 120.6 ($OCH_2CH\underline{C}H_2$), 124.2 (q, J = 282.3 Hz, CF_3), 125.3 ($NCH_2\underline{C}_{arom,quat}$), 129.7 ($O(CH_{arom})_{meta}$), 130.4 ($OCH_2\underline{C}HCH_2$), 160.0 ($OC_{arom,quat}$), 161.9 (NC=O), 162.2 (OC=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -68.43 (3F, t, J = 8.9 Hz, CF_3).

Minor rotamer

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.81 (3H, s, OCH_3), 3.93 (2H, q, J = 8.8 Hz, CH_2CF_3), 4.71 (2H, s, NCH_2), 4.78-4.80 (2H, m, $OC\underline{H}_2CHCH_2$), 5.34 (1H, d × d, J = 10.2, 1.0 Hz, $OCH_2CH(\underline{H}CH)$), 5.43 (1H, d × q, J = 17.4, 1.7 Hz, $OCH_2CH(HC\underline{H})$), 5.90-6.01 (1H, m, $OCH_2C\underline{H}CH_2$), 6.89 and 7.19 (2 × 2H, 2 × d, J = 8.6 Hz, NCH_2 $(C\underline{H}_{arom})_{ortho}$ and $O(CH_{arom})_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 46.5 (q, J = 34.7 Hz, $\underline{C}H_2CF_3$), 48.2 ($N\underline{C}H_2Ar$), 55.33 (OCH_3), 67.0 ($O\underline{C}H_2CHCH_2$), 114.45 (2 × $O(CH_{arom})_{ortho}$), 120.4 ($OCH_2CH\underline{C}H_2$), 123.9 (q, J = 281.0 Hz, CF_3),126.3 ($NCH_2\underline{C}_{arom,quat}$), 130.1 ($O(CH_{arom})_{meta}$), 130.4 ($OCH_2\underline{C}HCH_2$), 159.7 ($OC_{arom,quat}$), 161.2 (NC=O), 161.4 (OC=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -69.79 (3F, t, J = 8.8 Hz, CF_3).

IR (ATR, cm^{-1}): $\nu_{OC=O}$ = 1742, $\nu_{NC=O}$ = 1675, ν_{max} = 1515, 1446, 1250, 1258, 1117, 1031, 832. GC-MS: *m/z* (%) = 331 (M^+, 7), 290 (60), 218 (20), 137 (72), 121 (100), 78 (13), 41 (10).

3-Chloropropyl 2-[(2,2-difluorovinyl)(4-methoxybenzyl)amino]-2-oxoacetate 3c



Yellow oil. HPLC (Supelco Ascentis C18, H_2O/CH_3CN, 43/57, flow rate 6 mL min^{-1}, detection at 220 nm, t_R = 32.72-33.30 min). Yield 42%. 2 rotamers 83/17

Major rotamer

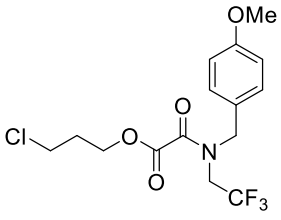
^{1}H NMR (400 MHz, $CDCl_3$): δ 2.10-2.20 (2H, m, $OCH_2C\underline{H}_2CH_2Cl$), 3.63 (2H, t, J = 6.2 Hz, $OCH_2CH_2C\underline{H}_2Cl$), 3.81 (3H, s, OCH_3), 4.42 (2H, t, J = 6.2 Hz, $OC\underline{H}_2CH_2CH_2Cl$), 4.62 (2H, s, NCH_2), 5.32 (1H, d × d, J = 18.1, 2.7 Hz, $CHCF_2$), 6.87 and 7.21 (2 × 2H, 2 × d, J = 8.5 Hz, $NCH_2(C\underline{H}_{arom})_{ortho}$ and $O(CH_{arom})_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 31.1 ($OCH_2\underline{C}H_2CH_2Cl$), 40.6 ($OCH_2CH_2C\underline{H}_2Cl$), 49.9 (t, J = 2.2 Hz, NCH_2), 55.28 (OCH_3), 62.8 ($O\underline{C}H_2CH_2CH_2Cl$), 85.5 (d × d, J = 48.9, 15.1 Hz, $\underline{C}HCF_2$), 114.2 (2 × $O(CH_{arom})_{ortho}$), 126.6 ($NCH_2\underline{C}_{arom,quat}$), 130.1 (2 × $O(CH_{arom})_{meta}$), 158.5 (d × d, J = 298.0, 293.1 Hz, CF_3), 159.6 ($OC_{arom,quat}$), 161.4 (t, J = 2.8 Hz, NC=O), 161.89 (OC=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -92.77 (1F, d × d, J = 2.7, 26.5 Hz, $\underline{F}CF$), -83.61 (1F, d × d, J = 26.5, 18.1 Hz, $FC\underline{F}$).

Minor rotamer

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.10-2.20 (2H, m, $OCH_2C\underline{H}_2CH_2Cl$), 3.56 (2H, t, J = 6.2 Hz, $OCH_2CH_2C\underline{H}_2Cl$), 3.81 (3H, s, OCH_3), 4.43 (2H, t, J = 6.2 Hz, $OC\underline{H}_2CH_2CH_2Cl$), 4.58 (2H, s, NCH_2), 5.55 (1H, d × d, J = 21.3, 1.1 Hz, $CHCF_2$), 6.89 and 7.18 (2 × 2H, 2 × d, J = 9.0 Hz, $O(CH_{arom})_{ortho}$ and $NCH_2(C\underline{H}_{arom})_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 31.0 ($OCH_2\underline{C}H_2CH_2Cl$), 40.6 ($OCH_2CH_2C\underline{H}_2Cl$), 52.1 (d, J = 3.6 Hz, NCH_2), 55.32 (OCH_3), 63.0 ($O\underline{C}H_2CH_2CH_2Cl$), 84.5 (d × d, J = 51.5, 12.7 Hz, $\underline{C}HCF_2$), 114.3 (2 × $O(CH_{arom})_{ortho}$), 126.4 ($NCH_2\underline{C}_{arom,quat}$), 128.9 (2 × $O(CH_{arom})_{meta}$), 155.5 (d × d, J = 295.6, 286.0 Hz, CF_3), 159.7 ($OC_{arom,quat}$), 160.8 (NC=O), 161.94 (OC=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -97.15 (1F, d, J = 41.7 Hz, $\underline{F}CF$), -82.57 (1F, d × d, J = 41.7, 21.3 Hz, $FC\underline{F}$).

IR (ATR, cm^{-1}): $\nu_{OC=O}$ = 1745, $\nu_{NC=O}$ = 1674, ν_{max} = 1513, 1417, 1244, 1173, 1031, 957, 801. MS (70eV): m/z (%): 370 (M^+ + 23, 20). HRMS (ESI) calcd for $C_{15}H_{17}ClF_2NO_4^+$: 348.0809 $[M + H]^+$. Found: 348.0814.

3-Chloropropyl 2-oxo-2-[(4-methoxybenzyl)(2,2,2-trifluoroethyl)amino]acetate 4c



Yellowish oil. HPLC (Supelco Ascentis C18, H_2O/CH_3CN, 43/57, flow rate 6 mL min^{-1}, detection at 220 nm, t_R = 38.47-38.97 min). Yield 10%. 2 rotamers 65/35

Major rotamer

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.14-2.23 (2H, m, $OCH_2C\underline{H}_2CH_2Cl$), 3.60 (2H, t, J = 6.2 Hz, $OCH_2CH_2C\underline{H}_2Cl$), 3.82 (3H, s, OCH_3), 3.90 (2H, q, J = 8.9 Hz, CH_2CF_3), 4.467 (2H, t, J = 6.2 Hz, $OC\underline{H}_2CH_2CH_2Cl$), 4.55 (2H, s, NCH_2), 6.91 and 7.21 (2 × 2H, 2 × d, J = 8.6 Hz, $NCH_2(C\underline{H}_{arom})_{ortho}$ and $O(CH_{arom})_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 31.0 ($OCH_2\underline{C}H_2CH_2Cl$), 40.64

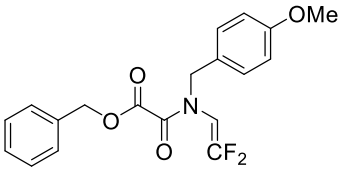
($OCH_2CH_2C\underline{H}_2Cl$), 43.1 (q, J = 34.3 Hz, $\underline{C}HCF_3$), 51.4 (NCH_2), 55.4 (OCH_3), 63.1 ($O\underline{C}H_2CH_2CH_2Cl$), 114.6 (2 × $O(CH_{arom})_{ortho}$), 124.1 (q, J = 281.5 Hz, CF_3), 125.4 ($NCH_2\underline{C}_{arom,quat}$), 129.5 (2 × $O(CH_{arom})_{meta}$), 160.0 ($OC_{arom,quat}$), 161.4 (NC=O), 162.0 (OC=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -68.49 (3F, t, J = 8.9 Hz, CF_3).

Minor rotamer

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.14-2.23 (2H, m, $OCH_2C\underline{H}_2CH_2Cl$), 3.65 (2H, t, J = 6.2 Hz, $OCH_2CH_2C\underline{H}_2Cl$), 3.81 (3H, s, OCH_3), 3.95 (2H, q, J = 8.8 Hz, $C\underline{H}_2CF_3$), 4.463 (2H, t, J = 6.2 Hz, $OC\underline{H}_2CH_2CH_2Cl$), 4.71 (2H, s, NCH_2), 6.90 and 7.19 (2 × 2H, 2 × d, J = 8.5 Hz, $NCH_2(C\underline{H}_{arom})_{ortho}$ and $O(CH_{arom})_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 31.1 ($OCH_2\underline{C}H_2CH_2Cl$), 40.62 ($OCH_2CH_2C\underline{H}_2Cl$), 46.6 (q, J = 35.0 Hz, $\underline{C}HCF_3$), 48.4 ($N\underline{C}H_2Ar$), 55.3 (OCH_3), 63.2 ($O\underline{C}H_2CH_2CH_2Cl$), 114.5 (2 × $O(CH_{arom})_{ortho}$), 126.2 ($NCH_2\underline{C}_{arom,quat}$), 126.7 (q, J = 282.4 Hz, CF_3), 130.0 (2 × $O(CH_{arom})_{meta}$), 159.7 ($OC_{arom,quat}$), 161.3 (NC=O), 162.3 (OC=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -69.95 (3F, t, J = 8.8 Hz, CF_3).

IR (ATR, cm^{-1}): $\nu_{OC=O}$ = 1740, $\nu_{NC=O}$ = 1673, ν_{max} = 1514, 1446, 1249, 1155, 1113, 1025, 831, 656. MS (70eV): m/z (%): 368 (M^+ + 1, 8). HRMS (ESI) calcd for $C_{15}H_{18}ClF_3NO_4^+$: 368.0871 [M + H]$^+$. Found: 368.0857.

Benzyl 2-[(2,2-difluorovinyl)(4-methoxybenzyl)amino]-2-oxoacetate 3d



White solid. Mp 32 °C. HPLC (Supelco Ascentis C18, H_2O/CH_3CN, 55/45, flow rate 6 mL min^{-1}, detection at 220 nm, t_R = 65.01-66.96 min). Yield 50%. 2 rotamers 82/18

Major rotamer

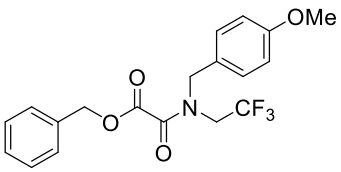
^{1}H NMR (400 MHz, $CDCl_3$): δ 3.78 (3H, s, OCH_3), 4.59 (2H, s, NCH_2), 5.19 (1H, d × d, J = 18.1, 3.5 Hz, $CHCF_2$), 5.27 (2H, s, OCH_2), 6.85 and 7.18 (2 × 2H, 2 × d, J = 8.7 Hz, $NCH_2(C\underline{H}_{arom})_{ortho}$ and $O(CH_{arom})_{ortho}$), 7.33-7.37 (5H, m, CH_{arom}). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 49.8 (t, J = 1.7 Hz, NCH_2), 55.3 (OCH_3), 67.8 (OCH_2), 85.3 (d × d, J = 49.1, 14.9 Hz, $\underline{C}HCF_2$), 114.16 (2 × $O(CH_{arom,ortho})$), 126.7 ($NCH_2\underline{C}_{arom,quat}$), 128.72, 128.76, 128.86 (5 × $OCH_2\underline{C}H_{arom}$), 130.1 (2 × $O(CH_{arom})_{ortho}$), 134.3 ($OCH_2\underline{C}_{arom,quat}$), 158.5 (d × d, J = 305.1, 299.5 Hz, CF_2), 159.5 ($OC_{arom,quat}$), 161.5 (t, J = 2.3 Hz, NC=O), 161.9 (OC=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -92.77 (1F, d × d, J = 26.1, 3.5 Hz, $\underline{F}CF$), -83.17 (1F, d × d, J = 26.1, 18.1 Hz, $FC\underline{F}$).

Minor rotamer

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.79 (3H, s, OCH_3), 4.48 (2H, s, NCH_2), 5.30 (2H, s, OCH_2), 5.50 (1H, d × d, J = 21.3, 1.2 Hz, $CHCF_2$), 6.83 and 7.11 (2 × 2H, 2 × d, J = 8.3 Hz, $NCH_2(C\underline{H}_{arom})_{ortho}$ and $O(CH_{arom})_{ortho}$), 7.33-7.37 (5H, m, CH_{arom}). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 51.9 (d, J = 3.7 Hz, NCH_2), 55.3 (OCH_3), 68.1 (OCH_2), 84.3 (d × d, J = 51.4, 12.8 Hz, $\underline{C}HCF_2$), 114.20 (2 × $O(CH_{arom})_{ortho}$), 126.3 ($NCH_2\underline{C}_{arom,quat}$), 128.74, 128.94, 128.96 (5 × CH_{arom}), 130.1 (2 × $O(CH_{arom})_{ortho}$), 134.1 ($OCH_2\underline{C}H_{arom,quat}$), 154.1 (d, J = 296.2 Hz, CF_2), 159.7 ($OC_{arom,quat}$), 160.8 (NC=O), 161.9 (OC=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -92.16 (1F, d, J = 41.6 Hz, $\underline{F}CF$), -82.56 (1F, d × d, J = 41.6, 21.3 Hz, $FC\underline{F}$).

IR (ATR, cm^{-1}): $\nu_{OC=O}$ = 1744, $\nu_{NC=O}$ = 1674, ν_{max} = 1513, 1416, 1243, 1169, 1031, 801, 746, 697. MS (70eV): m/z (%): 362 (M^+ + 1, 5). HRMS (ESI) calcd for $C_{19}H_{18}F_2NO_4^+$: *m/z* calcd: 362.1198 $[M + H]^+$. Found: 362.1200.

Benzyl 2-oxo-2-[(4-methoxybenzyl)(2,2,2-trifluoroethyl)amino]acetate 4d



Yellowish oil. HPLC (Supelco Ascentis C18, H_2O/CH_3CN, 55/45, flow rate 6 mL min^{-1}, detection at 220 nm, t_R = 77.04-77.39 min). Yield 11%. 2 rotamers 68/32

Major rotamer

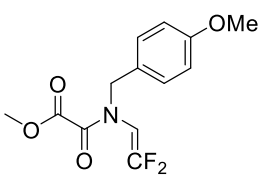
^{1}H NMR (400 MHz, $CDCl_3$): δ 3.80 (3H, s, OCH_3), 3.862 (2H, q, J = 8.9 Hz, CH_2CF_3), 4.45 (2H, s, NCH_2), 5.321 (2H, s, OCH_2), 6.86 and 7.14 (2 × 2H, 2 × d, J = 8.7 Hz, $NCH_2(C\underline{H}_{arom})_{ortho}$ and $O(CH_{arom})_{ortho}$), 7.32-7.42 (5H, m, CH_{arom}). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 42.9 (q, J = 34.5 Hz, $\underline{C}H_2CF_3$), 51.2 ($N\underline{C}H_2Ar$), 55.3 (OCH_3), 68.1 (OCH_2), 114.5 (2 × $O(CH_{arom})_{ortho}$), 124.2 (q, J = 280.9 Hz, CF_3), 125.3 ($NCH_2\underline{C}_{arom,quat}$), 128.72, 128.74, 128.8 (5 × $\underline{C}H_{arom}$), 129.6 (2 × $O(CH_{arom})_{meta}$), 134.07 ($OCH_2\underline{C}_{arom,quat}$), 159.9 ($OCH_{arom,quat}$), 162.0 (OC=O), 162.3 (NC=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -68.43 (3F, t, J = 8.9 Hz, CF_3).

Minor rotamer

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.80 (3H, s, OCH_3), 3.858 (2H, q, J = 8.8 Hz, CH_2CF_3), 4.69 (2H, s, NCH_2), 5.316 (2H, s, OCH_2), 6.88 and 7.18 (2 × 2H, 2 × d, J = 8.4 Hz, $NCH_2(C\underline{H}_{arom})_{ortho}$ and $O(CH_{arom})_{ortho}$), 7.32-7.42 (5H, m, CH_{arom}). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 46.5 (q, J = 34.4 Hz, $\underline{C}H_2CF_3$), 48.2 ($N\underline{C}H_2Ar$), 55.3 (OCH_3), 68.2 ($O\underline{C}H_2$), 114.5 (2 × $O(CH_{arom})_{ortho}$), 123.8 (q, J = 280.8 Hz, CF_3), 126.3 ($NCH_2\underline{C}_{arom,quat}$), 128.9, 129.0 (5 × CH_{arom}), 130.1 (2 × $O(CH_{arom})_{meta}$), 134.10 ($OCH_2\underline{C}_{arom,quat}$), 159.7 ($OC_{arom,quat}$), 161.37 (OC=O), 161.43 (NC=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -68.78 (3F, t, J = 8.8 Hz, CF_3).

IR (ATR, cm^{-1}): $\nu_{OC=O}$ = 1739, $\nu_{NC=O}$ = 1672, ν_{max} = 1514, 1445, 1266, 1248, 1153, 1111, 1026, 831, 736, 696. MS (70eV): m/z (%): 382 (M^+ + 1, 10). HRMS (ESI) calcd for $C_{19}H_{22}F_3N_2O_4^+$: *m/z* calcd: 399.1526 $[M + NH_4]^+$. Found: 399.1523.

Methyl 2-[(2,2-difluorovinyl)(4-methoxybenzyl)amino]-2-oxoacetate 3e



Yellow oil. HPLC (Supelco Ascentis C18, H_2O/CH_3CN, 55/45, flow rate 6 mL min^{-1}, detection at 220 nm, t_R = 54.99-66.94 min). Yield 33%. 2 rotamers 82/18

Major rotamer

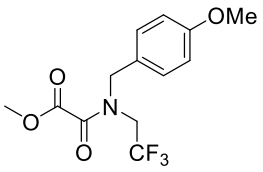
^1H NMR (400 MHz, $CDCl_3$): δ 3.80 (3H, s, OCH_3), 3.86 (3H, s, $COOCH_3$), 4.63 (2H, s, NCH_2), 5.32 (1H, d × d, *J* = 18.3, 3.0 Hz, $CHCF_2$), 6.87 and 7.20 (2 × 2H, 2 × d, *J* = 8.6 Hz, $NCH_2(C\underline{H}_{arom})_{ortho}$ and $O(CH_{arom})_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 49.9 (t, *J* = 2.1 Hz, NCH_2), 52.8 ($COO\underline{C}H_3$), 55.28 (OCH_3), 85.5 (d × d, *J* = 49.2, 15.1 Hz, $\underline{C}HCF_2$), 114.2 (2 × $O(CH_{arom})_{ortho}$), 126.7 ($NCH_2\underline{C}_{arom,quat}$), 130.1 (2 × $O(CH_{arom})_{meta}$), 158.4 (d × d, *J* = 299.5, 292.7 Hz, CF_2), 159.6 ($OC_{arom,quat}$), 161.4 (t, *J* = 2.1 Hz, NC=O), 162.3 (OC=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -93.21 (1F, d × d, *J* = 27.4, 3.0 Hz, $\underline{F}CF$), -83.64 (1F, d × d, *J* = 27.4, 18.3 Hz, $FC\underline{F}$).

Minor rotamer

^1H NMR (400 MHz, $CDCl_3$): δ 3.81 (3H, s, OCH_3), 3.89 (3H, s, $COOCH_3$), 4.57 (2H, s, NCH_2), 5.50 (1H, d × d, *J* = 21.3, 1.4 Hz, $CHCF_2$), 6.89 and 7.19 (2 × 2H, 2 × d, *J* = 8.6 Hz, $NCH_2(C\underline{H}_{arom})_{ortho}$ and $O(CH_{arom})_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 52.1 (d, *J* = 3.5 Hz, NCH_2), 53.0 ($COO\underline{C}H_3$), 55.3 (OCH_3), 84.3 (d × d, *J* = 51.3, 12.8 Hz, $\underline{C}HCF_2$), 114.3 (2 × $O(CH_{arom})_{ortho}$), 126.3 ($NCH_2\underline{C}_{arom,quat}$), 129.1 (2 × $O(CH_{arom})_{meta}$), 155.6 (d × d, *J* = 297.2, 286.2 Hz, CF_2), 159.7 ($OC_{arom,quat}$), 160.8 (NC=O), 162.5 (OC=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -97.04 (1F, d, *J* = 41.2 Hz, $\underline{F}CF$), -82.51 (1F, d × d, *J* = 41.2, 21.3 Hz, $FC\underline{F}$).

IR (ATR, cm^{-1}): $\nu_{OC=O}$ = 1745, $\nu_{NC=O}$ = 1674, ν_{max} = 1513, 1412, 1243, 1200, 1031, 800. MS (70eV): m/z (%): 286 (M^+ + 1, 5). HRMS (ESI) calcd for $C_{13}H_{14}F_2NO_4^+$: *m/z* calcd: 286.0885 $[M + H]^+$. Found: 286.0885.

Methyl 2-oxo-2-[(4-methoxybenzyl)(2,2,2-trifluoroethyl)amino]acetate 4e



Yellowish oil. HPLC (Supelco Ascentis C18, H_2O/CH_3CN = 55:45, flow rate 6 mL min^{-1}, detection at 220 nm, t_R = 73.28-86.52 min). Yield 7%. 2 rotamers 66/34

Major rotamer

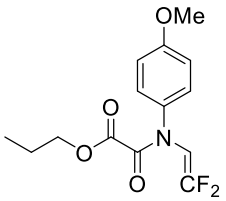
^{1}H NMR (400 MHz, $CDCl_3$): δ 3.82 (3H, s, OCH_3), 3.88 (2H, q, J = 8.9 Hz, CH_2CF_3), 3.912 (3H, s, $COOCH_3$), 4.53 (2H, s, NCH_2), 6.91 and 7.22 (2 × 2H, 2 × d, J = 8.9 Hz, $NCH_2(C\underline{H}_{arom})_{ortho}$ and $O(CH_{arom})_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 42.8 (q, J = 34.7 Hz, $\underline{C}HCF_3$), 51.4 ($N\underline{C}H_2Ar$), 53.0 ($COO\underline{C}H_3$), 55.4 (OCH_3), 114.6 (2 × $O(CH_{arom})_{ortho}$), 124.1 (q, J = 282.9 Hz, CF_3), 125.4 ($NCH_2\underline{C}_{arom,quat}$), 129.6 (2 × $O(CH_{arom})_{meta}$), 160.0 ($OC_{arom,quat}$), 162.3 (NC=O), 162.6 (OC=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -68.44 (3F, t, J = 8.9 Hz, CF_3).

Minor rotamer

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.81 (3H, s, OCH_3), 3.906 (3H, s, $COOCH_3$), 3.96 (2H, q, J = 8.8 Hz, CH_2CF_3), 4.71 (2H, s, NCH_2), 6.90 and 7.19 (2 × 2H, 2 × d, J = 8.6 Hz, $NCH_2(C\underline{H}_{arom})_{ortho}$ and $O(CH_{arom})_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 46.6 (q, J = 34.4 Hz, $\underline{C}HCF_3$), 48.4 ($N\underline{C}H_2Ar$), 53.2 ($COO\underline{C}H_3$), 55.3 (OCH_3), 114.5 (2 × $O(CH_{arom})_{ortho}$), 124.0 (q, J = 283.7 Hz, CF_3), 126.3 ($NCH_2\underline{C}_{arom,quat}$), 130.0 (2 × $O(CH_{arom})_{meta}$), 159.7 ($OC_{arom,quat}$), 161.3 (NC=O), 161.9 (OC=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -69.97 (3F, t, J = 8.8 Hz, CF_3).

IR (ATR, cm^{-1}): $\nu_{OC=O}$ = 1744, $\nu_{NC=O}$ = 1672, ν_{max} = 1514, 1249, 1153, 1113, 1028, 829. MS (70eV): m/z (%): 306 (M^+ + 1, 10). HRMS (ESI) calcd for $C_{13}H_{15}F_3NO_4^+$: *m/z* calcd: 306.0948 $[M + H]^+$. Found: 306.0940.

Propyl 2-[(2,2-difluorovinyl)(4-methoxyphenyl)amino]-2-oxoacetate 3f



Yellow oil. R_f = 0.19 (PE/EtOAc, 15/1). Yield 30%. 2 rotamers 86/14

Major rotamer

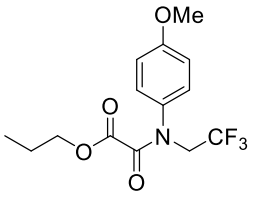
^{1}H NMR (400 MHz, $CDCl_3$): δ 0.80 (3H, t, J = 7.1 Hz, $OCH_2CH_2C\underline{H}_3$), 1.45 (2H, sextet, J = 7.1 Hz, $OCH_2C\underline{H}_2CH_3$), 3.82 (3H, s, OCH_3), 3.93 (2H, t, J = 7.1 Hz, $OC\underline{H}_2CH_2CH_3$), 6.08 (1H, d, J = 19.2 Hz, $CHCF_2$), 6.89 and 7.21 (2 × 2H, 2 × d, J = 8.9 Hz, $N(CH_{arom})_{ortho}$ and $O(CH_{arom})_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 10.2 ($OCH_2CH_2\underline{C}H_3$), 21.5 ($OCH_2\underline{C}H_2CH_3$), 55.5 ($OCH_3$), 67.6 ($O\underline{C}H_2CH_2CH_3$), 87.2 (d × d, J = 51.3, 10.3 Hz, $\underline{C}HCF_2$), 114.6 (2 × $O(CH_{arom})_{ortho}$), 128.7 (2 × $O(CH_{arom})_{meta}$), 130.8 ($NC_{arom,quat}$), 155.3 (d × d, J = 296.8, 284.2 Hz, CF_2), 159.9 ($OC_{arom,quat}$), 161.1 (d, J = 1.8 Hz, NC=O), 161.8 (OC=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -98.70 (1F, d, J = 42.2 Hz, $\underline{F}CF$), -84.40 (1F, d × d, J = 42.2, 19.2 Hz, $FC\underline{F}$).

Minor rotamer (detectable signals)

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.01 (3H, t, J = 7.2 Hz, $OCH_2CH_2C\underline{H}_3$), 1.78 (2H, sextet, J = 7.2 Hz, $OCH_2C\underline{H}_2CH_3$), 3.82 (3H, s, OCH_3), 4.28 (2H, t, J = 7.2 Hz, $OC\underline{H}_2CH_2CH_3$), 5.73 (1H, d × d, J = 17.4, 3.4 Hz, $CHCF_2$), 6.93 and 7.25 (2 × 2H, 2 × d, J = 9.0 Hz, $N(CH_{arom})_{ortho}$ and $O(CH_{arom})_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 10.2 ($OCH_2CH_2\underline{C}H_3$), 21.8 ($OCH_2\underline{C}H_2CH_3$), 55.5 ($OCH_3$), 67.9 ($O\underline{C}H_2CH_2CH_3$), 87.8 (d × d, J = 64.2, 15.7 Hz, $\underline{C}HCF_2$), 114.6 (2 × $O(CH_{arom})_{ortho}$), 126.6 (2 × $O(CH_{arom})_{meta}$), 131.4 ($NC_{arom,quat}$), 158.9 ($OC_{arom,quat}$), 161.4 (d, J = 2.9 Hz, NC=O), 162.4 (OC=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -93.58 (1F, d × d, J = 26.4, 3.4 Hz, $\underline{F}CF$), -84.15 (1F, d × d, J = 26.4, 17.4 Hz, $FC\underline{F}$).

IR (ATR, cm^{-1}): $\nu_{OC=O}$ = 1743, $\nu_{NC=O}$ = 1681, ν_{max} = 1509, 1236, 1030, 922, 839, 795, 672. MS (70eV): m/z (%): 300 (M^+ + 1, 100). HRMS (ESI) calcd for $C_{14}H_{16}F_2NO_4^+$: 300.1042 $[M + H]^+$. Found: 300.1054.

Propyl 2-oxo-2-[(4-methoxyphenyl)(2,2,2-trifluoroethyl)amino]acetate 4f

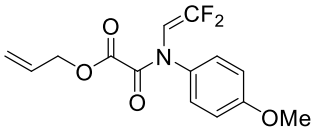


Yellowish oil. R_f = 0.18 (PE/EtOAc, 15/1). Yield 9%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.80 (3H, t, J = 7.1 Hz, $OCH_2CH_2C\underline{H}_3$), 1.45 (2H, sextet, J = 7.1 Hz, $OCH_2C\underline{H}_2CH_3$), 3.82 (3H, s, OCH_3), 3.91 (2H, t, J = 7.1 Hz, $OC\underline{H}_2CH_2CH_3$), 4.34 (2H, q, J = 8.6 Hz, CH_2CF_3), 6.90 and 7.21 (2 × 2H, 2 × d, J = 8.9 Hz, $N(CH_{arom})_{ortho}$ and $O(CH_{arom})_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 10.2 ($OCH_2CH_2\underline{C}H_3$), 21.5 ($OCH_2\underline{C}H_2CH_3$), 48.7 (q, J = 34.3 Hz, $\underline{C}HCF_3$), 55.5 (OCH_3), 67.5 ($O\underline{C}H_2CH_2CH_3$), 114.8 (2 × $O(CH_{arom})_{ortho}$), 123.7 (q, J = 280.5 Hz, CF_3), 129.4 (2 × $O(CH_{arom})_{meta}$), 131.4 ($NC_{arom,quat}$), 160.1 ($OC_{arom,quat}$), 161.9 (OC=O), 162.7 (NC=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -68.78 (3F, t, J = 8.6 Hz, CF_3).

IR (ATR, cm^{-1}): $\nu_{OC=O}$ = 1744, $\nu_{NC=O}$ = 1682, ν_{max} = 1510, 1248, 1217, 1134, 1029, 838, 573. MS (70eV): m/z (%): 320 (M^+ + 1, 20). HRMS (ESI) calcd for $C_{14}H_{17}F_3NO_4^+$: 320.1104 $[M + H]^+$. Found: 320.1112.

Allyl 2-[(2,2-difluorovinyl)(4-methoxyphenyl)amino]-2-oxoacetate 3g



Yellow oil. R_f = 0.19 (PE/EtOAc, 18/1). Yield 35%. 2 rotamers 85/15

Major rotamer

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.82 (3H, s, OCH_3), 4.45 (2H, d × t, J = 6.1, 1.2 Hz, $OC\underline{H}_2CHCH_2$), 5.17 (1H, d × q, J = 10.7, 1.2 Hz, $OCH_2CH(\underline{H}CH)$), 5.19 (1H, d × q, J = 17.0, 1.2 Hz, $OCH_2CH(HC\underline{H})$), 5.62 (1H, d × d × t, J = 17.0, 10.7, 6.1 Hz, $OCH_2C\underline{H}CH_2$), 6.07

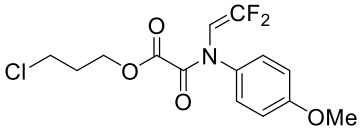
(1H, d, J = 19.1 Hz, $CHCF_2$), 6.88 and 7.20 (2 × 2H, 2 × d, J = 8.9 Hz, $N(CH_{arom})_{ortho}$ and $O(CH_{arom})_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 55.5 (OCH_3), 66.4 ($O\underline{C}H_2CHCH_2$), 87.1 (d × d, J = 51.3, 10.4 Hz, $\underline{C}HCF_2$), 114.6 (2 × $O(CH_{arom})_{ortho}$), 119.9 ($OCH_2CH\underline{C}H_2$), 128.7 (2 × $N(CH_{arom})_{ortho}$), 130.4 ($OCH_2\underline{C}HCH_2$), 130.7 ($NC_{arom,quat}$), 155.3 (d × d, J = 296.8, 284.3 Hz, CF_2), 159.9 ($OC_{arom,quat}$), 160.8 (NC=O), 161.3 (OC=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -98.59 (1F, d, J = 42.0 Hz, $\underline{F}CF$), -84.27 (1F, d × d, J = 42.0, 19.1 Hz, $FC\underline{F}$).

Minor rotamer (detectable signals)

^1H NMR (400 MHz, $CDCl_3$): δ 3.82 (3H, s, OCH_3), 4.80 (2H, d, J = 5.7 Hz, $OC\underline{H}_2CHCH_2$), 5.36 (1H, d, J = 11.2 Hz, $OCH_2CH(\underline{H}CH)$), 5.45 (1H, d, J = 16.9 Hz, $OCH_2CH(HC\underline{H})$), 5.72 (1H, d × d, J = 17.3, 3.1 Hz, $CHCF_2$), 5.98 (1H, d × d × t, J = 16.9, 11.2, 5.7 Hz, $OCH_2C\underline{H}CH_2$), 6.93 and 7.25 (2 × 2H, 2 × d, J = 8.8 Hz, $O(CH_{arom})_{ortho}$ and $N(CH_{arom})_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 55.5 (OCH_3), 66.7 ($O\underline{C}H_2CHCH_2$), 87.8 (d, J = 33.6 Hz, $\underline{C}HCF_2$), 114.6 (2 × $O(CH_{arom})_{ortho}$), 120.5 ($OCH_2CH\underline{C}H_2$), 126.6 (2 × $N(CH_{arom})_{ortho}$), 130.5 ($OCH_2\underline{C}HCH_2$), 131.3 ($NC_{arom,quat}$), 158.9 ($OCH_{arom,quat}$), 161.9 (OC=O).^{19}F NMR (376.5 MHz, $CDCl_3$): δ -93.36 (1F, d × d, J = 25.9, 3.1 Hz, $\underline{F}CF$), -83.90 (1F, d × d, J = 25.9, 17.3 Hz, $FC\underline{F}$).

IR (ATR, cm^{-1}): $\nu_{OC=O}$ = 1745, $\nu_{NC=O}$ = 1681, ν_{max} = 1510, 1386, 1345, 1236, 1120, 1030, 920, 839, 794, 674. MS (70eV): *m/z* (%): 298 (M^+ + 1, 100). HRMS (ESI) calcd for $C_{14}H_{14}F_2NO_4^+$: 298.0885 $[M + 1]^+$. Found: 298.0892.

3-Chloropropyl 2-[(2,2-difluorovinyl)(4-methoxyphenyl)amino]-2-oxoacetate 3h



Yellow oil. R_f = 0.1 (PE/EtOAc, 9/1). Yield 38%. 2 rotamers 88/12

Major rotamer

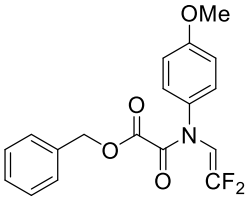
^1H NMR (400 MHz, $CDCl_3$): δ 1.88 (2H, quintet, J = 6.2 Hz, $OCH_2C\underline{H}_2CH_2Cl$), 3.34 (2H, t, J = 6.2 Hz, $OCH_2CH_2C\underline{H}_2Cl$), 3.83 (3H, s, OCH_3), 4.13 (2H, t, J = 6.2 Hz, $OC\underline{H}_2CH_2CH_2Cl$), 6.06 (1H, d × d, J = 19.1, 0.7 Hz, $CHCF_2$), 6.91 and 7.21 (2 × 2H, 2 × d, J = 9.3 Hz, $N(CH_{arom})_{ortho}$ and $O(CH_{arom})_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 31.1 ($OCH_2\underline{C}H_2CH_2Cl$), 40.5 ($OCH_2CH_2C\underline{H}_2Cl$), 55.5 ($OCH_3$), 62.5 ($O\underline{C}H_2CH_2CH_2Cl$), 87.1 (d × d, J = 51.3, 10.4 Hz, $\underline{C}HCF_2$), 114.8 (2 × $O(CH_{arom})_{ortho}$), 128.6 (2 × $O(CH_{arom})_{meta}$), 130.6 ($NC_{arom,quat}$), 155.4 (d × d, J = 297.0, 284.7 Hz, CF_3), 160.0 ($OC_{arom,quat}$), 160.7 (NC=O), 161.6 (OC=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -98.36 (1F, d, J = 41.2 Hz, $\underline{F}CF$), -84.04 (1F, d × d, J = 41.2, 19.1 Hz, $FC\underline{F}$).

Minor rotamer (detectable signals)

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.22 (2H, quintet, J = 6.2 Hz, $OCH_2C\underline{H}_2CH_2Cl$), 3.67 (2H, t, J = 6.2 Hz, $OCH_2CH_2C\underline{H}_2Cl$), 3.83 (3H, s, OCH_3), 4.48 (2H, t, J = 6.2 Hz, $OC\underline{H}_2CH_2CH_2Cl$), 5.74 (1H, d × d, J = 17.2, 3.3 Hz, $CHCF_2$), 6.94 and 7.25 (2 × 2H, 2 × d, J = 7.9 Hz, $N(CH_{arom})_{ortho}$ and $O(CH_{arom})_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 31.1 ($OCH_2\underline{C}H_2CH_2Cl$), 40.6 ($OCH_2CH_2C\underline{H}_2Cl$), 52.5 ($OCH_3$), 62.9 ($O\underline{C}H_2CH_2CH_2Cl$), 87.8 (d, J = 30.5 Hz, $\underline{C}HCF_2$), 114.7 (2 × $O(CH_{arom})_{ortho}$), 126.1 ($NC_{arom,quat}$), 126.6 (2 × $O(CH_{arom})_{meta}$), 159.0 ($OC_{arom,quat}$). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -93.13 (1F, d × d, J = 26.6, 3.3 Hz, $\underline{F}CF$), -84.28 (1F, d × d, J = 26.6, 17.2 Hz, $FC\underline{F}$).

IR (ATR, cm^{-1}): $\nu_{OC=O}$ = 1745, $\nu_{NC=O}$ = 1679, ν_{max} = 1509, 1372, 1237, 1029, 921, 839, 793, 672, 554. MS (70eV): m/z (%): 334 (M^+ + 1, 60). HRMS (ESI) calcd for $C_{14}H_{15}ClF_2NO_4^+$: 334.0652 [M + H]$^+$. Found: 334.0653.

Benzyl 2-[(2,2-difluorovinyl)(4-methoxyphenyl)amino]-2-oxoacetate 3i



Yellow oil. R_f = 0.26 (PE/EtOAc, 15/1). Yield 50%. 2 rotamers 87/13

Major rotamer

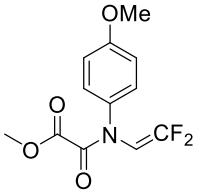
^{1}H NMR (400 MHz, $CDCl_3$): δ 3.78 (3H, s, OCH_3), 5.00 (2H, s, $OC\underline{H}_2Ph$), 6.04 (1H, d × d, J = 19.1, 0.6 Hz, $CHCF_2$), 6.72 (2H, d, J = 9.0 Hz, $O(CH_{arom})_{ortho}$), 7.08-7.11 (4H, m, $N(CH_{arom})_{ortho}$ and $CH_2C\underline{H}_{arom}$), 7.25-7.33 (3H, m, $CH_2C\underline{H}_{arom}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 55.4 (OCH_3), 67.6 ($O\underline{C}H_2Ph$), 87.1 (d × d, J = 51.3, 10.4 Hz, $\underline{C}HCF_2$), 114.5 (2 × $O(CH_{arom})_{ortho}$), 128.48, 128.54, 128.6 (5 × $CH_2\underline{C}H_{arom}$), 128.87 (2 × $N(CH_{arom})_{ortho}$), 130.4 ($NC_{arom,quat}$), 134.0 ($OCH_2\underline{C}_{arom,quat}$), 155.3 (d × d, J = 296.9, 284.4 Hz, CF_2), 159.8 ($OC_{arom,quat}$), 160.8 (d, J = 2.0 Hz, NC=O), 161.5 (OC=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -95.58 (1F, d, J = 41.6 Hz, $\underline{F}CF$), -84.22 (1F, d × d, J = 41.6, 19.1 Hz, $FC\underline{F}$).

Minor rotamer (detectable signals)

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.80 (3H, s, OCH_3), 5.33 (2H, s, $OC\underline{H}_2Ph$), 5.60 (1H, d × d, J = 17.1, 3.4 Hz, $CHCF_2$), 6.91 and 7.22 (2 × 2H, 2 × d, J = 8.4 Hz, $N(CH_{arom})_{ortho}$ and $O(CH_{arom})_{ortho}$), 7.36-7.43 (5H, m, $CH_2C\underline{H}_{arom}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 55.5 (OCH_3), 68.0 ($O\underline{C}H_2Ph$), 87.8 (d, J = 15.2 Hz, $\underline{C}HCF_2$), 114.6 (2 × $O(CH_{arom})_{ortho}$), 126.6 (2 × $N(CH_{arom})_{ortho}$), 128.8, 128.9 (5 × $CH_2\underline{C}H_{arom}$), 131.3 ($NC_{arom,quat}$), 134.3 ($CH_2\underline{C}_{arom,quat}$), 158.9 ($OC_{arom,quat}$), 161.1 (NC=O), 162.1 (OC=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -93.13 (1F, d × d, J = 25.1, 3.4 Hz, $\underline{F}CF$), -83.79 (1F, d × d, J = 25.1, 17.1 Hz, $FC\underline{F}$).

IR (ATR, cm^{-1}): $\nu_{OC=O}$ = 1743, $\nu_{NC=O}$ = 1680, ν_{max} = 1509, 1361, 1235, 1030, 919, 838, 735, 696. MS (70eV): m/z (%): 348 (M^+ + 1, 100). HRMS (ESI) calcd for $C_{18}H_{16}F_2NO_4^+$: 348.1042 $[M + H]^+$. Found: 348.1034.

Methyl 2-[(2,2-difluorovinyl)(4-methoxyphenyl)amino]-2-oxoacetate 3j



Yellow oil. HPLC (Supelco Ascentis C18, H_2O/CH_3CN, 55/45, flow rate 6 mL min^{-1}, detection at 220 nm, t_R = 85.11-90.56 min). Yield 42%. 2 rotamers 83/17

Major rotamer

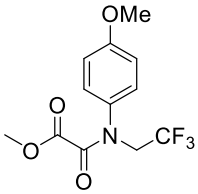
^{1}H NMR (400 MHz, $CDCl_3$): δ 3.58 (3H, s, $COOCH_3$), 3.82 (3H, s, OCH_3), 6.06 (1H, d × d, J = 19.1, 0.5 Hz, $CHCF_2$), 6.89 and 7.20 (2 × 2H, 2 × d, J = 8.9 Hz, $N(CH_{arom})_{ortho}$ and $O(CH_{arom})_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 52.5 ($COO\underline{C}H_3$), 55.5 (OCH_3), 87.2 (d × d, J = 51.3, 10.4 Hz, $\underline{C}HCF_2$), 114.6 (2 × $O(CH_{arom})_{ortho}$), 128.6 (2 × $N(CH_{arom})_{ortho}$), 130.7 ($NC_{arom,quat}$), 155.4 (d × d, J = 295.9, 283.4 Hz, CF_2), 159.9 ($OC_{arom,quat}$), 160.8 (d, J = 1.7 Hz, NC=O), 162.0 (OC=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -98.52 (1F, d, J = 41.8 Hz, $\underline{F}CF$), -84.20 (1F, d × d, J = 41.8, 19.1 Hz, $FC\underline{F}$).

Minor rotamer

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.58 (3H, s, $COOCH_3$), 3.92 (3H, s, OCH_3), 5.75 (1H, d × d, J = 17.3, 3.0 Hz, $CHCF_2$), 6.93 and 7.24 (2 × 2H, 2 × d, J = 9.2 Hz, $N(CH_{arom})_{ortho}$ and $O(CH_{arom})_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 53.0 ($COO\underline{C}H_3$), 55.5 (OCH_3), 87.8 (d × d, J = 48.9, 14.2 Hz, $\underline{C}HCF_2$), 114.6 (2 × $O(CH_{arom})_{ortho}$), 126.7 (2 × $N(CH_{arom})_{ortho}$), 131.4 ($NC_{arom,quat}$), 158.8 (d × d, J = 298.7, 293.3 Hz, CF_2), 159.0 ($OC_{arom,quat}$), 161.0 (NC=O), 162.5 (OC=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -93.61 (1F, d × d, J = 26.4, 3.0 Hz, $\underline{F}CF$), -84.29 (1F, d × d, J = 26.4, 17.3 Hz, $FC\underline{F}$).

IR (ATR, cm^{-1}): $\nu_{OC=O}$ = 1746, $\nu_{NC=O}$ = 1681, ν_{max} = 1509, 1380, 1238, 1122, 1029, 839, 794, 673. MS (70eV): m/z (%): 272 (M^+ + 1, 100). HRMS (ESI) calcd for $C_{12}H_{12}F_2NO_4^+$: 272.0729 $[M + H]^+$. Found: 272.0726.

Methyl 2-oxo-2-[(4-methoxyphenyl)(2,2,2-trifluoroethyl)amino]acetate 4j



Yellow oil. HPLC (Supelco Ascentis C18, H_2O/CH_3CN, 55/45, flow rate 6 mL min^{-1}, detection at 220 nm, t_R = 99.55-105.33 min). Yield 5%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.57 (3H, s, $COOCH_3$), 3.83 (3H, s, OCH_3), 4.34 (2H, q, J = 8.7 Hz, CH_2CF_3), 6.90 and 7.20 (2 × 2H, 2 × d, J = 8.9 Hz, $N(CH_{arom})_{ortho}$ and $O(CH_{arom})_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 48.8 (q, J = 34.3 Hz, $\underline{C}H_2CF_3$),

52.4 ($COO\underline{C}H_3$), 55.5 (OCH_3), 114.8 (2 × $O(CH_{arom})_{ortho}$), 123.6 (q, J = 280.6 Hz, $CH\underline{C}F_3$), 129.3 (2 × $N(CH_{arom})_{ortho}$), 131.3 ($NC_{arom,quat}$), 160.1 ($OC_{arom,quat}$), 162.1 (NC=O), 162.5 (OC=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -68.80 (3F, t, J = 8.7 Hz, CF_3). IR (ATR, cm^{-1}): $\nu_{OC=O}$ = 1748, $\nu_{NC=O}$ 1682, ν_{max} = 1510, 1395, 1249, 1132, 1028, 838, 781, 676. MS (70eV): m/z (%): 292 (M^+ + 1, 100). HRMS (ESI) calcd for $C_{12}H_{13}F_3NO_4^+$: 292.0791 $[M + H]^+$. Found: 292.0783.

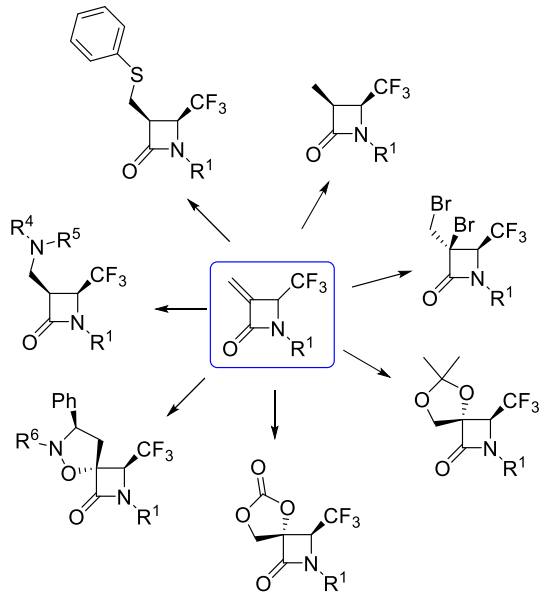
PART IV

Synthesis and application of 3-methylene-4-(trifluoromethyl)azetidin-2-ones as novel building blocks for the preparation of mono- and spirocyclic 4-CF_3-β-lactams

Abstract

3-Methylene-4-(trifluoromethyl)azetidin-2-ones were efficiently prepared from the corresponding 3-oxo-4-trifluoromethyl-β-lactams and successfully evaluated as novel building blocks in organic synthesis. In particular, Michael additions, electrophilic additions and cycloadditions were applied to allow an easy access to a broad variety of stereodefined mono- and spirocyclic 4-CF_3-β-lactams as useful synthetic intermediates *en route* to a variety of biologically relevant CF_3-functionalized target structures.

Graphical abstract



Reference

Dao Thi, H., Danneels, B., Desmet, T., Van Hecke, K., Van Nguyen, T., D'hooghe, M. "Synthesis and applications of 3-methylene-4-(trifluoromethyl)azetidin-2-ones as building blocks for the preparation of mono- and spirocyclic 4-CF_3-β-lactams". *Asian J. Org. Chem.* **2016**, *5*, 1480-1491. (I.F. 2.79).

1. Introduction

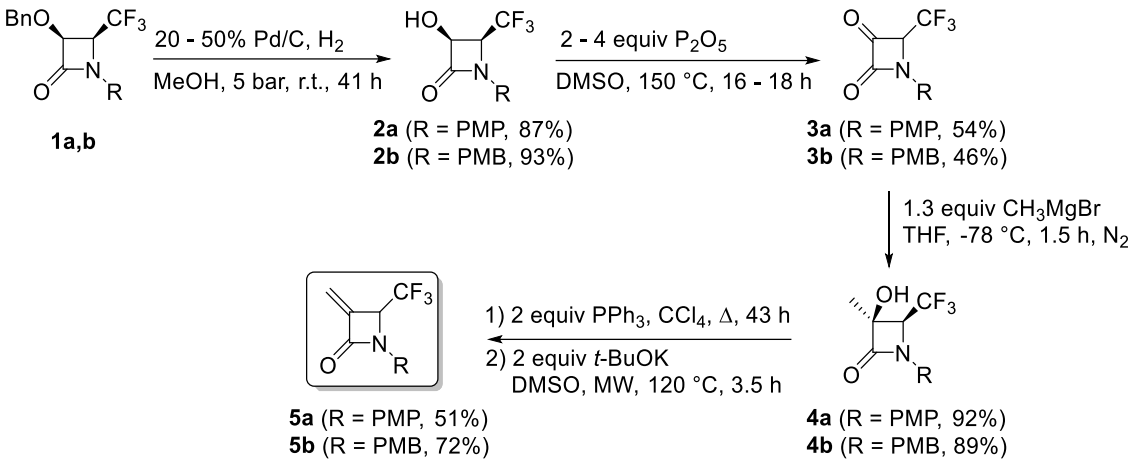
Small-ring azaheterocycles are known to entail a certain inherent reactivity associated with their high ring-strain energy, rendering the trifluoromethylation of such substrates delicate. The inherent reactivity of these synthons allows for the construction of a plethora of valuable heterocycles upon careful synthetic manipulation, providing theoretical access to a broad diversity of novel molecular scaffolds. In that respect, we embarked on the preparation and exploration of several classes of CF_3-functionalized small rings as novel substrates in organic synthesis a few years ago.[28a,18,51,94] In particular, β-lactams or azetidin-2-ones represent a versatile class of four-membered azaheterocycles,[95a,16b,95b,95c,30d] as these compounds are celebrated for both their diverse biological activities and their synthetic potential as precursors for further synthetic elaboration. In the present work, the preparation and exploration of 3-methylene-4-trifluoromethyl-β-lactams as novel and versatile building blocks is pursued, *en route* to the construction of new C3-functionalized (spirocyclic) β-lactams. The presence of an exocyclic carbon-carbon double bond as part of a constrained α,β-unsaturated amide fragment bearing a CF_3-group allows for a multilateral application of these new synthons in different synthetic directions. More precisely, the susceptibility of the alkene moiety with respect to nucleophiles, electrophiles and dipolarophiles will be scrutinized with the intention to effect Michael additions, electrophilic additions and cycloadditions, respectively. The installation of an electron-withdrawing group at C4 in β-lactams has been suggested to be beneficial with respect to the antibacterial properties of these compounds,[96,13a] and thus the replacement of the traditional CH_3 substituent (as in the established antibiotic Aztreonam) with a CF_3 group might provide an interesting new approach in antibacterial agent development.

2. Synthesis of 3-methylene-4-(trifluoromethyl)azetidin-2-one building blocks

In spite of their occurrence in several bioactive natural products (exemplified by the β-lactamase inhibitor Asparenomycin A1 and the herbical agent Phyllostictine A),[97] the chemistry of 3-alkylidene-β-lactams has received relatively little attention in the literature so far. Synthetic approaches to 3-alkylidene-β-lactams rely on different strategies to construct the four-membered framework, such as [2+2]-cycloadditions,[98] ring-closing or cross-metathesis reactions,[99,97d] palladium-catalyzed oxidative carbonylations,[100] and Kinugasa reactions,[101] or concern

elaborations of preformed β-lactam systems.[102] In this study, we pursued the latter strategy to provide access to the hitherto unknown 3-methylene-4-trifluoromethyl-β-lactam scaffold.

A well-established and general entry into olefins relates to the conversion of carbonyl compounds upon treatment with phosphorus ylides *via* intermediate oxaphosphetanes (Wittig reaction).[103] From a retrosynthetic point of view, the premised 3-methylene-β-lactams could thus be accessed from the corresponding 3-oxo-β-lactams.[102d,104] In a previous communication, *cis*-3-benzyloxy-4-(trifluoromethyl)azetidin-2-ones **1** were selected as eligible substrates for the preparation of the desired 3-oxo-β-lactams **3** *via* a debenzylation-oxidation sequence. The first step was accomplished upon palladium on carbon-mediated hydrogenolysis (5 bar) in methanol at room temperature, providing alcohols **2** in high yields. Subsequent Albright-Onodera oxidation using the P_2O_5/DMSO combination afforded the contemplated new 3-oxo-4-(trifluoromethyl)azetidin-2-ones **3** in acceptable yields (Scheme 1). The latter ketones **3** proved to be unstable upon prolonged preservation and should therefore be used immediately for further elaboration. Once in hand, 3-oxo-β-lactams **3** were evaluated as substrates for a Wittig olefination upon treatment with methylenetriphenylphosphorane, albeit without any success (formation of complex mixtures). In order to circumvent this unexpected obstacle, a short detour was proposed based on addition of methylmagnesium bromide across the cyclic ketone, followed by alcohol activation and elimination. Thus, treatment of azetidine-2,3-diones **3** with methylmagnesium bromide in THF at -78 °C efficiently provided tertiary alcohols **4**. It should be noted that reactions at room temperature or 0 °C resulted in decomposition of the substrates **3**. Subsequently, alcohols **4** were treated with PPh_3 in CCl_4 to prepare the corresponding intermediate chlorides followed by microwave-assisted dehydrochlorination by means of KO*t*Bu in DMSO (Scheme 1). Fortunately, this approach furnished the desired 3-methylene-4-(trifluoromethyl)azetidin-2-ones **5** in good yields as a new class of β-lactam building blocks for further elaboration.

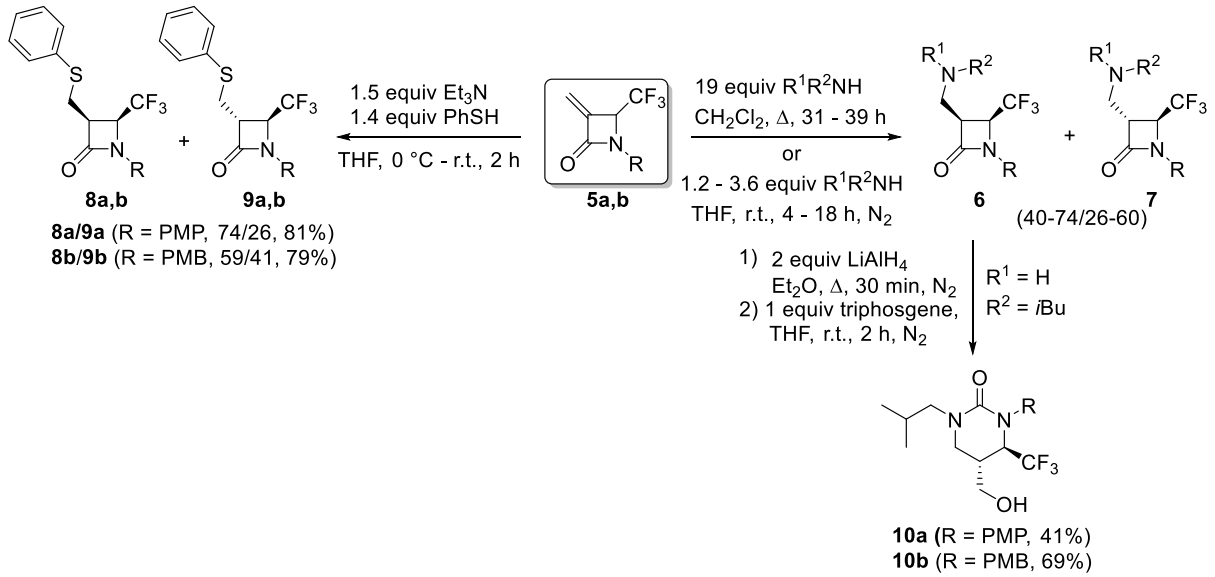


Scheme 1. Synthesis of 3-methylene-4-(trifluoromethyl)azetidin-2-ones **5**.

3. Conjugate addition of sulfur and nitrogen nucleophiles across 3-methylene-4-trifluoromethyl-β-lactams

Because of the cyclic acrylamide motif in 3-methylene-β-lactams **5**, in combination with the electron-withdrawing CF_3-group, the electron-poor C-C double bond might facilitate conjugate addition of nucleophiles as a suitable route to 3-functionalized azetidin-2-ones. In that respect, the Michael addition of nitrogen and sulfur nucleophiles was assessed next. The addition of benzenethiol in THF at room temperature proceed smoothly, but resulted in inseparable mixtures of *cis*- and *trans*-3-phenylthiomethyl-4-(trifluoromethyl)azetidin-2-ones **8**/**9** (ratio 59-74/26-41, Scheme 2). On the other hand, conjugate addition of primary and secondary amines provided separable mixtures of *cis*- and *trans*-3-aminomethyl-4-(trifluoromethyl)azetidin-2-ones **6**/**7**, with *cis*-β-lactams **6** being the major isomers in most cases (Scheme 2, Table 1). The 1,4-addition of isobutylamine was realized for 31-39 hours in CH_2Cl_2 at reflux temperature, whereas pyrrolidine and piperidine successfully effected this conjugate addition in THF after 4-18 hours at room temperature. The *cis*-/*trans*-relationship of the β-lactam substituents in compounds **6** and **7** was deduced based on the vicinal H-H coupling constants ($CDCl_3$), in accordance with literature information, and full characterization of all isomers **6**/**7** was made possible after isolation of pure material by means of preparative TLC chromatography (SiO_2). Finally, 3-isobutylaminomethyl-β-lactams **6a** and **6d** were selected for further elaboration, involving reductive β-lactam ring opening to intermediate 3-amino-2-(isobutylaminomethyl)butan-1-ols followed by cyclization. Thus, consecutive treatment of azetidin-2-ones **6a**,**d** with $LiAlH_4$ in Et_2O and triphosgene in THF afforded the contemplated new 4-CF_3-tetrahydropyrimidin-2-ones **10a**,**b** in good yields (Scheme 2).

Pyrimidinones in general are known to have a long track record in medicinal chemistry, for example as kinase inhibitors or as anti-HIV agents.[105,1a]



Scheme 2. Conjugate addition of sulfur and nitrogen nucleophiles across 3-methylene-4-CF_3-β-lactams **5**.

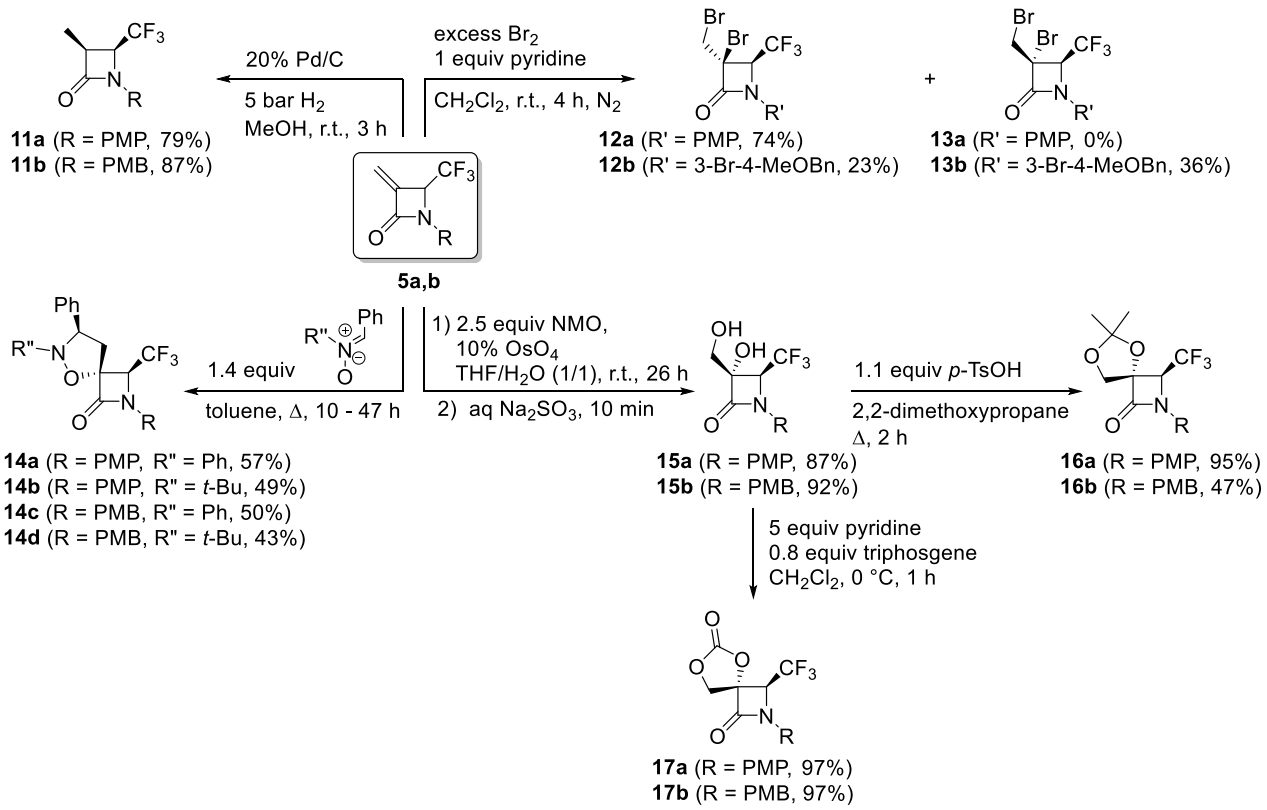
Table 1. Synthesis of 3-aminomethyl-4-(trifluoromethyl)azetidin-2-ones **6/7**.

Compound	R	R^1, R^2	Ratio **6/7**	Yield **6** [%][a]	Yield **7** [%][a]
6a,7a	PMP	H, *i*Bu	67/33	60	29
6b,7b	PMP	-$(CH_2)_4$-	69/31	39	13
6c, 7c	PMP	-$(CH_2)_5$-	74/26	44	6
6d, 7d	PMB	H, *i*Bu	53/47	38	25
6e, 7e	PMB	-$(CH_2)_4$-	62/38	18	12
6f, 7f	PMB	-$(CH_2)_5$-	40/60	15	15

[a] Yields of isolated products after preparative TLC (SiO_2)

4. Evaluation of electrophilic additions and cycloadditions of 3-methylene-4-trifluoromethyl-β-lactams

In the second part, the tendency of 3-methylene-4-trifluoromethyl-β-lactams **5** to undergo classical addition reactions across the C-C double bond was investigated. First, hydrogenation on Pd/C was evaluated, providing easy and selective access to *cis*-3-methyl-4-CF_3-azetidin-2-ones **11** in MeOH at room temperature (Scheme 3). Also electrophilic bromine addition in CH_2Cl_2 was studied, resulting in clean and stereoselective formation of dibrominated 1-(4-methoxyphenyl)-β-lactam **12a** from the corresponding alkene **5a**. In the case of 1-(4-methoxybenzyl)-substituted substrate **5b**, however, a separable mixture of isomers **12b** and **13b** was formed, in which also the *N*-PMB group experienced bromination. The difference in stereoselectivity between bromination of **5a** and **5b** is remarkable and might be attributable to the interacting steric effects exerted by the *N*-PMB group and the CF_3 group in **5b**, whereas in **5a** the steric influence of the more rigid and planar *N*-PMP substituent is negligible and the bromination is only controlled by the CF_3 group. In a third approach, Upjohn dihydroxylation of substrates **5** was assessed, involving a OsO_4-mediated oxidation using *N*-methylmorpholine-*N*-oxide (NMO) in a THF/H_2O (1/1) solvent system. This method smoothly produced vicinal diols **15** in high yields and excellent stereoselectivity. The latter diols were subsequently considered to be eligible substrates for the preparation of unprecedented β-lactam-based spirocyclic building blocks. In a first example, acetalisation was effected upon treatment of diols **15** with *p*TsOH in 2,2-dimethoxypropane under reflux, furnishing 3-trifluoromethyl-5,7-dioxa-2-azaspiro[3.4]octan-1-ones **16**. As a second class of target spirocyclic structures, the 5,7-dioxa-2-azaspiro[3.4]octane-1,6-dione scaffold **17** was pursued by reaction of diols **15** with triphosgene in CH_2Cl_2 in the presence of pyridine, affording a convenient entry into these new CF_3-substituted spirocycles **17** (Scheme 3).



Scheme 3. Evaluation of 3-methylene-4-trifluoromethyl-β-lactams **5** for electrophilic additions and cycloadditions.

The synthetic exploration of these novel 3-methylene-4-CF_3-β-lactam building blocks **5** was finalized by evaluating their susceptibility toward cycloaddition reactions. An important strategy in that respect comprises the 1,3-dipolar nitrone-olefin cycloaddition to generate isoxazolidines,[106a,106b,102b,106c,106d,25] which was selected here in order to provide access to novel spiro-fused β-lactam isoxazolidine systems. Thus, treatment of 3-methylene-β-lactams **5** with either *N*-phenyl- or *N*-*tert*-butyl-α-phenylnitrone in toluene under reflux afforded a convenient entry to 7-phenyl-3-trifluoromethyl-5-oxa-2,6-diazaspiro[3.4]octan-1-ones **14**, as exemplified by the synthesis and characterization of four new derivatives **14a-d** (Scheme 3). The major (3*S**,4*R**,7*R**)-isomers **14** were accompanied by small amount of their 7-epimers, some of which were also isolated and characterized spectroscopically.

An important aspect of these studies concerned the assignment of the correct structures to all these new compounds, especially with respect to their relative stereochemistry. In order to secure their molecular architecture, a few representative model compounds were selected for single crystal X-ray analysis, providing irrefutable evidence for the chemical structure of β-lactams **14**,

16 and **17** (see Fig. 1 for X-ray structure of compounds **14b** and **16a**). Furthermore, it was also observed that β-lactams with a *cis*-configured methylene group and a CF_3 group are characterized by a distinct long-range coupling between one of the two methylene protons at C3 and the fluorine atoms from the C4 CF_3-group (quartet, J = 1-3 Hz, $CDCl_3$), which is not present in the diastereomeric counterparts, allowing for an unequivocal stereochemistry assignment of all compounds shown in Scheme 3.

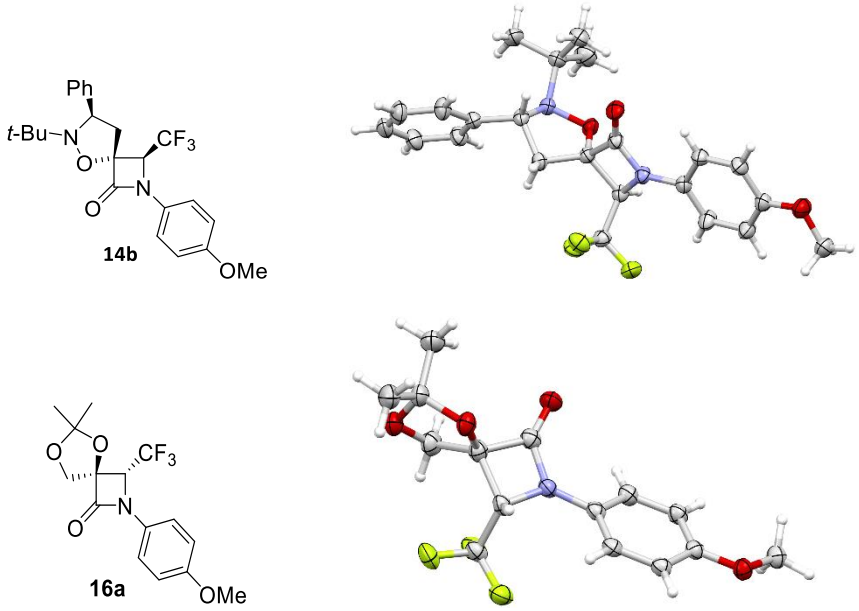


Fig. 1. Schematic representation and molecular structures of spirocycles **14b** and **16a**.

As indicated in the Introduction, β-lactams are considered to be the cornerstones of contemporary antibacterial therapy, but the rapid emergence of resistant strains necessitates a persistent search for new analogues and derivatives. On the other hand, β-lactams also represent flexible precursors in organic synthesis, providing access to a broad range of complex target structures. In that respect, spirocyclic β-lactams have attracted considerable interest in recent years, both from a chemical and a biological point of view.[102e,107] Indeed, further synthetic elaboration allows the preparation of various highly functionalized (hetero)cycles, in particular focused on the synthesis of cyclic amino acid derivatives, and spiroazetidin-2-ones are also associated with diverse biological effects, such as antimicrobial, antiviral, and cholesterol absorption inhibition activity. Bearing the general importance of CF_3-substituted heterocycles within the field of

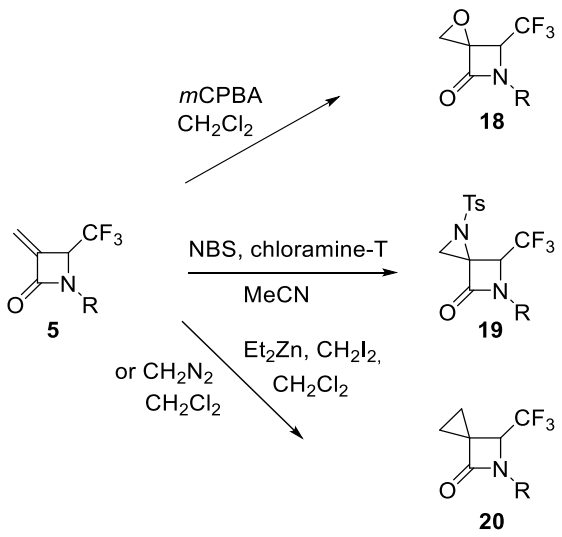
medicinal chemistry in mind, β-lactam-based spirocycles **14**, **16** and **17** accommodating a CF_3-group can thus be considered as valuable new building blocks for diverse applications.

5. Conclusion

3-Methylene-4-(trifluoromethyl)azetidin-2-ones were efficiently prepared *via* intermediate 3-oxo-4-trifluoromethyl-β-lactams and successfully deployed as novel substrates for Michael additions, electrophilic additions and cycloadditions. In this way, a broad variety of new and stereodefined 4-CF_3-β-lactams were produced, including 3-phenylthiomethyl-4-(trifluoromethyl)azetidin-2-ones, 3-aminomethyl-4-(trifluoromethyl)azetidin-2-ones, 3-methyl-4-(trifluoromethyl)azetidin-2-ones, 3-bromo-3-bromomethyl-4-(trifluoromethyl)azetidin-2-ones, 3-hydroxy-3-hydroxymethyl-4-(trifluoromethyl)azetidin-2-ones and 3-trifluoromethyl-5-oxa-2,6-diazaspiro[3.4]octan-1-ones, providing many opportunities for further elaboration as shown by the synthesis of 4-(trifluoromethyl)tetrahydropyrimidin-2-ones, 3-trifluoromethyl-5,7-dioxa-2-azaspiro[3.4]octan-1-ones and 3-trifluoromethyl-5,7-dioxa-2-azaspiro[3.4]octane-1,6-diones. In light of the increasing demand for new CF_3-substituted azaheterocyclic scaffolds from a medicinal chemistry perspective, 3-methylene-4-(trifluoromethyl)azetidin-2-ones can indeed be considered as eligible building blocks for the construction of a broad variety of mono- and spirocyclic 4-CF_3-β-lactams with diverse applications.

6. Perspectives

Next to the aforementioned reactivities, the presence of an alkene moiety at the C3 position in 3-methylene-4-(trifluoromethyl)azetidin-2-ones **5** allows for many other chemical transformations to access several types of biologically interesting β-lactam derivatives (Scheme 4). For example, treatment of 3-methylene-β-lactams **5** with *m*CPBA in CH_2Cl_2 could afford 6-trifluoromethyl-1-oxa-5-azaspiro[2.3]hexan-4-ones **18**.[108] In analogy with the epoxidation of CF_3-nonsubstituted 3-methylene-β-lactams **5**, the direct aziridination of the double bond could lead to the formation of new 1-tosyl-6-trifluoromethyl-1,5-diazaspiro[2.3]hexan-4-ones **19** upon the treatment with NBS and chloroamine-T.[109] In addition, treatment of 3-methylene-β-lactams **5** under either Simmon-Smith conditions (Et_2Zn, CH_2I_2) or CH_2N_2 in CH_2Cl_2 could give rise to novel 6-trifluoromethyl-5-azaspiro[2.3]hexan-4-ones **20**.[110,25]



Scheme 4

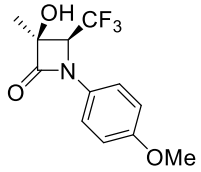
The deployment of 3-methylene-4-CF_3-β-lactam **5** as building blocks toward the synthesis of novel β-lactam-based spirocycles bearing a trifluoromethyl group might be an appealing field from both synthesis and application points of view.

7. Experimental details

Synthesis of 3-hydroxy-3-methyl-4-(trifluoromethyl)azetidin-2-ones 4

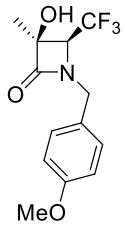
As a representative example, the synthesis of *cis*-3-hydroxy-1-(4-methoxybenzyl)-3-methyl-4-(trifluoromethyl)azetidin-2-one **4b** is described. A solution of methylmagnesium bromide (0.26 mL, 2.38 mmol, 3M in Et_2O, 1.3 equiv) was added to a solution of 1-(4-methoxybenzyl)-4-trifluoromethyl-3-oxoazetidin-2-one **3b** (0.50 g, 1.83 mmol, 1 equiv) in dry THF (10 mL) at -78 °C under a nitrogen atmosphere. The resulting mixture was stirred for 1.5 hours at the same temperature. The mixture was quenched by adding a 5% solution of NH_4Cl (3 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic phases were washed with brine (2 x 10 mL). Drying ($MgSO_4$), filtration of the drying agent, and removal of the solvent *in vacuo* afforded *cis*-3-hydroxy-1-(4-methoxybenzyl)-3-methyl-4-(trifluoromethyl)azetidin-2-one **4b**, which was further purified by means of column chromatography (PE/EtOAc, 4/1) to furnish pure **4b** in a yield of 89%.

Cis-3-hydroxy-1-(4-methoxyphenyl)-3-methyl-4-(trifluoromethyl)azetidin-2-one 4a



Yellowish crystals. Mp 123 °C. Recrystallization in Et_2O/Hex, 2/1. Yield 92%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.73 (3H, s, CH_3), 3.44 (1H, s, OH), 3.80 (3H, s, OCH_3), 4.34 (1H, q, J = 5.9 Hz, $CHCF_3$), 6.90 and 7.40 (2 × 2H, 2 × d, J = 9.0 Hz, $N(CH_{arom})_{ortho}$ and $O(CH_{arom})_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 22.2 ($C\underline{C}H_3$), 55.5 (OCH_3), 63.9 (q, J = 31.7 Hz, $\underline{C}HCF_3$), 83.0 ($\underline{C}CH_3$), 114.5 (2 × $O(CH_{arom})_{ortho}$), 119.6 (2 × $N(CH_{arom})_{ortho}$), 123.7 (q, J = 280.5 Hz, CF_3), 129.4 ($N(CH_{arom})_{ortho}$), 157.4 ($OC_{arom,quat}$), 167.4 (C=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -68.75 (3F, d, J = 5.9 Hz, CF_3). IR (ATR, cm^{-1}): ν_{OH} = 3364, $\nu_{C=O}$ = 1745, ν_{max} = 1513, 1289, 1252, 1140, 1091, 1032, 825. MS (70eV): m/z (%): 276 (M^+ + 1, 100). HRMS (ESI) calcd for $C_{12}H_{13}F_3NO_3^+$: 276.0842 $[M + H]^+$. Found: 276.0838.

Cis-3-hydroxy-1-(4-methoxybenzyl)-3-methyl-4-(trifluoromethyl)azetidin-2-one 4b



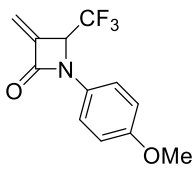
White crystals. Mp 82 °C. R_f = 0.17 (PE/EtOAc, 4/1). Yield 89%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.51 (3H, s, CH_3), 3.56 (1H, q, J = 6.4 Hz, $CHCF_3$), 3.81 (3H, s, OCH_3), 3.90 (1H, d, J = 14.8 Hz, (<u>H</u>CH)N), 3.92 (1H, s, OH), 4.85 (1H, d, J = 14.8 Hz, (HC<u>H</u>)N), 6.89 and 7.15 (2 × 2H, 2 × d, J = 8.5 Hz, $NCH_2(C\underline{H}_{arom})_{ortho}$ and $O(CH_{arom})_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 21.4 ($C\underline{C}H_3$), 44.6 ($Ar\underline{C}H_2N$), 55.3 (OCH_3), 62.4 (q, J = 31.4 Hz, $\underline{C}HCF_3$), 83.4 ($\underline{C}CH_3$), 114.5 (2 × $O(HC_{arom})_{ortho}$), 123.9 (q, J = 280.0 Hz, CF_3), 125.9 ($NCH_2\underline{C}_{arom,quat}$), 129.9 (2 × $NCH_2(H\underline{C}_{arom})_{ortho}$), 159.6 ($OC_{arom,quat}$), 170.4 (C=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -69.86 (3F, d, J = 6.4 Hz, CF_3). IR (ATR, cm^{-1}): ν_{OH} = 3335, $\nu_{C=O}$ = 1729, ν_{max} = 1515, 1282, 1253, 1212, 1162, 1139, 1080, 1033, 810. MS (70eV): m/z (%): 121 (100), 290 (M^+ + 1, 45). HRMS (ESI) calcd for $C_{13}H_{15}F_3NO_3^+$: 290.0999 $[M + H]^+$. Found: 290.0993.

Synthesis of 3-methylene-4-(trifluoromethyl)azetidin-2-ones 5

As a representative example, the synthesis of 1-(4-methoxybenzyl)-3-methylene-4-(trifluoromethyl)azetidin-2-one **5b** is described. A solution of 3-hydroxy-1-(4-methoxybenzyl)-3-methyl-4-(trifluoromethyl)azetidin-2-one **4b** (0.27 g, 0.94 mmol, 1 equiv) and triphenylphosphine (0.49 g, 1.87 mmol, 2 equiv) in carbon tetracholoride (4 mL) was heated under reflux for 43 hours. The reaction mixture was then filtered through a small pad of Celite® and concentrated under reduced pressure to afford the crude product. The LC-MS and ^{1}H NMR of the crude product showed it to be a mixture of 1-(4-methoxybenzyl)-3-methylene-4-(trifluoromethyl)azetidin-2-one **4b** and 3-chloro-1-(4-methoxybenzyl)-3-methyl-4-(trifluoromethyl)azetidin-2-one in a ratio of 65:35, which was separated by flash column chromatography (PE/EtOAc, 9/1) to give pure 1-(4-methoxybenzyl)-3-methylene-4-(trifluoromethyl)azetidin-2-one **5b** in a yield of 51% as white

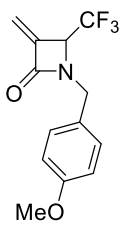
crystals and 3-chloro-1-(4-methoxybenzyl)-3-methyl-4-(trifluoromethyl)azetidin-2-one in a yield of 34% as a yellow oil. In the next step, to a solution of 3-chloro-1-(4-methoxybenzyl)-3-methyl-4-(trifluoromethyl)azetidin-2-one (0.10 g, 0.33 mmol, 1 equiv) in dry dimethyl sulfoxide (10 mL), KO*t*Bu (0.07 g, 0.66 mmol, 2 equiv) was slowly added and the mixture was subjected to microwave heating for 3.5 hours at 120 °C. Afterward, the reaction mixture was cooled to room temperature and was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed five times with brine (5 × 10 mL) to remove the excess of DMSO, then, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by means of column chromatography (PE/EtOAc, 9/1) to furnish pure 1-(4-methoxybenzyl)-3-methylene-4-(trifluoromethyl)azetidin-2-one **5b** in a yield of 21%.

1-(4-Methoxyphenyl)-3-methylene-4-(trifluoromethyl)azetidin-2-one 5a



Yellow crystals. Mp 68 °C. R_f = 0.15 (PE/EtOAc, 9/1). Yield 51%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.81 (3H, s, OCH_3), 4.89 (1H, q × t, J = 5.0, 1.3 Hz, $CHCF_3$), 5.56 and 6.02 (2 × 1H, 2 × s, C(HCH)), 6.91 and 7.42 (2 × 2H, 2 × d, J = 9.1 Hz, $N(CH_{arom})_{ortho}$ and $O(CH_{arom})_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 55.5 (OCH_3), 59.2 (q, J = 35.6 Hz, $CHCF_3$), 114.1 (CCH_2), 114.5 (2 × $O(CH_{arom})_{ortho}$), 119.0 (2 × $N(CH_{arom})_{ortho}$), 123.6 (q, J = 281.5 Hz, CF_3), 130.0 ($NC_{arom,quat}$), 140.4 (CCH_2), 157.1 ($OC_{arom,quat}$), 159.5 (C=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -71.87 (3F, d, J = 5.0 Hz, CF_3). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1742, ν_{max} = 1510, 1380, 1279, 1248, 1128, 1024, 866, 826, 715. MS (70eV): m/z (%): 258 (M^+ + 1, 100). HRMS (ESI) calcd for $C_{12}H_{11}F_3NO_2^+$: 258.0736 $[M + H]^+$. Found: 258.0731.

1-(4-Methoxybenzyl)-3-methylene-4-(trifluoromethyl)azetidin-2-one 5b

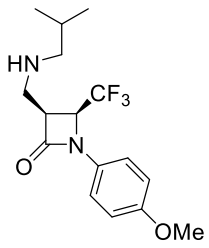


White crystals. Mp < 50 °C. R_f = 0.19 (PE/EtOAc, 9/1). Yield 72%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.81 (3H, s, OCH_3), 4.05 (1H, d, J = 15.0 Hz, (HCH)N), 4.19 (1H, q, J = 5.6 Hz, $CHCF_3$), 4.90 (1H, d, J = 15.0 Hz, (HCH)N), 5.37 and 5.87 (2 × 1H, 2 × s, C(HCH)), 6.89 and 7.19 (2 × 2H, 2 × d, J = 8.5 Hz, $NCH_2(CH_{arom})_{ortho}$ and $O(CH_{arom})_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 45.0 ($ArCH_2N$), 55.3 (OCH_3), 57.6 (q, J = 35.2 Hz, $CHCF_3$), 113.0 (CCH_2), 114.4 (2 × $O(HC_{arom})_{ortho}$), 123.7 (q, J = 279.5 Hz, CF_3), 126.3 ($NCH_2C_{arom,quat}$), 129.9 (2 × $NCH_2(HC_{arom})_{ortho}$), 141.4 (CCH_2), 159.6 ($OC_{arom,quat}$), 162.4 (C=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -73.28 (3F, d, J = 5.6 Hz, CF_3). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1766, ν_{max} = 1514, 1384, 1278, 1246, 1126, 1032, 866, 714. MS (70eV): m/z (%): 272 (M^+ + 1, 10). HRMS (ESI) calcd for $C_{13}H_{13}F_3NO_2^+$: 272.0893 $[M + H]^+$. Found: 272.0888.

Synthesis of 3-aminomethyl-4-(trifluoromethyl)azetidin-2-ones 6-7

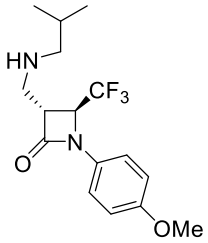
As a representative example, the synthesis of *cis*-1-(4-methoxybenzyl)-3-(pyrrolidin-1-ylmethyl)-4-(trifluoromethyl)azetidin-2-one **6e** and *trans*-1-(4-methoxybenzyl)-3-(pyrrolidin-1-ylmethyl)-4-(trifluoromethyl)azetidin-2-one **7e** is described. Pyrolidine (0.02 mL, 0.22 mmol, 1.2 equiv) was added to an ice-cooled solution of 1-(4-methoxybenzyl)-3-methylene-4-(trifluoromethyl)azetidin-2-one **5b** (0.05 g, 0.18 mmol, 1 equiv) in dry THF (5 mL). Then, the reaction mixture was stirred at room temperature for four hours. After completion of the reaction, the reaction mixture was extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with brine (3 × 5 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent *in vacuo* afforded a mixture of *cis*-1-(4-methoxybenzyl)-3-(pyrrolidin-1-ylmethyl)-4-(trifluoromethyl)azetidin-2-one **6e** (18%) and *trans*-1-(4-methoxybenzyl)-3-(pyrrolidin-1-ylmethyl)-4-(trifluoromethyl)azetidin-2-one **7e** (12%) in a ratio of 62:38. The two isomers were separated by preparative TLC (PE/EtOAc, 1/1) to obtain analytically pure samples.

Cis-3-[(isobutylamino)methyl]-1-(4-methoxyphenyl)-4-(trifluoromethyl)azetidin-2-one 6a



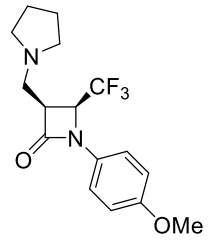
Yellowish solid. Mp 80 °C. R_f = 0.08 (PE/EtOAc/Et_3N, 1/1/0.01). Yield 60%. ^1H NMR (400 MHz, $CDCl_3$): δ 0.93 and 0.94 (2 × 3H, 2 × d, J = 6.7 Hz, CH($C\underline{H}_3$)$_2$), 1.77 (1H, nonet, J = 6.7 Hz, C$\underline{H}$(CH_3)$_2$), 2.48 and 2.52 (2H, 2 × (d × d), J = 11.4, 6.7 Hz, ($\underline{H}C\underline{H}$)$CHCH_3$), 3.03 (1H, d × d, J = 12.3, 6.2 Hz, CHCH(HC$\underline{H}$)NH), 3.19 (1H, d × d × q, J = 12.3, 8.9, 1.7 Hz, CHCH($\underline{H}$CH)NH), 3.80 (3H, s, OCH_3), 3.84 (1H, d × t, J = 8.9, 6.2 Hz, C$\underline{H}CHCF_3$), 4.59 (1H, quintet, J = 6.2 Hz, $CHCF_3$), 6.89 and 7.35 (2 × 2H, 2 × d, J = 9.0 Hz, O(CH_{arom})$_{ortho}$ and N(CH_{arom})$_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 20.53, 20.54 (2 × CH($\underline{C}H_3$)$_2$), 28.2 ($\underline{C}$H(CH_3)$_2$), 44.9 (q, J = 2.4 Hz CHCH$\underline{C}H_2$NH), 52.0 (CH$\underline{C}$HCH_2NH), 54.6 (q, J = 34.1 Hz, $\underline{C}HCF_3$), 55.5 (OCH_3), 58.0 (NH$\underline{C}H_2CHCH_3$), 114.4 (2 × O(HC_{arom})$_{ortho}$), 119.7 (2 × N(HC_{arom})$_{ortho}$), 124.3 (q, J = 282.5 Hz, CF_3), 129.6 ($NC_{arom,quat}$), 157.1 ($OC_{arom,quat}$), 165.7 (C=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -67.79 (3F, d, J = 6.2 Hz, CF_3). IR (ATR, cm^{-1}): ν_{NH} = 2961, $\nu_{C=O}$ = 1742, ν_{max} = 1512, 1285, 1240, 1140, 1130, 831, 810, 694, 517. MS (70eV): 331 (M^+ + 1, 100). HRMS (ESI) for $C_{16}H_{22}F_3N_2O_2^+$: 331.1628 $[M + H]^+$. Found: 331.1632.

Trans-3-[(isobutylamino)methyl]-1-(4-methoxyphenyl)-4-(trifluoromethyl)azetidin-2-one 7a



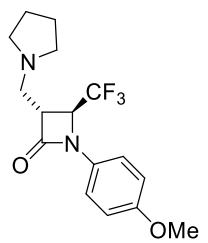
Yellow oil. R_f = 0.23 (PE/EtOAc/Et_3N, 1/10/01). Yield 29%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 and 0.88 (6H, 2 × d, J = 6.7 Hz, CH($C\underline{H}_3$)$_2$), 1.68 (1H, nonet, J = 6.7 Hz, C$\underline{H}$(CH_3)$_2$), 2.41 (1H, d × d, J = 11.5, 6.7 Hz, ($\underline{H}$CH)$CHCH_3$), 2.48 (1H, d × d, J = 11.5, 6.7 Hz, (HC$\underline{H}$)$CHCH_3$), 2.95 (1H, d × d, J = 12.9, 5.4 Hz, ($\underline{H}$CH)NH), 3.16 (1H, d × d, J = 12.9, 5.4 Hz, (HC$\underline{H}$)NH), 3.53 (1H, t × d, J = 5.4, 2.2 Hz, C$\underline{H}$CHCF_3), 3.80 (3H, s, OCH_3), 4.52 (1H, q × d, J = 5.6, 2.2 Hz, $CHCF_3$), 6.89 and 7.35 (2 × 2H, 2 × d, J = 9.0 Hz, O(CH_{arom})$_{ortho}$ and N(CH_{arom})$_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 20.4 and 20.5 (2 × CH($\underline{C}H_3$)$_2$), 28.3 (C$\underline{H}$(CH_3)$_2$), 46.1 (CH$\underline{C}H_2$NH), 52.5 ($\underline{C}$HCH_2NH), 54.7 (q, J = 34.8 Hz, $\underline{C}$HCF_3), 55.5 (OCH_3), 58.0 (NH$\underline{C}H_2$$CHCH_3$), 114.4 (2 × O($CH_{arom}$)$_{ortho}$), 119.6 (2 × N($CH_{arom}$)$_{ortho}$), 124.6 (q, J = 278.3 Hz, CF_3), 129.8 ($NC_{arom,quat}$), 157.0 ($OC_{arom,quat}$), 165.2 (C=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -72.45 (3F, d, J = 5.6 Hz, CF_3). IR (ATR, cm^{-1}): ν_{NH} = 2957, $\nu_{C=O}$ = 1759, ν_{max} = 1512, 1279, 1246, 1159, 1136, 1113, 1032, 829, 694, 519. MS (70eV): 331 (M^+ + 1, 100).

Cis-1-(4-methoxyphenyl)-3-(pyrrolidin-1-ylmethyl)-4-(trifluoromethyl)azetidin-2-one 6b



White crystals. Mp 104 °C. R_f = 0.07 (PE/EtOAc, 1/1). Yield 39%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.78-1.85 (4H, m, N(CH_2($C\underline{H}_2$)$_2$), 2.54-2.60 and 2.67-2.74 (2 × 2H, 2 × m, N($C\underline{H}_2$)$_2$(CH_2)$_2$), 2.88 (1H, d × d × q, J = 13.3, 7.8, 1.4 Hz, CH($\underline{H}$CH)N), 3.10 (1H, d × d × q, J = 13.3, 6.0, 1.3 Hz, CH($\underline{H}$CH)N), 3.80 (3H, s, OCH_3), 3.82 (1H, d × t, J = 7.8, 6.0 Hz, C$\underline{H}$CHCF_3), 4.61 (1H, quintet, J = 6.0 Hz, $CHCF_3$), 6.89 and 7.36 (2 × 2H, 2 × d, J = 9.0 Hz, O(CH_{arom})$_{ortho}$ and N(CH_{arom})$_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 23.7 (NCH_2($\underline{C}H_2$)$_2$), 50.1 (q, J = 2.5 Hz, CH$\underline{C}H_2$N), 52.2 ($\underline{C}$HCH_2N), 54.5 (N($\underline{C}H_2$)$_2$(CH_2)$_2$), 54.7 (q, J = 33.6 Hz, $\underline{C}$HCF_3), 55.5 (OCH_3), 114.4 (2 × O(CH_{arom})$_{ortho}$), 119.8 (2 × N(CH_{arom})$_{ortho}$), 124.4 (q, J = 281.2 Hz, CF_3), 129.7 ($NC_{arom,quat}$), 157.0 ($OC_{arom,quat}$), 165.4 (C=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -68.04 (3F, d, J = 6.0 Hz, CF_3). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1749, ν_{max} = 1514, 1277, 1248, 1138, 1109, 1030, 839, 808, 694, 521. MS (70eV): 329 (M^+ +1, 100). HRMS (ESI) for $C_{16}H_{20}F_3N_2O_2^+$: 329.1471 $[M + H]^+$. Found: 329.1477.

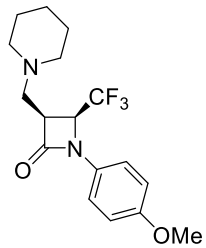
Trans-1-(4-methoxyphenyl)-3-(pyrrolidin-1-ylmethyl)-4-(trifluoromethyl)azetidin-2-one 7b



Pale solid. Mp 80 °C. R_f = 0.21 (PE/EtOAc, 1/1). Yield 13%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.74-1.81 (4H, m, N(CH_2($C\underline{H}_2$)$_2$), 2.52-2.63 (4H, m, N($C\underline{H}_2$)$_2$(CH_2)$_2$), 2.91 (1H, d × d, J = 12.9, 5.6 Hz, CH(HC$\underline{H}$)N), 2.96 (1H, d × d, J = 12.9, 7.8 Hz, CH($\underline{H}$CH)N), 3.55 (1H, d × d × d, J = 7.8, 5.6, 2.1 Hz, C$\underline{H}$CHCF_3), 3.80 (3H, s, OCH_3), 4.52 (1H, q × d, J = 5.5, 2.1 Hz, $CHCF_3$), 6.89 and 7.36 (2 × 2H, 2 × d, J

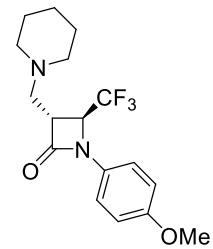
= 9.0 Hz, O(CH_{arom})$_{ortho}$ and N(CH_{arom})$_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 23.7 ($NCH_2(\underline{C}H_2)_2$), 52.1 ($\underline{C}HCH_2N$), 53.0 ($CH\underline{C}H_2N$), 54.5 ($N(\underline{C}H_2)_2(CH_2)_2$), 55.50 ($OCH_3$), 55.53 (q, J = 34.2 Hz, $\underline{C}HCF_3$), 114.4 (2 × O(CH_{arom})$_{ortho}$), 119.4 (2 × N(CH_{arom})$_{ortho}$), 124.4 (q, J = 280.5 Hz, CF_3), 130.0 ($NC_{arom,quat}$), 156.9 ($OC_{arom,quat}$), 165.1 (C=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -72.35 (3F, d, J = 5.5 Hz, CF_3). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1748, ν_{max} = 1516, 1275, 1254, 1161, 1134, 1028, 837, 808, 696, 517. MS (70eV): 329 (M^+ +1, 100).

Cis-1-(4-methoxyphenyl)-3-(piperidin-1-ylmethyl)-4-(trifluoromethyl)azetidin-2-one 6c



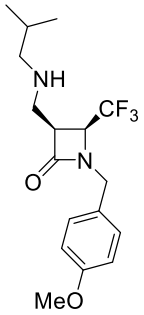
White crystals. Mp 110 °C. R_f = 0.18 (PE/EtOAc, 1/1). Yield 44%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.41-1.47 (2H, m, $N((CH_2)_2(CH_2)_2C\underline{H}_2)$, 1.53-1.67 (4H, m, $N((CH_2)_2(C\underline{H}_2)_2)$, 2.37-2.43 and 2.59-2.64 (2 × 2H, 2 × m, $N(C\underline{H}_2)_2(CH_2)_2$), 2.79 (1H, d × d × q, J = 13.6, 6.0, 1.4 Hz, CH($\underline{H}$CH)N), 2.88 (1H, d × d × q, J = 13.6, 6.0, 1.4 Hz, CH($\underline{H}$CH)N), 3.79 (3H, s, OCH_3), 3.82 (1H, d × t, J = 6.3, 6.0 Hz, $C\underline{H}CHCF_3$), 4.59 (1H, quintet, J = 6.3 Hz, $CHCF_3$), 6.88 and 7.34 (2 × 2H, 2 × d, J = 9.0 Hz, O(CH_{arom})$_{ortho}$ and N(CH_{arom})$_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 24.1 ($NCH_2(CH_2)_2(\underline{C}H_2)_2$), 26.0 ($N(CH_2)_2(\underline{C}H_2)_2$), 51.5 ($\underline{C}HCH_2N$), 53.0 (q, J = 2.2 Hz, $CH\underline{C}H_2N$), 54.6 ($N(\underline{C}H_2)_2(CH_2)_2$), 54.9 (q, J = 33.5 Hz, $\underline{C}HCF_3$), 55.5 (OCH_3), 114.4 (2 × O(HC_{arom})$_{ortho}$), 119.8 (2 × N(HC_{arom})$_{ortho}$), 124.4 (q, J = 281.3 Hz, CF_3), 129.7 ($N(C_{arom,quat})$, 157.0 ($OC_{arom,quat}$), 165.7 (C=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -68.15 (3F, d, J = 6.3 Hz, CF_3). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1746, ν_{max} = 1514, 1285, 1248, 1136, 1032, 839, 808, 656, 521. MS (70eV): 343 (M^+ + 1, 100). HRMS (ESI) for $C_{17}H_{22}F_3N_2O_2^+$: 343.1628 $[M + H]^+$. Found: 343.1634.

Trans-1-(4-methoxyphenyl)-3-(piperidin-1-ylmethyl)-4-(trifluoromethyl)azetidin-2-one 7c



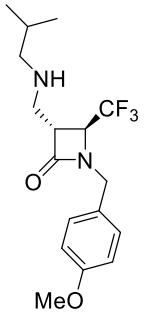
Yellow sticky oil. R_f = 0.46 (PE/EtOAc, 1/1). Yield 6%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.38-1.44 (2H, m, $N(CH_2)_2(CH_2)_2C\underline{H}_2$), 1.52-1.57 (4H, m, $N(CH_2)_2(C\underline{H}_2)_2$), 2.38-2.43 and 2.46-2.51 (2 × 2H, 2 × m, $N(C\underline{H}_2)_2(CH_2)_2$), 2.77 (2H, d, J = 6.7 Hz, CH($\underline{H}C\underline{H}$)N), 3.56 (1H, t × d, J = 6.7, 2.0 Hz, $C\underline{H}CHCF_3$), 3.80 (3H, s, OCH_3), 4.42 (1H, q × d, J = 5.4, 2.0 Hz, $CHCF_3$), 6.89 and 7.35 (2 × 2H, 2 × d, J = 9.0 Hz, O(CH_{arom})$_{ortho}$ and N(CH_{arom})$_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 24.1 ($NCH_2(CH_2)_2(\underline{C}H_2)_2$), 26.0 ($N(CH_2)_2(\underline{C}H_2)_2$), 50.9 ($\underline{C}HCH_2N$), 54.9 ($N(\underline{C}H_2)_2(CH_2)_2$), 55.5 ($OCH_3$), 55.8 (q, J = 34.4 Hz, $\underline{C}HCF_3$), 56.0 ($CH\underline{C}H_2N$), 114.4 (2 × O(CH_{arom})$_{ortho}$), 119.5 (2 × N(CH_{arom})$_{ortho}$), 124.6 (q, J = 276.1 Hz, CF_3), 130.0 ($N(C_{arom,quat})$, 156.9 ($OC_{arom,quat}$), 165.4 (C=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -72.34 (3F, d, J = 5.4 Hz, CF_3). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1778, ν_{max} = 1499, 1398, 1283, 1252, 1161, 1132, 1109, 1056, 810, 509, 403. MS (70eV): 343 (M^+ + 1, 100).

Cis-3-[(isobutylamino)methyl]-1-(4-methoxybenzyl)-4-(trifluoromethyl)azetidin-2-one 6d



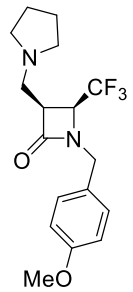
White solid. Mp < 46 °C. R_f = 0.11 (PE/EtOAc/Et_3N, 2/1/0.01). Yield 38%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.898 and 0.902 (6H, 2 × d, J = 6.7 Hz, CH(C<u>H</u>$_3$)$_2$), 1.72 (1H, nonet, J = 6.7 Hz, C<u>H</u>(CH$_3$)$_2$), 2.41 (1H, d × d, J = 11.3, 6.7 Hz, (<u>H</u>CH)CHCH$_3$), 2.46 (1H, d × d, J = 11.3, 6.7 Hz, (HC<u>H</u>)CHCH$_3$), 2.91 (1H, d × d, J = 12.4, 6.0 Hz, CH$_3$CH(<u>H</u>CH)NH), 3.09 (1H, d × d × q, J = 12.4, 8.8, 1.7 Hz, CHCH(HC<u>H</u>)NH), 3.58 (1H, d × t, J = 8.8, 6.0 Hz, C<u>H</u>CHCF$_3$), 3.81 (3H, s, OCH$_3$), 3.86 (1H, q × d, J = 7.1, 6.0 Hz, CHCF$_3$), 3.90 and 4.79 (2 × 1H, 2 × d, J = 15.0, (<u>H</u>C<u>H</u>N)), 6.88 and 7.17 (2 × 2H, 2 × d, J = 8.6 Hz, O(CH$_{arom}$)$_{ortho}$ and NCH$_2$(C<u>H</u>$_{arom}$)$_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 20.5 (2 × CH(<u>C</u>H$_3$)$_2$), 28.2 (<u>C</u>H(CH$_3$)$_2$), 44.8 (N<u>C</u>H$_2$CHCH$_3$, N<u>C</u>H$_2$C$_{arom}$), 52.5 (<u>C</u>HCHCF$_3$), 53.1 (q, J = 33.7 Hz, <u>C</u>HCF$_3$), 55.3 (OCH$_3$), 57.9 (<u>C</u>H$_2$CH(CH$_3$)$_2$), 114.3 (2 × O(HC$_{arom}$)$_{ortho}$), 124.5 (q, J = 280.3 Hz, CF$_3$), 126.6 (NCH$_2$(<u>C</u>$_{arom,quat}$), 129.8 (2 × NCH$_2$(<u>C</u>H$_{arom}$)$_{ortho}$), 159.5 (OC$_{arom,quat}$), 168.2 (C=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -68.81 (3F, d, J = 7.1 Hz, CF$_3$). IR (ATR, cm^{-1}): ν_{NH} = 2949, $\nu_{C=O}$ = 1749, ν_{max} = 1514, 1246, 1134, 1113, 1032, 839, 806. MS (70eV): 345 (M^+ + 1, 100). HRMS (ESI) calcd for $C_{17}H_{24}F_3N_2O_2^+$: 345.1784 $[M + H]^+$. Found: 345.1788.

Trans-3-[(isobutylamino)methyl]-1-(4-methoxybenzyl)-4-(trifluoromethyl)azetidin-2-one 7d



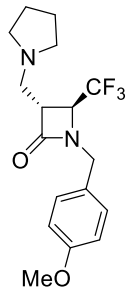
Yellow oil. R_f = 0.40 (PE/EtOAc/Et_3N, 2/1/0.01). Yield 25%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.847 and 0.853 (2 × 3H, 2 × d, J = 6.6 Hz, CH(C<u>H</u>$_3$)$_2$), 1.62 (1H, nonet, J = 6.6 Hz, C<u>H</u>(CH$_3$)$_2$), 2.31 (1H, d × d, J = 11.4, 6.6 Hz, (HC<u>H</u>)CHCH$_3$), 2.43 (1H, d × d, J = 11.4, 6.6 Hz, (<u>H</u>CH)CHCH$_3$), 2.78 (1H, d × d, J = 12.9, 5.1 Hz, CHCH(<u>H</u>CH)NH), 3.01 (1H, d × d , J = 12.9, 5.1 Hz, CHCH(HC<u>H</u>)NH), 3.40 (1H, t × d, J = 5.1, 2.5 Hz, C<u>H</u>CHCF$_3$), 3.80 (3H, s, OCH$_3$), 3.82 (1H, q × d, J = 5.8, 2.5 Hz, CHCF$_3$), 3.90 and 4.82 (2 × 1H, 2 × d, J = 15.0, (<u>H</u>C<u>H</u>N)), 6.87 and 7.21 (2 × 2H, 2 × d, J = 8.6 Hz, O(CH$_{arom}$)$_{ortho}$ and NCH$_2$(C<u>H</u>$_{arom}$)$_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 20.48 and 20.51 (2 × CH(<u>C</u>H$_3$)$_2$), 28.5 (<u>C</u>H(CH$_3$)$_2$), 44.9 (N<u>C</u>H$_2$C$_{arom}$), 46.0 (COCH<u>C</u>H$_2$N), 52.6 (<u>C</u>HCHCF$_3$), 53.3 (q, J = 34.2 Hz, <u>C</u>HCF$_3$), 55.3 (OCH$_3$), 58.0 (<u>C</u>H$_2$CH(CH$_3$)$_2$), 114.2 (2 × O(CH$_{arom}$)$_{ortho}$), 124.7 (q, J = 279.2 Hz, CF$_3$), 126.7 (NCH$_2$(<u>C</u>$_{arom,quat}$), 129.8 (2 × NCH$_2$(<u>C</u>H$_{arom}$)$_{ortho}$), 159.4 (OC$_{arom,quat}$), 167.7 (C=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -73.65 (3F, d, J = 5.8 Hz, CF$_3$). IR (ATR, cm^{-1}): ν_{NH} = 2953, $\nu_{C=O}$ = 1761, ν_{max} = 1514, 1283, 1246, 1136, 1032, 839, 808, 656, 513. MS (70eV): 345 [M^+ + 1, 100].

Cis-1-(4-methoxybenzyl)-3-(pyrrolidin-1-ylmethyl)-4-(trifluoromethyl)azetidin-2-one 6e



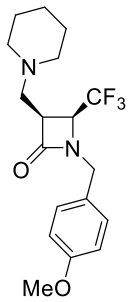
White crystals. Mp 66 °C. R_f = 0.12 (PE/EtOAc, 1/1). Yield 18%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.74-1.81 (4H, m, $N(CH_2(C\underline{H}_2)_2)$, 2.47-2.55 and 2.61-2.68 (2 × 2H, 2 × m, $N(C\underline{H}_2)_2CH_2$), 2.77 (1H, d × d × q, J = 13.0, 8.3, 1.7 Hz, $CH(HC\underline{H})N$), 2.98 (1H, d × d, J = 13.0, 5.4 Hz, $CH(\underline{H}CH)N$), 3.57 (1H, d × t, J =8.3, 5.4 Hz, $C\underline{H}CHCF_3$), 3.81 (3H, s, OCH_3), 3.86 (1H, q × d, J = 6.9, 5.4 Hz, $CHCF_3$), 3.91 and 4.80 (2 × 1H, 2 × d, J = 14.9 Hz, $(\underline{H}C\underline{H})N$), 6.88 and 7.17 (2 × 2H, 2 × d, J = 8.6 Hz, $O(CH_{arom})_{ortho}$ and $NCH_2(C\underline{H}_{arom})_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 23.6 ($NCH_2(\underline{C}H_2)_2$), 44.8 ($N\underline{C}H_2C_{arom}$), 50.1 (q, J = 2.0 Hz, $CH\underline{C}H_2N$), 52.6 ($\underline{C}HCH_2N$), 53.2 (q, J = 33.3 Hz, $\underline{C}HCF_3$), 54.4 ($N(\underline{C}H_2)_2(CH_2)_2$), 55.3 ($OCH_3$), 114.3 (2 × $O(CH_{arom})_{ortho}$), 124.6 (q, J = 280.5 Hz, CF_3), 126.7 ($NCH_2(\underline{C}_{arom,quat})$, 129.9 (2 × $NCH_2(H\underline{C}_{arom})_{ortho}$), 159.4 ($OC_{arom,quat}$), 167.9 (C=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -68.96 (3F, d, J = 6.9 Hz, CF_3). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1751, ν_{max} = 1514, 1288, 1246, 1126, 1111, 1036, 833, 673, 575, 515. MS (70eV): m/z (%): 343 (M^+ + 1, 100). HRMS (ESI) calcd for $C_{17}H_{22}F_3N_2O_2^+$: 343.1628 $[M + H]^+$. Found: 343.1638.

Trans-1-(4-methoxybenzyl)-3-(pyrrolidin-1-ylmethyl)-4-(trifluoromethyl)azetidin-2-one 7e



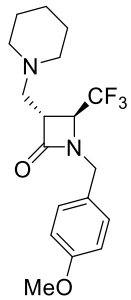
Yellowish oil. R_f = 0.43 (PE/EtOAc, 1/1). Yield 12%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.69-1.74 (4H, m, $N(CH_2(C\underline{H}_2)_2)$, 2.47-2.52 (4H, m, $N(C\underline{H}_2)_2CH_2$, 2.75 (1H, d × d, J = 13.3, 7.5 Hz, $CH(\underline{H}CH)N$), 2.80 (1H, d × d, J = 13.3, 5.2 Hz, $CH(HC\underline{H})N$), 3.40 (1H, d × d × d, J = 7.5, 5.2, 2.0 Hz, $C\underline{H}CHCF_3$), 3.77 (1H, q × d, J = 6.1, 2.0 Hz, $CHCF_3$), 3.81 (3H, s, OCH_3), 3.88 and 4.83 (2 × 1H, 2 × d, J = 15.0 Hz, $(\underline{H}C\underline{H})N$), 6.88 and 7.19 (2 × 2H, 2 × d, J = 8.6 Hz, $O(CH_{arom})_{ortho}$ and $NCH_2(C\underline{H}_{arom})_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 23.6 ($NCH_2(\underline{C}H_2)_2$), 44.8 ($NCH_2$), 52.3 ($\underline{C}HCH_2N$), 52.6 ($CH\underline{C}H_2N$), 54.2 (q, J = 33.8 Hz, $\underline{C}HCF_3$), 54.6 ($N(\underline{C}H_2)_2(CH_2)_2$), 55.3 ($OCH_3$), 114.2 (2 × $O(CH_{arom})_{ortho}$), 124.6 (q, J = 279.5 Hz, CF_3), 126.7 ($NCH_2(\underline{C}_{arom,quat})$, 129.8 (2 × $NCH_2(H\underline{C}_{arom})_{ortho}$), 159.4 ($OC_{arom,quat}$), 167.7 (C=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -73.48 (3F, d, J = 6.1 Hz, CF_3). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1767, ν_{max} = 1514, 1277, 1246, 1128, 1115, 1034, 843, 820, 563, 513. MS (70eV): 343 (M^+ +1, 100).

Cis-1-(4-methoxybenzyl)-3-(piperidin-1-ylmethyl)-4-(trifluoromethyl)azetidin-2-one 6f



White crystals. Mp 76 °C. R_f = 0.13 (PE/EtOAc, 1/1). Yield 15%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.38-1.44 (2H, m, $N(CH_2)_2(CH_2)_2C\underline{H}_2$), 1.49-1.63 (4H, m, $N(CH_2)_2(C\underline{H}_2)_2$), 2.31-2.36 and 2.52-2.59 (2 × 2H, 2 × m, $N(C\underline{H}_2)_2(CH_2)_2$), 2.69 (1H, d × d × q, J = 13.5, 7.2, 1.5 Hz, CH(HC$\underline{H}$)N), 2.77 (1H, d × d, J = 13.5, 5.5 Hz, CH($\underline{H}$CH)N), 3.58 (1H, d × t, J = 7.2, 5.5 Hz, C$\underline{H}$CHCF$_3$), 3.81 (3H, s, OCH_3), 3.84 (1H, q × d, J = 7.1, 5.5 Hz, $CHCF_3$), 3.90 and 4.79 (2 × 1H, 2 × d, J = 15.0, ($\underline{H}$C$\underline{H}$)N), 6.87 and 7.17 (2 × 2H, 2 × d, J = 8.6 Hz, $NCH_2(C\underline{H}_{arom})_{ortho}$ and $O(CH_{arom})_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 24.1 ($N(CH_2)_2(CH_2)_2\underline{C}H_2$), 26.0 ($N(CH_2)_2(\underline{C}H_2)_2$), 44.8 ($N\underline{C}H_2$), 51.5 ($\underline{C}HCH_2N$), 53.1 (q, J = 2.0 Hz, $CH\underline{C}H_2N$), 53.4 (q, J = 33.1 Hz, $\underline{C}HCF_3$), 54.5 ($N(\underline{C}H_2)_2(CH_2)_2$), 55.3 ($OCH_3$), 114.3 (2 × $O(CH_{arom})_{ortho}$), 124.6 (q, J = 281.7 Hz, CF_3), 126.7 (2 × $NCH_2(\underline{C}_{arom,quat})$, 129.8 ($NCH_2(\underline{C}H_{arom})_{ortho}$), 159.4 ($OC_{arom,quat}$), 168.1 (C=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -68.99 (3F, d, J = 7.1 Hz, CF_3). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1749, ν_{max} = 1514, 1277, 1244, 1150, 1128, 1111, 1038, 972, 943, 831, 806, 673, 577, 513. MS (70eV): 357 (M^+ + 1, 100). HRMS (ESI) calcd for $C_{18}H_{24}F_3N_2O_2^+$: 357.1784 [M + H]$^+$. Found: 357.1779.

Trans-1-(4-methoxybenzyl)-3-(piperidin-1-ylmethyl)-4-(trifluoromethyl)azetidin-2-one 7f



Yellow oil. R_f = 0.45 (PE/EtOAc, 1/1). Yield 15%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.35-1.40 (2H, m, $N(CH_2)_2(CH_2)_2C\underline{H}_2$), 1.45-1.52 (4H, m, $N(CH_2)_2(C\underline{H}_2)_2$), 2.36-2.39 (4H, m, $N(C\underline{H}_2)_2(CH_2)_2$), 2.61 (2H, d, J = 6.0 Hz, CH($\underline{H}$C$\underline{H}$)N), 3.41 (1H, t × d, J = 6.0, 2.0 Hz, C$\underline{H}$CHCF$_3$), 3.72 (1H, q × d, J = 6.1, 2.0 Hz, $CHCF_3$), 3.81 (3H, s, OCH_3), 3.88 and 4.83 (2 × 1H, 2 × d, J = 15.0, ($\underline{H}$C$\underline{H}$)N), 6.89 and 7.21 (2 × 2H, 2 × d, J = 8.6 Hz, $O(CH_{arom})_{ortho}$ and $NCH_2(C\underline{H}_{arom})_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 24.0 ($N(CH_2)_2(CH_2)_2\underline{C}H_2$), 25.9 ($N(CH_2)_2(\underline{C}H_2)_2$), 44.8 ($N\underline{C}H_2$), 51.3 ($\underline{C}HCH_2N$), 54.2 (q, J = 33.8 Hz, $\underline{C}HCF_3$), 55.1 ($N(\underline{C}H_2)_2(CH_2)_2$), 55.3 ($CH\underline{C}H_2N$), 55.4 ($OCH_3$), 114.3 (2 × $O(CH_{arom})_{ortho}$), 124.6 (q, J = 281.9 Hz, CF_3), 126.8 ($NCH_2(\underline{C}_{arom,quat})$, 129.8 (2 × $NCH_2(H\underline{C}_{arom})_{ortho}$), 159.4 ($OC_{arom,quat}$), 167.9 (C=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -74.42 (3F, d, J = 6.1 Hz, CF_3). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1767, ν_{max} = 1514, 1277, 1244, 1155, 1130, 1107, 1034, 955, 841, 820, 565, 511. MS (70eV): 357 (M^+ + 1, 100).

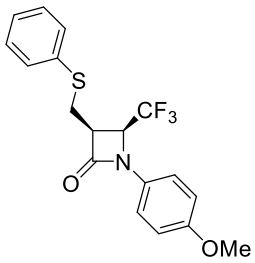
Synthesis of 3-phenylthiomethyl-4-(trifluoromethyl)azetidin-2-ones 8-9

As a representative example, the synthesis of *cis*-1-(4-methoxybenzyl)-3-phenylthiomethyl-4-(trifluoromethyl)azetidin-2-one **8b** and *trans*-1-(4-methoxybenzyl)-3-phenylthiomethyl-4-(trifluoromethyl)azetidin-2-one **9b** is described. Triethylamine (0.04 mL, 0.28 mmol, 1.5 equiv) was

added dropwise to a stirred solution of 1-(4-methoxybenzyl)-3-methylene-4-(trifluoromethyl)azetidin-2-one **5b** (0.05 g, 0.18 mmol, 1 equiv) and benzenethiol (0.03 mL, 0.26 mmol, 1.4 equiv) in dry THF (5 mL) at 0 °C, and the reaction mixture was allowed to continue for two hours at room temperature. After completion of the reaction as monitored by LC-MS, the reaction mixture was extracted with EtOAc (3 × 5 mL), then the organic layers were dried over $MgSO_4$. The solvent was evaporated, which resulted in a mixture of *cis*-1-(4-methoxybenzyl)-3-phenylthiomethyl-4-(trifluoromethyl)azetidin-2-one **8b** and *trans*-1-(4-methoxybenzyl)-3-phenylthiomethyl-4-(trifluoromethyl)azetidin-2-one **9b** in a ratio of 59:41. The mixture was purified by preparative TLC (PE/EtOAc, 12/1) to provide the desired sulfides **8b** and **9b** as white crystals in a yield of 79%.

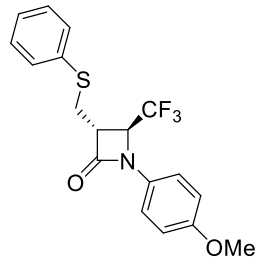
***Cis*-1-(4-methoxyphenyl)-3-phenylthiomethyl-4-(trifluoromethyl)azetidin-2-one 8a and *trans*-1-(4-methoxyphenyl)-3-phenylthiomethyl-4-(trifluoromethyl)azetidin-2-one 9a**: White crystals. Mp 87 °C. R_f = 0.27 (PE/EtOAc, 9/1). Yield 81%. *Cis*:*trans*, 74:26. IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1749, ν_{max} = 1512, 1287, 1250, 1142, 1125, 1086, 1030, 950, 831, 806, 737, 689, 521, 475. MS (70eV): 368 [M^+ + 1].

***Cis*-1-(4-methoxyphenyl)-3-phenylthiomethyl-4-(trifluoromethyl)azetidin-2-one 8a**



^{1}H NMR (400 MHz, $CDCl_3$): δ 3.30 (1H, d × d, J = 14.4, 7.5 Hz, CH(HCH)S), 3.46 (1H, d × d, J = 14.4, 7.5 Hz, CH(HCH)S), 3.78 (1H, t × d, J = 7.5, 6.1 Hz, CHCHCF$_3$), 3.79 (3H, s, OCH_3), 4.60 (1H, quintet, J = 6.1 Hz, $CHCF_3$), 6.877 (2H, d, J = 9.1 Hz, O(CH_{arom})$_{ortho}$), 7.24-7.46 (7H, m, N(CH_{arom})$_{ortho}$ and SCH_{arom}). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 28.8 (q, J = 2.3 Hz, $CHCH_2S$), 51.3 ($CHCH_2S$), 55.3 (q, J = 33.6 Hz, $CHCF_3$), 55.5 (OCH_3), 114.4 (2 × O(HC_{arom})$_{ortho}$), 119.8 (2 × N(HC_{arom})$_{ortho}$), 124.2 (q, J = 281.5 Hz, CF_3), 127.2 (SC_{arom}), 129.3 ($NC_{arom,quat}$), 129.4, 130.8 and 134.4 (SC_{arom}), 157.2 ($OC_{arom,quat}$), 164.4 (C=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -67.57 (3F, d, J = 6.1 Hz, CF_3).

***Trans*-1-(4-methoxyphenyl)-3-phenylthiomethyl-4-(trifluoromethyl)azetidin-2-one 9a**

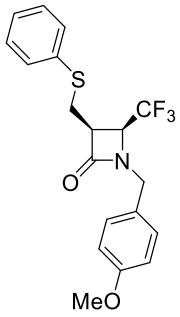


^{1}H NMR (400 MHz, $CDCl_3$): δ 3.20 (1H, d × d, J = 13.9, 9.3 Hz, CH(HCH)S), 3.49 (1H, d × d, J = 13.9, 4.2 Hz, CH(HCH)S), 3.59 (1H, d × d × d, J = 9.3, 4.2, 2.1 Hz, CHCHCF$_3$), 3.80 (3H, s, OCH_3), 4.39 (1H, q × d, J = 5.4, 2.1 Hz, $CHCF_3$), 6.883 (2H, d, J = 9.2 Hz, O($CH_{arom,ortho}$)), 7.24-7.46 (7H, m, N(CH_{arom})$_{ortho}$ and SCH_{arom}). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 32.3 ($CHCH_2S$), 51.5 ($CHCH_2S$), 55.5 (OCH_3), 56.5 (q, J = 34.7 Hz, $CHCF_3$), 114.4 (2 ×

$O(CH_{arom})_{ortho}$), 119.6 (2 × $N(CH_{arom})_{ortho}$), 124.1 (q, J = 289.7 Hz, CF_3), 127.5 (SC_{arom}), 129.3 ($NC_{arom,quat}$), 129.6, 130.9 and 133.8 (SC_{arom}), 157.2 ($OC_{arom,quat}$), 163.8 (C=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -72.16 (3F, d, J = 5.4 Hz, CF_3).

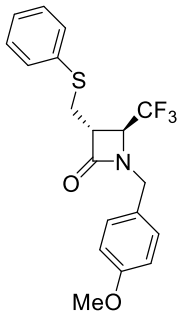
***Cis*-1-(4-methoxybenzyl)-3-phenylthiomethyl-4-(trifluoromethyl)azetidin-2-one 8b and *trans*-1-(4-methoxybenzyl)-3-phenylthiomethyl-4-(trifluoromethyl)azetidin-2-one 9b**: White crystals. Mp 60 °C. R_f = 0.09 (PE/EtOAc, 12/1). Yield 79%. *Cis*:*trans*, 59:41. IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1751, ν_{max} = 1514, 1288, 1246, 1177, 1159, 1150, 1132, 1123, 1090, 1035, 829, 816, 739, 691, 669, 515, 474. MS (70eV): 382 [M^+ +1, 100].

***Cis*-1-(4-methoxybenzyl)-3-phenylthiomethyl-4-(trifluoromethyl)azetidin-2-one 8b**



^1H NMR (400 MHz, $CDCl_3$): δ 3.20 (1H, d × d, J = 14.1, 7.7 Hz, CH(HCH)S), 3.38 (1H, d × d, J = 14.1, 7.7 Hz, CH(HCH)S), 3.53 (1H, t × d, J = 7.7, 6.3 Hz, CHCHCF$_3$), 3.79 (3H, s, OCH_3), 3.86 (1H, quintet, J = 6.3 Hz, $CHCF_3$), 3.89 and 4.81 (2 × 1H, J = 14.8 Hz, (HCH)N), 6.86 and 7.15 (2 × 2H, 2 × d, J = 8.6 Hz, $O(CH_{arom})_{ortho}$ and $NCH_2(CH_{arom})_{ortho}$), 7.21-7.32 and 7.36-7.39 (5H, 2 × m, SCH_{arom}). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 28.7 (q, J = 2.2 Hz, $CHCH_2S$), 44.9 (NCH_2), 51.7 ($CHCH_2S$), 53.8 (q, J = 33.3 Hz, $CHCF_3$), 55.3 (OCH_3), 114.36 (2 × $O(CH_{arom})_{ortho}$), 124.4 (q, J = 280.7 Hz, CF_3), 126.4 ($NCH_2C_{arom,quat}$), 127.0 (SC_{arom}), 129.2 (SC_{arom}), 129.89 ($NCH_2(HC_{arom})_{ortho}$), 130.52 (SC_{arom}), 134.5 ($SC_{arom,quat}$), 159.51 ($OC_{arom,quat}$), 166.8 (C=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -68.40 (3F, d, J = 6.3 Hz, CF_3).

***Trans*-1-(4-methoxybenzyl)-3-phenylthiomethyl-4-(trifluoromethyl)azetidin-2-one 9b**

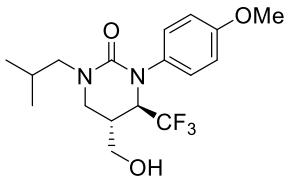


^1H NMR (400 MHz, $CDCl_3$): δ 2.97 (1H, d × d, J = 13.9, 9.5 Hz, CH(HCH)S), 3.37 (1H, d × d, J = 13.9, 3.9 Hz, CH(HCH)S), 3.45 (1H, d × d × d, J = 9.5, 3.9, 2.0 Hz, CHCHCF$_3$), 3.64 (1H, q × d, J =5.8, 2.0 Hz, $CHCF_3$), 3.82 (3H, s, OCH_3), 3.88 and 4.81 (2 × 1H, J = 15.0 Hz, (HCH)N), 6.89 and 7.19 (2 × 2H, d, J = 8.6 Hz, $NCH_2(CH_{arom})_{ortho}$ and $O(CH_{arom})_{ortho}$), 7.21-7.32 and 7.36-7.39 (5H, 2 × m, SCH_{arom}). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 31.8 ($CHCH_2S$), 45.0 (NCH_2), 51.5 ($CHCH_2S$), 55.1 (q, J = 34.3 Hz, $CHCF_3$), 55.3 (OCH_3), 114.37 (2 × $O(CH_{arom})_{ortho}$), 124.2 (q, J = 279.7 Hz, CF_3), 126.5 ($NCH_2C_{arom,quat}$), 127.2 (SC_{arom}), 129.2 (SC_{arom}), 129.95 (2 × $NCH_2(HC_{arom})_{ortho}$), 130.48 (SC_{arom}), 134.1 ($SC_{arom,quat}$), 159.53 ($OC_{arom,quat}$), 166.4 (C=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -73.34 (3F, d, J = 5.8 Hz, CF_3).

Synthesis of 5-hydroxymethyl-1-isobutyl-4-(trifluoromethyl)tetrahydropyrimidin-2(1*H*)-ones 10

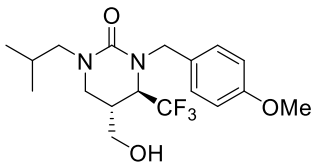
As a representative example, the synthesis of *trans*-5-hydroxymethyl-1-isobutyl-3-(4-methoxybenzyl)-4-(trifluoromethyl)tetrahydropyrimidin-2(1*H*)-one **10b** is described. $LiAlH_4$ (0.30 mL, 0.30 mmol, 1M in Et_2O, 2 equiv) was added in small portions to a solution of *cis*-3-[(isobutylamino)methyl]-1-(4-methoxybenzyl)-4-(trifluoromethyl)azetidin-2-one **6d** (0.05 g, 0.15 mmol, 1 equiv) in dry Et_2O (5 mL) at 0 °C. After heating for 30 minutes at reflux temperature under a nitrogen atmosphere, the reaction mixture was cooled to 0 °C, quenched with water (5 mL) and extracted with Et_2O (3 × 5 mL). Drying ($MgSO_4$), filtration of the drying agent, and evaporation of the solvent *in vacuo* produced the crude product, then, dry THF (5 mL) and triphosgene (0.02 mL, 1 equiv) were added to the crude product. The resulting mixture was stirred for two hours at room temperature, after which the reaction mixture was extracted with EtOAc (3 × 5 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent *in vacuo* afforded *trans*-5-hydroxymethyl-1-isobutyl-3-(4-methoxybenzyl)-4-(trifluoromethyl)tetrahydropyrimidin-2(1*H*)-one **10b** (69%), which was purified by preparative TLC (PE/EtOAc, 1/1) to obtain an analytically pure sample.

Trans-5-hydroxymethyl-1-isobutyl-3-(4-methoxyphenyl)-4-(trifluoromethyl)tetrahydropyrimidin-2(1*H*)-one 10a



White crystals. Mp 142 °C. R_f = 0.17 (PE/EtOAc, 1/1). Yield 41%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 and 0.90 (2 × 3H, 2 × d, J = 6.8 Hz, $CH(C\underline{H}_3)_2$), 1.97 (1H, nonet, J = 7.0 Hz, $C\underline{H}(CH_3)_2$), 2.31 (1H, t, J = 4.7 Hz, OH), 2.42-2.47 (1H, m, $CH_2C\underline{H}CHCF_3$), 3.00 (1H, d × d, J = 13.6, 7.0 Hz, $N(\underline{H}CH)CHCH_3$), 3.08 (1H, d, J = 12.7 Hz, $N(\underline{H}CH)CHCH_2OH$), 3.36 (1H, d × d, J = 13.6, 7.5 Hz, $N(HC\underline{H})CHCH_3$), 3.69 (1H, d × d, J = 12.7, 4.7 Hz, $N(HC\underline{H})CHCH_2OH$), 3.74-3.85 (5H, m, $CHC\underline{H}_2OH$ and $OC\underline{H}_3$), 4.43 (1H, q, J = 7.6 Hz, $C\underline{H}CF_3$), 6.86 and 7.16 (2 × 2H, 2 × d, J = 8.9 Hz, $O(CH_{arom})_{ortho}$ and $N(CH_{arom})_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 19.7 and 20.2 (2 × $CH(\underline{C}H_3)_2$), 26.8 ($\underline{C}H(CH_3)_2$), 32.3 ($CH_2\underline{C}HCHCF_3$), 44.9 (q, J = 1.5 Hz, $N\underline{C}H_2CHCH_2OH$), 55.4 ($OCH_3$), 56.1 ($\underline{C}H_2CH(CH_3)_2$), 60.1 (q, J = 29.2 Hz, $\underline{C}HCF_3$), 61.5 ($\underline{C}H_2OH$), 114.1 (2 × $O(HC_{arom})_{ortho}$), 125.4 (q, J = 285.3 Hz, CF_3), 129.3 (2 × $N(CH_{arom})_{ortho}$), 136.1 ($NC_{arom,quat}$), 154.0 (C=O), 158.1 ($OC_{arom,quat}$). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -72.03 (3F, d, J = 7.6 Hz, CF_3). IR (ATR, cm^{-1}): ν_{OH} = 3368, $\nu_{C=O}$ = 1628, ν_{max} = 1514, 1501, 1466, 1225, 1161, 1134, 1084, 1067, 824, 746, 700, 669, 571. MS (70eV): 361 (M^+ + 1, 100). HRMS (ESI) calcd for $C_{17}H_{24}F_3N_2O_3^+$: 361.1734 $[M + H]^+$. Found: 361.1736.

Trans-5-hydroxymethyl-1-isobutyl-3-(4-methoxybenzyl)-4-(trifluoromethyl)tetrahydropyrimidin-2(1*H*)-one 10b

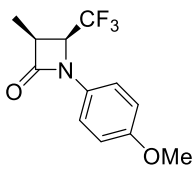


Brownish sticky oil. R_f = 0.28 (PE/EtOAc, 1/1). Yield 69%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.82 (1H, t, J = 5.4 Hz, OH), 0.89 and 0.91 (2 × 3H, 2 × d , J = 6.4 Hz, $CH(C\underline{H}_3)_2$), 1.94 (1H, nonet, J = 7.2 Hz, $C\underline{H}(CH_3)_2$), 2.21-2.26 (1H, m, $CH_2C\underline{H}CHCF_3$), 2.92 (1H, d, J = 12.6 Hz, $N(\underline{H}CH)CHCH_2OH$), 2.95 (1H, d × d, J = 13.6, 7.2 Hz, $N(\underline{H}CH)CHCH_3$), 3.10-3.17 (1H, m, $CH(HC\underline{H})OH$), 3.35 (1H, d × t, J = 10.4, 5.4 Hz, $CH(\underline{H}CH)OH$), 3.42 (1H, d × d, J = 13.6, 7.2 Hz, $N(HC\underline{H})CHCH_3$), 3.57 (1H, d × d, J = 12.6, 5.2 Hz, $N(HC\underline{H})CHCH_2OH$), 3.72 (1H, d, J = 14.7 Hz, $N(\underline{H}CH)$, 3.77-3.83 (4H, m, $C\underline{H}CF_3$ and OCH_3), 5.63 (1H, d, J = 14.7 Hz, $N(HC\underline{H})$, 6.88 and 7.28 (2 × 2H, 2 × d, J = 8.4 Hz, $O(CH_{arom})_{ortho}$ and $NCH_2(C\underline{H}_{arom})_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 19.7 and 20.2 (2 × $CH(\underline{C}H_3)_2$), 26.7 ($\underline{C}H(CH_3)_2$), 31.8 ($CH_2\underline{C}HCHCF_3$), 44.4 ($N\underline{C}H_2CHCH_2OH$), 49.3 ($NCH_2$), 53.8 (q, J = 29.6 Hz, $\underline{C}HCF_3$), 55.3 (OCH_3), 56.1 ($\underline{C}H_2CH(CH_3)_2$), 61.4 ($CH\underline{C}H_2OH$), 114.1 (2 × $O(HC_{arom})_{ortho}$), 126.0 (q, J = 285.4 Hz, CF_3), 129.9 ($NCH_2\underline{C}_{arom,quat}$), 130.5 (2 × $NCH_2(CH_{arom})_{ortho}$), 154.4 (C=O), 159.3 ($OC_{arom,quat}$). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -71.70 (3F, d, J = 7.6 Hz, CF_3). IR (ATR, cm^{-1}): ν_{OH} = 3387, $\nu_{C=O}$ = 1620, ν_{max} = 1506, 1466, 1265, 1234, 1157, 1136, 1123, 1055, 1038, 812, 756, 743, 700, 581. MS (70eV): 375 (M^+ + 1, 100). HRMS (ESI) calcd for $C_{18}H_{26}F_3N_2O_3^+$: 375.1890 $[M + H]^+$. Found: 375.1888.

Synthesis of *cis*-3-methyl-4-(trifluoromethyl)azetidin-2-ones 11

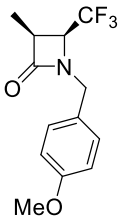
As a representative example, the synthesis of *cis*-1-(4-methoxybenzyl)-3-methyl-4-(trifluoromethyl)azetidin-2-one **11b** is described. palladium on activated carbon (20% w/w) was added to a solution of 1-(4-methoxybenzyl)-3-methylene-4-(trifluoromethyl)azetidin-2-one **5b** (0.04 g, 0.15 mmol, 1 equiv) in MeOH (2 mL). The resulting mixture was placed in a Parr apparatus. The inside of the Parr apparatus was then degassed and filled with hydrogen gas, after which the mixture was stirred for three hours at room temperature while applying 5 bar of hydrogen gas. Filtration of the heterogenous mixture through Celite® and evaporation of the solvent *in vacuo* afforded *cis*-1-(4-methoxybenzyl)-3-methyl-4-(trifluoromethyl)azetidin-2-one **11b** (87%) as an analytically pure sample.

Cis-1-(4-methoxyphenyl)-3-methyl-4-(trifluoromethyl)azetidin-2-one 11a



White crystals. Mp 86 °C. R_f = 0.36 (PE/EtOAc, 41). Yield 79%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.45 (3H, d × q, J = 7.7, 1.7 Hz, CHC$\underline{H}_3$), 3.68 (1H, q × d, J = 7.7, 5.9 Hz, C$\underline{H}$CH$_3$), 3.79 (3H, s, OCH_3), 4.52 (1H, quintet, J = 5.9 Hz, $CHCF_3$), 6.89 and 7.36 (2 × 2H, 2 × d, J = 9.0 Hz, O(CH_{arom})$_{ortho}$ and N(CH_{arom})$_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 9.1 (q, J = 2.4 Hz, CH$\underline{C}H_3$), 46.9 ($\underline{C}HCH_3$), 55.1 (q, J = 33.2 Hz, $\underline{C}HCF_3$), 55.5 (OCH_3), 114.4 (2 × O(CH_{arom})$_{ortho}$), 119.6 (2 × N (CH_{arom})$_{ortho}$), 124.4 (q, J = 281.0 Hz, CF_3), 129.8 ($NC_{arom,quat}$), 157.0 ($OC_{arom,quat}$), 166.8 (C=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -67.67 (3F, d, J = 5.9 Hz, CF_3). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1743, ν_{max} = 1513, 1394, 1281, 1246, 1137, 1025, 830. MS (70eV): m/z (%): 260 (M^+ + 1, 100). HRMS (ESI) calcd for $C_{12}H_{13}F_3NO_2^+$: 260.0893 $[M + H]^+$. Found: 260.0886.

Cis-1-(4-methoxybenzyl)-3-methyl-4-(trifluoromethyl)azetidin-2-one 11b



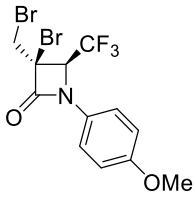
White solid. Mp 46 °C. Yield 87%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.34 (3H, d × q, J = 7.6, 1.6 Hz, CHC$\underline{H}_3$), 3.43 (1H, q × d, J = 7.6, 5.4 Hz, C$\underline{H}$CH$_3$), 3.80 (1H, q × d, J = 7.0, 5.4 Hz, $CHCF_3$), 3.81 (3H, s, OCH_3), 3.90 and 4.79 (2 × 1H, 2 × d, J = 15.0 Hz, ($\underline{H}$C$\underline{H}$)N), 6.88 and 7.18 (2 × 2H, 2 × d, J = 8.6 Hz, O(CH_{arom})$_{ortho}$ and NCH_2($C\underline{H}_{arom}$)$_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 8.9 (q, J = 1.6 Hz, CH$\underline{C}H_3$), 44.7 (Ar$\underline{C}H_2$N), 47.2 ($\underline{C}HCH_3$), 53.6 (q, J = 32.7 Hz, $\underline{C}HCF_3$), 55.3 (OCH_3), 114.3 (2 × O(HC_{arom})$_{ortho}$), 124.6 (q, J = 280.3 Hz, CF_3), 126.8 ($NCH_2\underline{C}_{arom,quat}$), 129.8 (2 × NCH_2($\underline{C}H_{arom}$)$_{ortho}$), 159.4 ($OC_{arom,quat}$), 169.2 (C=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -68.74 (3F, d, J = 7.0 Hz, CF_3). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1750, ν_{max} = 1514, 1248, 1131, 1034, 964, 828, 752, 659. MS (70eV): m/z (%): 121 (100), 274 (M^+ + 1, 10). HRMS (ESI) calcd for $C_{13}H_{15}F_3NO_2^+$: 274.1049 $[M + H]^+$. Found: 274.1055.

Synthesis of 3-bromo-3-bromomethyl-4-(trifluoromethyl)azetidin-2-ones 12-13

As a representative example, the synthesis of *cis*-3-bromo-3-bromomethyl-1-(4-methoxyphenyl)-4-(trifluoromethyl)azetidin-2-one **12a** is described. Pyridine (0.02 mL, 1 equiv) was added to a solution of 1-(4-methoxyphenyl)-3-methylene-4-(trifluoromethyl)azetidin-2-one **5a** (0.05 g, 0.19 mmol, 1 equiv) in dry CH_2Cl_2 (7 mL) under a nitrogen atmosphere, then an excess of bromine was slowly added. The reaction was stirred for four hours at room temperature. The mixture was quenched with water (10 mL) and extracted with dichloromethane (3 x 7 mL), the combined organic phases were washed with brine (2 x 10 mL). Drying ($MgSO_4$), filtration of the drying agent, and removal of the solvent *in vacuo* afforded *cis*-3-bromo-3-bromomethyl-1-(4-methoxyphenyl)-4-

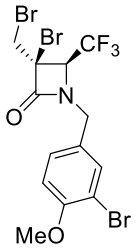
(trifluoromethyl)azetidin-2-one **12a** (74%), which was further purified by means of column chromatography (PE/EtOAc, 15/1) in order to obtain an analytically pure compound.

***Cis*-3-bromo-3-bromomethyl-1-(4-methoxyphenyl)-4-(trifluoromethyl)azetidin-2-one 12a**



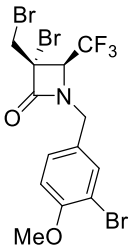
Brown oil. R_f = 0.10 (PE/EtOAc, 15/1). Yield 74%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.81 (3H, s, OCH_3), 3.93 and 4.09 (2 × 1H, 2 × d, J = 11.3 Hz, BrC(HCH)Br), 4.87 (1H, q, J = 5.7 Hz, $CHCF_3$), 6.92 and 7.38 (2H, 2 × d, J = 9.0 Hz, $O(CH_{arom})_{ortho}$ and $N(CH_{arom})_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 32.6 ($BrCCH_2Br$), 55.5 (OCH_3), 57.9 ($BrCCH_2Br$), 60.7 (q, J = 34.1 Hz, $CHCF_3$), 114.6 (2 × $O(CH_{arom})_{ortho}$), 121.0 (2 × $N(CH_{arom})_{ortho}$), 122.8 (q, J = 281.0 Hz, CF_3), 127.8 ($NC_{arom,quat}$),158.2 ($OC_{arom,quat}$), 160.1 (C=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -67.48 (3F, d, J = 5.7 Hz, CF_3). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1776, ν_{max} = 1510, 1389, 1248, 1169, 1142, 1028, 831, 557, 523. GC-MS: *m/z* (%) = 257 (84), 203 (31), 188 (16), 149 (100), 134 (65).

***Cis*-3-bromo-1-(3-bromo-4-methoxybenzyl)-3-bromomethyl-4-(trifluoromethyl)azetidin-2-one 12b**



Yellowish crystals. Mp 96 °C. R_f = 0.25 (PE/EtOAc, 15/1). Yield 23%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.78 (1H, d, J = 11.4 Hz, BrC(HCH)Br), 3.91 (3H, s, OCH_3), 3.94 (1H, d, J = 15.0 Hz, (HCH)N), 3.97 (1H, d, J = 11.4 Hz, BrC(HCH)Br), 4.23 (1H, q, J = 6.1 Hz, $CHCF_3$), 4.85 (1H, d, J = 15.0 Hz, (HCH)N), 6.87 (1H, d, J = 8.5 Hz, $O(CH_{arom})_{ortho}$), 7.25 (1H, d × d, J = 8.5, 2.2 Hz, $O(CH_{arom})_{meta}$) and 7.55 (1H, d, J = 2.2 Hz, $NCH_2(CH_{arom})_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 32.0 ($BrCCH_2Br$), 45.2 ($ArCH_2N$), 56.3 (OCH_3), 58.0 ($BrCCH_2Br$), 59.0 (q, J = 34.2 Hz, $CHCF_3$), 111.8, 111.9 (2 × $O(CH_{arom})_{ortho}$), 122.8 (q, J = 279.0 Hz, CF_3), 126.4 ($NCH_2C_{arom,quat}$), 129.6 ($OCH_{arom,meta}$), 134.2 ($NCH_2(CH_{arom})_{ortho}$), 156.1 ($OC_{arom,quat}$), 162.2 (C=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -68.29 (3F, d, J = 6.1 Hz, CF_3). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1786, ν_{max} = 1497, 1391, 1285, 1252, 1163, 1109, 1053, 1018, 970, 941, 814, 754, 691, 627, 596, 554, 486, 436, 409. GC-MS: *m/z* (%) = 509 (M^+, 6), 351 (12), 270 (16), 201 (100), 105 (9), 77 (19).

Trans-3-bromo-1-(3-bromo-4-methoxybenzyl)-3-bromomethyl-4-(trifluoromethyl)azetidin-2-one 13b

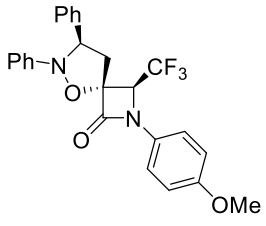


White crystals. Mp 110 °C. R_f = 0.27 (PE/EtOAc, 15/1). Yield 36%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.88 (1H, d, J = 12.1 Hz, BrC(HCH)Br), 3.92 (3H, s, OCH_3), 3.929 (1H, d, J = 12.1 Hz, BrC(HCH)Br), 3.933 (1H, d, J = 15.1 Hz, (HCH)N), 4.14 (1H, q, J = 6.4 Hz, $CHCF_3$), 4.88 (1H, d, J = 15.1 Hz, (HCH)N), 6.91 (1H, d, J = 8.4 Hz, $O(CH_{arom})_{ortho}$), 7.19 (1H, d × d, J = 8.4, 2.1 Hz, $O(CH_{arom})_{meta}$) and 7.45 (1H, d, J = 2.1 Hz, $NCH_2(CH_{arom})_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 30.2 (q, J = 2.5 Hz, BrCCH$_2$Br), 44.8 (ArCH$_2$N), 56.3 (OCH_3), 63.3 (BrCCH$_2$Br), 64.8 (q, J = 34.3 Hz, CHCF$_3$), 112.2, 112.3 (2 × $O(HC_{arom})_{ortho}$), 124.3 (q, J = 281.3 Hz, CF_3), 126.1 ($NCH_2C_{arom,quat}$), 128.8 ($O(CH_{arom})_{meta}$), 133.4 ($NCH_2(CH_{arom})_{ortho}$), 156.2 ($OC_{arom,quat}$), 162.6 (C=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -68.37 (3F, d, J = 6.4 Hz, CF_3). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1778, ν_{max} = 1497, 1396, 1285, 1250, 1184, 1171, 1128, 1109, 1053, 968, 939, 883, 814, 706, 683, 619, 596, 554, 507, 434, 403. GC-MS: *m/z* (%) = 511 (M^+, 3), 349 (11), 270 (15), 199 (100), 105 (11), 77 (22).

Synthesis of 3-trifluoromethyl-5-oxa-2,6-diazaspiro[3.4]octan-1-ones 14

As a representative example, the synthesis of (*3S**,*4R**,*7R**)-6-*tert*-butyl-2-(4-methoxybenzyl)-7-phenyl-3-trifluoromethyl-5-oxa-2,6-diazaspiro[3.4]octan-1-one **14d** is described. *N*-*tert*-butyl-α-phenylnitrone (0.07 g, 0.42 mmol, 1.4 equiv) was added to a solution of 1-(4-methoxybenzyl)-3-methylene-4-(trifluoromethyl)azetidin-2-one **5b** (0.08 g, 0.30 mmol, 1 equiv) in dry toluene (7 mL). The mixture was stirred for 47 hours at reflux temperature. After completion of the reaction, the reaction mixture was extracted with EtOAc (3 × 10 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent *in vacuo* afforded 6-*tert*-butyl-2-(4-methoxybenzyl)-7-phenyl-3-trifluoromethyl-5-oxa-2,6-diazaspiro[3.4]octan-1-one **14d** (43%), which was purified by means of flash chromatography on silica gel (PE/EtOAc, 20/1) to obtain an analytically pure sample.

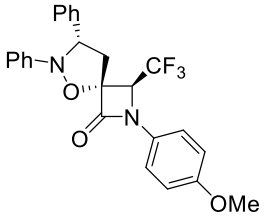
(3*S**,4*R**,7*R**)-2-(4-Methoxyphenyl)-6,7-diphenyl-3-trifluoromethyl-5-oxa-2,6-diazaspiro[3.4]octan-1-one 14a



White crystals. Mp 135 °C. Recrystallization in Et_2O. Yield 57%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.96 (1H, d × d, J = 13.4, 9.0 Hz, PhCH(HCH)), 3.19 (1H, d × d, J = 13.4, 6.7 Hz, PhCH(HCH)), 3.81 (3H, s, OCH_3), 4.73 (1H, d × d, J = 9.0, 6.7 Hz, PhCHCH$_2$), 4.79 (1H, q, J = 6.0 Hz, $CHCF_3$), 6.92 (2H, d, J = 9.0 Hz, $N(CH_{arom})_{ortho}$), 7.03-7.07 (3H, m, CH_{arom}), 7.18-7.22 (2H, m, CH_{arom}), 7.31-7.38 (3H, m, CH_{arom}), 7.39 (2H, d, J = 9.0 Hz, $O(CH_{arom})_{ortho}$), 7.45-7.47 (2H, m,

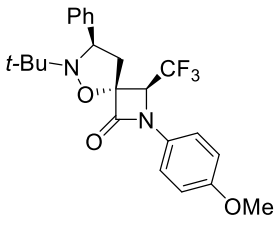
CH_{arom}). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 41.4 (q, J = 1.5 Hz, PhCH<u>C</u>H_2), 55.5 (OCH_3), 63.9 (q, J = 33.1 Hz, <u>C</u>HCF_3), 71.2 (Ph<u>C</u>HCH_2), 91.3 (<u>C</u>CHCF_3), 114.5 (2 × O(CH_{arom})$_{ortho}$), 118.7, 120.6 (2 × CH_{arom}), 123.4 (q, J = 281.2 Hz, CF_3), 124.7, 127.2 (2 × CH_{arom}), 128.3, 128.67 (2 × CH_{arom}), 128.74 ($NC_{arom,quat}$), 129.0 (2 × N(CH_{arom})$_{ortho}$), 138.0 (CH<u>C</u>$_{arom,quat}$), 149.3 ($ONC_{arom,quat}$), 157.6 ($OC_{arom,quat}$), 164.4 (C=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -69.00 (3F, d, J = 6.0 Hz, CF_3). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1760, ν_{max} = 1515, 1396, 1256, 1140, 1079, 1027, 688. MS (70eV): m/z (%): 182 (100%), 455 (M^+ + 1, 50). HRMS (ESI) calcd for $C_{25}H_{22}F_3N_2O_3^+$: 455.1577 $[M + H]^+$. Found: 455.1586.

(3*S,4*R**,7*S**)-2-(4-Methoxyphenyl)-6,7-diphenyl-3-trifluoromethyl-5-oxa-2,6-diazaspiro[3.4]octan-1-one**



Yellow sticky oil. Yield 13% (HPLC). ^1H NMR (400 MHz, $CDCl_3$): δ 3.00 (1H, d × d, J =13.6, 8.0 Hz, PhCH(<u>H</u>CH)), 3.24 (1H, d × d, J = 13.6, 7.7 Hz, PhCH(HC<u>H</u>)), 3.81 (3H, s, OCH_3), 4.70 (1H, t, J = 7.8 Hz, PhC<u>H</u>CH_2), 4.71 (1H, q, J = 5.8 Hz, $CHCF_3$), 6.91 (2H, d, J = 9.0 Hz, O(CH_{arom})$_{ortho}$), 6.98-7.02 (3H, m, CH_{arom}), 7.20-7.24 (2H, m, CH_{arom}), 7.30-7.34 (1H, m, CH_{arom}), 7.39 (1H, d, J = 9.0 Hz, N(CH_{arom})$_{ortho}$), 7.37-7.41 (2H, m, CH_{arom}), 7.54-7.56 (2H, m, CH_{arom}). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 41.2 (q, J = 1.0 Hz, PhCH<u>C</u>H_2), 55.5 (OCH_3), 64.2 (q, J = 32.9 Hz, <u>C</u>HCF_3), 69.0 (Ph<u>C</u>HCH_2), 91.6 (<u>C</u>CHCF_3), 114.5 (2 × O(CH_{arom})$_{ortho}$), 116.6, 120.5 (2 × CH_{arom}), 123.4, 123.6 (q, J = 281.5 Hz, CF_3), 127.2 (2 × CH_{arom}), 128.2, 128.77 (2 × CH_{arom}), 128.82 ($NC_{arom,quat}$), 129.0 (2 × N(CH_{arom})$_{ortho}$), 139.1 (CH<u>C</u>$_{arom,quat}$), 149.4 ($ONC_{arom,quat}$), 157.6 ($OC_{arom,quat}$), 163.6 (C=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -68.78 (3F, d, J = 5.8 Hz, CF_3). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1773, ν_{max} = 1510, 1389, 1248, 1136, 1028, 835, 756, 692, 525. MS (70eV): *m/z* (%): 182 (100%), 455 (M^+ + 1, 20). HRMS (ESI) calcd for $C_{25}H_{22}F_3N_2O_3^+$: 455.1577 $[M + H]^+$. Found: 455.1589.

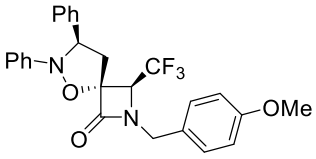
(3*S,4*R**,7*R**)-6-*Tert*-butyl-2-(4-methoxyphenyl)-7-phenyl-3-trifluoromethyl-5-oxa-2,6-diazaspiro[3.4]octan-1-one 14b**



White crystals. Mp 175 °C. Recrystallization from Et_2O. Yield 49%. ^1H NMR (400 MHz, $CDCl_3$): δ 1.04 (9H, s, C(C<u>H</u>$_3$)$_3$), 2.78 (1H, d × d, J = 13.3, 10.4 Hz, PhCH(<u>H</u>CH)), 3.00 (1H, d × d, J = 13.3, 6.8 Hz, PhCH(HC<u>H</u>)), 3.80 (3H, s, OCH_3), 4.47 (1H, d × d, J = 10.4, 6.8 Hz, PhC<u>H</u>CH_2), 4.66 (1H, q, J = 6.0 Hz, $CHCF_3$), 6.91 (2H, d, J = 9.0 Hz, O(CH_{arom})$_{ortho}$), 7.24-7.28 and 7.31-7.34 (3H, 2 × m, CH_{arom}), 7.39 (2H, d, J = 9.0 Hz, N(CH_{arom})$_{ortho}$), 7.45-7.47 (2H, 2 × m,

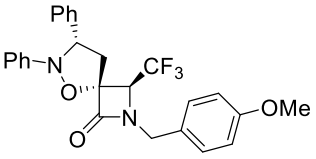
CH_{arom}). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 26.4 C($\underline{C}H_3)_3$), 43.8 (q, J = 2.4 Hz, PhCH$\underline{C}H_2$), 55.5 (OCH_3), 59.9 ($\underline{C}(CH_3)_3$), 63.9 (Ph$\underline{C}$HCH$_2$), 64.1 (q, J = 32.7 Hz, $\underline{C}HCF_3$), 90.5 ($\underline{C}CHCF_3$), 114.4 (2 × O$(CH_{arom})_{ortho}$), 120.5 ($NC_{arom,quat}$), 123.5 (q, J = 281.3 Hz, CF_3), 127.2, 127.7, 128.7 (5 × CH_{arom}), 129.0 (2 × N$(CH_{arom})_{ortho}$), 140.9 (CH$\underline{C}_{arom,quat}$), 157.4 ($OC_{arom,quat}$), 165.3 (C=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -68.87 (3F, d, J = 6.0 Hz, CF_3). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1751, ν_{max} = 1514, 1392, 1250, 1163, 1136, 1134, 829, 766, 731, 702, 521. MS (70eV): m/z (%): 435 (M^+ + 1, 100). HRMS (ESI) calcd for $C_{23}H_{26}F_3N_2O_3^+$: 435.1890 $[M + H]^+$. Found:435.1902.

(3*S,4*R**,7*R**)-2-(4-Methoxybenzyl)-6,7-diphenyl-3-trifluoromethyl-5-oxa-2,6-diazaspiro[3.4]octan-1-one 14c**



White crystals. Mp 104 °C. Recrystallization from Et_2O. Yield 50%. ^1H NMR (400 MHz, $CDCl_3$): δ 2.83 (1H, d × d, J = 13.5, 8.9 Hz, PhCH($\underline{H}$CH)), 3.10 1H, d × d, J = 13.5, 6.9 Hz, PhCH(HC$\underline{H}$)), 3.82 (3H, s, OCH_3), 3.97 (1H, d, J = 15.0 Hz,($\underline{H}$CH)N), 4.09 (1H, q, J = 6.5 Hz , $CHCF_3$), 4.66 (1H, d × d, J = 8.9, 6.9 Hz, PhC$\underline{H}$CH$_2$), 4.90 (1H, d, J = 15.0 Hz,(HC$\underline{H}$)N), 6.91 (2H, d, J = 8.7 Hz, O$(CH_{arom})_{ortho}$), 7.03-7.06 (3H, m, CH_{arom}), 7.18-7.23 (2H, m, CH_{arom}), 7.22 (2H, d, J = 8.7 Hz, $NCH_2(C\underline{H}_{arom})_{ortho}$), 7.28-7.36 (3H, m, CH_{arom}), 7.39-7.42 (2H, m, CH_{arom}). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 41.2 (PhCH$\underline{C}$H$_2$), 44.9 (N$\underline{C}$H$_2$Ar), 55.3 (OCH_3), 62.4 (q, J = 32.9 Hz, $\underline{C}HCF_3$), 71.1 (Ph$\underline{C}$HCH$_2$), 91.6 ($\underline{C}CHCF_3$), 114.5 (2 × O$(CH_{arom})_{ortho}$), 118.7 (CH_{arom}), 123.5 (q, J = 283.9 Hz, CF_3), 124.7 (CH_{arom}), 125.8 ($NC_{arom,quat}$), 127.2, 128.2, 128.6, 128.9 (CH_{arom}), 129.8 (2 × N$(CH_{arom})_{ortho}$), 138.1 (CH$\underline{C}_{arom,quat}$), 149.4 (ON$C_{arom,quat}$), 159.6 ($OC_{arom,quat}$), 167.0 (C=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -70.13 (3F, d, J = 6.5 Hz, CF_3). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1773, ν_{max} = 1512, 1398, 1246, 1145, 1084, 1030, 754, 693. MS (70eV): m/z (%): 469 (M^+ + 1, 20). HRMS (ESI) calcd for $C_{26}H_{24}F_3N_2O_3^+$: 469.1734 $[M + H]^+$. Found: 469.1755.

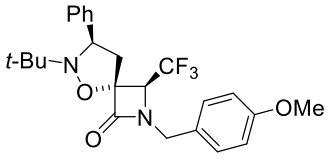
(3*S,4*R**,7*S**)-2-(4-Methoxybenzyl)-6,7-diphenyl-3-trifluoromethyl-5-oxa-2,6-diazaspiro[3.4]octan-1-one**



Colorless oil. Yield 10% (HPLC). ^1H NMR (400 MHz, $CDCl_3$): δ 2.89 (1H, d × d, J = 13.4, 7.9 Hz, PhCH($\underline{H}$CH)), 3.12 1H, d × d, J = 13.4, 7.9 Hz, PhCH(HC$\underline{H}$)), 3.83 (3H, s, OCH_3), 3.96 (1H, d, J = 15.2 Hz,($\underline{H}$CH)N), 4.02 (1H, q, J = 6.4 Hz , $CHCF_3$), 4.62 (1H, t, J = 7.9 Hz, PhC$\underline{H}$CH$_2$), 4.90 (1H, d, J = 15.2 Hz,(HC$\underline{H}$)N), 6.92 (2H, d, J = 8.7 Hz, O$(CH_{arom})_{ortho}$, 6.89-7.00 (3H, m, CH_{arom}), 7.15-7.19 (2H, m, CH_{arom}), 7.23 (2H, d, J = 8.7 Hz, $NCH_2(C\underline{H}_{arom})_{ortho}$), 7.29-7.33 and 7.35-7.39 (3H, 2 × m, CH_{arom}), 7.51-7.53 (2H, m, CH_{arom}) . ^{13}C NMR (100.6 MHz, $CDCl_3$): δ

40.7 (q, *J* = 1.7 Hz, PhCH<u>C</u>H$_2$), 45.0 (N<u>C</u>H$_2$Ar), 55.3 (OCH$_3$), 62.3 (q, *J* = 33.0 Hz, <u>C</u>HCF$_3$), 69.1 (Ph<u>C</u>HCH$_2$), 92.0 (<u>C</u>CHCF$_3$), 114.4 (2 × O(CH$_{arom}$)$_{ortho}$), 116.5 (CH$_{arom}$), 123.3 (CH$_{arom}$), 125.8 (NC$_{arom,quat}$), 125.9 (q, *J* = 284.6 Hz, CF$_3$), 127.1, 128.1, 128.7, 128.9 (CH$_{arom}$), 129.9 (O(CH$_{arom}$)$_{ortho}$), 139.2 (CH<u>C</u>$_{arom,quat}$), 149.5 (ONC$_{arom,quat}$), 159.6 (OC$_{arom,quat}$), 166.3 (C=O). ^{19}F NMR (376.5 MHz, CDCl$_3$): *δ* -70.08 (3F, d, *J* = 6.4 Hz, CF$_3$). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1783, ν_{max} = 1513, 1249, 1175, 758, 695. MS (70eV): m/z (%): 121 (100%), 182 (60%), 469 (M^+ + 1, 20). HRMS (ESI) calcd for $C_{26}H_{24}F_3N_2O_3^+$: 469.1734 $[M + H]^+$. Found: 469.1737.

(3*S,4*R**,7*R**)-6-*Tert*-butyl-2-(4-methoxybenzyl)-7-phenyl-3-trifluoromethyl-5-oxa-2,6-diazaspiro[3.4]octan-1-one 14d**



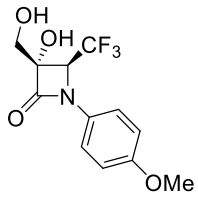
Yellowish crystals. Mp 89 °C. R_f = 0.25 (PE/EtOAc, 20/1). Yield 43%. ^{1}H NMR (400 MHz, CDCl$_3$): *δ* 1.02 (9H, s, C(C<u>H</u>$_3$)$_3$), 2.65 (1H, d × d, *J* = 12.8, 9.9 Hz, PhCH(<u>H</u>CH)), 2.92 (1H, d × d, *J* = 12.8, 6.7 Hz, PhCH(HC<u>H</u>)), 3.82 (3H, s, OCH$_3$), 3.96 (1H, d, *J* = 15.1 Hz, (<u>H</u>CH)N), 3.97 (1H, q, *J* = 6.4 Hz, CHCF$_3$), 4.39 (1H, d × d, *J* = 9.9, 6.7 Hz, PhC<u>H</u>CH$_2$), 4.84 (1H, d, *J* = 15.1 Hz, (HC<u>H</u>)N), 6.90 and 7.20 (2 × 2H, 2 × d, *J* = 8.6 Hz, O(CH$_{arom}$)$_{ortho}$ and NCH$_2$(C<u>H</u>$_{arom}$)$_{ortho}$), 7.23-7.32 (3H, m, CH$_{arom}$), 7.40-7.42 (2H, m, CH$_{arom}$). ^{13}C NMR (100.6 MHz, CDCl$_3$): *δ* 26.3 C(<u>C</u>H$_3$)$_3$), 43.6 (PhCH<u>C</u>H$_2$), 44.7 (N<u>C</u>H$_2$Ar), 55.3 (OCH$_3$), 59.8 (<u>C</u>(CH$_3$)$_3$), 62.9 (q, *J* = 32.5 Hz, <u>C</u>HCF$_3$), 63.7 (Ph<u>C</u>HCH$_2$), 90.8 (<u>C</u>CHCF$_3$), 114.3 (2 × O(CH$_{arom}$)$_{ortho}$), 123.6 (q, *J* = 280.3 Hz, CF$_3$), 126.1 (NCH$_2$<u>C</u>$_{arom,quat}$), 127.2, 127.6, 128.6 (5 × CH$_{arom}$), 129.7 (NCH$_2$(<u>C</u>H$_{arom}$)$_{ortho}$), 141.0 (CH<u>C</u>$_{arom,quat}$), 159.5 (OC$_{arom,quat}$), 168.0 (C=O). ^{19}F NMR (376.5 MHz, CDCl$_3$): *δ* -70.03 (3F, d, *J* = 6.4 Hz, CF$_3$). MS (70eV): *m/z* (%): 449 (M^+ + 1, 100). HRMS (ESI) calcd for $C_{24}H_{28}F_3N_2O_3^+$: 449.2047 $[M + H]^+$. Found: 449.2056.

Synthesis of 3-hydroxy-3-hydroxymethyl-4-(trifluoromethyl)azetidin-2-ones 15

As a representative example, the synthesis of *trans*-3-hydroxy-3-hydroxymethyl-1-(4-methoxybenzyl)-4-(trifluoromethyl)azetidin-2-one **15b** is described. *N*-methylmorpholine-*N*-oxide (0.11 g, 0.93 mmol, 2.5 equiv) and OsO_4 (10% mol, 0.22 mL, 4% in water) were added to a solution of 1-(4-methoxybenzyl)-3-methylene-4-(trifluoromethyl)azetidin-2-one **5b** (0.10 g, 0.37 mmol, 1 equiv) in THF-H_2O (1:1, 10 mL), and the mixture was stirred for 26 hours at room temperature. Subsequently, an aqueous saturated solution of $Na_2S_2O_3$ (1 mL) was added and the mixture was stirred for 10 min. The reaction mixture was filtered and the filtrate was extracted with ethyl acetate (3 x 15 mL). The combined extracts were washed with brine (2 x 10 mL). Drying $MgSO_4$, filtration of the drying agent and evaporation of the solvent *in vacuo* afforded *trans*-3-hydroxy-3-

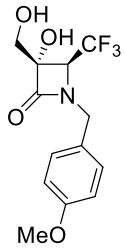
hydroxymethyl-1-(4-methoxybenzyl)-4-(trifluoromethyl)azetidin-2-one **15b** (92%), which was purified by recrystallization in Et_2O.

***Trans*-3-hydroxy-3-hydroxymethyl-1-(4-methoxyphenyl)-4-(trifluoromethyl)azetidin-2-one 15a**



White solid. Mp 151 °C. Recrystallization from Et_2O. Yield 87%. ^{1}H NMR (400 MHz, CD_3OD): δ 3.79 (3H, s, OCH_3), 3.93 and 3.98 (2 × 1H, 2 × d, J = 12.1 Hz, $C\underline{H}_2OH$), 4.66 (1H, q, J = 6.9 Hz, $CHCF_3$), 6.95 and 7.35 (2 × 2H, 2 × d, J = 9.0 Hz, $O(CH_{arom})_{ortho}$ and $N(CH_{arom})_{ortho}$). ^{13}C NMR (100.6 MHz, CD_3OD): δ 54.5 (OCH_3), 60.3 (q, J = 2.5 Hz, CH_2OH), 64.6 (q, J = 33.7 Hz, $\underline{C}HCF_3$), 86.7 (COH), 114.0 (2 × $O(CH_{arom})_{ortho}$), 121.0 (2 × $N(CH_{arom})_{ortho}$), 123.9 (q, J = 280.3 Hz, CF_3), 128.6 ($NC_{arom,quat}$), 157.8 ($OC_{arom,quat}$), 167.0 (C=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -68.16 (3F, d, J = 6.9 Hz, CF_3). IR (ATR, cm^{-1}): ν_{OH} = 3462, $\nu_{C=O}$ = 1735, ν_{max} = 1516, 1256, 1173, 1130, 1096, 1082, 1028, 997, 835, 808, 698. MS (70eV): m/z (%): 292 (M^+ + 1, 100). HRMS (ESI) for calcd for $C_{12}H_{13}F_3NO_4^+$: 292.0791. Found: 292.0801 $[M + H]^+$.

***Trans*-3-hydroxy-3-hydroxymethyl-1-(4-methoxybenzyl)-4-(trifluoromethyl)azetidin-2-one 15b**



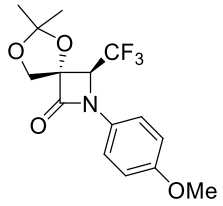
Colorless solid. Mp 93 °C. Recrystallization from Hex/Et_2O, 1/2. Yield 92%. ^{1}H NMR (400 MHz, CD_3OD): δ 3.81 (3H, s, OCH_3), 3.86 (1H, q, J = 7.4 Hz, $CHCF_3$), 3.87 and 3.90 (2 × 1H, 2 × d, J = 12.1 Hz, $H\underline{C}H\underline{O}H$), 4.09 and 4.74 (2 × 1H, 2 × d, J = 15.2 Hz, $H\underline{C}H\underline{N}$), 6.94 and 7.24 (2 × 2H, 2 × d, J = 8.7 Hz, $O(CH_{arom})_{ortho}$ and $NCH_2(C\underline{H}_{arom})_{ortho}$). ^{13}C NMR (100.6 MHz, CD_3OD): δ 44.2 (NCH_2), 54.3 (OCH_3), 60.3 (q, J = 2.1 Hz, CH_2OH), 63.2 (q, J = 33.8 Hz, $\underline{C}HCF_3$), 87.0 ($CH_2\underline{C}OH$), 113.8 (2 × $O(CH_{arom})_{ortho}$), 123.8 (q, J = 279.4 Hz, CF_3), 126.5 (2 × $NCH_2(\underline{C}H_{arom})_{ortho}$), 129.5 ($NCH_2\underline{C}_{arom,quat}$), 159.7 ($OC_{arom,quat}$), 169.6 (C=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -69.72 (3F, d, J = 7.4 Hz, CF_3). IR (ATR, cm^{-1}): ν_{OH} = 3433, $\nu_{C=O}$ = 1732, ν_{max} =1516, 1290, 1254, 1130, 1099, 1053, 1030, 885, 821, 698, 522, 438. MS (70eV): m/z (%): 306 (M^+ + 1, 100). HRMS (ESI) calcd for $C_{13}H_{15}F_3NO_4^+$: 306.0948. Found: 306.0944 [*M* + H]$^+$.

Synthesis of 6,6-dimethyl-3-trifluoromethyl-5,7-dioxa-2-azaspiro[3.4]octan-1-ones 16

As a representative example, the synthesis of *trans*-2-(4-methoxyphenyl)-6,6-dimethyl-3-trifluoromethyl-5,7-dioxa-2-azaspiro[3.4]octan-1-one **16a** is described. A solution of diol **15a** (0.05 g, 0.17 mmol, 1 equiv) and *p*-toluenesulfonic acid (0.03 g, 0.19 mmol, 1.1 equiv) in dimethoxypropane (3 mL) was heated for two hours at reflux temperature. The reaction mixture

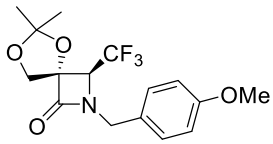
was cooled to room temperature and extracted with ethyl acetate (3 x 7 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent *in vacuo* afforded *trans*-2-(4-methoxyphenyl)-6,6-dimethyl-3-trifluoromethyl-5,7-dioxa-2-azaspiro[3.4]octan-1-one **16a** (95%), which was purified by recrystallization (Hex/Et_2O, 2/1) to obtain an analytically pure sample.

***Trans*-2-(4-methoxyphenyl)-6,6-dimethyl-3-trifluoromethyl-5,7-dioxa-2-azaspiro[3.4]octan-1-one 16a**



Brownish crystals. Mp 89 °C. Recrystallization in Hex/Et_2O, 2/1. Yield 95%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.50 and 1.53 (2 × 3H, 2 × s, C($C\underline{H}_3)_2$), 3.80 (3H, s, OCH_3), 4.37 (1H, d × q, J = 10.2, 0.6 Hz, C(HC$\underline{H}$)O), 4.43 (1H, d × q, J = 10.2, 1.3 Hz, C($\underline{H}$CH)O), 4.61 (1H, q, J = 6.1 Hz, $CHCF_3$), 6.90 and 7.35 (2 × 2H, 2 × d, J = 9.0 Hz, O($CH_{arom})_{ortho}$ and N($CH_{arom})_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 25.4 and 25.7 (C($\underline{C}H_3)_2$), 55.5 (OCH_3), 64.1 (q, J = 33.2 Hz, $\underline{C}HCF_3$), 65.2 (q, J = 3.2 Hz, $\underline{C}H_2OC$), 89.8 ($\underline{C}CHCF_3$), 112.4 (OCO), 114.5 (2 × O($CH_{arom})_{ortho}$), 120.5 (2 × N($CH_{arom})_{ortho}$), 123.5 (q, J = 280.7 Hz, CF_3), 128.7 ($NC_{arom,quat}$), 157.6 ($OC_{arom,quat}$), 164.9 (C=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -69.25 (3F, d, J = 6.1 Hz, CF_3). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1778, ν_{max} = 1499, 1398, 1285, 1252, 1171, 1128, 1110, 1055, 970, 814, 621, 596, 407. MS (70eV): m/z (%): 332 (M^+ + 1, 100). HRMS (ESI) calcd for $C_{15}H_{17}F_3NO_4^+$: 332.1104 $[M + H]^+$. Found: 332.1103.

***Trans*-2-(4-methoxybenzyl)-6,6-dimethyl-3-trifluoromethyl-5,7-dioxa-2-azaspiro[3.4]octan-1-one 16b**

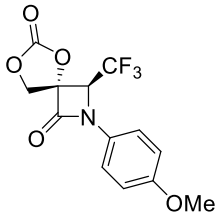


Yellow oil. R_f = 0.31 (Hex/Et_2O, 5/1). Yield 47%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.40 and 1.50 (2 × 3H, 2 × s, C($C\underline{H}_3)_2$), 3.81 (3H, s, OCH_3), 3.91 (1H, q, J = 6.6 Hz, $CHCF_3$), 3.92 (1H, d, J = 14.9 Hz, (HC$\underline{H}$)N), 4.28 (1H, d, J = 10.1 Hz, C($\underline{H}$CH)O), 4.32 (1H, d × q, J = 10.1, 1.3 Hz, C(HC$\underline{H}$)O), 4.87 (1H, d, J = 14.9 Hz, ($\underline{H}$CH)N), 6.90 and 7.19 (2 × 2H, 2 × d, J = 8.7 Hz, O($CH_{arom})_{ortho}$ and NCH_2($C\underline{H}_{arom})_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 25.49 and 25.51 (C($\underline{C}H_3)_2$), 44.8 (NCH_2), 55.3 (OCH_3), 62.2 (q, J = 32.9 Hz, $\underline{C}HCF_3$), 65.0 (q, J = 2.8 Hz, O$\underline{C}H_2$C), 90.0 ($\underline{C}CHCF_3$), 112.2 (OCO), 114.4 (2 × O($CH_{arom})_{ortho}$), 123.6 (q, J = 280.0 Hz, CF_3), 125.8 (NCH_2($\underline{C}_{arom,quat}$), 129.9 (2 × NCH_2(H$\underline{C}_{arom})_{ortho}$), 159.6 ($OC_{arom,quat}$), 167.4 (C=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -70.35 (3F, d, J = 6.6 Hz, CF_3). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1778, ν_{max} = 1514, 1285, 1246, 1167, 1150, 1069, 1032, 843, 691, 586, 511. MS (70eV): m/z (%): 346 (M^+ + 1, 100). HRMS (ESI) calcd for $C_{16}H_{19}F_3NO_4^+$: 346.1261 $[M + H]^+$. Found: 346.1268.

Synthesis of 3-trifluoromethyl-5,7-dioxa-2-azaspiro[3.4]octane-1,6-diones 17

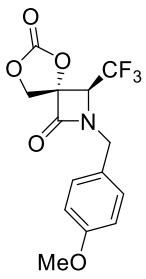
As a representative example, the synthesis of *trans*-2-(4-methoxybenzyl)-3-trifluoromethyl-5,7-dioxa-2-azaspiro[3.4]octane-1,6-dione **17b** is described. To a solution of diol **15b** (0.05 g, 0.16 mmol, 1 equiv) in dry dichloromethane (3 mL) at 0 °C was treated with pyridine (0.06 mL, 0.80 mmol, 5 equiv) and triphosgene (0.02 mL, 0.13 mmol, 0.80 equiv). The mixture was stirred for one hour at 0 °C, quenched with a saturated solution of NH_4Cl (1 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were washed with an aqueous solution of HCl (2 mL, 1 M) and brine (3 × 5 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure to obtained pure *trans*-2-(4-methoxybenzyl)-3-trifluoromethyl-5,7-dioxa-2-azaspiro[3.4]octane-1,6-dione **17b** in a yield of 97%.

Trans-2-(4-methoxyphenyl)-3-trifluoromethyl-5,7-dioxa-2-azaspiro[3.4]octane-1,6-dione 17a



Light-brown solid. Mp 116 °C. Yield 97%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.82 (3H, s, OCH_3), 4.81 (1H, d × q, J = 10.7, 1.3 Hz, C(HC<u>H</u>)O), 4.86 (1H, d, J = 10.7 Hz, C(<u>H</u>CH)O), 4.88 (1H, q, J = 5.7 Hz, $CHCF_3$), 6.94 and 7.36 (2 × 2H, 2 × d, J = 9.0 Hz, $O(CH_{arom})_{ortho}$ and $N(CH_{arom})_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 55.6 (OCH_3), 63.2 (q, J = 34.0 Hz, <u>C</u>HCF_3), 64.3 (q, J = 3.3 Hz, <u>C</u>H_2OC), 87.7 (<u>C</u>$CHCF_3$), 114.8 (2 × $O(CH_{arom})_{ortho}$), 120.8 (2 × $N(CH_{arom})_{ortho}$), 122.6 (q, J = 281.5 Hz, CF_3), 127.5 ($NC_{arom,quat}$), 151.4 (OC=O), 158.4 ($OC_{arom,quat}$), 159.1 (C=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -69.00 (3F, d, J = 5.7 Hz, CF_3). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1825, $\nu_{C=O}$ = 1763, ν_{max} = 1514, 1290, 1252, 1140, 1032, 839, 820, 760, 729, 700, 640, 523. MS (70eV): 335 [M^+ + 18]. HRMS (ESI) calcd for $C_{13}H_{11}F_3NO_5^+$: 318.0584. Found: 318.0575 [M + H]$^+$.

Trans-2-(4-methoxybenzyl)-3-trifluoromethyl-5,7-dioxa-2-azaspiro[3.4]octane-1,6-dione 17b



Yellowish solid. Mp 93 °C. Yield 97%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.82 (3H, s, OCH_3), 3.97 (1H, d, J = 15.0 Hz, N(<u>H</u>CH), 4.15 (1H, q, J = 6.1 Hz, $CHCF_3$), 4.69 (1H, d × q, J = 10.5, 1.2 Hz, C(<u>H</u>CH)O), 4.76 (1H, d, J = 10.5, C(HC<u>H</u>)O), 4.92 (1H, d, J = 15.0 Hz, N(HC<u>H</u>)), 6.92 and 7.19 (2 × 2H, 2 × d, J = 8.6 Hz, $O(CH_{arom})_{ortho}$ and $NCH_2(C\underline{H}_{arom})_{ortho}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 45.5 (NCH_2), 55.4 (OCH_3), 61.0 (q, J = 33.9 Hz, <u>C</u>HCF_3), 64.2 (q, J = 2.9 Hz, C<u>C</u>H_2O), 88.0 (<u>C</u>$CHCF_3$), 114.7 (2 × $O(CH_{arom})_{ortho}$), 122.7 (q, J = 280.5 Hz, CF_3), 124.4 ($NCH_2\underline{C}_{arom,quat}$), 129.9 (2 × $NCH_2(\underline{C}H_{arom})_{ortho}$), 151.5 (O(C=O)O), 160.0 ($OC_{arom,quat}$), 161.9 (C=O). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ -70.22 (3F, d,

J = 6.1 Hz, CF_3). IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1840, $\nu_{C=O}$ = 1773, ν_{max} = 1514, 1281, 1256, 1177, 1146, 1078, 1063, 1034, 947, 820, 752, 692, 586, 525. MS (70eV): 349 [M^+ + 18]. HRMS (ESI) calcd for $C_{14}H_{13}F_3NO_5^+$: 332.0740. Found: 332.0740 $[M + H]^+$.

Single crystal X-ray diffraction

X-ray analysis was performed by Prof. Kristof Van Hecke (XStruct, Department of Inorganic and Physical Chemistry, Faculty of Sciences, Ghent University).

For the structures of compounds **14b** and **16a**, X-ray intensity data were collected at 293 K and 100 K, respectively, on a Supernova Dual Source (Cu at zero) diffractometer equipped with an Atlas CCD detector using ω scans and CuKα (λ = 1.54184 Å) radiation. The images were interpreted and integrated with the program CrysAlisPro. Using Olex2, the structures were solved by direct methods using the ShelXS structure solution program and refined by full-matrix least-squares on F^2 using the ShelXL program package. Non-hydrogen atoms were anisotropically refined and the hydrogen atoms in the riding mode and isotropic temperature factors fixed at 1.2 times U(eq) of the parent atoms (1.5 times for methyl group).

CCDC 1529989-1529991 contains the supplementary crystallographic data for these molecules and can be obtained free of charge *via* www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44-1223-336033; or deposit@ccdc.cam.ac.uk).

Crystal data for compound 14b:

$C_{23}H_{25}F_3N_2O_3$, M = 434.45, monoclinic, space group $P2_1/c$ (No. 14), a = 19.5141(5) Å, b = 6.07188(13) Å, c = 18.6214(4) Å, β = 105.212(3)°, V = 2129.09(9) $Å^3$, Z = 4, T = 293 K, D_{calc} = 1.355 g cm^{-3} , μ(Cu-Kα) = 0.909 mm^{-1}, F(000) = 912, 31426 reflections measured, 4365 unique (R_{int} = 0.0798) which were used in all calculations. The final R_1 was 0.0552 (I >2σ (I)) and wR_2 was 0.1735 (all data). The asymmetric unit has chirality at C1(*S*), C3(*S*) and C14(*R*). Obviously, because of the centro-symmetric space group $P2_1/c$, also the inverse configuration is present in the crystal structure.

Crystal data for compound 16a:

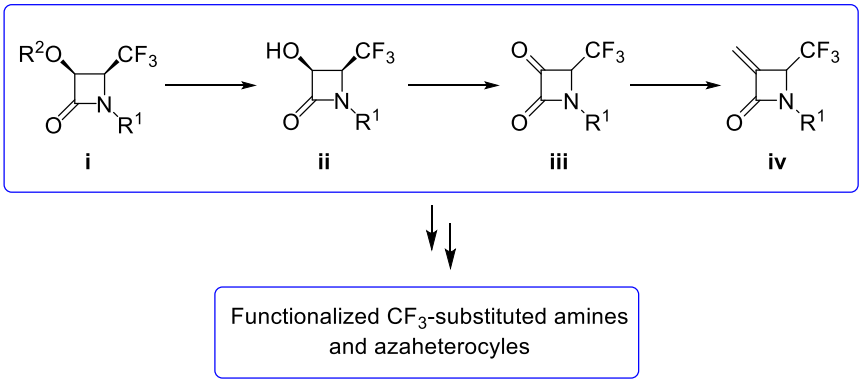
$C_{15}H_{16}F_3NO_4$, M = 331.29, monoclinic, space group $P2_1/c$ (No. 14), a = 16.0443(13) Å, b = 6.2322 (3) Å, c = 16.7935(11) Å, β = 115.517(10)°, V = 1515.4(2) $Å^3$, Z = 4, T = 100 K, D_{calc} = 1.452 g cm^{-3} , μ(Cu-Kα) = 1.120 mm^{-1}, F(000) = 688, 14467 reflections measured, 2957 unique (R_{int} =

0.1022) which were used in all calculations. The final R_1 was 0.0584 (I >2σ (I)) and wR_2 was 0.1763 (all data). The asymmetric unit has chirality at C1(*S*) and C6(*S*). Obviously, because of the centro-symmetric space group $P2_1/c$, also the inverse configuration is present in the crystal structure.

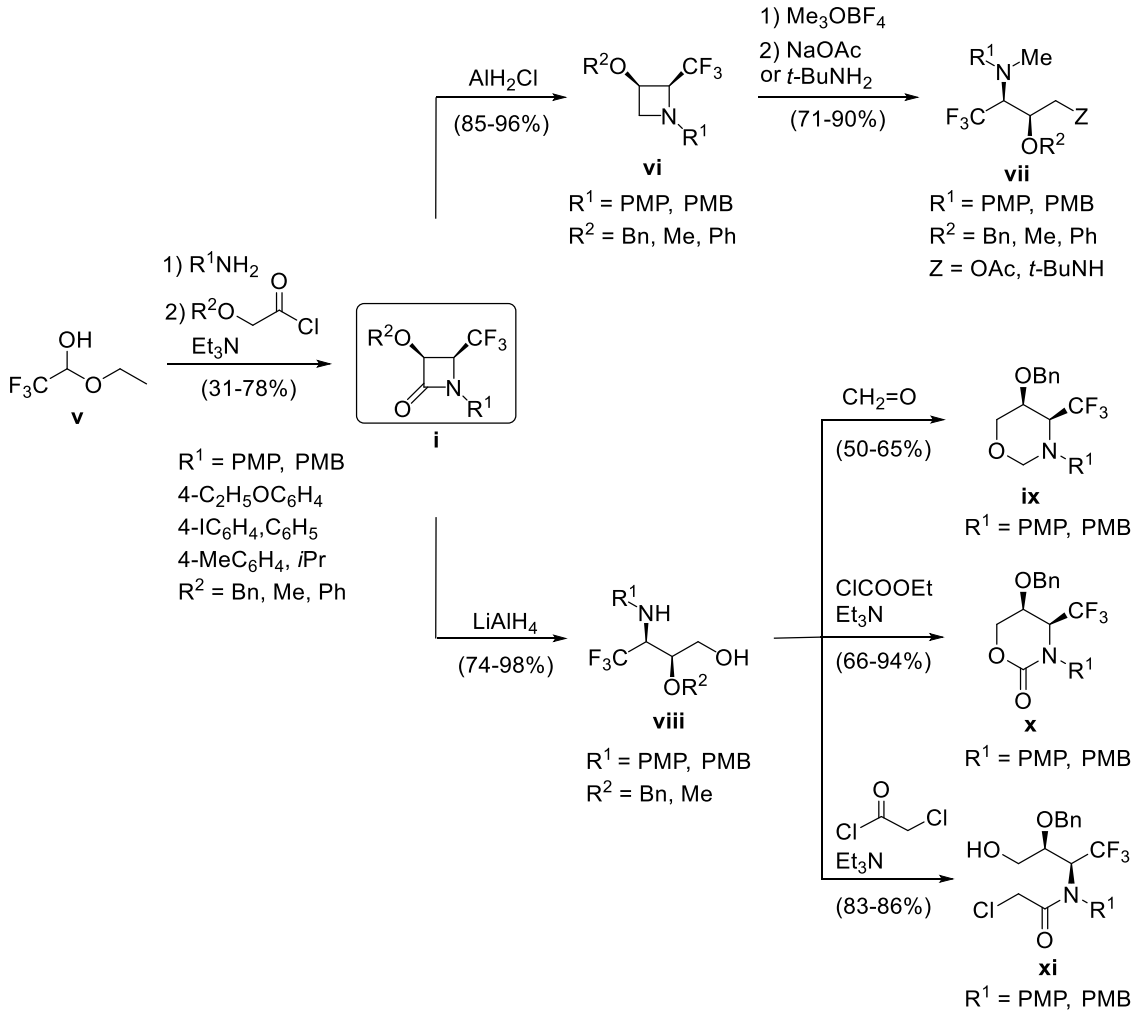
SUMMARY

In recent years, organofluorine compounds have been increasingly used in organic and medicinal chemistry. Indeed, the inclusion of fluorine into organic molecules is known to alter chemical and biological properties such as pKa, lipophilicity, metabolic stability and bioavailability. The increasing interest in fluorinated compounds has stimulated the development of novel methods to incorporate one or more fluorine atoms, for example a trifluoromethyl group, into organic molecules. The preparation of CF_3-substituted molecules can be accomplished by either the deployment of CF_3-containing building blocks or by using trifluoromethylating agents. However, the incorporation of a trifluoromethyl group into small molecules such as β-lactams or azetidine-2-ones has been accompanied with a considerable challenge to handle trifluoromethylating agents during the synthesis (harsh conditions, hazardous reactions…). Therefore, the building block approach has been deployed here as an efficient alternative.

In addition to their well-known pharmacological properties, β-lactams represent potential intermediates for organic synthesis due to the inherent strain of the four-membered ring, which allows for further elaboration toward a variety of nitrogen-containing acyclic and heterocyclic target compounds. In light of the pronounced effect of fluorine introduction, β-lactams containing a trifluoromethyl group can be considered as interesting entities for the construction of novel targets with promising applications. Nevertheless, the chemistry of CF_3-substituted β-lactams has not been explored as intensively as that of their lower homologs, CF_3-aziridines, which have already demonstrated their broad applicability as versatile building blocks through ring-opening and ring-transformation reactions. The synthesis and deployment of 4-trifluoromethyl-β-lactams **i**, **ii**, **iii**, **iv** as novel building blocks (fluorinated synthon approach) was accomplished in this PhD thesis, resulting in a broad spectrum of functionalized CF_3-amines and CF_3-azaheterocycles upon further synthetic manipulation.

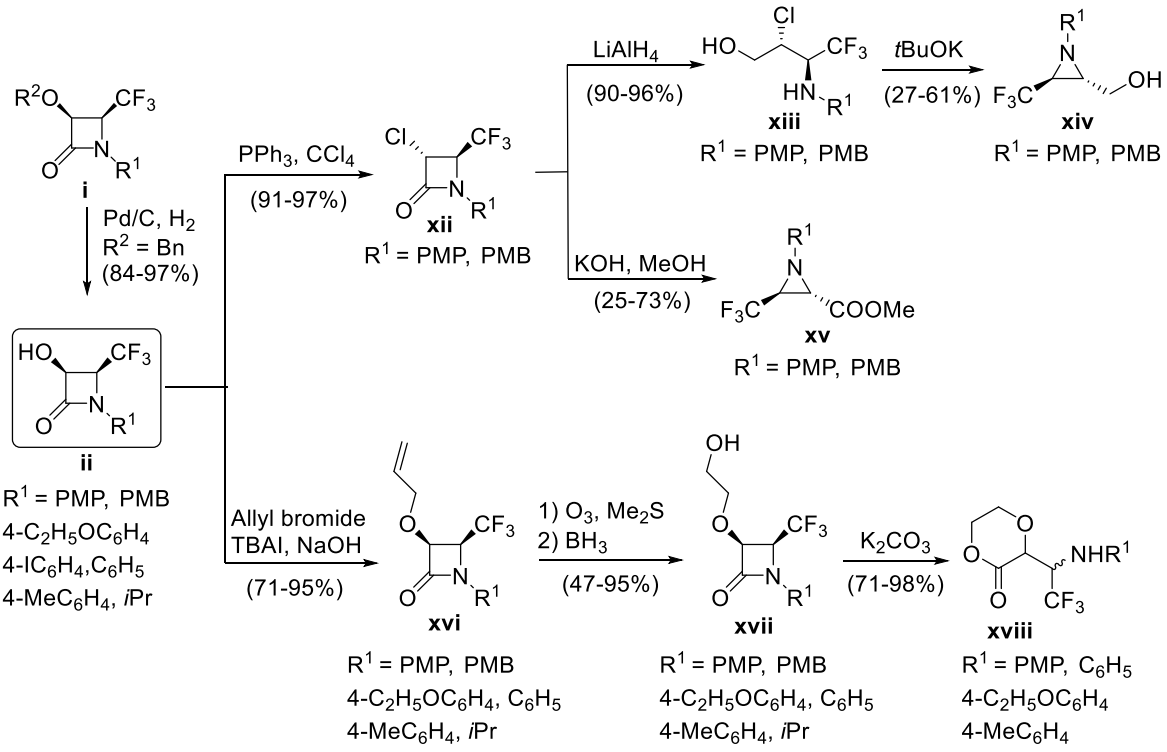


In the first part, 3-alkoxy/aryloxy-4-CF_3-azetidin-2-one **i** building blocks were efficiently prepared starting from commercially available 1-ethoxy-2,2,2-trifluoroethanol **v** *via* imination and subsequent Staudinger synthesis with alkyl/aryloxyacetyl chlorides. The synthetic potential of the resulting 4-CF_3-β-lactams **i** toward C2-N ring-opening reactions was evaluated based on an indirect or a direct approach. In the indirect approach, 4-CF_3-β-lactams **i** were subjected to initial carbonyl removal upon treatment with AlH_2Cl, providing azetidine intermediates **vi**. Activation of the latter azetidines **vi** by trimethyloxonium tetrafluoroborate and subsequent ring opening using different oxygen and nitrogen nucleophiles gave rise to a variety of functionalized α-(trifluoromethyl)amines **vii**. On the other hand, the direct reductive ring opening of 4-CF_3-β-lactams **i** was accomplished upon treatment with $LiAlH_4$, furnishing 3-aminopropan-1-ols **viii**. Cyclization of the latter γ-amino alcohols **viii** employing formaldehyde or ethyl chloroformate was evaluated leading to new 1,3-oxazinanes **ix** and 1,3-oxazinan-2-ones **x**, respectively. Besides that, attempts were made to synthesize 1,4-oxazepane analogs through cyclization of the corresponding amides **xi**, derived from 3-aminopropan-1-ols **viii** through *N*-acylation, albeit without success.

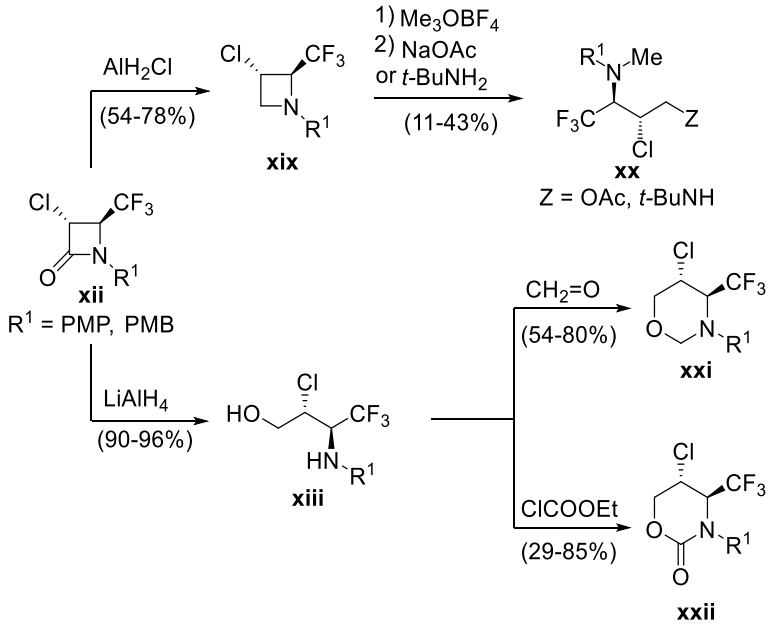


In the second part, a set of new 3-hydroxy-4-CF_3-β-lactams **ii** as a second type of building blocks was successfully synthesized from the corresponding 3-benzyloxy-4-CF_3-β-lactams **i** (R^2 = Bn) in high yields through hydrogenolysis. 2-Hydroxy-4-CF_3-β-lactams **ii** were shown to be suitable substrates 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 alcohols **ii** with Ph_3P in CCl_4 afforded *trans*-3-chloro-4-CF_3-β-lactams **xii**. The $LiAlH_4$-mediated reductive ring opening of chlorides **xii** provided γ-amino alcohols **xiii** in high yields (90-96%). The latter alcohols **xiii** were subjected to *t*BuOK-induced ring closure, furnishing 3-trifluoromethylated 2-(hydroxymethyl) aziridines **xiv** in 27-61% yield. On the other hand, direct treatment of chlorides **xii** with KOH in methanol resulted in the corresponding aziridine-2-carboxylates **xv** in 25-73% yield.

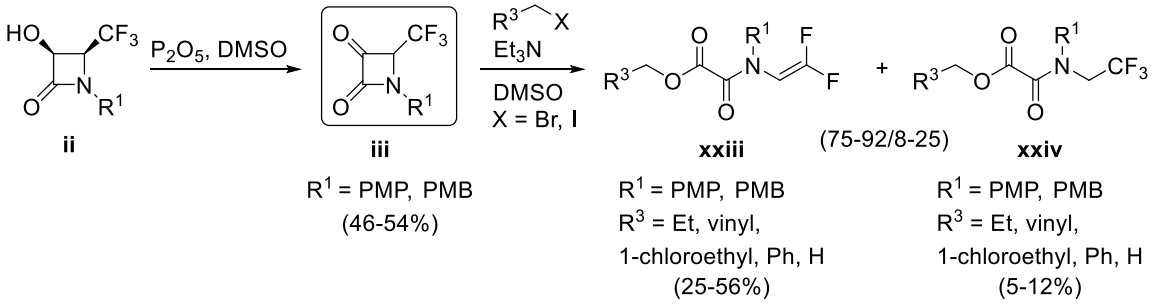
Furthermore, alcohols **ii** proved to be suitable substrates for the synthesis of novel 3-[2,2,2-trifluoro-1-(arylamino)ethyl]-1,4-dioxan-2-ones **xviii** in high yields *via* intramolecular cyclization of 3-(2-hydroxyethoxy)-β-lactam intermediates **xvii** upon treatment with an excess of K_2CO_3. The 3-(2-hydroxyethoxy)-β-lactams **xvii** were prepared from allyloxy products **xvi** through an ozonolysis reaction, followed by a reduction sequence with Me_2S and BH_3.



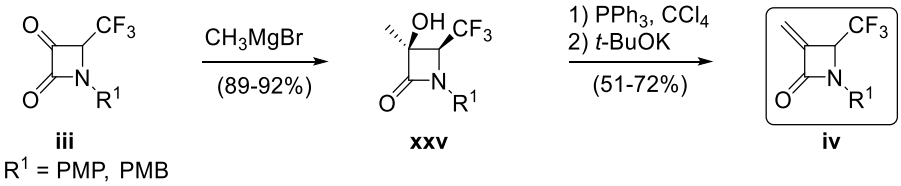
In analogy with 4-CF_3-azetidin-2-ones **i**, 3-chloro-4-CF_3-β-lactams **xii** were shown to be eligible substrates for the preparation of new α-CF_3-substituted aminopropane derivatives **xx**. Ring opening of azetidine intermediates **xix**, derived from chlorides **xii**, was performed by treatment with sodium acetate or *tert*-butylamine. In addition, the cyclization of amino alcohols **xiii** with formaldehyde and ethyl chloroformate also furnished the corresponding new functionalized 1,3-oxazinanes **xxi** and 1,3-oxazinan-2-ones **xxii**.



In the next part, the oxidation of alcohols **ii** using P_2O_5/DMSO gave rise to 3-oxo-4-(trifluoromethyl)azetidin-2-ones **iii** as a third class of new building blocks. Ring opening of 3-oxo-β-lactams **iii** through C3-C4 bond fission was unexpectedly observed in attempts to form and trap the corresponding 2,3-dioxoazetidin-4-yl anions, resulting in 2-[(2,2-difluorovinyl)amino]-2-oxoacetates **xxiii** as major products (25-56%) accompanied by minor amounts of 2-oxo-2-[(2,2,2-trifluoroethyl)amino]acetates **xxiv** (5-12%) upon treatment with alkyl halides and triethylamine in DMSO. This extraordinary 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.



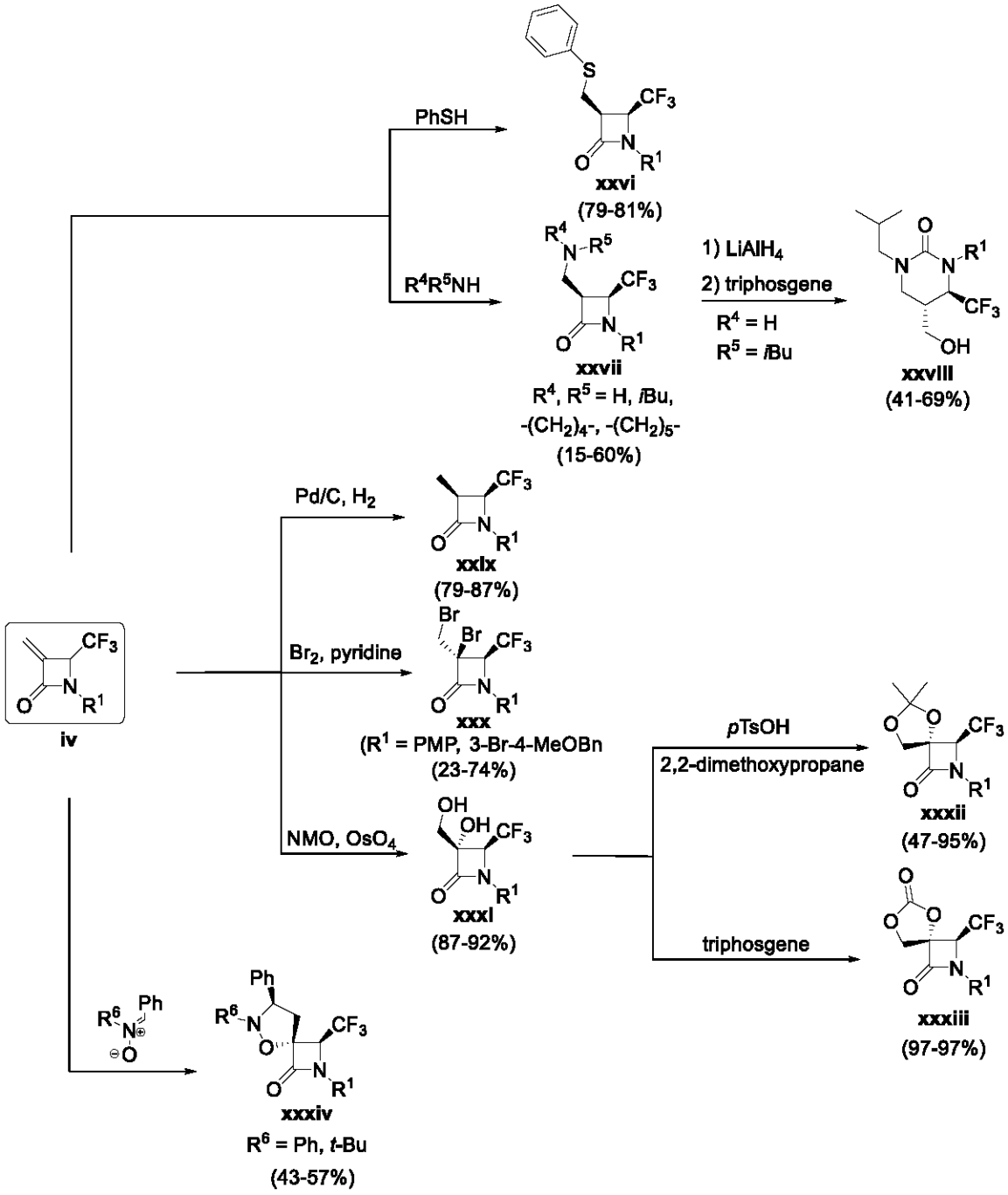
In the final part of this PhD thesis, treatment of azetidine-2,3-diones **iii** with methylmagnesium bromide provided tertiary alcohols **xxv** in excellent yields. Subsequently, these alcohols **xxv** were treated with PPh_3 in CCl_4 to prepare the corresponding intermediate chlorides, followed by microwave-assisted dehydrochlorination by means of KO*t*Bu in DMSO, to furnish 3-methylene-4-(trifluoromethyl)azetidin-2-ones **iv** in good yields as a fourth new class of β-lactam building blocks for further elaborations.



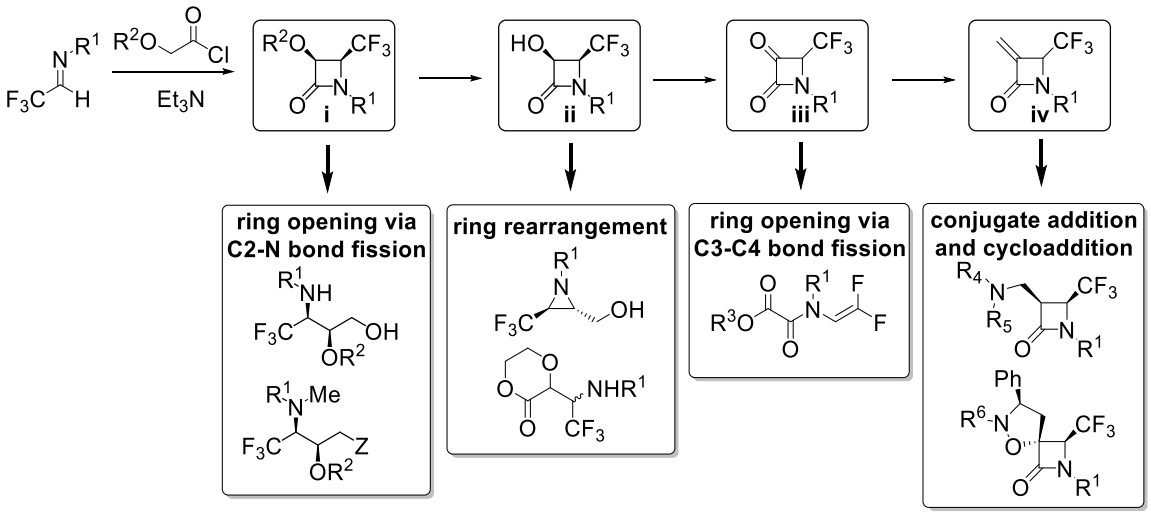
The presence of an exocyclic carbon-carbon double bond in 3-methylene-4-(trifluoromethyl)azetidin-2-ones **iv** allowed for the deployment of different synthetic strategies. In particular, the Michael addition of sulfur and nitrogen nucleophiles onto 4-CF_3-β-lactams **iv** furnished the corresponding 3-phenylthiomethyl-4-(trifluoromethyl)azetidin-2-ones **xxvi** and 3-aminomethyl-4-(trifluoromethyl)azetidin-2-ones **xxvii**. 3-Isobutylaminomethyl-β-lactams **xxvi** were then selected for further elaboration, involving reductive β-lactam ring opening using $LiAlH_4$, followed by cyclization with triphosgene, leading to new 4-CF_3-tetrahydropyrimidin-2-ones **xxviii** in good yields. The aptitude of 3-methylene-4-trifluoromethyl-β-lactams **iv** to undergo classical addition reactions across the C-C double bond was also investigated. First, hydrogenation of 3-methylene-4-(trifluoromethyl)azetidin-2-ones **iv** on Pd/C provided a selective access to 3-methyl-4-(trifluoromethyl)azetidin-2-ones **xxix** in good yields. Furthermore, electrophilic bromine addition to 4-CF_3-β-lactams **iv** in the presence of pyridine resulted in 3-bromo-3-bromomethyl-4-(trifluoromethyl)azetidin-2-ones **xxx**. In addition, 3-trifluoromethyl-5,7-dioxa-2-azaspiro[3.4]octan-1-ones **xxxii** and 3-trifluoromethyl-5,7-dioxa-2-azaspiro[3.4]octane-1,6-diones **xxxiii** were prepared upon treatment of the corresponding diols **xxxi**, derived from the OsO_4-mediated oxidation of 3-methylene-β-lactams **iv**, with *p*TsOH in 2,2-dimethoxypropane and with triphosgene, respectively.

Furthermore, 4-CF_3-β-lactams **iv** were shown to be susceptible to 1,3-dipolar nitrone-olefin cycloaddition reactions to generate isoxazolidine systems. Treatment of 3-methylene-β-lactams **iv** with either *N*-phenyl- or *N*-*tert*-butyl-α-phenylnitrone afforded a convenient entry to 7-phenyl-3-

trifluoromethyl-5-oxa-2,6-diazaspiro[3.4]octan-1-ones **xxxiv**, which were assigned as (3*S**,4*R**,7*R**)-isomers by means of single crystal X-ray analysis.



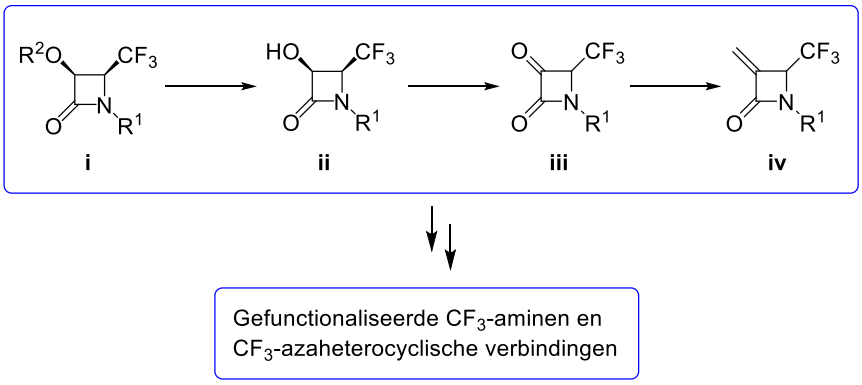
In conclusion, a set of four new 4-trifluoromethyl-β-lactam building blocks was successfully synthesized in this PhD thesis. These compounds have been shown to be powerful substrates for ring-opening reactions, ring-rearrangement reactions, Michael additions, electrophilic additions and cycloadditions *en route* to a broad variety of functionalized CF_3-amines and CF_3-azaheterocycles. In light of the fascinating properties of the CF_3 group introduction, 4-CF_3-β-lactams can indeed be considered as very promising structures for further development in the field of medicinal chemistry and chemical biology.



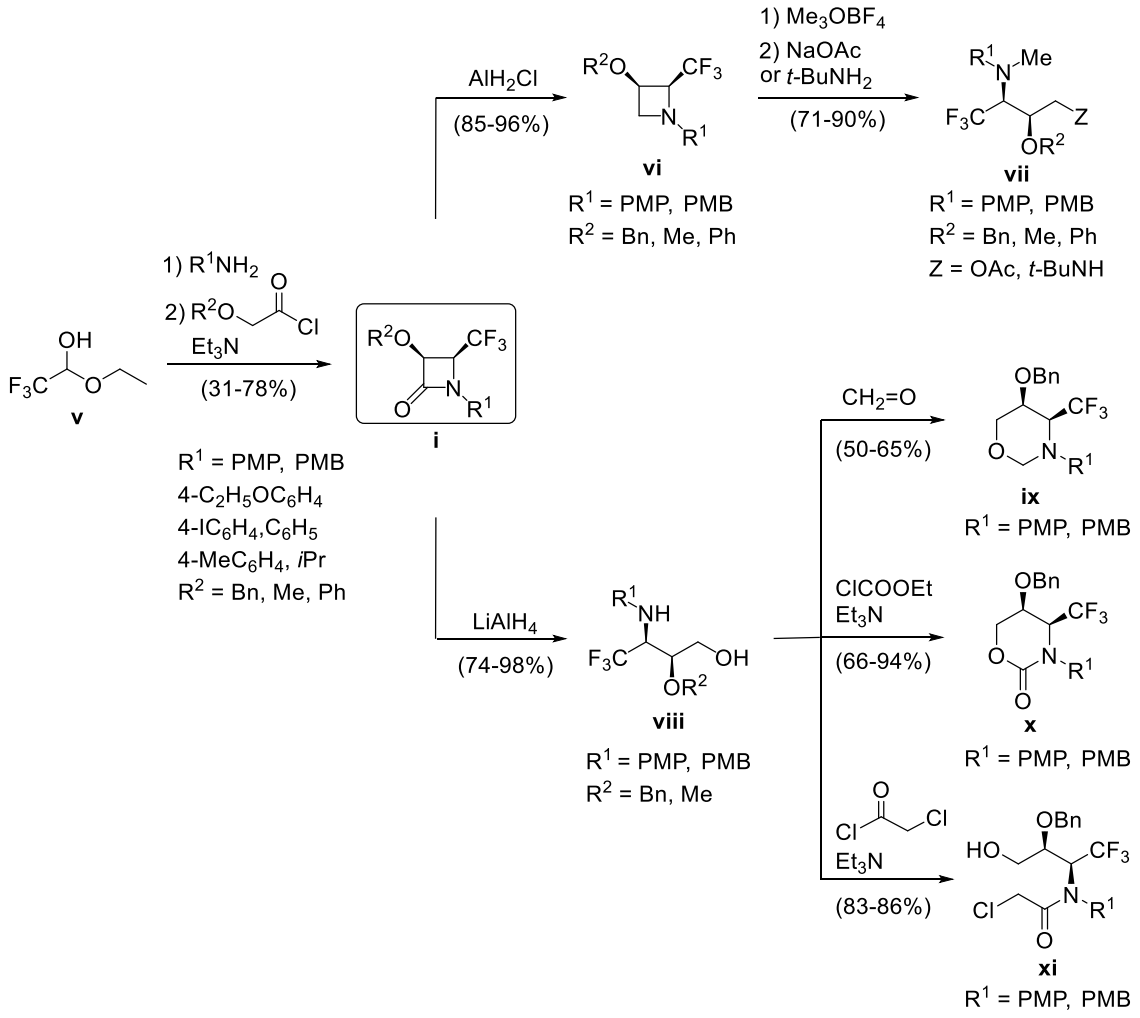
SAMENVATTING

Organofluorverbindingen worden steeds meer gebruikt in de organische en medicinale chemie. Het incorporeren van fluor in organische moleculen beïnvloedt chemische en biologische eigenschappen zoals pKa, lipofiliciteit, metabolische stabiliteit en biologische beschikbaarheid. De toenemende interesse in gefluoreerde verbindingen heeft de ontwikkeling van nieuwe methoden om één of meerdere fluoratomen, bijvoorbeeld een trifluormethylgroep, in organische moleculen te introduceren, gestimuleerd. De bereiding van CF_3-gesubstitueerde moleculen kan verwezenlijkt worden door ofwel bouwstenen die een CF_3-groep bevatten te gebruiken, ofwel door trifluormethyleringsreagentia te benutten. Echter, het incorporeren van een trifluormethylgroep in een kleine molecule (zoals een β-lactam of een azetidin-2-on) gaat gepaard met een aanzienlijk risico tijdens de synthese door de condities en de gevaren verbonden aan het gebruik van trifluormethyleringsreagentia. Daarom wordt het gebruik van gefluoreerde bouwstenen hier aangewend als een efficiënt alternatief.

β-lactamen vertonen, naast hun welgekende farmacologische eigenschappen, potentieel om als intermediairen gebruikt te worden in de organische synthese. Dit omwille van de inherente spanning in de vierring, die verdere omzetting naar acyclische en heterocyclische stikstofverbindingen toelaat. β-lactamen met een trifluormethylgroep kunnen, omwille van het uitgesproken effect van fluor op de eigenschappen, als interessante bouwstenen voor de ontwikkeling van nieuwe doelstructuren met veelbelovende toepassingen beschouwd worden. Echter, de chemie van CF_3-gesubstitueerde β-lactamen werd nog niet zo uitvoerig onderzocht als die van CF_3-aziridinen, hun driering-homologen. Voor deze laatste werd reeds een brede toepasbaarheid als veelzijdige bouwstenen voor ring-openingsreacties en ring-transformatiereacties aangetoond. De synthese en het gebruik van 4-trifluormethyl-β-lactamen **i, ii, iii, iv** als nieuwe bouwstenen (“gefluoreerde synthon strategie”) werd in deze doctoraatsthesis verwezenlijkt, hetgeen resulteerde in een breed spectrum van gefunctionaliseerde CF_3-aminen en CF_3-azaheterocyclische verbindingen na verdere synthetische modificaties.

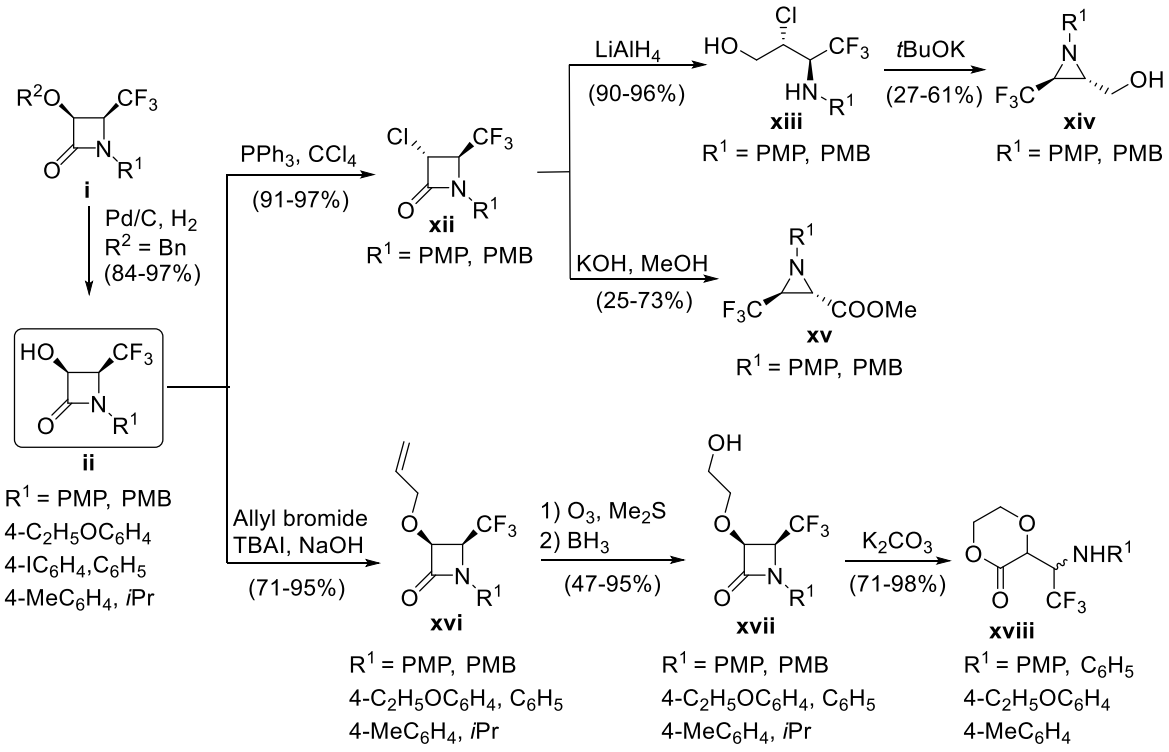


In het eerste deel werden 3-alkoxy/aryloxy-4-CF_3-azetidin-2-on-bouwstenen **i** op een efficiënte wijze bereid startende van het commercieel beschikbare 1-ethoxy-2,2,2-trifluorethanol **v** *via* iminering en daaropvolgende Staudingersynthese met alkyl/aryloxyacetylchlorides. Het synthetisch potentieel van de resulterende 4-CF_3-β-lactamen **i** m.b.t C2-N ringopeningsreacties werd geëvalueerd op een indirecte of een directe wijze. Op de indirecte wijze werden 4-CF_3-β-lactamen **i** onderworpen aan een initieel verwijderen van de carbonylgroep door behandeling met AlH_2Cl, hetgeen resulteerde in de azetidine-intermediairen **vi**. Activatie van deze azetidinen **vi** met trimethyloxoniumtetrafluorboraat en daaropvolgende ringopeningsreactie door verschillende zuurstof- en stikstofbevattende nucleofielen resulteerde in een waaier aan gefunctionaliseerde α-(trifluormethyl)aminen **vii**. De directe reductieve ring-openingsreactie van 4-CF_3-β-lactamen **i** werd gerealiseerd door behandeling met $LiAlH_4$, resulterend in 3-aminopropaan-1-olen **viii**. Cyclisatie van deze 3-aminopropaan-1-olen **viii** met formaldehyde of ethylchloorformiaat werd geëvalueerd, hetgeen leidde tot nieuwe 1,3-oxazinanen **ix** en 1,3-oxazinan-2-onen **x**, respectievelijk. Daarnaast werd gepoogd om 1,4-oxazepaananalogen te synthetiseren door cyclisatie van de overeenkomstige amiden **xi**, afgeleid van de 3-aminopropaan-1-olen **viii** door N-acylering. Dit was echter zonder succes.

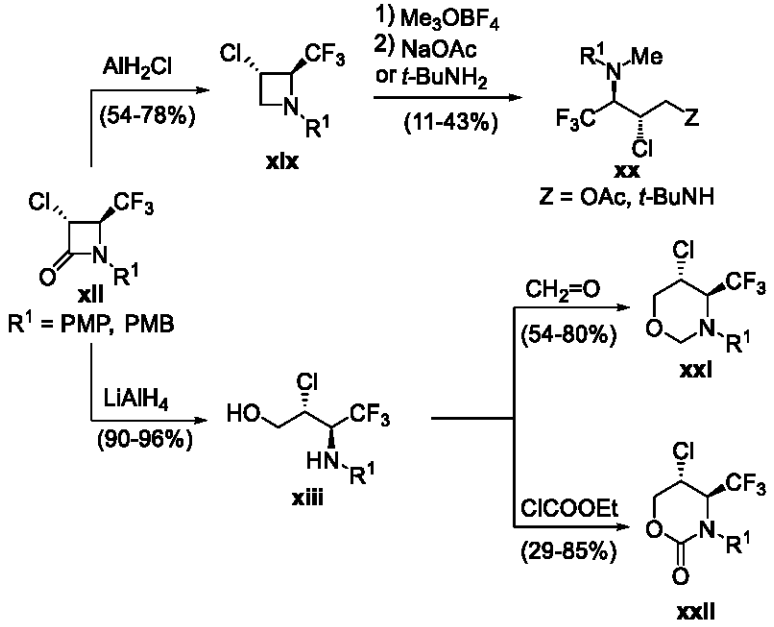


In het tweede deel werd met succes een reeks nieuwe 3-hydroxy-4-CF_3-β-lactamen **ii** gesynthetiseerd met hoge opbrengsten door de hydrogenolyse van de overeenkomstige 3-benzyloxy-4-CF_3-β-lactamen **i** (R^2 = Bn). Er werd aangetoond dat 2-hydroxy-4-CF_3-β-lactamen **ii** geschikte substraten zijn voor ringcontractie, leidend tot de synthese van 2-gesubstitueerde 3-(trifluormethyl)aziridinen *via* 3-chloor-4-CF_3-β-lactamintermediairen. Hier resulteerde behandeling van de alcoholen **ii** met Ph_3P in CCl_4 in *trans*-3-chloor-4-CF_3-β-lactamen **xii**. De ringopeningsreactie met behulp van de chloriden **xii** leverde hoge opbrengsten (90-96%) aan γ-amino-alcoholen **xiii**. Deze alcoholen werden onderworpen aan *t*BuOK-geïnduceerde ringsluiting, hetgeen aanleiding gaf tot 3-trifluorgemethyleerde 2-(hydroxymethyl)aziridinen **xiv** in 27-61% rendement. Anderzijds resulteerde de directe behandeling van de chloriden **xii** met KOH in methanol in de overeenkomstige aziridine-2-carboxylaten **xv** in 25-73% rendement.

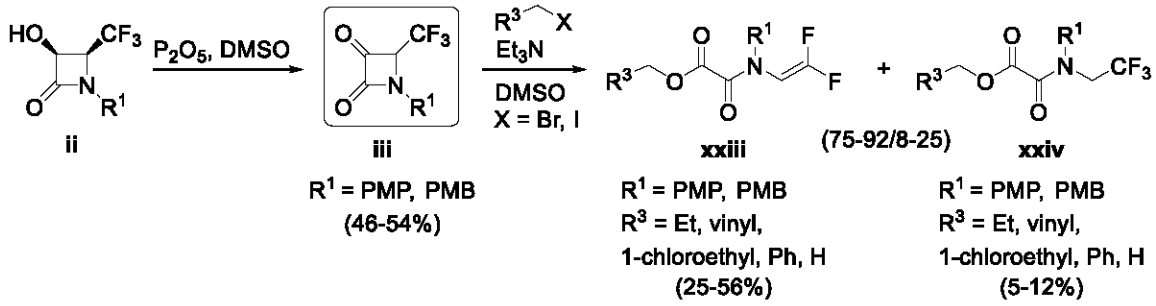
Verder werd aangetoond dat de alcoholen **ii** geschikte substraten zijn voor de synthese van nieuwe 3-[2,2,2-trifluor-1-(arylamino)ethyl]-1,4-dioxan-2-onen **xviii** in hoge opbrengsten *via* intermoleculaire cyclisatie van de 3-(2-hydroxyethoxy)-β-lactamintermediairen **xvii** na behandeling met een overmaat K_2CO_3. De 3-(2-hydroxyethoxy)-β-lactamen **xvii** werden bereid vanuit de allyloxyproducten **xvi** door ozonolyse, gevolgd door een reductiesequentie met Me_2S en BH_3.



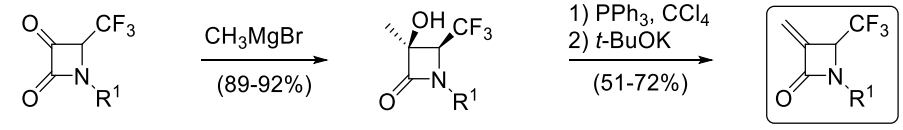
In analogie met de 4-CF_3-azetidin-2-onen **i** werd er voor de 3-chloor-4-CF_3-β-lactamen **xii** aangetoond dat het geschikte substraten zijn voor de bereiding van nieuwe α-CF_3-gesubstitueerde aminopropaanderivaten **xx**. Een ringopeningsreactie van de azetidine-intermediairen **xix**, afgeleid van de chloriden **xii**, werd uitgevoerd door behandeling met natriumacetaat of *tert*-butylamine. Hiernaast leverde de cyclisatie van de amino-alcoholen **xiii** met formaldehyde en ethylchloorformaat de overeenkomstige, gefunctionaliseerde 1,3-oxazinanen **xxi** en 1,3-oxazinaan-2-onen **xxii**.



In het volgende deel werden de alcoholen **ii** geoxideerd met behulp van P_2O_5/DMSO, resulterend in 3-oxo-4-(trifluormethyl)azetidin-2-onen **iii** als een derde klasse van nieuwe bouwstenen. De ringopeningsreactie van 3-oxo-β-lactamen **iii** door splitsing van de C3-C4-binding werd onverwachts waargenomen toen gepoogd werd om de overeenkomstige 2,3-dioxoazetidine-4-yl-anionen te vormen. Dit resulteerde in 2-[(2,2-difluorvinyl)amino]-2-oxoacetaten **xxiii** als belangerijkste producten (25-56%), met kleine hoeveelheden 2-oxo-2-[(2,2,2-trifluorethyl)amino]acetaten **xxiv** (5-12%) na behandeling met alkylhaliden en triethylamine in DMSO. Deze uitzonderlijke reactiviteit werd dieper onderzocht, zowel experimenteel als computationeel, om het onderliggende reactiemechanisme te ontrafelen.



In het laatste deel van deze doctoraatsthesis werden uitstekende opbrengsten aan tertiaire alcoholen **xxv** bekomen door behandeling van de azetidin-2,3-dionen **iii** met methylmagnesiumbromide. Daaropvolgend werden deze alcoholen **xxv** behandeld met PPh_3 in CCl_4 om de overeenkomstige intermediaire chloriden te bekomen. Dit werd gevolgd door een microgolfgeassisteerde dehydrochlorering met KO*t*Bu in DMSO, hetgeen leidde tot 3-methyleen-4-(trifluormethyl)azetidin-2-onen **iv** in goede rendementen, als een vierde nieuwe klasse van β-lactambouwstenen.



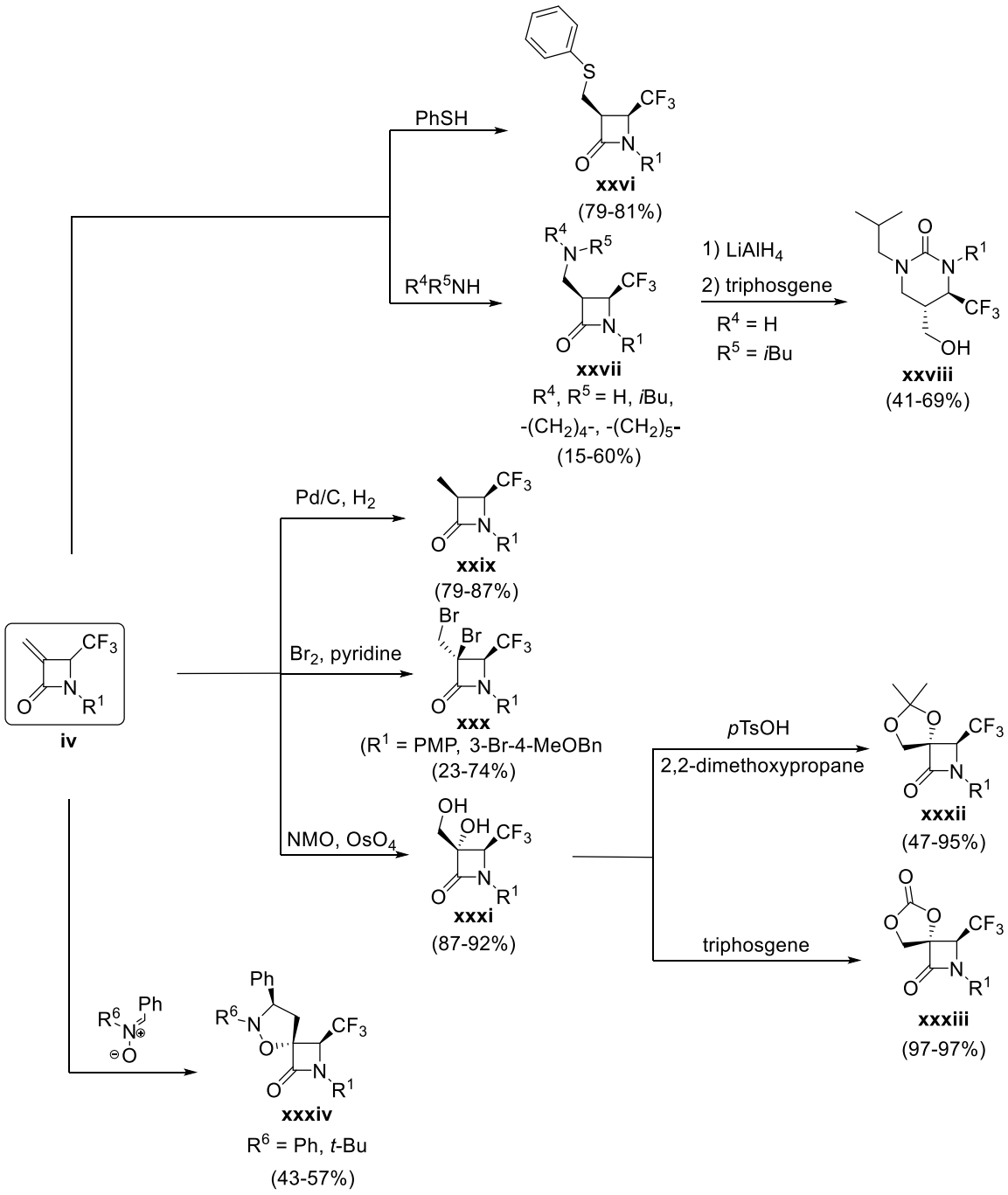
iii R^1 = PMP, PMB

xxv

iv

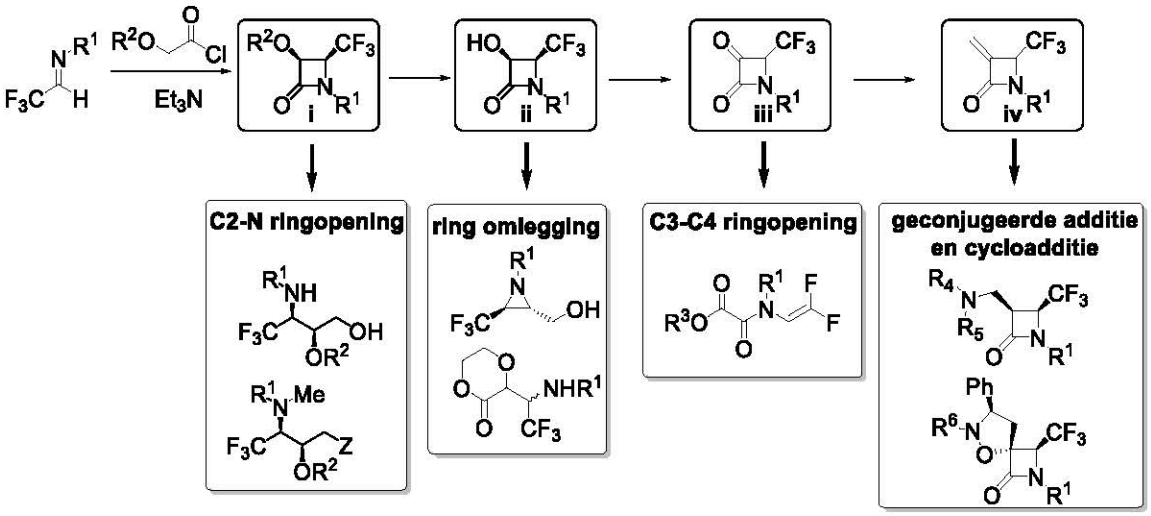
De aanwezigheid van een exocyclische koolstof-koolstof dubbele binding in 3-methyleen-4-(trifluormethyl)azetidin-2-onen **iv** maakte het mogelijk om verschillende synthetische strategieën toe te passen. Michaeladditie van zwavel- en stikstofbevattende nucleofielen op 4-CF_3-β-lactamen **iv** leverde de overeenkomstige 3-fenylthiomethyl-4-(trifluormethyl)azetidin-2-onen **xxvi** en 3-aminomethyl-4-(trifluormethyl)azetidin-2-onen **xxvii**. De 3-isobutylaminomethyl-β-lactamen **xxvi** werden dan geselecteerd voor een reductieve β-lactam ringopeningsreactie met $LiAlH_4$, gevolgd door cyclisatie met trifosgeen, hetgeen resulteerde in nieuwe 4-CF_3-tetrahydropyrimidin-2-onen **xxviii** in goede opbrengsten. Verder resulteerde de elektrofiele additie van broom aan 4-CF_3-β-lactamen **iv** (in aanwezigheid van pyridine) in 3-broom-3-broommethyl-4-(trifluormethyl)azetidin-2-onen **xxx**. Daarnaast werden de 3-trifluormethyl-5,7-dioxa-2-azaspiro[3.4]octaan-1-onen **xxxii** en 3-trifluormethyl-5,7-dioxa-2-azaspiro[3.4]octaan-1,6-dionen **xxxiii** bereid door behandeling van de overeenkomstige diolen **xxxi**, afgeleid van de OsO_4-gemedieerde oxidatie van de 3-methyleen-β-lactamen **iv**, met pTsOH in 2,2-dimethoxypropaan en met trifosgeen, respectievelijk.

Verder werd aangetoond dat 1,3-dipolaire nitron-olefien-cycloadditiereacties op 4-CF_3-β-lactamen **iv** mogelijk waren die leiden tot isoxazolidinesystemen. Behandeling van de 3-methyleen-β-lactamen **iv** met ofwel *N*-fenyl- ofwel *N-tert*-butyl-α-phenylnitron resulteerde in een handige route tot 7-fenyl-3-trifluormethyl-5-oxa-2,6-diazaspiro[3.4]octaan-1-onen **xxxiv**, dewelke als (3*S**,4*R**,7*R**)-isomeren werden toegewezen op basis van *single crystal X-ray* analyse.



In deze doctoraatsthesis werden met succes vier nieuwe 4-trifluormethyl-β-lactambouwstenen gesynthetiseerd. Er werd aangetoond dat deze verbindingen krachtige substraten vormen voor reacties waarbij de ring geopend of herschikt wordt, alsook Michaeladdities, elektrofiele addities en cycloaddities. Deze leidden allen tot een brede waaier aan gefunctionaliseerde CF_3-aminen en CF_3-azaheterocyclische verbindingen. In het licht van de uitzonderlijke eigenschappen die de CF_3-groep aan een molecule geeft, kunnen we hier inderdaad besluiten dat de 4-CF_3-β-lactamen als

veelbelovende structuren voor verdere ontwikkelingen in de medicinale chemie en chemische biologie beschouwd kunnen worden.



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SCIENTIFIC PUBLICATIONS IN INTERNATIONAL PEER-REVIEWED JOURNALS

1) **Dao Thi, H.**, Decuyper, L., Mollet, K., Kenis, S., De Kimpe, N., Van Nguyen, T., D'hooghe, M. "Synthesis of trifluoromethylated azetidines, aminopropanes, 1,3-oxazinanes and 1,3-oxazinan-2-ones starting from 4-trifluoromethyl-β-lactam building blocks". *Synlett* **2016**, *27*, 1100. (I.F. 2.42).

2) **Dao Thi, H.**, Le Nhat Thuy, G., Catak, S., Van Speybroeck, V., Van Nguyen, T., D'hooghe, M. "Use of 3-hydroxy-4-(trifluoromethyl)azetidin-2-ones as building blocks for the preparation of trifluoromethyl-containing aminopropanes, 1,3-oxazinan(2-on)es, aziridines and 1,4-dioxan-2-ones". *Synthesis* **2018**, *50*, 1439-1456. (I.F. 2.65).

3) **Dao Thi, H.**, Goossens, H., Hertsen, D., Otte, V., Van Nguyen, T., Van Speybroeck, V., D'hooghe, M. "Formation of fluorinated amido esters through unexpected C3-C4 bond fission in 4-trifluoromethyl-3-oxo-β-lactams". *Chem. Asian J.* **2018***, 13*, 421-431. (I.F. 4.08).

4) **Dao Thi, H.**, Danneels, B., Desmet, T., Van Hecke, K., Van Nguyen, T., D'hooghe, M. "Synthesis and applications of 3-methylene-4-(trifluoromethyl)azetidin-2-ones as building blocks for the preparation of mono- and spirocyclic 4-CF_3-β-lactams". *Asian J. Org. Chem.* **2016**, *5*, 1480-1491. (I.F. 2.79).

5) **Dao Thi, H.**, Van Nguyen, T., D'hooghe, M. "Synthesis and reactivity of 4-(trifluoromethyl)azetidin-2-ones". *Monatsh. Chem.* **2018**, *149*, 687-700. (I.F.1.28).

ACTIVE PARTICIPATIONS AT CONFERENCES

1) **Dao Thi, H.**, Decuyper, L., Mollet, K., Kenis, S., De Kimpe, N., Van Nguyen, T., D'hooghe, M. "Synthesis of trifluoromethylated azetidines, aminopropanes, 1,3-oxazinanes, and 1,3-oxazinan-2-ones starting from 4-trifluoromethyl-β-lactam building blocks" (poster), *18th Sigma Aldrich Organic Synthesis Meeting* (December 4-5, **2014**, Blankenberge, Belgium).

2) **Dao Thi, H.**, Decuyper, L., Mollet, K., Kenis, S., De Kimpe, N., Van Nguyen, T., D'hooghe, M. "Synthesis of trifluoromethylated azetidines, aminopropanes, 1,3-oxazinanes, and 1,3-oxazinan-2-ones starting from 4-trifluoromethyl-β-lactam building blocks" (poster), *Chemical research in Flanders symposium CRF-1* (October 24-26, **2016**, Blankenberge, Belgium).

3) **Dao Thi, H.**, Van Nguyen, T., D'hooghe, M. "Synthesis of 4-(trifluoromethyl)azetidin-2-one building blocks and transformations into novel CF_3-substituted amines and heterocyclic systems" (poster), MOCS *symposium* (December 7-8, **2017**, Blankenberge, Belgium).

4) **Dao Thi, H.**, Van Nguyen, T., D'hooghe, M. "Synthesis of 4-(trifluoromethyl)azetidin-2-one building blocks and transformations into novel CF_3-substituted amines and heterocyclic systems" (oral presentation), ChemCYS (February 21-23, **2018**, Blankenberge, Belgium).

TUTORING OF MASTER THESIS STUDENTS

Otte, V. "C3-C4 ring opening of 3-oxo-4-trifluoromethyl-beta-lactams: a computational study" (2016-2017).