"Will fluorine ever have practical applications?

It is very difficult to answer this question. I may, however, say in all sincerity that I gave this subject little thought when I undertook my researches, and I believe that all the chemists whose attempts preceded mine gave it no more consideration.

A scientific research is a search after truth, and it is only after discovery that the question of applicability can be usefully considered."

Henri Moissan

(Nobel Prize winner Chemistry in 1906 for the isolation of the element fluorine)

Members of the Jury

Prof. Dr. ir. Stefaan De Smet (Chairman)

Prof. Dr. Troels Skrydstrup

Prof. Dr. ir. Kourosch Abbaspour Tehrani

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Prof. Dr. ir. Matthias D'hooghe (Promoter)

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Rector: Prof. Dr. Anne De Paepe

MSc. Matthias Moens

New strategies for the synthesis of fluorinated carbo- and heterocyclic compounds

Thesis submitted in fulfillment of the requirements

for the degree of Doctor (PhD) in Applied Biological Sciences:

Chemistry and Bioprocess Technology

Dutch translation of the title:

Ontwikkeling van nieuwe strategieën voor de synthese van gefluoreerde carbo- en heterocyclische verbindingen.

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Ghent, September 2014

The author, The promoters,

Matthias Moens Prof. Dr. ir. N. De Kimpe Prof. Dr. ir. M. D'hooghe

Woord vooraf

Vier jaar geleden vatte ik mijn doctoraat aan op het voor mij relatief onbekend terrein '*het boerekot*' genaamd, het territorium van de toekomstige bio-ingenieur. Niettegenstaande deze nieuwe omgeving voelde ik me er al snel thuis en de jaren van onderzoek vlogen voorbij. Het was vooral een periode van ontdekking waarin ik veel heb bijgeleerd over fluorchemie, het begeleiden van studenten en samenwerking. De vele fijne herinneringen geassocieerd met deze faculteit, zowel op professioneel vlak als daarbuiten zal ik dan ook steeds koesteren.

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Vooreerst zou ik mijn promotor Prof. Dr. ir. Norbert De Kimpe willen bedanken voor het gestelde vertrouwen en om mij de kans te geven dit doctoraal onderzoek te voeren. Uw kritische zin en brede chemische kennis brachten steeds weer nieuwe oplossingen en mogelijkheden naar voor om de gestelde problemen aan te pakken. Vervolgens wil ik ook graag Prof. Dr. ir. Matthias D'hooghe bedanken om het promotorschap op zich te nemen na het emeritaat van Prof. De Kimpe. Naast het grondig nalezen van manuscripten, stond uw deur altijd open om even tijd te maken en mijn talloze vragen te beantwoorden.

Furthermore, I would like to thank the members of the jury: Prof. Troels Skrydstrup, Prof. Kourosch Abbaspour Tehrani, Prof. Johan Van der Eycken, Prof. Tom Desmet and Prof. Stefaan De Smet for all the efforts you have done by reading this PhD-thesis in a very detailed way.

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of voor de eindeloze discussies over onze bouwprojecten. Andy, Ans, Els en Pieter Z. om steeds paraat te staan voor ons en voor al het werk dat jullie achter de schermen doen zodat wij ons kunnen focussen op het onderzoek. Bouchra, Jenny, Julie en Yeter die er voor zorgden dat we altijd in een propere omgeving konden werken. En tenslotte Prof. Christian Stevens om mij de opportuniteit te geven mijn schouders onder een nieuw project te kunnen zetten binnen zijn onderzoeksgroep.

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Tenslotte is er nog mijn allerliefste. Iris, reeds vijf prachtige jaren mocht ik delen in jouw liefde en warmte en steeds weet jouw glimlach mij volledig op te fleuren na een dag vol teleurstellende resultaten. 2014 zal voor altijd in ons geheugen gegraveerd staan als het jaar van 'den bouw en onze trouw', ik kijk dan ook uit naar onze toekomst om met jou deze en toekomstige uitdagingen aan te gaan.

Matthias Moens,

12 September 2014

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List of Abbreviations

ADA: American Dental Association

AIBN: azabisisobutyronitrile

aq: aqueous

Ar: Aryl

Bn: benzyl

cat: catalytic

*c*Hex: cyclohexyl

DAST: diethylaminosulfur trifluoride

Deoxofluor®: bis(2-methoxyethyl)aminosulfur trifluoride

DIBAL: diisobutylaluminium hydride

DMF: *N,N*-dimethylformamide

DMM: dimethoxymethane

DMSO: dimethyl sulfoxide

dr: diastereomeric ratio

EDTA: ethylenediaminetetraacetic acid

ee: enantiomeric excess

EI: electron impact ionisation

equiv: equivalent

ES: electrospray ionisation

GC: gas chromatography

IR: infrared spectroscopy

KHMDS: potassium bis(trimethylsilyl)amide

LC: liquid chromatography

LDA: lithium diisopropylamide

LiHMDS: lithium bis(trimethylsilyl)amide

MIRC: michael induced ring closure

Mes: methanesulfonyl

Mol. siev.: molecular sieves

Morph-DAST: morpholinosulfur trifluoride

MS: mass spectrometry

NBS: *N*-bromosuccinimide

NCS: *N*-chlorosuccinimide

n.d.: not determined

NFS: *N*-fluorosuccinimide

NFSI: *N*-fluorobenzenesulfonimide

NMR: nuclear magnetic resonance

PG: protecting group

Ph: phenyl

pyr: pyridine

ref: reference

rt: room temperature

Selectfluor®: 1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane ditetrafluoroborate

TBAT: tetrabutylammonium triphenyldifluorosilicate

TBDMS: *tert*-butyldimethylsilyl

THF: tetrahydrofuran

TMS: trimethylsilyl or tetramethylsilane

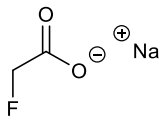
Tos: 4-toluenesulfonyl

XtalFluor-E®: (diethylamino)difluorosulfonium tetrafluoroborate

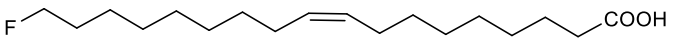
XtalFluor-M®: difluoro(morpholino)sulfonium tetrafluoroborate

1 Introduction and Goals

Fluorine, as the 13th most abundant element in the earth's crust, bears such a reactivity that any free fluorine in the atmosphere of the early earth was immediately bound to surface rocks. These minerals, such as fluorspar (CaF_2) and fluorapatite ($Ca_5(PO_4)_3F$), are the main sources of commercial fluorine nowadays. The relative insolubity of fluorine-containing minerals hinders the uptake and metabolism by living organisms, explaining the limited number of naturally occurring fluorinated compounds isolated up till now, despite bulky amounts of fluorine present in the earth's crust. The majority of these natural products are homologues of fluoroacetate **1**, e.g. ω-fluorooleic acid **2**.[1] Not only enzymes have difficulties to introduce fluorine into natural products, also synthetic chemists experienced severe problems in handling fluorine. It took till 1886 when Henri Moissan achieved the isolation of elemental fluorine at the University of Paris. The extreme reactivity of F_2 still limits widespread laboratory use.[2]

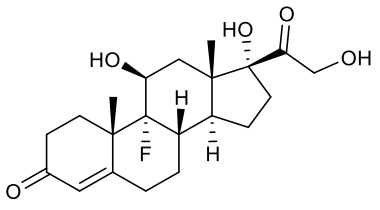


1



2

Over the years a broad range of applications of fluorinated compounds have been developed in as well inorganic as organic chemistry fields. As with other scientific discoveries, the research in handling and employing fluorine exploded by large investments of governmental institutions in the weapons industry. In this specific case, during the Manhattan Project naturally occurring monoisotopic fluorine was applied in the enrichment of ^{235}U as uranium hexafluoride (UF_6) in the development and production of atomic bombs. After World War II the American Dental Association (ADA) approved the use of fluoride in low doses in toothpaste to reduce tooth decay. Simultaneously, some organic applications were developed, for example, freons as cooling gases and inert thermoplastic polymers (Teflon®). More recently, the focus shifted toward organofluorine chemistry, establishing unique properties in the pharmaceutical and agrochemical domain. In the early 1950's, the interest in organic fluorine was triggered by the discovery of Fried that 9-α-fluoro derivatives of cortisone and hydrocortisone had enhanced biological activities compared to the non-fluorinated hormones. This resulted in the development of the first applications of fluorinated compounds in medicinal chemistry, e.g. Fludrocortisone **3** and 5-fluorouracil **4** as anti-inflammatory and antitumor compounds, respectively.



3
Fludrocortisone

4
5-fluorouracil

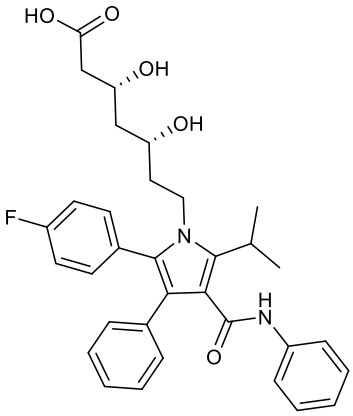
However, until the 1970's, due to challenging procedures for the incorporation of fluorine, the percentage of fluorinated compounds on the pharmaceutical market remained limited (about 2%). Drastic improvements were made when safe and selective fluorinating agents were developed, facilitating the synthetic approaches toward fluorine-containing drugs, enabling an intensive growth over several decades. In 2014, the share of fluorinated drugs has grown to 25%, with 40 new fluorine-containing drugs introduced on the market from 2001 to 2011.[3]

The success of organofluorine compounds can be attributed to the combination of the unique physical properties of fluorine, such as high electronegativity, very low polarizability due to the small size of the fluorine atom and an excellent overlap between the fluorine 2s and 2p orbitals with the corresponding orbitals of carbon, resulting in a strong polar bond.[4] Due to this charge distribution, a C-F bond usually interacts with its environment through electrostatic/dipole interactions, and is thus able to change the conformation of the molecule.[5] This polarisation and the presence of three electron lone pairs suggests that fluorine can play an important role in the formation of hydrogen bonds. However, the high electronegativity of fluorine holds the free lone pairs tightly bonded, rendering poor donor abilities.

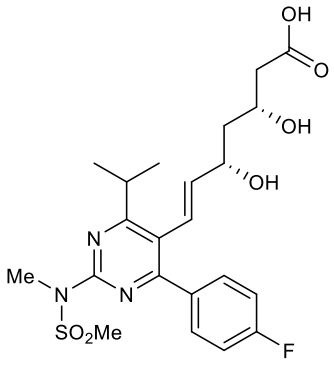
The strong electron-withdrawing character of fluorine can dramatically alter the acidity and basicity of neighbouring functional groups. For example, amines become much less basic upon β-, γ- and even δ-fluoro substitution, while the acidity of alcohols and carboxylic acids increases with adjacent fluorine substitution. Changes in pK_a can have effects on a number of different parameters in lead compounds, including physicochemical properties (solubility, lipophilicity), binding affinities (potency and selectivity), absorption (membrane penetration), distribution, metabolic stability and excretion.[6] So it can be well understood that the replacement of a hydrogen atom in bioactive compounds by even a single fluorine atom can tremendously influence the chemical reactivity and the biological and pharmacological properties.[7]

During almost a decade, Atorvastatin **5** (Lipitor®) was the top-selling prescription drug in the United States as a cholesterol-lowering drug. In 2013, rosuvastatin **6** (Crestor®) and Fluticasone propionate **7**

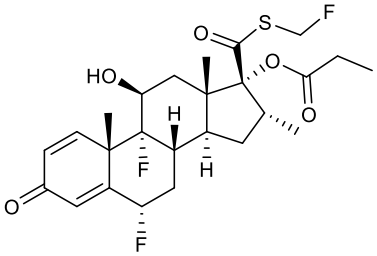
(Advair Diskus) occupied the fourth and fifth position, respectively, and a total of five fluorinated compounds were present in the top 20.[8]



5
Lipitor®, Pfizer
Cholesterol regulator



6
Crestor®, AstraZeneca
Cholesterol regulator

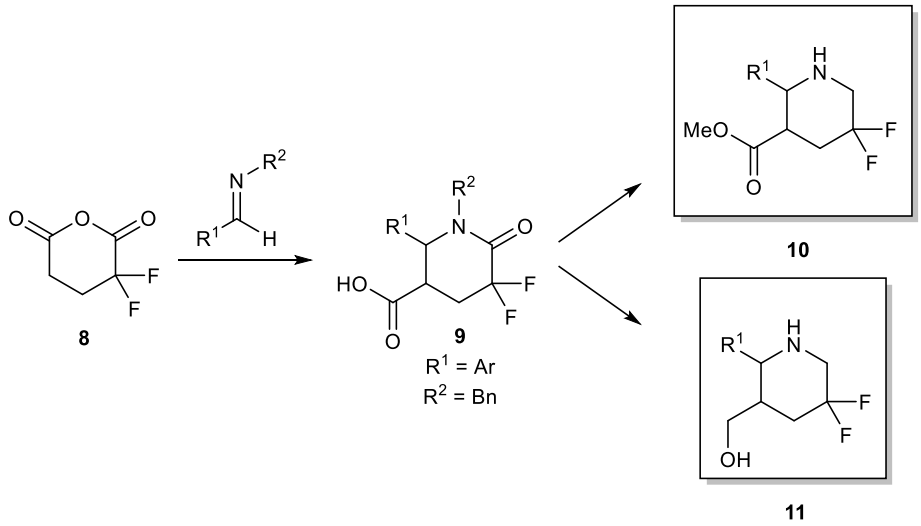


7
Advair Diskus, GlaxoSmithKline
Asthma

With a constant need for innovation in the pharmaceutical and the agrochemical sector, it is of vital essence to keep developing synthetic approaches toward new and potentially active fluorinated molecules. These compounds can be immediately tested as potential drug candidates or can be used as building blocks to be incorporated in larger systems. In that perspective, functionalized azaheterocycles are interesting molecules. While the chemistry of non-fluorinated azaheterocyles has received a lot of attention in the past decades, the research on the synthesis of their ring-fluorinated or trifluoromethylated analogues remains limited.

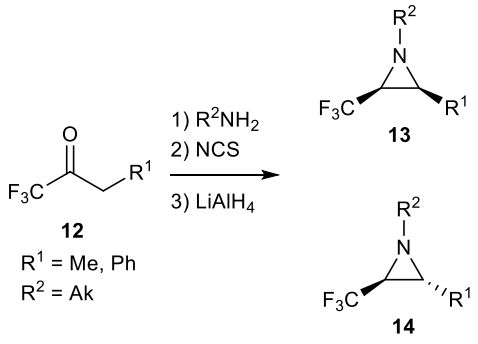
Because of the large demand for new building blocks, the focus in this PhD-thesis was set on the development of entries toward a broad range of ring-fluorinated and trifluorinated cyclic structures with considerable potential as building blocks for pharmaceutical applications.

Piperidines, as six-membered azaheterocycles, recently gained special interest as they are recognized as T-type calcium channel antagonists,[9] anti-Alzheimer's agents[10] and glycosidase inhibitors.[11] In that respect, a new approach is attempted toward interesting fluorinated nipecotic acid derivatives starting from a difluorinated building block using 2,2-difluoroglutaric anhydride **8** as a key intermediate. Addition of an imine to 2,2-difluoroglutaric anhydride **8** could result in the formation of fluorinated piperidinones **9**. Further transformations such as esterifications, separation of diastereomers, (selective) reduction and removal of the *N*-protecting group could lead to the *cis*- and/or *trans*-structures of 3-alkoxycarbonyl- and 3-hydroxymethyl 5,5-difluoropiperidines **10** and **11**, respectively (Scheme 1).



Scheme 1

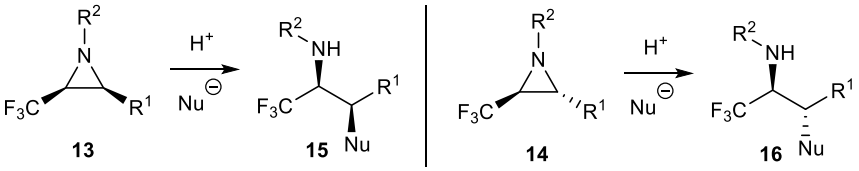
Small-ring heterocyclic systems, such as aziridines comprise an important group of constrained reactive compounds, making them useful as versatile synthons in the preparation of functionalized amines.[12] As a result, trifluoromethylated aziridines are often employed as eligible substrates in the synthesis of fluorinated building blocks.[13] However, the pathways toward the stereoselective synthesis of 2-substituted 3-(trifluoromethyl)aziridines remain scarce.[14] As most of these methods use precarious diazo compounds (ethyl diazoacetate[14a,14b] or (trifluoromethyl)diazomethane[14c-e]) or require drastic circumstances[14f] a new stereoselective approach toward *cis*- and *trans*-2-substituted 3-(trifluoromethyl)aziridines will be evaluated. Imination of suitable trifluoromethylketones **12** followed by α-chlorination with *N*-chlorosuccinimide (NCS) and hydride-induced ring closure using lithium aluminium hydride ($LiAlH_4$) could provide *cis*-and/or *trans*-aziridines **13** and **14** (Scheme 2).



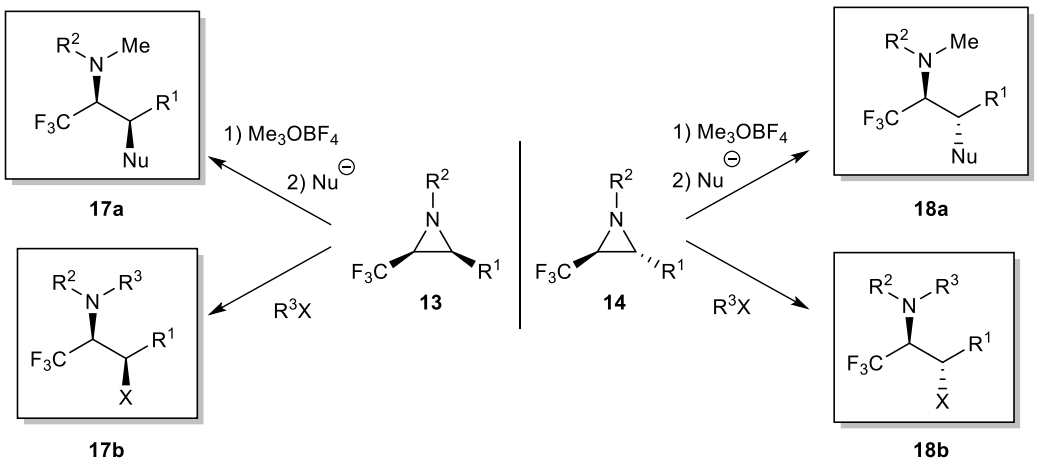
Scheme 2

Additionally, the potential of these novel aziridines **13** and **14** as fluorinated synthons will be studied. Ring-opening reactions of single substituted 2-(trifluoromethyl)aziridines has been explored to some extent.[13b,15] However, the aptitude of 2-substituted 1-alkyl-3-(trifluoromethyl)aziridines toward

further elaboration remains mainly unexplored.[13c,13d] Prior to ring-opening reactions with a series of *C*-, *N*-, *O*-, *S*- or halogen nucleophiles, activation of these *N*-alkyl-aziridines **13** will be required. Activation of aziridines **13** and **14** will be performed via quaternisation of the nitrogen atom, either by means of protonation, leading toward secondary amines **15** and **16** (Scheme 3), or by alkyl activation resulting in tertiary amines **17a,b** and **18a,b** (Scheme 4). Based on literature reports, the ring opening of these activated aziridines is expected to proceed via a S_N2 process, which would preserve the diastereoselective outcome of previous reactions.[13c]



Scheme 3

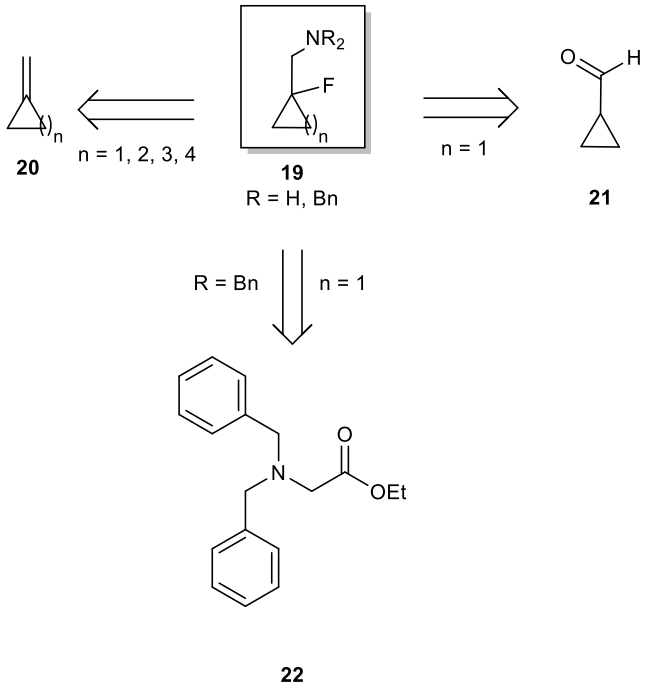


Scheme 4

In another part of this PhD-thesis, new synthetic approaches toward 1-aminomethyl-1-fluorocycloalkanes **19** are evaluated. Bromofluorination of methylenecycloalkane **20** (n = 1, 2, 3 and 4) should lead selectively toward the Markovnikov product, 1-bromomethyl-1-fluorocyclopropane, which could then be converted toward the intended 1-aminomethyl-1-fluorocycloalkanes **19** by azide displacement of the bromine and subsequent reduction by hydrogenation.

Additionally, some specific alternative direct fluorination approaches are evaluated toward the synthesis of *N*-protected 1-aminomethyl-1-fluorocyclopropanes **19** (n = 1). At the Department of Sustainable Organic Chemistry and Technology, Ghent University, a general method for the preparation of α-fluorinated imines,[16] as versatile substrates for the synthesis of β-fluorinated amines, was developed.[17] Starting from cyclopropanecarboxaldehyde **21**, iminiation and α-

fluorination followed by reduction could afford *N*-protected 1-aminomethyl-1-fluorocyclopropane **19** (n = 1). A final approach consists of a Kulinkovich-cyclopropanation starting from ethyl *N,N*-dibenzylglycinate **22**,[18] followed by direct fluorination of *N,N*-dibenzyl-1-aminomethyl-1-cyclopropanol using deoxofluorinating agents could lead to 1-aminomethyl-1-fluorocyclopropane **19** (n = 1) (Scheme 5).



Scheme 5

2 Literature Overview

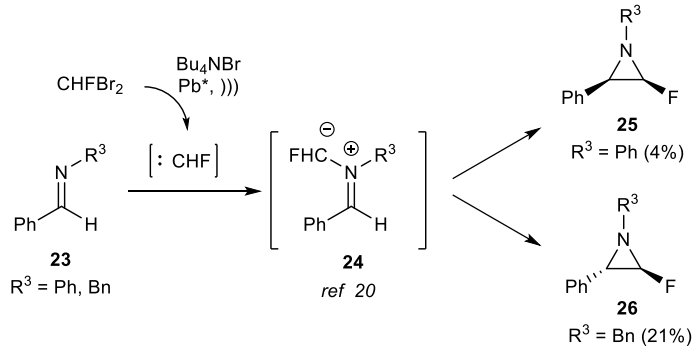
2.1 General approaches toward the synthesis of fluorinated heterocyclic compounds

In this section, a short literature overview is presented, in which the synthetic availability of saturated mono- and geminal difluorinated aza- and oxaheterocycles is evaluated. Accessibility of three- to six-membered rings is mainly determined by the ring strain in these cyclic compounds. As the ring-strain decreases for larger ring systems, the number of synthetic pathways toward fluorinated heterocyclic compounds increases tremendously from three- to six-membered ring systems and by consequence the number of synthesized fluorinated compounds.

2.1.1 Three-membered rings

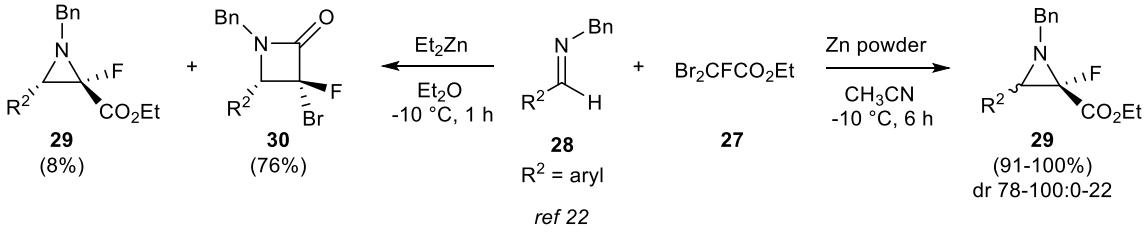
2.1.1.1 Synthesis of mono- and difluorinated aziridines

Aziridines are reactive compounds, which make them useful and versatile substrates in the synthesis of functionalized amines.[12a-c] In the literature, introduction of fluorine always precedes ring-closing steps, probably because of the fact that the high reactivity of aziridines makes it hard to introduce fluorine immediately onto the aziridine ring. Generally, monofluorinated aziridines are prepared through the addition of a fluorocarbene across an imine.[19] As an example, the synthetic approach, developed by Konev et al., is presented here (Scheme 6).[20] Imines **23** reacted with *in situ* prepared fluorocarbene. The reaction involves attack of the electron lone pair of the imine nitrogen onto the fluorocarbene to give azomethine ylides **24**, followed by ring closure to the monofluorinated aziridines **25** and **26**. A stereoselective outcome was obtained by altering the *N*-protecting group. With *N*-aryl groups the reaction furnished *cis*-monofluorinated aziridines **25**, while *N*-alkyl groups gave rise to *trans*-monofluorinated aziridines **26**.[21]



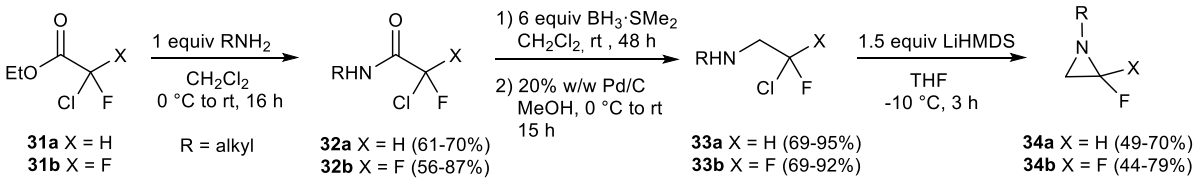
Scheme 6

Monofluorinated aziridines **29** were first obtained as side products in a Reformatsky-type aza-Darzens reaction with ethyl dibromofluoroacetate **27** and imines **28** in the presence of Et_2Zn, affording α-bromo-α-fluoro-β-lactams **30**. Optimisation of the reaction conditions (switching the solvent from Et_2O to CH_3CN and changing the Zn source from Et_2Zn to unactivated Zn powder) gave rise to quantitative formation of *cis*- and *trans*-3-aryl-2-fluoroaziridine-2-carboxylates **29** in a high stereoselectivity ranging from 72:28 to 100:0 (*cis*:*trans*) (Scheme 7).[22]



Scheme 7

Two alternative approaches toward fluorinated aziridines have been developed at the Department of Sustainable Organic Chemistry and Technology, Ghent University, in which these aziridines were formed via the intramolecular nucleophilic substitution of a halogen atom (Scheme 8 and 9).[23] Firstly, the synthesis of 3-unsubstituted 2-fluoroaziridines **34a** was achieved, starting from the commercially available ethyl chlorofluoroacetate **31a** (X = H). Treatment with primary amines resulted in the corresponding α-chloro-α-fluorocarboxylic amides **32a**, which were reduced with $BH_3{\cdot}SMe_2$ toward chlorofluoroamines **33a**.[23a] Basic treatment of β-chloro-β-fluoroamine **33a** with lithium bis(trimethylsilyl)amide (LiHMDS) yielded the desired 3-unsubstituted 2-fluoroaziridines **34a** in good yields (49-70%).

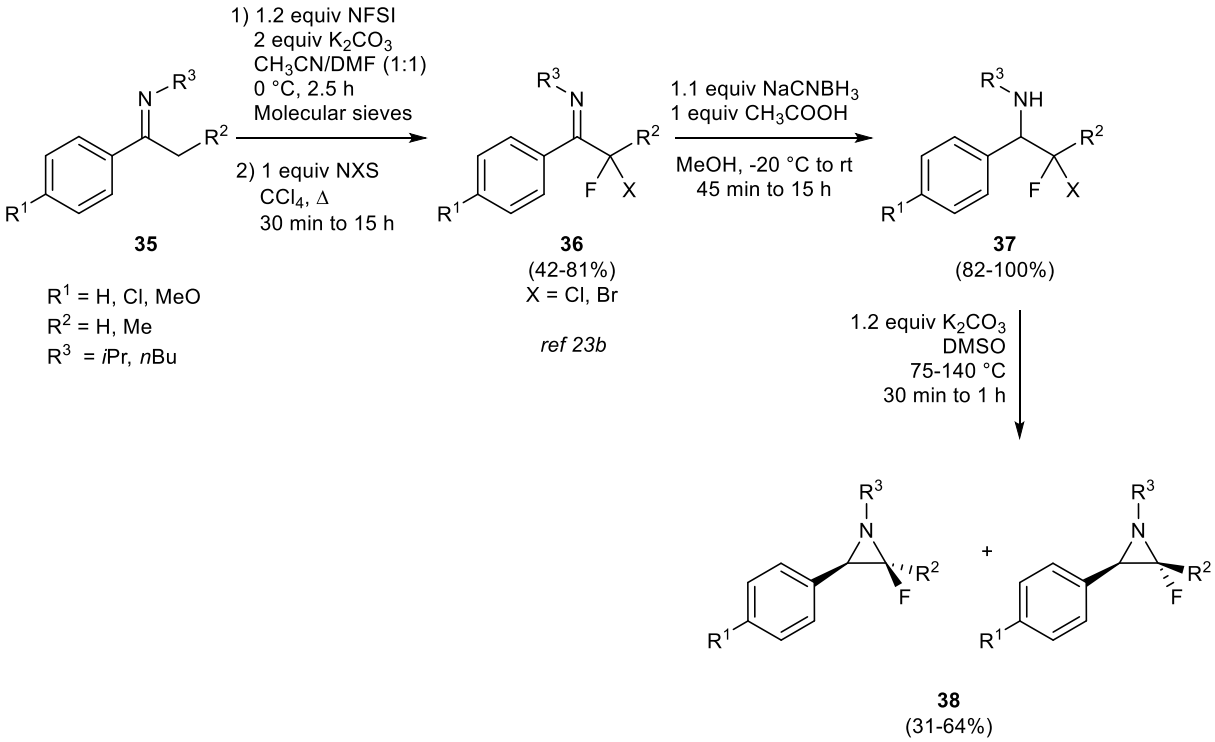


ref 23a

Scheme 8

The scope of this reaction could be broadened toward 3-unsubstituted 2,2-difluoroaziridines **34b**, starting from ethyl chlorodifluoroacetate **31b** (X = F), applying the same synthetic pathway.

Secondly, 3-substituted 2-fluoroaziridines were prepared from aromatic ketimines **35**, which were α-fluorinated and subsequently α-chlorinated or α-brominated (Scheme 9). Reduction of the α-bromo- and α-chloro-α-fluoroimines **36** with sodium cyanoborohydride ($NaCNBH_3$) afforded β-bromo- and β-chloro-β-fluoroamines **37**. Base-induced ring closure with K_2CO_3 gave rise to a mixture of *cis*- and *trans*-3-substituted 2-fluoroaziridines **38** in acceptable to good yields (31-64%).[23b]

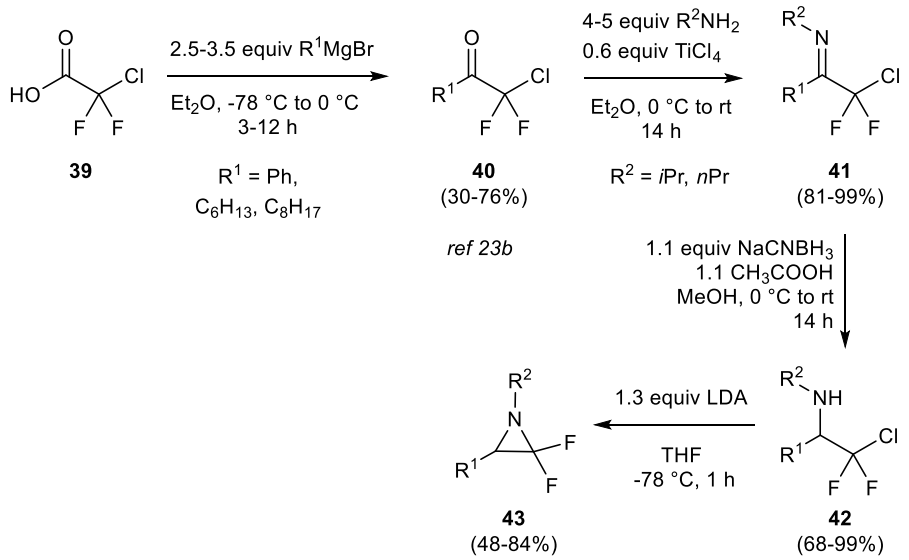


ref 23b

Scheme 9

Despite the successful synthesis of 3-substituted monofluorinated aziridines **38,** the extension toward 3-substituted difluorinated aziridines could not be achieved by α-difluorination and subsequent α-chlorination of the corresponding imines (R^2 = H, Scheme 9). α-Chloro-α,α-difluoroimines **41** were synthesised starting from α-chloro-α,α-difluoroacetic acid **39** by treatment with a Grignard reagent to yield α-chloro-α,α-difluoroketones **40**, followed by imination with an

appropriate primary amine (Scheme 10). Subsequent reduction ($NaCNBH_3$) and base-induced (LDA) ring closure led toward 3-substituted 2,2-difluoroaziridines **43** in good yields (48-84%).[23b]

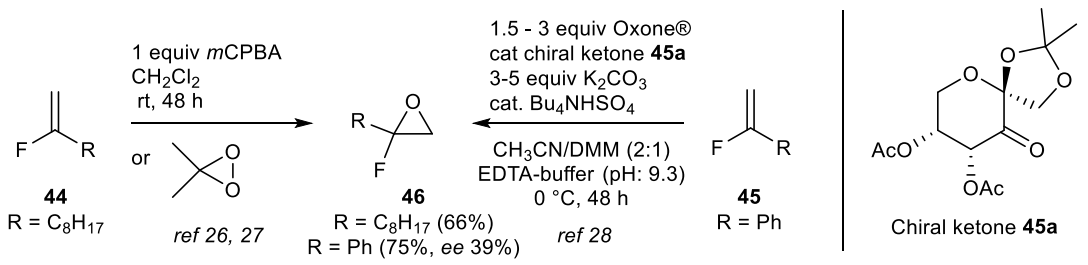


Scheme 10

Up till now, these two methods are the only available synthetic approaches toward difluorinated aziridines.

2.1.1.2 Synthesis of mono- and difluorinated epoxides

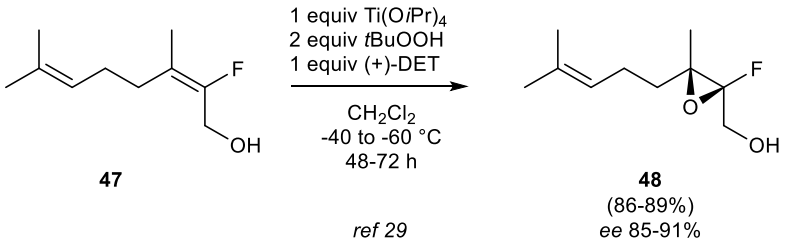
In contrast to the limited access to fluorinated aziridines, numerous pathways to monofluorinated epoxides have been investigated. Analogous to fluoroaziridines, some approaches have been reported for the synthesis of monofluorinated epoxides, *i.e.*, (Reformatsky-type) Darzen condensations[24] and reduction of α-chloro-α-fluoroketones followed by intramolecular substitution.[25] However, the utmost popular method toward 2-fluorooxiranes **46** is the immediate epoxidation of suited fluoroolefins **44** with mCPBA[26] or dimethyldioxirane (Scheme 11).[27]



Scheme 11

Optically active monofluorinated epoxides have been prepared via direct addition to fluoroolefins with oxone® in the presence of a catalytic amount of a chiral ketone **45a**[28] (Scheme 11) or via

Sharpless epoxidation of monofluoroallylic alcohol **47** using (+)-diethyl tartrate as chiral inducer (Scheme 12).[29]



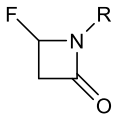
Scheme 12

Despite many approaches yielding perfluorinated peroxides,[30] up till now, no approaches have been reported for the synthesis of *gem*-difluorinated epoxides.

2.1.2 Four-membered rings

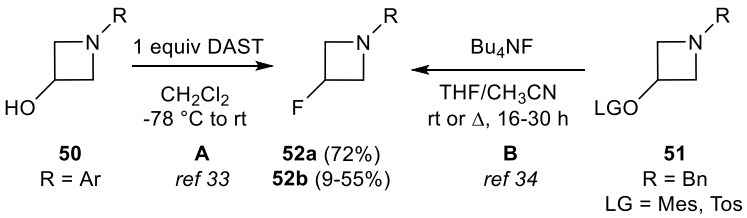
2.1.2.1 Synthesis of monofluorinated azetidines

3-Fluoroazetidines are much more accessible than their 2-fluoroazetidine analogues.[31] Except for the synthesis of some 4-fluoro-β-lactams **49**,[32] the synthesis of 2-fluoroazetidines has not yet been reported.



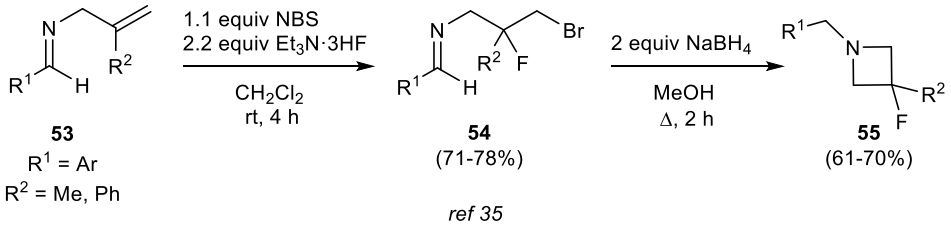
49

In comparison with fluorinated aziridines, direct fluorination of azetidines, for example by substitution of an appropriate leaving group, is possible. Principally, the alcohol function of 3-hydroxyazetidines **50** was first transformed into a good leaving group and then replaced by nucleophilic fluorine toward 3-fluoroazetidines **52** (Scheme 13). The leaving group transformation of the hydroxyl function could occur *in situ* with a deoxofluorination reagents (Method A),[33] *i.e.* DAST or Deoxofluor®, or in a separate step toward isolable mesyloxy- or tosyloxyazetidines **51** (Method B).[34]



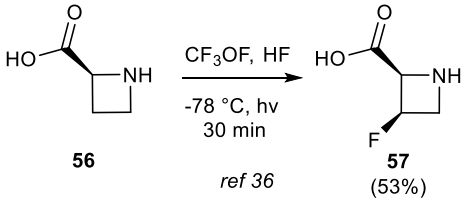
Scheme 13

Next to direct fluorination, a second valuable, less abundantly used approach, is known.[35] Firstly, fluorine and bromine were introduced by means of a bromofluorination of *N*-allyl imines **53**, after which hydride-induced ring closure yielded 3-substituted 3-fluoroazetidines **55** in good yields (61-70%) (Scheme 14).



Scheme 14

Radical fluorination steps are quiet scarce in the literature, although a stereoselective, direct radical fluorination of a C-H bond has been described.[36] L-C*is*-3-fluoroazetidine-2-carboxylic acid **57** was prepared in a single step approach from the corresponding amino acid **56** by photofluorination with fluoroxytrifluoromethane as the fluorine radical source in 53% yield (Scheme 15).



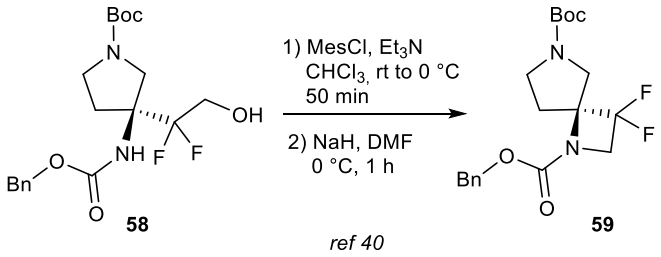
Scheme 15

2.1.2.2 Synthesis of difluorinated azetidines

Apart from the perfluorinated azetidines[37] and 4,4-difluorinated azetidin-2-ones,[38] no synthetic pathways toward 2,2-difluoroazetidines are known up to now.

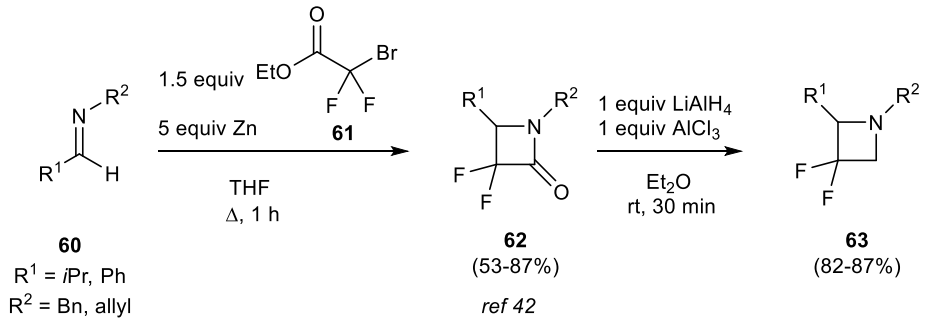
For the synthesis of 3,3-difluoroazetidines, next to frequently used deoxofluorination[33d,33f,39] and base-induced intramolecular ring closure methods (Scheme 16), an alternative approach has been developed starting from a difluorinated building block, ethyl bromodifluoroacetate **61** (Scheme 17).

Treatment of difluorinated alcohol **58** with mesyl chloride in the presence of triethylamine, afforded 3,3-difluoroazetidine **59**, after intramolecular displacement of the mesyl group by deprotonation of the secondary amide with sodium hydride (NaH) (Scheme 16).[40]



Scheme 16

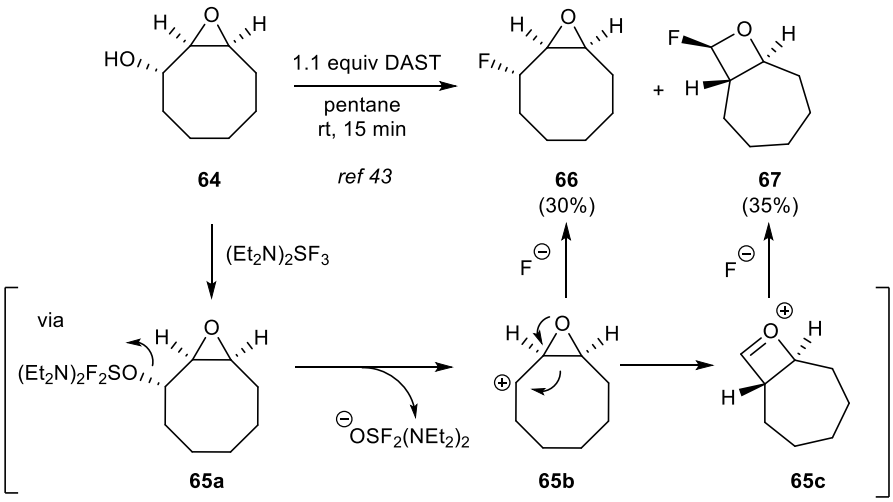
A Reformatsky reaction of ethyl bromodifluoroacetate **61** with appropriate imines **60** in the presence of activated Zn led to 3,3-difluoro-β-lactams **62**.[41] Removal of the carbonyl unit was performed by reduction with monochloroalane ($AlClH_2$), formed by combining one equivalent of lithium aluminium hydride ($LiAlH_4$) and one equivalent of $AlCl_3$, resulting in 3,3-difluoroazetidines **63** in excellent yields (82-87%).[42]



Scheme 17

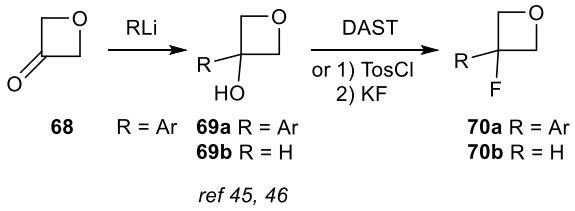
2.1.2.3 Synthesis of monofluorinated oxetanes

Monofluorinated oxetanes have only been obtained so far as (side) products in direct fluorination of suited alcohols with DAST or Deoxofluor®.[43] 2-Fluorooxetane **67** was observed as side product in the reaction with epoxyalcohol **64**. Presumably, the reaction occurs via skeletal rearrangement, with formation of intermediates **65b** and **65c**, which are trapped by a fluoride ion to give rise to the desired fluoroepoxide **66** and bicyclic oxetane **67** as a side product in a 1:1 ratio (Scheme 18).



Scheme 18

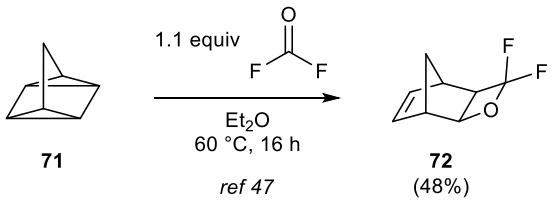
The synthesis of 3-substituted 3-fluorooxetanes **70a** was achieved by nucleophilic addition to oxetan-3-ones **68**, leading toward 3-aryl-3-hydroxyoxetanes **69a** (Scheme 19). Deoxofluorination of the hydroxyl group yielded the desired 3-substituted 3-fluorooxetanes **70a**.[44] When 3-unsubstituted 3-fluorooxetanes **70b** were required, the pathway started from oxetan-3-ol **69b**. Two different approaches have been reported for the preparation of these 3-unsubstituted 3-fluorooxetanes **70b**, *i.e.*, direct deoxofluorination with DAST[45] or tosylation followed by nucleophilic substitution with KF[46] (Scheme 19).



Scheme 19

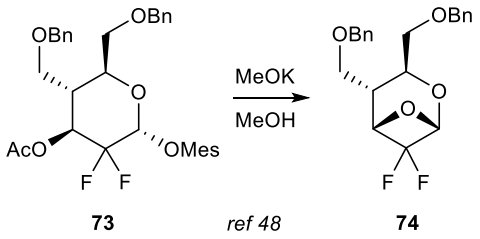
2.1.2.4 Synthesis of difluorinated oxetanes

Only one method has been reported for the synthesis of 2,2-difluorooxetane. A [2+2+2] cycloaddition reaction of quadricyclane **71** with COF_2 yielded the *exo*-4,4-difluoro-3-oxatricyclo[4.2.1.$0^{2,5}$]non-7-ene **72** in good yields (48%) (Scheme 20).[47]



Scheme 20

In constrast to the many reported examples for the synthesis of 3,3-difluoroazetidines and 3,3-difluoro-β-lactams,[41-42] almost no synthetic methods for the preparation of 3,3-difluorooxetanes[48] or 3,3-difluoro-β-propiolactones are available.[49] The only successful synthesis of a 3,3-difluorooxetane **74** involves an intramolecular substitution reaction of a mesyl group in tetrahydropyran **73** by prior cleavage of the acetate ester with potassium methoxide toward the alkoxy anion (Scheme 21).[48]

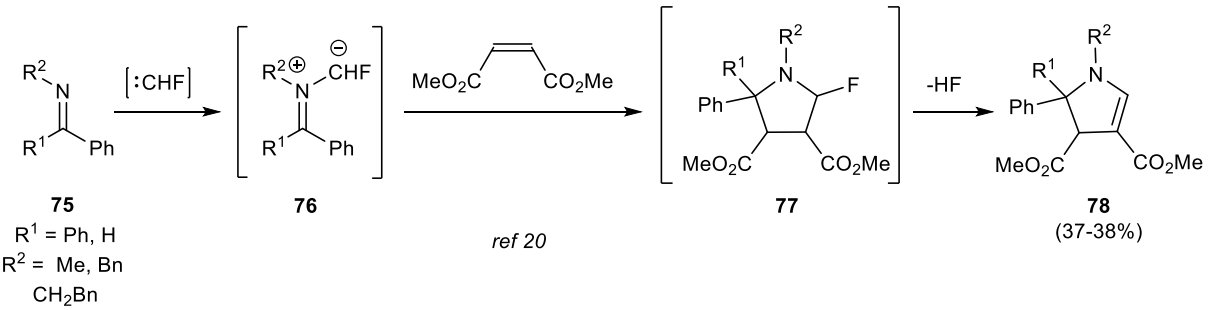


Scheme 21

2.1.3 Five-membered rings

2.1.3.1 Synthesis of monofluorinated pyrrolidines

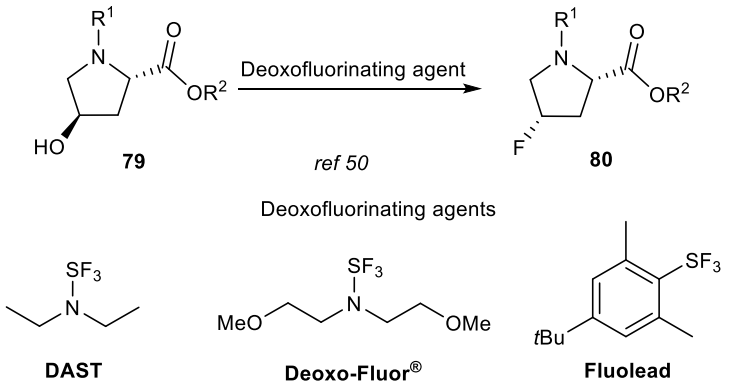
As noticed before for the synthesis of fluorinated azetidines (see paragraph 2.1.2.2), the accessibility of 2-fluoroazaheterocycles is low. The only reported 2-fluoropyrrolidine was observed during a 1,3-dipolar cycloaddition reaction of imines **75** with fluorocarbenes, in the presence of appropriate alkenes. Due to immediate elimination of hydrogen fluoride to non-fluorinated 2,3-dihydro-1*H*-pyrrole **78**, the 2-fluoropyrrolidines **77** could not be isolated as such (Scheme 22).[20]



Scheme 22

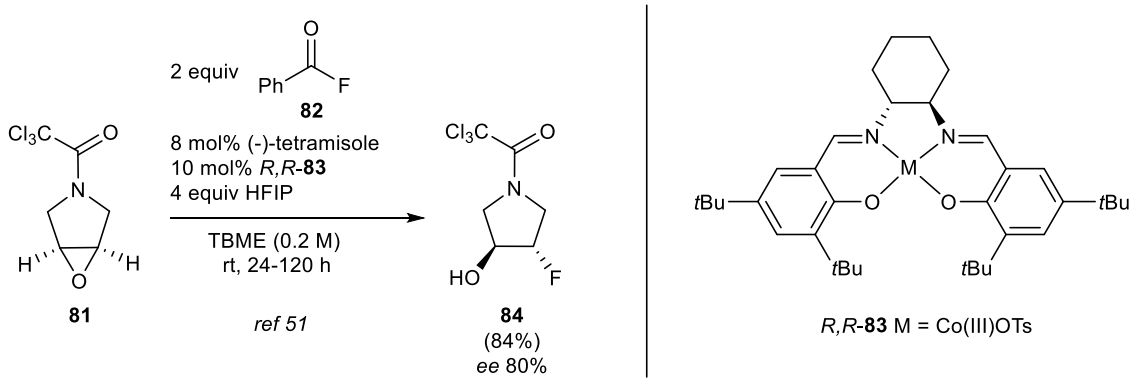
Known syntheses to 3-fluoropyrrolidines are quite diverse, including nucleophilic fluorination of hydroxylated precursors,[50] ring opening of suitably functionalized 3,4-epoxypyrrolidines with fluoride sources,[51] 1,3-dipolar cycloaddition of 2-fluoroacrylates,[52] rearrangement of 2-(hydroxyalkyl)azetidines,[53] electrophilic fluorination of γ-lactams[54] and iodocyclisation of allylic fluorides.[55]

3-Hydroxyprolines **79** are popular substrates in the direct stereoselective fluorination with different deoxofluorinating agents such as DAST, Deoxofluor® and Fluolead, yielding interesting fluorinated amino acid derivatives **80** (Scheme 23).[50a-d] Inversion of the stereocenter in hydroxyprolines **79** can be rationalized by introduction of fluorine considering a S_N2-mechanism.



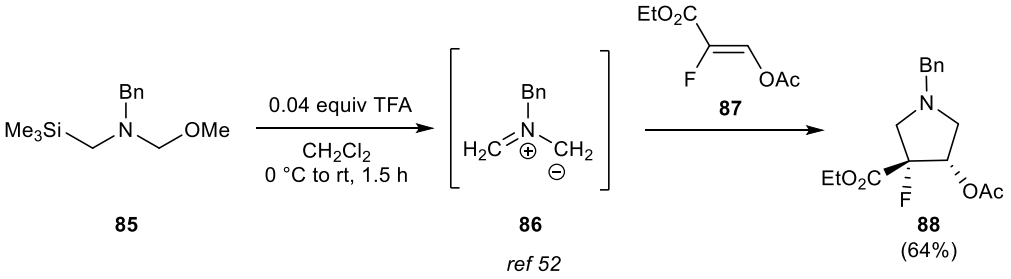
Scheme 23

3,4-Epoxypyrrolidine **81** underwent efficient hydrofluorination in the presence of 1,1,1,3,3,3-hexafluoroisopropanol (HFIP), benzoyl fluoride **82** and catalytic amounts of 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), resulting in β-fluoroalcohols **84**. When (-)-tetramisole, instead of DBN, and a chiral salen-type Co-complex **83** were added to the reaction mixture, an enantioselective outcome of the reaction was obtained (Scheme 24).[51]



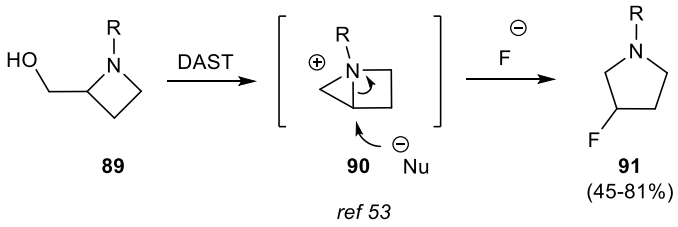
Scheme 24

As mentioned earlier for the synthesis of 2-fluoroaziridines and 2-fluoropyrrolidines, azomethine ylides react with alkenes toward functionalized pyrrolidines. 1,3-Dipolar cycloaddition reaction between (*Z*)-fluoroacrylate **87** and a non-fluorinated azomethine ylide **86**, generated *in situ* from *N*-methoxymethyl-*N*-(trimethylsilylmethyl)benzylamine **85**, gave *cis*-3-fluoropyrrolidine **88** in a concerted process in a good yield (64%) (Scheme 25).[52]



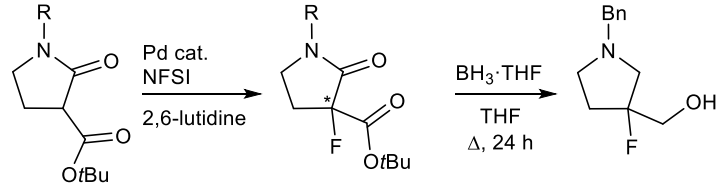
Scheme 25

In a fourth approach, ring expansion of 2-(hydroxymethyl)azetidines **89** with DAST turned out to be an effective method toward 3-fluoropyrrolidines **91**.[53] During the deoxofluorination reaction, the *in situ* formed leaving group was expelled by the azetidine nitrogen atom, as nitrogen is more nucleophilic than the fluoride ion,[56] leading to an aziridinium intermediate **90** (Scheme 26). Ring opening of this strained intermediate **90** took place by cleavage of the C–N bond induced by nucleophilic attack of the fluoride anion, affording 3-fluoropyrrolidines **91**.



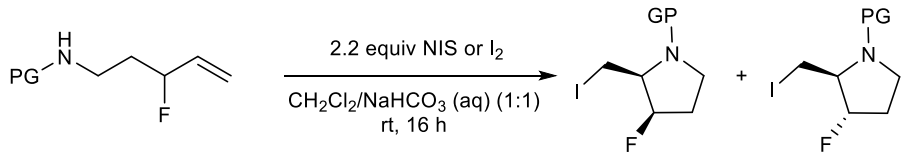
Scheme 26

A Pd-catalyzed enantioselective approach was established by electrophilic fluorination of γ-lactams **92a,b** with *N*-fluorobenzenesulfonimide (NFSI) yielding fluorinated pyrrolidinones **93a,b** in excellent yields and enantiomeric excess. Subsequent selective reduction with BH_3·THF complex of 3-fluoro-γ-lactams **93a** afforded 3-fluoropyrrolidine **94** (Scheme 27).[54]



Scheme 27

A final method consisted of a diastereoselective approach by iodoamination onto suited allylic fluorides (Scheme 28).[55] Activation of alkenes **95a,b**, by formation of an iodonium ion upon treatment with *N*-iodosuccinimide (NIS) or iodine, led to intramolecular attack of nitrogen in a 5-exo-trig cyclisation in good to excellent diastereomeric ratios depending on the used *N*-protective group.



95a PG = Ts
95b PG = Boc

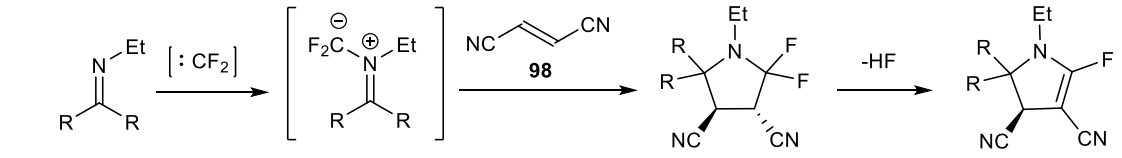
96a (82-88%, dr 12:1 to 14:1)
96b (42 %, dr 4:1)

Scheme 28

2.1.3.2 Synthesis of difluorinated pyrrolidines

Again, the accessibility of 2-fluoro five-membered azaheterocycles is quite low, as witnessed by only two approaches leading toward unstable 2,2-difluorinated pyrrolidines.[57]

The first method comprises the addition of difluorocarbene across the C=N bond of imine **97,** in the presence of an appropriate alkene **98,** to give rise to 2,2-difluorinated pyrrolidine **99**.[57a] In absence of alkene **98** fluorinated aziridines were formed (see 2.1.1.1, *vide supra*). Due to the extreme instability of 2,2-difluoropyrrolidines, only *trans*-methyl 2-(3,4-dicyano-5,5-difluoro-2,2-diphenyl-pyrrolidin-1-yl)acetate **99** was isolated in 38% yield. In all other cases, hydrogen fluoride elimination took place, eventually assisted by addition of anhydrous triethylamine, yielding 5-fluoro-2,3-dihydro-1*H*-pyrrole **100** (Scheme 29).



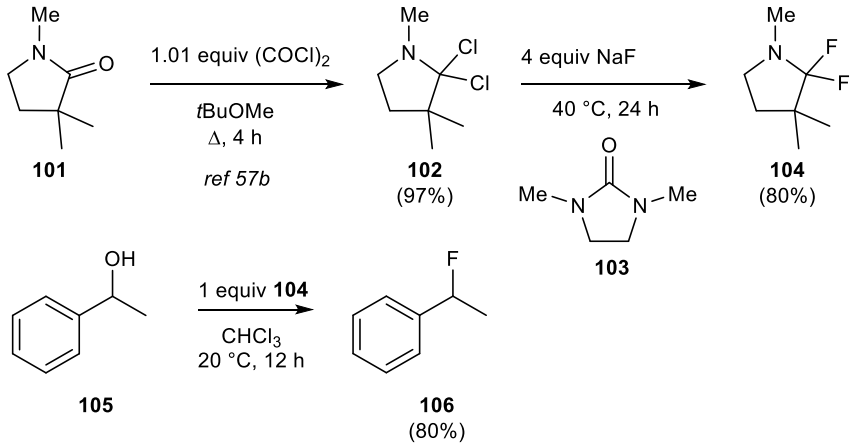
97
RR = 2,2'-biphenyl

99
(38%)

100
(64%)

Scheme 29

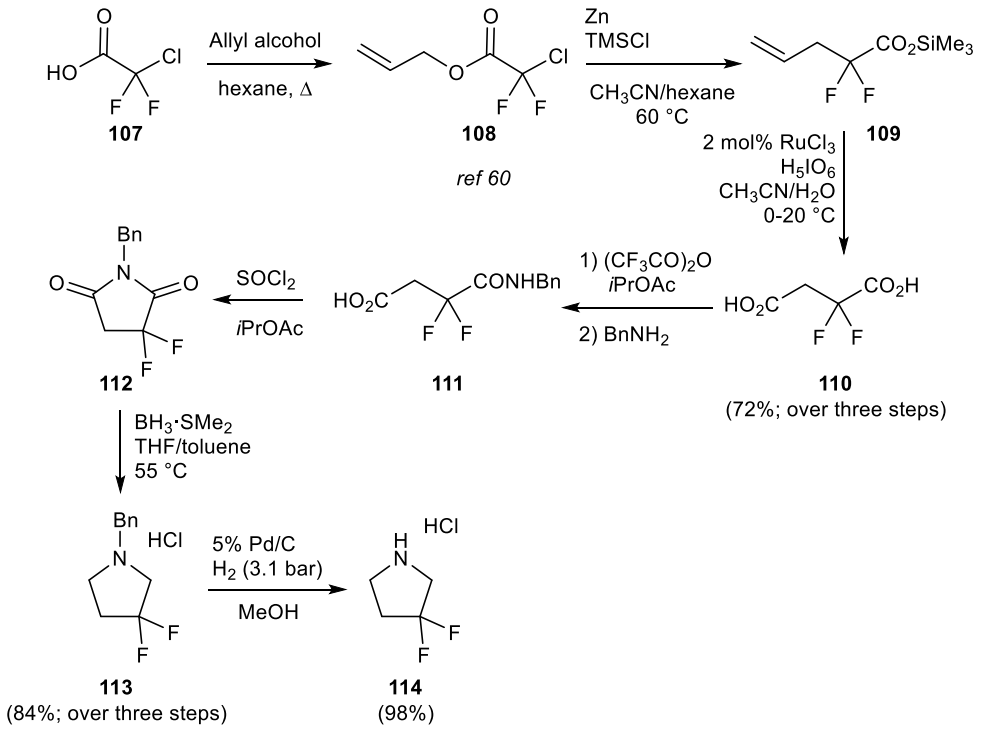
A second strategy implies the preparation of a fluorinating agent **104** by nucleophilic substitution of *geminal* dichloropyrrolidines **102**, starting from pyrrolidin-2-one **101**. Treatment of 1,3,3-trimethylpyrrolidin-2-one **101** with oxalyl chloride resulted in 2,2-dichloro-1,3,3-trimethylpyrrolidine **103**.[57b] Replacement of chlorine by fluorine was obtained with sodium fluoride (NaF) in 1,3-dimethylimidazolidinone **103** under mild conditions, affording 2,2-difluoro-1,3,3-trimethylpyrrolidine **104**. Smooth fluorination of 1-phenylethan-1-ol **105** with **104** as fluorinating agent was achieved to deliver (1-fluoroethyl)benzene **106** (Scheme 30).



Scheme 30

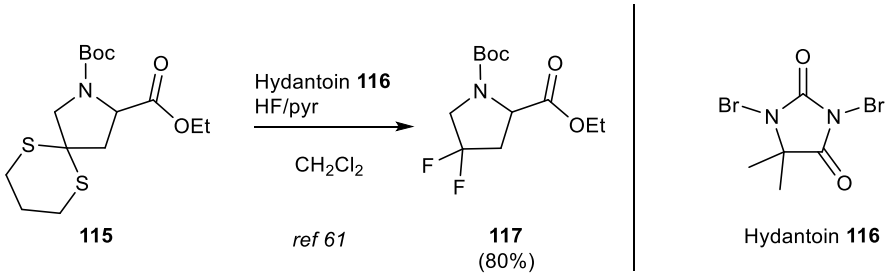
Next to general, earlier mentioned methods, such as deoxofluorination,[58] electrophilic fluorination of γ-lactams and reduction of the carbonyl[54b] or 1,3 cycloaddition onto 2,2-difluorovinyl structures,[59] some interesting alternative procedures have been reported for the preparation of 3,3-difluoropyrrolidines, namely a building block approach,[60] a method involving substitution of dithianes with fluorine,[61] radical ring closure steps[62] and even dehydrofluorination reactions of trifluoromethyl groups.[63]

3,3-Difluoropyrrolidine **114** was synthesized in a 7-step approach, starting from the commercially available chlorodifluoroacetic acid **107** as fluorinated building block.[60] After a condensation reaction of **107** with allyl alcohol toward ester **108**, this ester was subjected to a Claisen rearrangement with Zn dust to obtain difluoroester **109**. Ru(VIII)-catalyzed oxidation gave the desired dicarboxylic acid **110**. The *in situ* formed anhydride, by adding trifluoroacetic anhydride, reacted with benzylamine yielding amide **111**. Cyclisation with thionyl chloride, followed by reduction of the carbonyl functions in 2,2-difluorosuccinimide **112** and removal of the benzyl group resulted in 3,3-difluoropyrrolidine **114** (Scheme 31). The overall yield for this chromatography-free synthesis is 59%.



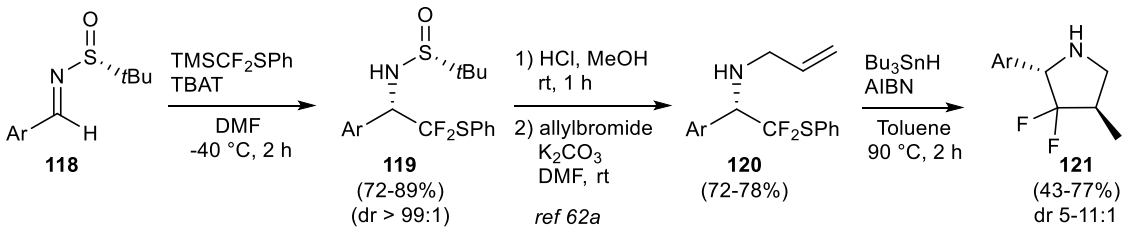
Scheme 31

Dithianes can be easily converted into their difluoromethylidene equivalents by treatment with a fluorine source and an oxidant.[61,64] In particular, when 4,4-dithianepyrrolidine **115** was treated with Olah's reagent and 1,3-dibromo-5,5-dimethylhydantoin **116**, 4,4-difluoropyrrolidine **117** was obtained in excellent yields (80%) (Scheme 32).



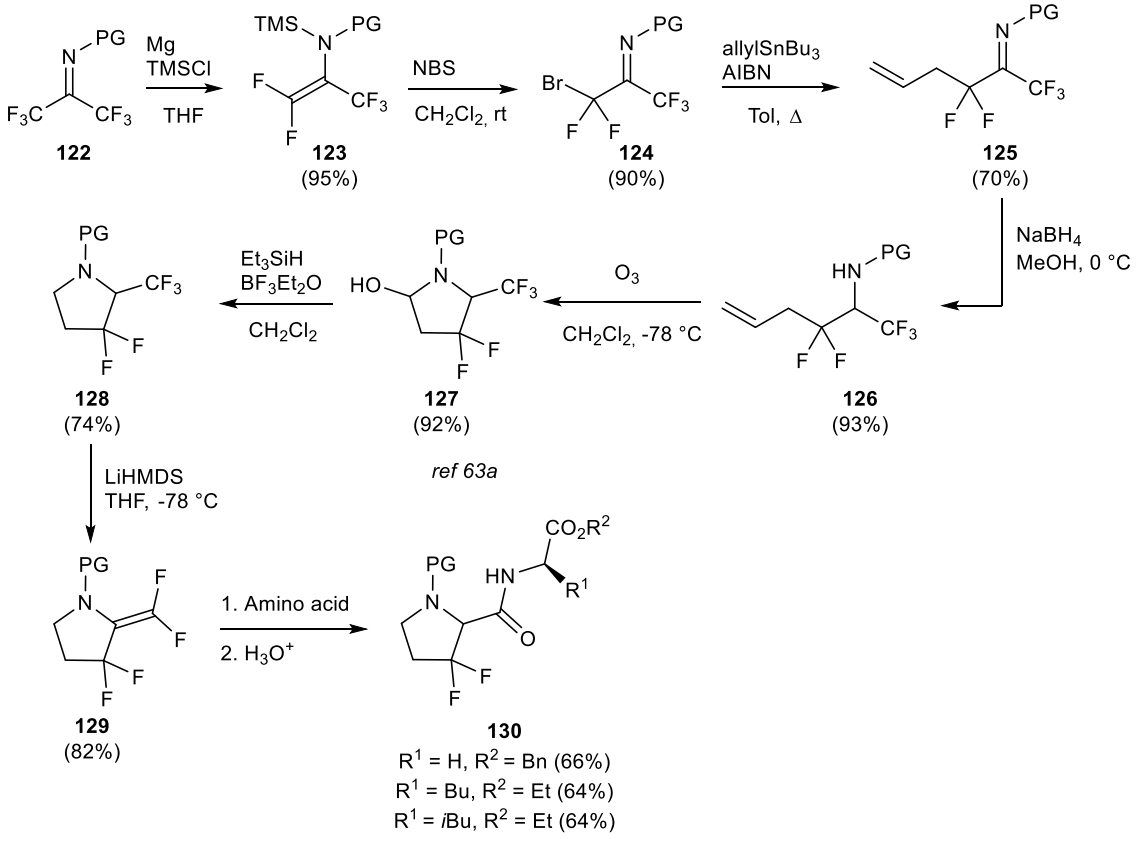
Scheme 32

In 2007, the use of [difluoro(phenylthio)methyl]trimethylsilane ($TMSCF_2SPh$), as latent difluoromethylene radical anion, has been evaluated in the synthesis of difluorinated compounds[62a] (Scheme 33). A Lewis base initiator (Tetrabutylammonium triphenyldifluorosilicate, TBAT) induced a highly diastereoselective nucleophilic addition onto *N*-sulfinyl imines **118** toward amines **119**. Substitution of the *N*-sulfinyl group by an allylic moiety allowed for further transformation of the allylamines **120** into *trans*-2,4-disubstituted 3,3-difluoropyrrolidines **121** through radical cyclisation.[62]



Scheme 33

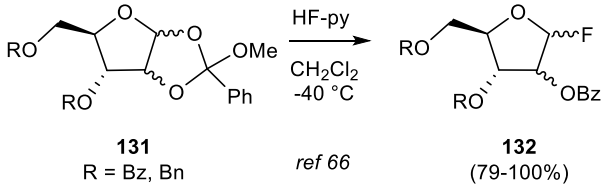
A far less explored technique is dehydrofluorination of trifluoromethyl groups (Scheme 34).[63] So far only two examples have been reported, and the synthesis starting from hexafluoroacetone imine **122** is depicted here (Scheme 34). Generally, these methods can be summarized as elimination of hydrogen fluoride with metallic Mg[63a] or Li-bases[63b] (BuLi or LiHMDS) toward difluoroenamine **123**. Electrophilic addition of bromine onto *gem*-difluoroalkene **123** was followed by a radical allylation with allyltributyltin. Reduction with sodium borohydride in methanol afforded amine **126** in 93% yield. Ring closure was accomplished upon ozonolysis to cyclic aminal **127**, which was dehydroxylated with triethylsilane toward 2-trifluoromethyl-3,3-difluoropyrrolidine **128**. The second trifluoromethyl group in **128** was intended as a synthon for a carboxylic acid, which was further used in the synthesis of peptides **130**.



Scheme 34

2.1.3.3 Synthesis of monofluorinated tetrahydrofurans

Although many structures contain a 2-fluorotetrahydrofuran moiety, only two synthetic approaches toward 2-fluorotetrahydrofurans **132** are known. These general approaches consist of deoxofluorination of hemiacetals[65] and acid-induced ring opening of furanose-derived 1,2-orthoesters **131** (Scheme 35).[66]



131
R = Bz, Bn

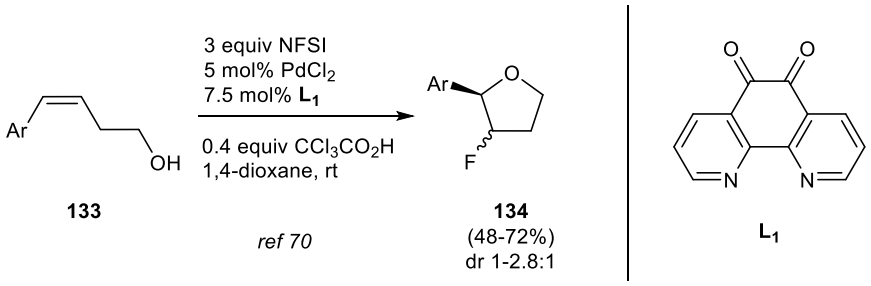
ref 66

132
(79-100%)

Scheme 35

Besides commonly used approaches such as deoxofluorination,[67] nucleophilic intramolecular substitution[68] or radical-promoted cyclisation of appropriate allyl ethers[69] to 3-fluorotetrahydrofurans, some interesting alternatives have been reported, *i.e.*, fluorooxylation of styrenes **133** (Scheme 36),[70] an unexpected ring expansion of epoxides (Scheme 37)[71] and a method for [^{18}F]-labelling of furanoses (Scheme 38).[73]

Fluorooxylation of styrenes **133** concerned a Pd-catalyzed introduction of fluorine onto the double bond. Subsequent ring closure by attack of the hydroxyl function led to 3-fluorotetrahydrofuran **134** (Scheme 36).[70]



133

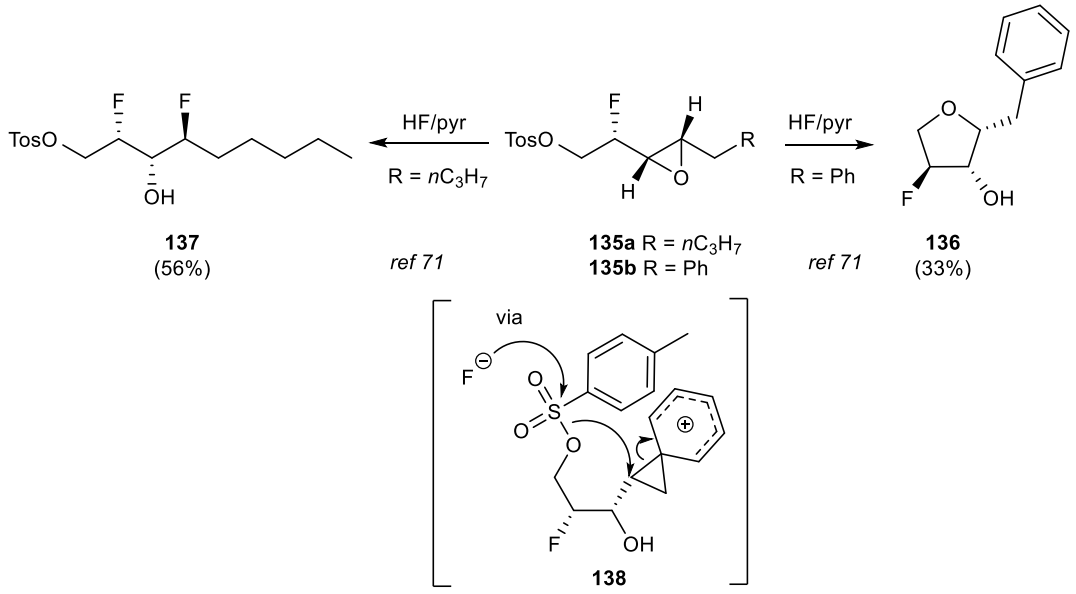
ref 70

134
(48-72%)
dr 1-2.8:1

L$_1$

Scheme 36

Treatment of epoxide **135a** with HF/pyridine led to the regio- and stereoselective ring opening of the epoxide moiety. However, when the same reaction conditions were applied to **135b**, 2-benzyl-4-fluorotetrahydrofuran-3-ol **136** was obtained. A possible reaction mechanism consists of the formation of a bicyclic cationic intermediate **138**. Fluoride ion-triggered tosyl cleavage afforded cyclisation to 2-benzyl-4-fluorotetrahydrofuran-3-ol **136** (Scheme 37).[71]

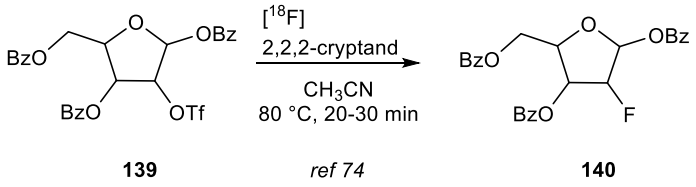


137 (56%) — *ref 71* — **135a** R = nC_3H_7, **135b** R = Ph — *ref 71* — **136** (33%)

138

Scheme 37

Furanoses, as five-membered carbohydrates, are of special interest for late stage introduction of radiolabeled fluorine, allowing *in vivo* imaging (of gene expression).[72] With a life time of 110 min, the need for a fast and clean late stage fluorination is of vital importance, eliminating overnight deoxofluorination reactions.[73] [^{18}F]-Radiolabeling of these five-membered sugars **140** can be smoothly achieved by a short reaction of furanose **139** with the anhydrous fluoride atom in a S_N2 substitution reaction (Scheme 38).[72,74] Often 2,2,2-cryptand was added to enhance the nucleophilic character of the fluoride atom.

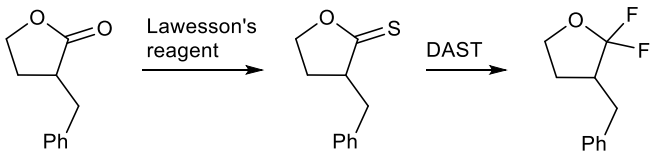


139 — *ref 74* — **140**

Scheme 38

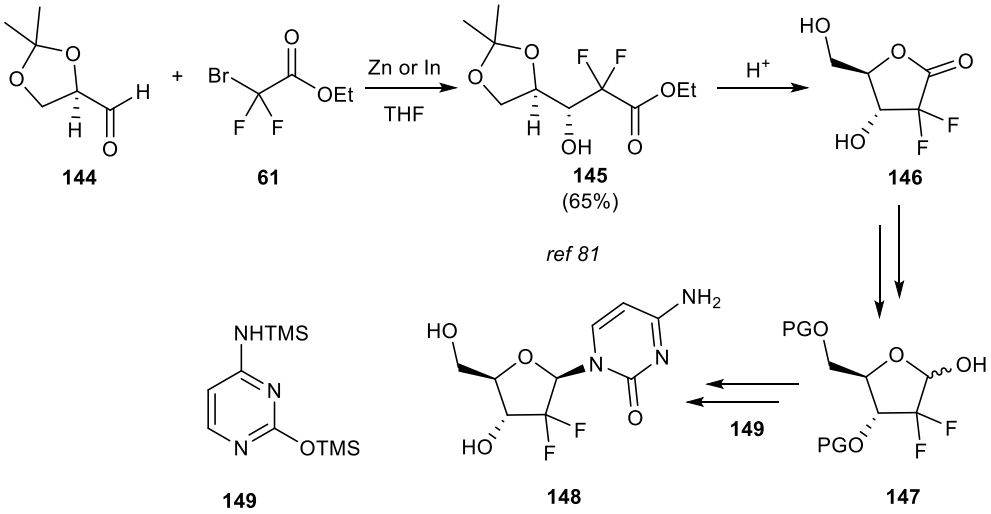
2.1.3.4 Synthesis of difluorinated tetrahydrofurans

Analogous to previously mentioned 2-fluoro substituted heterocycles, the synthetic methods to 2,2-difluorotetrahydrofurans remain limited. Only one single synthetic approach has been developed toward 2,2-difluorotetrahydrofurans. Prior to a treatment with DAST, the propiolactone substrate **141** was converted with Lawesson's reagent to the thioester derivative **142** (Scheme 39).[75] Albeit the generality of these reactions the overall yield is rather low (7%), probably due to the instability of the formed 2,2-difluorotetrahydrofuran **143**.



Scheme 39

Practically all synthetic approaches with regard to 3,3-difluorotetrahydrofurans can be specified to the synthesis of fluorinated furanoses/riboses, which are applicable in the further synthesis toward (deoxy-)ribonucleosides, as potential antitumor agents.[76] Known procedures for the preparation of 3,3-difluorofuranoses are deoxofluorination,[77] electrophilic fluorine introduction in the α-position of carbonyl functions,[78] radical cyclisation,[79] dithiane removal with Olah's reagent,[80] but the most popular approach is Hertel's method for the synthesis of 2-deoxy-2,2-difluororibonucleosides.[81] This building block approach starts with a Reformatsky reaction with Zn or In of ethyl bromodifluoroacetate **61** with isopropylidene glyceraldehyde **144** (Scheme 40).[76b,82] Deprotection of the acetal **145** and simultaneous lactonisation under acidic conditions resulted in 2,2-difluororibolactones **146**. Reduction of lactone **146** provided a mixture of α- and β-2-deoxy-2,2-difluororibofuranoses **147**, which were separated by crystallisation. Hemiacetal **147** was trapped in its cyclic form by transforming the available hydroxyl function to a good leaving group. Subsequent substitution reaction with 2-*O*- and 4-*N*-protected cytosine **149** yielded 2-deoxy-2,2-difluororibonucleosides **148** (β-gemcitabine) after removal of all protective groups.

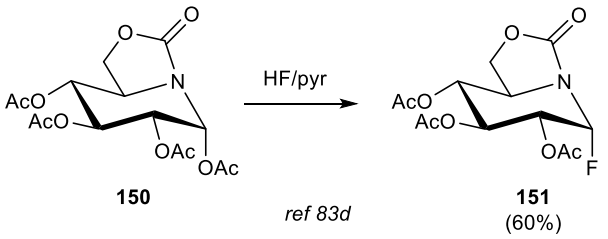


Scheme 40

2.1.4 Six-membered rings

2.1.4.1 Synthesis of monofluorinated piperidines

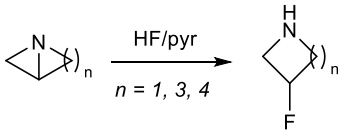
Synthetic methods toward 2-fluoropiperidines are scarce, demonstrated by only a few examples in the literature.[83] Next to deoxofluorination of appropriate piperidin-2-ols,[83a-c] a selective fluorination of azasugar **150** toward the stable aza-2-fluoroglucoside **151** with HF in pyridine is known (Scheme 41).[83d,83e]



150 *ref 83d* **151** (60%)

Scheme 41

3- and 4-Fluoropiperidines are of high interest as potential drug candidates as T-type calcium channel antagonists.[9,84] Many reports have been published on the synthesis toward well-studied 3-fluoropiperidines, involving deoxofluorination,[85] ring expansion of 2-(hydroxymethyl)pyrrolidines,[86] aminofluorination of appropriate alkenes,[87] triflate substitution by a fluoride ion[88] and electrophilic introduction of fluorine in the α-position of a carbonyl function[89] as major strategies in the synthesis of 3-fluoropiperidines. Noteworthy, 1-azabicyclo[n.1.0]alkanes **152** reacted with Olah's reagent (HF/pyridine) to racemic 3-fluoroazetidines (n = 1), 3-fluoropiperidines (n = 3) and 3-fluoroazepines (n = 4) **153** (Scheme 42).[90]

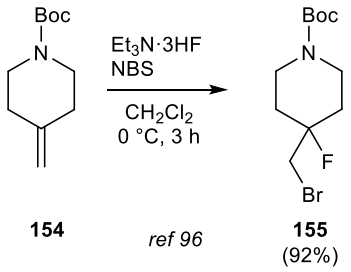


152 *ref 90* **153** (58-95%)

Scheme 42

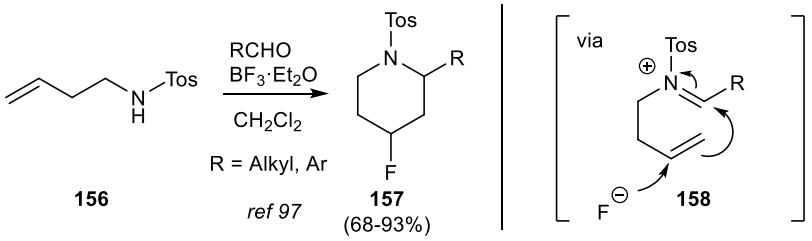
Besides the deoxofluorination of piperidin-4-ols toward 4-fluoropiperidines, which is frequently applied in patent literature,[91] some general applicable alternatives have been reported, such as a double nucleophilic substitution with $BnNH_2$ inducing ring closure,[92] nucleophilic substitution of a suitable sulfonyl group by fluorine,[93] ring opening of fused epoxides[94] and aziridines[95] on piperidine rings, direct fluorine introduction by bromofluorination on methylidenepiperidines **154** (Scheme 43),[96] and an aza-Prins cyclisation reaction (Scheme 44).[97]

Bromofluorination across γ-methylidenepiperidine **154** with triethylamine trihydrofluoride and *N*-bromosuccinimide led to the regioselective introduction of fluorine at the more substituted position, yielding 4-(bromomethyl)-4-fluoropiperidine **155** (Scheme 43).[96]



Scheme 43

N-tosyl-protected homoallylamines **156** reacted with aldehydes toward their corresponding iminium ions **158**. Treatment of **158** with borontrifluoride etherate ($BF_3 \cdot Et_2O$), as a fluoride source, then triggered a ring-closing step toward 4-fluoropiperidines **157**.[97]



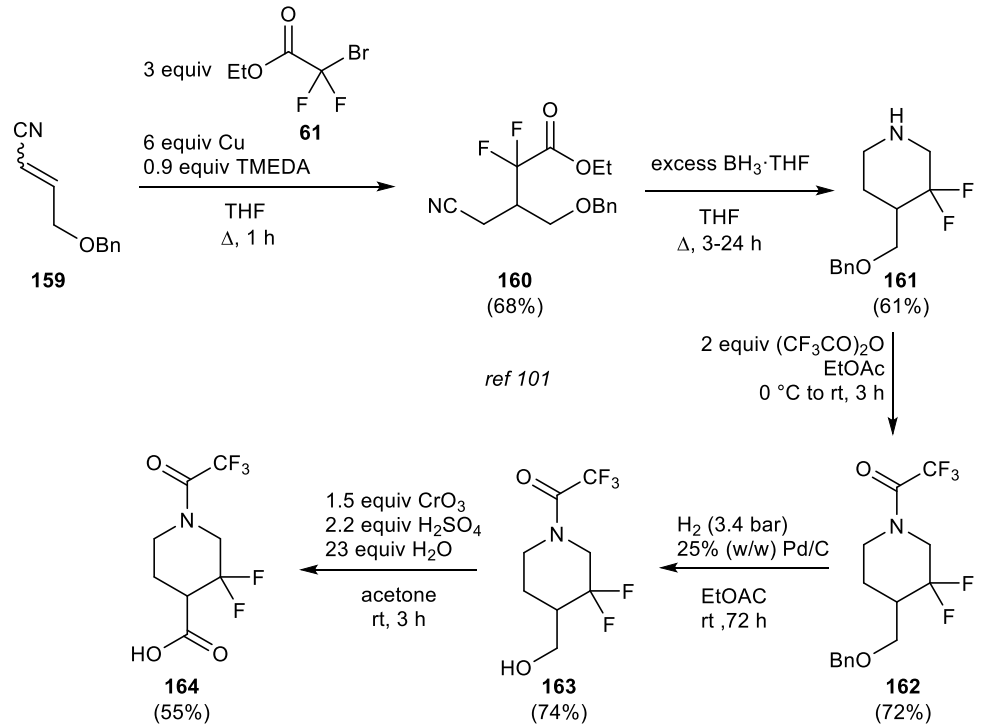
Scheme 44

2.1.4.2 Synthesis of difluorinated piperidines

The synthesis of 2,2-difluoropiperidines has been described in a single example by reaction of piperidin-2-one with DAST.[98]

On the other hand, many approaches toward 3,3-difluoropiperidines are known. In that respect, two major methods can be distinguished, namely the obvious deoxofluorination of a carbonyl unit [44c,99] and a building block approach.[100] Recently, the use of a building block approach has gained a lot of interest, because precarious deoxofluorinating agents can be avoided. Especially, ethyl bromodifluoroacetate **61** is commonly deployed as a cheap substrate in various syntheses. As a representative example the synthesis toward *N*-protected 3,3-difluoroisonipecotic acid **164** is depicted (Scheme 45).[101] 3-Substituted acrylonitrile **159** was treated with ethyl bromodifluoroacetate **61** in the presence of copper via a 1,4-addition toward ester **160**. Subsequent reduction of the nitrile induced ring closure toward a piperidin-2-one, which was immediately further reduced, yielding 3,3-difluoropiperidines **161**. Protection of the free amino group with a trifluoroacetyl group, followed by

hydrogenation of the benzyl group over Pd/C and final oxidation using chromium(VI) oxide of the hydroxymethyl piperidine **163**, afforded 3,3-difluoroisonipecotic acid **164**.



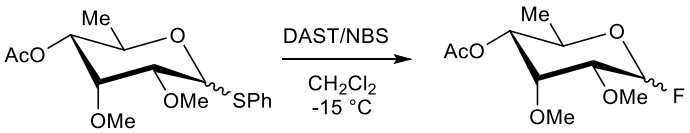
Scheme 45

Despite many reported methods to prepare 3,3-difluoropiperidines, the approaches toward 4,4-difluoropiperidines remain limited to the conversion of piperidin-4-ones by deoxofluorination[102] and *geminal* difluorination of dithiane systems.[103]

2.1.4.3 Synthesis of monofluorinated tetrahydropyrans

In contrast to other 2-fluoroheterocycles, a broad range of methods toward glycosyl fluorides, an important subclass of 2-fluorotetrahydropyrans, have been developed. Fluorine introduction at the anomeric carbon was achieved by treatment of 1-hydroxy-, 1-*O/S*-protected or 1-bromo sugars with hydrogen fluoride,[104] a deoxofluorinating agent,[105] metal fluorides (such as AgF, ZnF_2 or CF_3ZnBr and TiF_4),[106] TBAF,[107] DEAD/PPh_3/Et_3OBF_4[108] or 4-methyl(difluoroiodo)benzene.[109]

The conversion of thiol glycosides **165** into glycoside fluorides **166** can be demonstrated by the concomitant use of DAST and NBS (Scheme 46).[110]

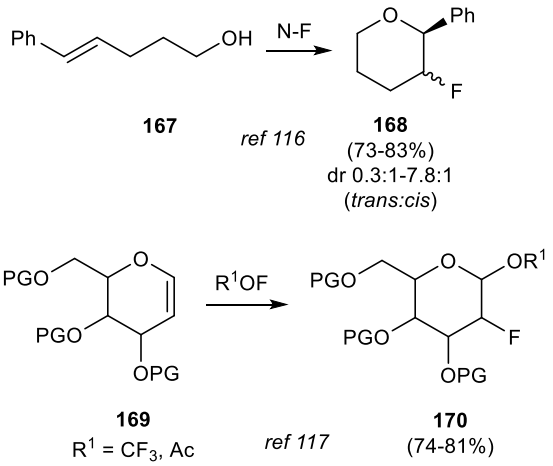


165 *ref 110* **166** (79%)

Scheme 46

Known procedures toward 3-fluorotetrahydropyrans can be summarized as deoxofluorination of suited tetrahydropyran-3-ols,[111] triflate displacement by a fluoride ion,[112] ring expansion of smaller cyclic structures,[113] Prins-type cyclisation reactions,[114] a building block approach,[115] or electrophilic addition of fluorine with Selectfluor®/NFSI[116] or hypofluorites ($FOCF_3$, CH_3CO_2F)[117] onto an appropriate double bond.

In the special case when *trans*-5-phenylpent-4-en-1-ol **167** reacted with Selectfluor® or *N*-fluorobenzenesulfonimide (NFSI), immediate intramolecular fluorocyclisation of the unsaturated alcohol took place to yield *cis*- and *trans*-3-fluorotetrahydropyrans **168** (Scheme 47).[118] Cyclic glycals **169** were transformed analogously in the presence of hypofluorites to 3-fluorohexoses **170**, in which the formed carbenium ion was trapped by the counterpart of the electrophilic fluorine, with in both cases exclusive fluorine introduction at the more nucleophilic C3-position (Scheme 47).[117]



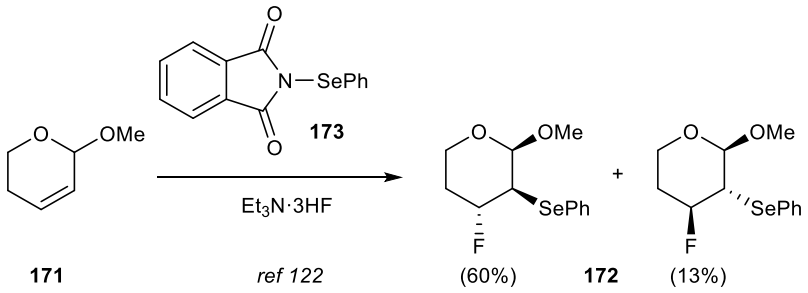
167 *ref 116* **168** (73-83%) dr 0.3:1-7.8:1 (*trans:cis*)

169 $R^1 = CF_3$, Ac *ref 117* **170** (74-81%)

Scheme 47

4-Fluorotetrahydropyrans are far less studied then their 3-fluoro analogues. Besides a deoxofluorinating step,[119] several Prins-fluorination cyclisation reactions, with different Lewis acids as the fluorine source ($BF_3{\cdot}Et_2O$, $HBF_4{\cdot}Et_2O$, TiF_4), are reported as useful alternatives.[97c,120] Sporadically, other methods were considered, like regioselective opening of 3,4-epoxytetrahydropyrans with KHF_2,[121] or phenylselenofluorination of alkenes **171** with *N*-

(phenylseleno)phtalimide **173** in the presence of triethylamine trihydrofluoride ($Et_3N{\cdot}3HF$) (Scheme 48).[122]

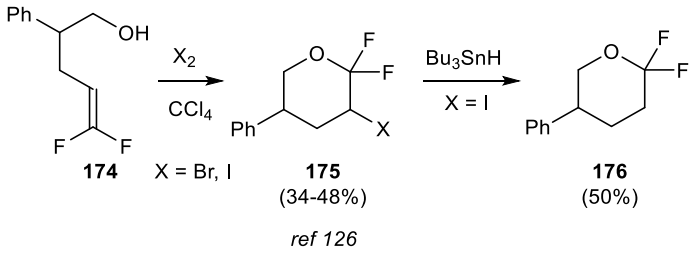


Scheme 48

2.1.4.4 Synthesis of difluorinated tetrahydropyrans

In comparison to their monofluorinated analogues, difluorinated tetrahydropyrans are far less studied. The low accessibility of 2,2-difluorotetrahydropyrans is reflected by the limited number of reports dealing with the synthesis of these difluorinated oxaheterocycles. Only a few standardized experiments such as deoxofluorination,[123] geminal difluorination of dithiane systems,[124] nucleophilic fluoride displacement of halogen atoms[125] and halogen-induced electrophilic cyclisation of *gem*-difluoroolefins toward 2,2-difluorotetrahydropyrans (Scheme 49) are reported.[126]

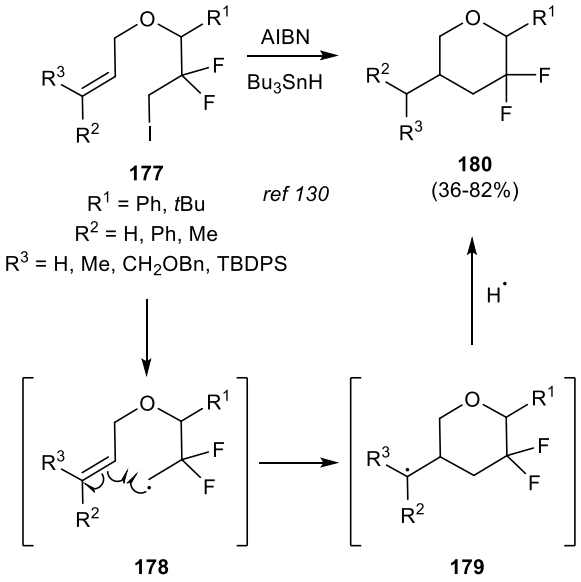
Halogen activation of alkene **174** by bromine and iodine triggered intramolecular ring closure to yield 3-halo-2,2-difluorotetrahydropyran **175**. Subsequent treatment with tributyltin hydride gave rise to the corresponding difluorinated tetrahydropyran **176** via a radical halogen-proton substitution (Scheme 49).[126]



Scheme 49

Furthermore, only a handful approaches toward 3,3-difluorotetrahydropyrans **180** are known, like deoxofluorination,[127] a building block approach,[128] dithiane substitution by fluorine[129] and the radical ring closure of suitably substituted alkenes **177**.[130]

Radical initiator azabisisobutyronitrile (AIBN) furnished iodide-removal leading to an unstable primary radical **178**. Radical ring closure, through a more stable tertiary radical intermediate **179** was followed by termination with tributyltin hydride as a radical proton source, yielding 3,3-difluorotetrahydropyran **180** (Scheme 50).[130]



Scheme 50

Finally, 4,4-difluorotetrahydropyrans can be prepared by deoxofluorination[131] or starting from ethyl bromodifluoroacetate **61** as fluorinated precursor.[132]

2.1.5 Conclusions

In general, it can be stated that over the years the use of precarious deoxofluorinating agents remains the utmost applied method to prepare mono- and difluorinated compounds, despite the growing number of available fluorinated building blocks. Next to deoxofluorination, the majority of the methods can be classified as nucleophilic introduction of fluorine, which is contradictory to the low nucleophilic character of the fluoride ion. Excluding other (better) nucleophiles and thorough activation of the substrates are therefore required to overcome this drawback.

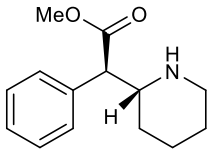
Direct fluorination of three-membered heterocyclic rings was not observed, probably due to the high reactivity, caused by ring strain in these cyclic systems.

3 Results and Discussion

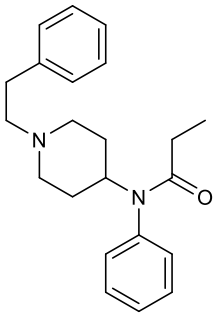
3.1 Synthesis of 3-substituted 5,5-difluoropiperidines

3.1.1 Fluorinated piperidines in medicinal chemistry

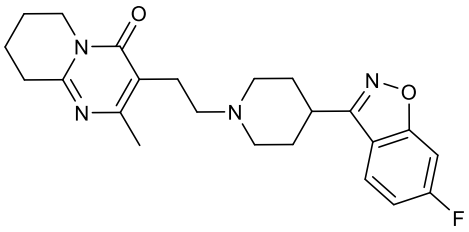
The piperidine motif is present in a variety of naturally occurring alkaloids[133] and is extensively used as core structure in medicinal chemistry, for example in Methylphenidate ER **181**, Fentanyl **182** and Risperdal ® **183**.[134]



181
Methylphenidate ER
Psychostimulants, Actavis

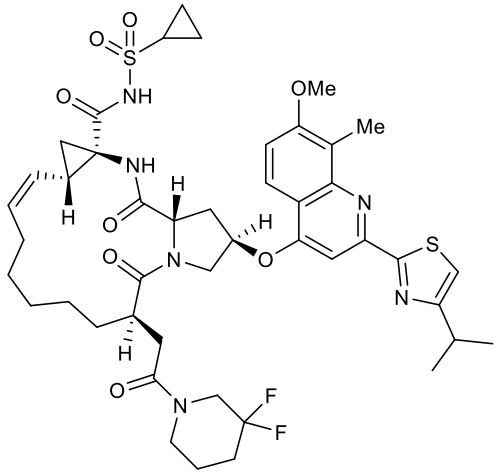


182
Fentanyl
Narcotic Analgesics, Mylan



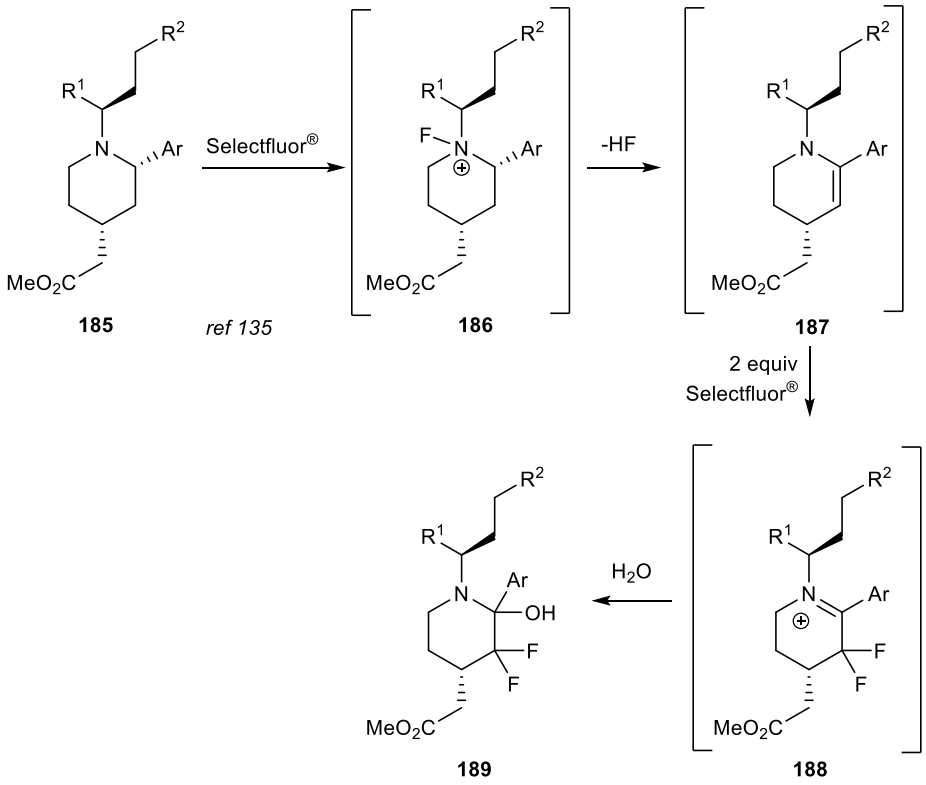
183
Risperdal®
Antipsychotics, Janssen Pharmaceutica

In numerous cases, the introduction of fluorine atoms in bioactive azaheterocyclic compounds has a pK_a lowering effect, leading to altered pharmacological profiles. This procedure has been applied to modulate the basicity of piperidine-containing anti-inflammatory drugs[135] and the difluorinated piperidine core has for example been used in the synthesis of Neceprevir **184**, a NS3 serine protease-inhibitor for the treatment of Hepatitis C.



184
Neceprevir

Besides the frequently applied deoxofluorination and fluorinated building block approaches (see Paragraph 2.1.4.2.), highly substituted 3,3-difluoropiperidines have been synthesized via electrophilic fluorination of an enamine species with Selectfluor® for the preparation of anti-Alzheimer's agents (Scheme 51).[136] As possible mechanism it was suggested that piperidine **185** is *N*-fluorinated to give ammonium intermediate **186**, followed by HF elimination to give an iminium ion that can tautomerize toward enamine **187**. Treatment of enamine **187** with Selectfluor® gave rise to the electrophilic introduction of fluorine toward iminium ion **188** that was hydrated during aqueous work up to provide the stable hemiaminal **189**.

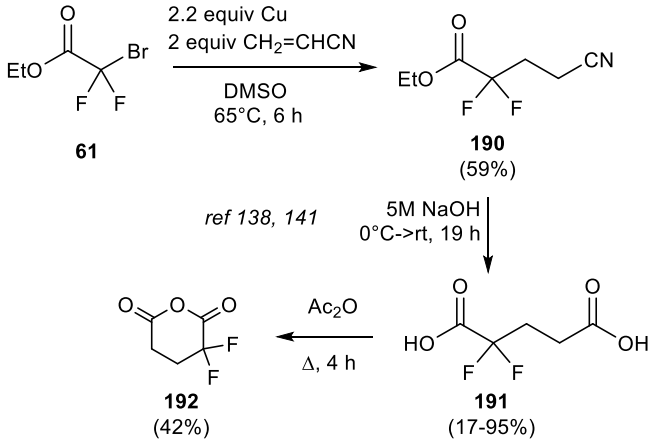


Scheme 51

Gem-difluorinated iminosugars, which are potential glycoside inhibitors, can be prepared from trifluoroethanol or 3-bromo-3,3-difluoropropene via tedious approaches.[11] Especially fluorinated piperidines substituted with an additional hydroxymethyl, aminomethyl, hydroxy or amino group are of interest as bifunctional building blocks toward bioactive compounds. Furthermore, fluorinated (hydroxymethyl)piperidines have shown to possess high potential for the treatment of metabolic syndrome,[137] a combination of several risk factors linked to obesity. In that respect, this PhD-work focused on the development of a new and general approach toward 3-methoxycarbonyl- and 3-hydroxymethyl-5,5-difluoropiperidines.

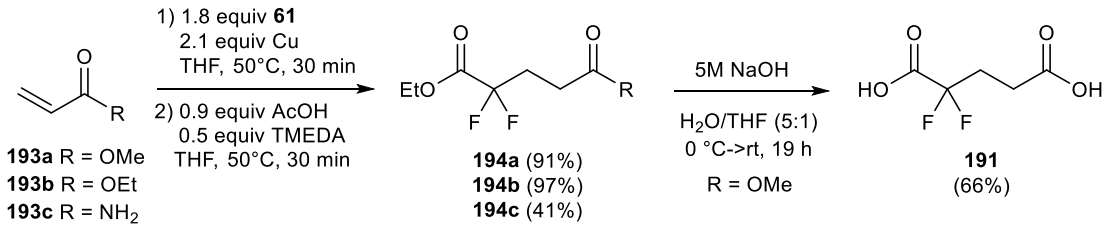
3.1.2 Synthesis of 3-functionalized 5,5-difluoropiperidines starting from ethyl bromodifluoroacetate

A convenient approach toward novel fluorinated piperidines was developed via reaction between 2,2-difluoroglutaric anhydride **192** and suitably substituted imines. The synthesis of 2,2-difluoroglutaric anhydride **192** was accomplished via a three-step pathway starting from commercially available ethyl bromodifluoroacetate **61**, following a literature procedure (Scheme 52).[138]



Scheme 52

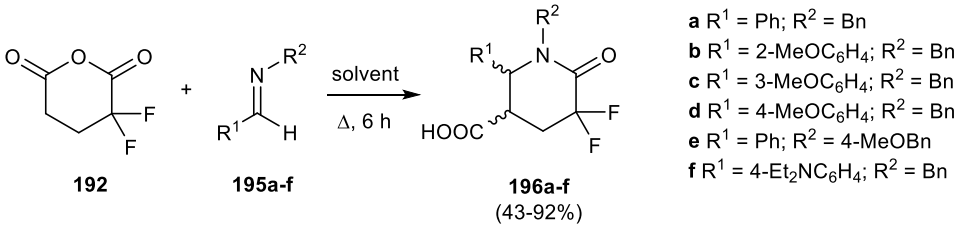
Ethyl 4-cyano-2,2-difluorobutanoate **190** was synthesized starting from ethyl bromodifluoroacetate **61** and acrylonitrile in the presence of copper via a Michael-type reaction in DMSO in 59% yield.[138a] Hydrolysis of nitrile **190** in aqueous NaOH (5M) provided 2,2-difluoroglutaric acid **191** in precarious yields (17-95%).[138b] After publication of the obtained results,[139] an improved copper-mediated 1,4-addition reaction has been reported.[140] This method was based on the addition of tetramethylethylenediamine (TMEDA) and a protic additive (AcOH) to the reaction mixture after 30 minutes at 50°C in THF and afforded the desired 1,4-adduct **190** in 91% yield within one hour. Performing the reaction in THF also avoided problematic work up of emulsifying mixtures with DMSO and Cu-salts. With this adapted procedure in hand, 1,4-addition onto acrylates **193a,b** and acrylamide **193c** was possible, yielding fluorinated esters **194a-c** (41-97%) (Scheme 53). Subsequent hydrolysis of ester **194a** furnished pure glutaric acid **191** after acidification and simple extraction with EtOAc in 66% yield. Due to the high solubility of glutaric acid in water (> 50%) the yield could eventually still be increased by repeated extraction of the aqueous layer (5 to 7 times instead of 3 times).



Scheme 53

Subsequent ring closure of 2,2-difluoroglutaric acid **191** in acetic anhydride after four hours under reflux conditions yielded 2,2-difluoroglutaric anhydride **192** in 42% (Scheme 52).[141]

Reaction of 2,2-difluoroglutaric anhydride **192** with benzaldehyde-derived imines **195a-f** in toluene or xylene under reflux for six hours afforded mixtures of *cis*- and *trans*-1-substituted 5,5-difluoropiperidin-6-one-3-carboxylic acids **196a-f** in moderate to good yields (43-92%) (Scheme 54, Table 1).



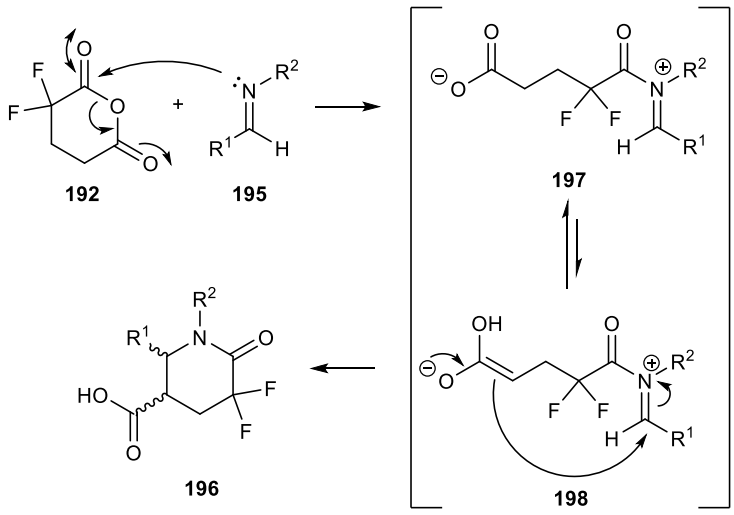
Scheme 54

Table 1. Influence of the imine substituents and the reaction temperature on the diastereomeric ratio of piperidinone carboxylic acids 196a-f.

Entry	R^1	R^2	Solvent	Product	Yield (%)[c]	*Trans*: *cis*
1	Ph	Bn	toluene	**196a**	74	5:1[a]
2			xylene		52	4:1[a]
3	2-$MeOC_6H_4$	Bn	toluene	**196b**	79	*Trans*
4			xylene		69	*Trans*
5	3-$MeOC_6H_4$	Bn	toluene	**196c**	67	12:1[b]
6			xylene		77	4:1[b]
7	4-$MeOC_6H_4$	Bn	toluene	**196d**	85	6:1[b]
8			xylene		80	3:1[b]
9	Ph	4-MeOBn	toluene	**196e**	45	6:1[b]
10			xylene		92	4:1[b]
11	4-$Et_2NC_6H_4$	Bn	toluene	**196f**	86	3:1[a]
12			xylene		43	2:1[a]

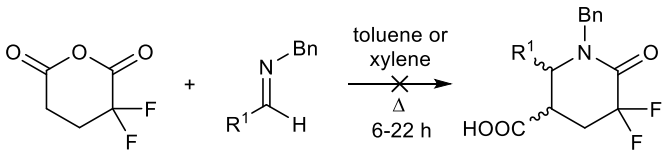
[a] Ratio determined by ^1H NMR based at the NCH-signal ($CDCl_3$). [b] Ratio determined by ^1H NMR based at the OMe-signal ($CDCl_3$). [c] Crude Yields.

The best results were obtained when electron-rich imines were used as reaction partners. The enhanced reactivity of these electron-rich imines supports a reaction mechanism in which the imine nitrogen serves as a nucleophile as a first step in the reaction cascade (Scheme 55). This nucleophilic attack leads to the formation of a zwitterionic intermediate **197,** which suffers ring closure caused by addition of the enolate to the iminium ion **198,** leading to the formation of *cis*- and *trans*-piperidinones **196**.[142] Repulsion between the carboxylate group and the phenyl ring controls the stereoselective outcome of this reaction, steering the reaction toward the *trans*-compounds as major diastereomers (vide infra), which is in agreement with literature data on analogous non-fluorinated piperidinones.[143]



Scheme 55

Indeed, reaction of anhydride **192** with electron-poor imines, such as *N*-(4-nitrobenzylidene)benzylamine **195g** or the *N*-benzylimine **195h** derived from ethyl glyoxalate was sluggish, and degradation of anhydride **192** proceeded faster than the formation of the corresponding fluorinated piperidinone-3-carboxylic acids **196g-h** (Scheme 56). Even when alkyl-derived imines such as *N*-(isobutylidene)benzylamine **195i** and *N*-(2-benzyloxyethylidene)benzylamine **195j** as electron-donating groups were evaluated instead of aryl-substituted imines, no formation of the desired fluorinated piperidinones **196i-j** could be detected (Scheme 56).



192 **195g** R^1 = 4-$NO_2C_6H_4$; **195h** R^1 = COOEt; **195i** R^1 = *i*Pr; **195j** R^1 = $BnOCH_2$ **196g-i**

Scheme 56

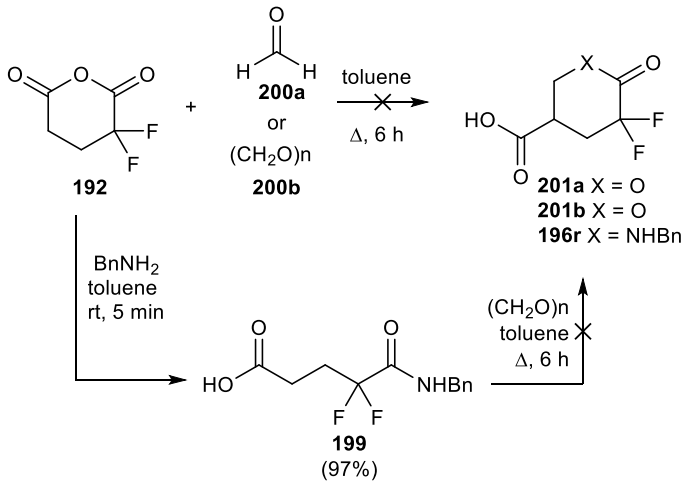
With this in mind, a series of electron-rich *N*-differentiated benzaldehyde derived imines were screened (Table 2). The reaction of 2,2-difluoroglutaric anhydride **192** with *N*-(benzylidene)phenylamine **195k** gave rise to degradation of the starting materials (Table 2, Entry 1). Reaction with oxime ether **195l** and *N*,*N*-dimethyl hydrazone **195m** resulted in the recovery and decomposition of the used starting materials, respectively (Table 2, Entries 2-3). On the other hand, *N*-alkylimines **195n,o** reacted successfully with 2,2-difluoroglutaric anhydride **192** toward 1-allyl- and 1-propyl-2-phenyl-5,5-difluoropiperidin-6-one-3-carboxylic acid **196n,o**, albeit in low to average yields (24-47%) (Table 2, Entries 4-5). Presumably the imine nitrogen in **195k** is too shielded by the bulky phenyl substituent, preventing nucleophilic attack of the imine onto anhydride **192** which seemed to be confirmed by the reaction with less sterically hindered *N*-alkyl-substituted imines (R = Bn, *n*Pr, Allyl).

Table 2. Evaluation of *N*-protecting group in the synthesis of piperidinonecarboxylic acids 196.

Entry	R^1	R^2	Imino derivative	Solvent	Time	Yield (%)	*Trans: cis*
1	Ph	Ph	**195k**	Tol	6h	0	/
2	Ph	OMe	**195l**	Tol	6h	SM	/
3	Ph	NMe_2	**195m**	Tol	6h	0	/
4	Ph	Allyl	**195n**	Tol	6h	24	4:1[a]
5	Ph	nPropyl	**195o**	Tol	6h	47	n.d.

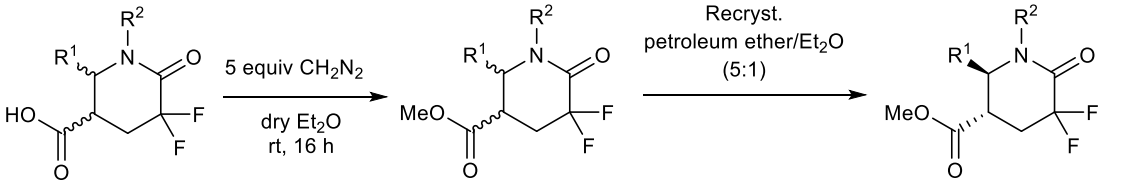
[a] Ratio determined by ^{1}H NMR based at the NCH-signal ($CDCl_3$). SM: recovery of starting materials.

Attempts to prepare fluorinated piperidinones **196** without the R^1-substituent failed. Firstly, anhydride **192** was easily ring opened by $BnNH_2$ toward fluorinated amide **199**, however subsequent addition of paraformaldehyde **200b** after six hours of reflux in toluene did not afford fluorinated piperidinone **196r** (Scheme 57).[143a] Also when the reaction was conducted with only formaldehyde **200a** or paraformaldehyde **200b** in the presence of 2,2-difluoroglutaric anhdyride **192,** no tetrahydropyranone carboxylic acids **201a-b** were formed.



Scheme 57

As the best results were obtained with electron-rich *N*-(benzylidene)benzylamine-derived imines **195a-e**, only their reaction products **196a-e** were considered in further reactions. The in Scheme 54 obtained crude *cis*- and *trans*-1-benzyl-2-aryl-5,5-difluoropiperidine-6-one-3-carboxylic acid mixtures **196a-e** reacted overnight in dry diethyl ether with five equivalents of diazomethane to yield a mixture of *cis*- and *trans*-methyl 1-benzyl-5,5-difluoro-6-oxo-2-arylpiperidine-3-carboxylates **202a-e** without any change in diastereomeric ratio (Scheme 58). This extra esterification step allowed for smooth purification via column chromatography. Subsequent fractional crystallisation in a petroleum ether/diethyl ether mixture (5/1) made isolation of *trans*-methyl 1-benzyl-2-aryl-5,5-difluoropiperidin-6-one-3-carboxylates **202a-e** as the major isomer possible.



a R^1 = Ph; R^2 = Bn
b R^1 = 2-$MeOC_6H_4$; R^2 = Bn
c R^1 = 3-$MeOC_6H_4$; R^2 = Bn
d R^1 = 4-$MeOC_6H_4$; R^2 = Bn
e R^1 = Ph; R^2 = 4-MeOBn

Scheme 58

The characterisation of both diastereomers was based on the analysis of H-2/H-3 coupling constants of methyl 1-benzyl-2-aryl-5,5-difluoropiperidin-6-one-3-carboxylates **202a-e** in ^{1}H NMR spectroscopy ($CDCl_3$), as these esters **202a-e** were easily isolated and analyzed (Scheme 58). The ^{1}H NMR spectra of methyl esters **202a-e** showed two sets of doublets, close to δ = 4.9 ppm, corresponding to the H-2

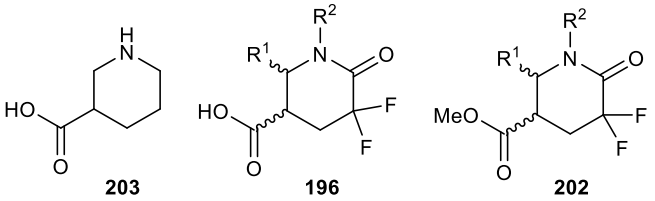
(NCH) protons of the *cis*- and *trans*-diastereomer, from which the diastereomeric ratio was deduced. The largest coupling constants were observed for the major diastereomers **202** (J_{trans} = 6.1-7.2 Hz), which indicates that the aryl group and the ester moiety occupy the *trans*-configuration, with H-2 and H-3 in the axial positions. This *trans*-configuration was confirmed by methyl ester **202b** for which a small coupling constant of J_{trans} = 4.4 Hz was observed. This change in conformational equilibrium can be explained by a diaxial positioning of the aryl group and the ester substituents, due to sterical hindrance between these functionalities. For all minor isomers **202a**,**c-e**, a coupling constant of J_{cis} = 5.5 Hz was observed, which indicates that H-2 and H-3 occupy a pseudoaxial-pseudoequatorial position, corresponding to the *cis*-configuration. The obtained diastereomeric ratio of *trans*- and *cis*-substituted piperidinone carboxylates **202a-f** ranged from 2:1 to 1:0 depending on the reaction temperature and the used substrates (Table 3). It was observed that the diastereomeric ratio of the obtained *trans*- and *cis*-piperidinone carboxylic acids **196a-f** could be improved by performing the reaction in a lower boiling solvent under reflux conditions, *i.e.*, in toluene instead of xylene, without a significant difference in the obtained yields. Indeed, when the reaction was conducted in benzene, the diastereomeric ratio of **196a** was improved from 5:1 to 10:1, although only a small amount (< 10%) of fluorinated piperidinone **196a** was observed. This could indicate that the ring-closing step requires forcing conditions at elevated temperatures (benzene *vs* toluene),[143a] but the diastereoselectivity is inversely related to the applied temperature (toluene *vs* xylene). This increase in diastereomeric ratio by applying lower reaction temperatures could indicate that the proposed mechanism is kinetically controlled toward *trans*-isomers. This was supported by an isomerisation reaction of a mixture of *trans*- and *cis*-**202a** with three equivalents of sodium hydride in dry tetrahydrofuran for 30 minutes, which resulted in a diastereomeric ratio shift from 5:1 to 1:1.

As a second effect on the diastereomeric ratio, the influence of the position of the substituent at the aromatic imine was evaluated. Replacement of an aryl hydrogen by a methoxy group at the 4-position of the aromatic ring to obtain *N*-(4-methoxybenzylidene)benzylamine **195d** and *N*-(benzylidene)-4-methoxybenzylamine **195e** did not significantly affect the diastereomeric ratio of the reaction (Table 3, Entries 1-2 and 7-10). A distinct increase in diastereomeric ratio was observed when the methoxy substituent was positioned closer to the imine functionality. An excellent diastereomeric ratio of 12:1 (*trans*/*cis*) was obtained for the 3-MeO derivative **196c** (Table 3, Entry 6). In the case of the 2-MeO-derivative **196b** only the *trans*-isomer was formed (Table 3, Entries 4-5). When *N*-[(4-diethylamino)benzylidene]benzylamine **195f** was used as substrate, the diastereomeric ratio even decreased compared to reaction with the non-substituted imines **195a** (Table 3, Entries 11-12).

Table 3.Esterification and its influence on the diastereomeric ratio of piperidinone carboxylates 202a-f.

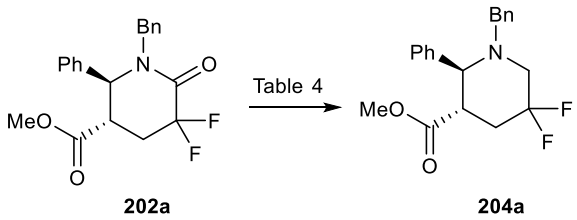
Entry	R^1	R^2	Solvent	Piperidinone carboxylate	Yield (%)	*Trans*: *cis*
1	Ph	Bn	toluene	**202a**	94	5:1[a]
2			xylene			4:1[a]
3	2-$MeOC_6H_4$	Bn	toluene	**202b**	43	*Trans*
4			xylene			*Trans*
5	3-$MeOC_6H_4$	Bn	toluene	**202c**	84	12:1[b]
6			xylene			4:1[b]
7	4-$MeOC_6H_4$	Bn	toluene	**202d**	58	6:1[b]
8			xylene			3:1[b]
9	Ph	4-MeOBn	toluene	**202e**	62	6:1[b]
10			xylene			4:1[b]
11	4-$Et_2NC_6H_4$	Bn	toluene	**202f**	48	3:1[a]
12			xylene			2:1[a]

[a] Ratio determined by ^{1}H NMR based at the NCH-signal ($CDCl_3$).
[b] Ratio determined by ^{1}H NMR based at the OMe-signal ($CDCl_3$).



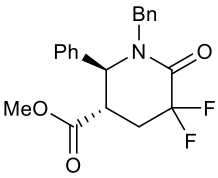
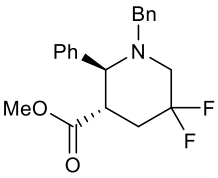
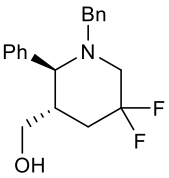
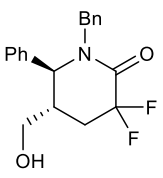
Compounds **196** and **202** show great similarity with nipecotic acid **203**, which is of high interest as a GABA uptake inhibitor.[143c] In order to obtain interesting fluorinated nipecotic acid derivatives **204**, some reduction reactions were evaluated to selectively reduce the amide carbonyl in the presence of the ester carbonyl (Scheme 59, Table 4). A selective reduction on analogous non-fluorinated substrates has been reported in the literature, using borane complexes ($BH_3{\cdot}SMe_2$ and $BH_3{\cdot}THF$) as reducing agents in tetrahydrofuran.[144] Treatment of *trans*-methyl 1-benzyl-2-phenyl-5,5-difluoropiperidin-6-one-3-carboxylate **202a** with borane dimethyl sulfide ($BH_3{\cdot}SMe_2$) in tetrahydrofuran only resulted in the total recovery of the used starting material **202a**. Piperidinone **202a** was converted into piperidine **204a** when the solvent was adapted from tetrahydrofuran to dichloromethane, although even at room temperature after one day the overreduced (hydroxymethyl)piperidine **205a** and (hydroxymethyl)piperidinone **206a** were present as undesired side products (Table 4, Entry 3). Also when the borane tetrahydrofuran complex ($BH_3{\cdot}THF$) as reductant was deployed, no complete conversion could be achieved. After four hours methyl piperidine carboxylate **204a** was isolated in 28% yield, along with 24% of the starting material **202a** (Table 4, entry 5). When prolonged reaction times or elevated reaction temperatures were applied,

overreduction of methyl piperidine carboxylate **204a** toward (hydroxymethyl)piperidine **205a** took place, resulting in decreased yields of the desired piperidine **204a** (11-18%) (Table 4, Entries 6-7). In a final attempt, monochloroalane was applied, as this reducing agents had already proven to be useful in the selective reduction of β-lactams to azetidines (Table 4, Entry 8).[145] Again the overreduced (hydroxymethyl)piperidine **205a** (17%) was obtained next to the desired methyl ester **204a** (1-22%).



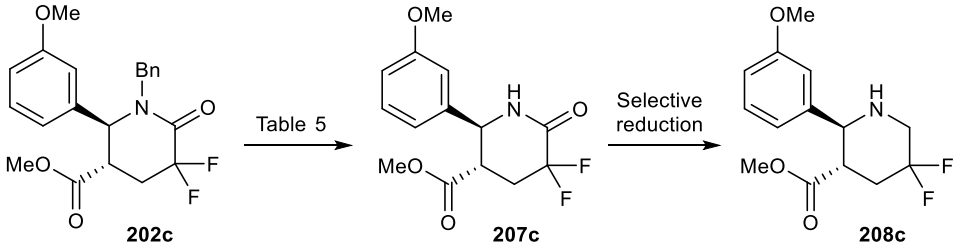
Scheme 59

Table 4. Selective reduction of methyl piperidinone carboxylate 202a.

Entry	Reaction conditions	 **202a** (%)	 **204a** (%)	 **205a** (%)	 **206a** (%)
1	20 equiv $BH_3{\cdot}SMe_2$ THF, rt, 2 h	100[a]	0	0	0
2	10 equiv $BH_3{\cdot}SMe_2$ THF, rt, 1 d	100[a]	0	0	0
3	2 equiv $BH_3{\cdot}SMe_2$ CH_2Cl_2, rt, 1 d	33[a]	48[a]	13[a]	6[a]
4	5 equiv $BH_3{\cdot}SMe_2$ CH_2Cl_2, Δ, 1 d	0	0	86[b]	n.d.
5	10 equiv $BH_3{\cdot}THF$ THF, rt, 4 h	24[b]	28[b]	0	n.d.
6	10 equiv $BH_3{\cdot}THF$ THF, rt, 16 h	10[b]	18[b]	11[b]	n.d.
7	10 equiv $BH_3{\cdot}THF$ THF, Δ, 4 h	0	11[b]	40[b]	n.d.
8	3 equiv AlH_2Cl Et_2O, Δ, 2 h	0	22[b]	17[b]	n.d.

[a] Based on GC-analysis of the reaction mixture. [b] Isolated yields. n.d.: not determined.

Hoping to improve the selectivity of the reduction reaction, debenzylation of the piperidine nitrogen was attempted to increase the accessibility of the amide carbonyl (Scheme 60, Table 5), after which subsequent selective reduction should lead toward the interesting fluorinated nipecotic acid derivatives **208c**. However, several Pd-sources (Pd/C and $Pd(OH)_2/C$; Table 5, Entries 1-3) and H_2-pressures were employed (4-5 bar *vs*. atmospheric pressure; Table 5, Entries 1-3 *vs*. Entries 4-5), and no conversion, even at elevated reaction temperatures (Table 5, Entry 3), toward *trans*-methyl 5,5-difluoro-6-oxo-2-(3-methoxyphenyl)piperidine-3-carboxylate **207c** could be obtained. Microwave-assisted debenzylation of *N*-benzylamides has been reported by Rombouts et al., by heating the *N*-benzyl-protected γ-lactam in the presence of four equivalents of triflic acid for 5-15 minutes in toluene at 150°C upon microwave irradiation.[146] For *trans*-methyl 5,5-difluoropiperidinone-3-carboxylate **202c** this method only resulted in a complex reaction mixture. Selective reduction of fluorinated methyl piperidinone-5-carboxylates **202a-e** to secondary δ-lactam **207c** did not prove to be possible, as reduction of the ester moiety already took place in an early stage and the removal of the benzyl group probably required more harsh reaction conditions.

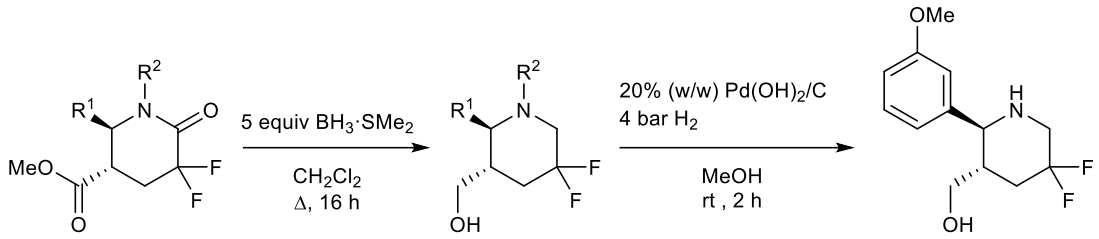


Scheme 60

Table 5. Attempts of debenzylation of *trans*-methyl 1-benzyl-5,5-difluoropiperidinone carboxylate 202c.

Entry	Reaction conditions	Result
1	4 bar H_2, 20% (w/w) $Pd(OH)_2/C$ MeOH, rt, 22 h	Recovery of starting material
2	4 bar H_2, 20% (w/w) Pd/C MeOH, rt, 16 h	Recovery of starting material
3	4 bar H_2, 40% (w/w) Pd/C toluene, 70 °C, 16 h	Recovery of starting material
4	5 equiv $HCOONH_4$, 10% (w/w) Pd/C MeOH, rt, 16 h	Recovery of starting material
5	5 equiv $HCOONH_4$, 10% (w/w) Pd/C MeOH, Δ, 3 h	Recovery of starting material
6	4 equiv CF_3SO_3H toluene, 150 °C, 15 min, μW	Complex reaction mixture

In order to overcome problems caused by non-selective reduction, complete reduction of the ester and amide moiety toward new 3-hydroxymethyl-5,5-difluoropiperidines **205a-e** was performed**.** *Trans*-methyl piperidinone carboxylates **202a-e** were smoothly reduced using five equivalents of $BH_3{\cdot}SMe_2$ in dichloromethane under reflux overnight yielding *trans*-2-aryl-1-benzyl-5,5-difluoro-3-(hydroxymethyl)piperidines **205a-e** (70-97%) (Scheme 61). As a representative example, *trans*-1-benzyl-5,5-difluoro-3-hydroxymethyl-2-(3-methoxyphenyl)piperidine **205c** was easily debenzylated under hydrogen atmosphere catalyzed by $Pd(OH)_2/C$ in methanol at room temperature after two hours, giving rise to *trans*-5,5-difluoro-3-hydroxymethyl-2-(3-methoxyphenyl)piperidine **209c** (Scheme 61). As a future perspective, treatment of (hydroxymethyl)piperidine **209c** with an appropriate oxidizing reagent should lead toward 2-aryl-5,5-difluoronipecotic acid.



202a R^1 = Ph; R^2 = Bn
202b R^1 = 2-$MeOC_6H_4$; R^2 = Bn
202c R^1 = 3-$MeOC_6H_4$; R^2 = Bn
202d R^1 = 4-$MeOC_6H_4$; R^2 = Bn
202e R^1 = Ph; R^2 = 4-MeOBn

204a (86%)
204b (75%)
204c (80%)
204d (70%)
204e (97%)

R^1 = 3-$MeOC_6H_4$
R^2 = Bn

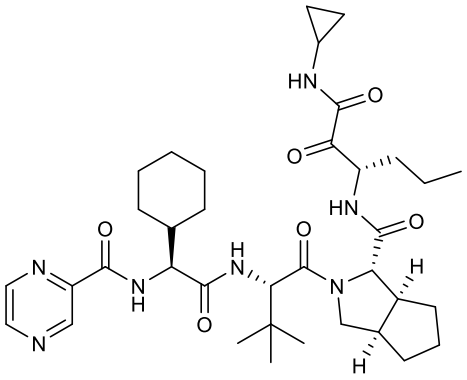
209c
(95%)

Scheme 61

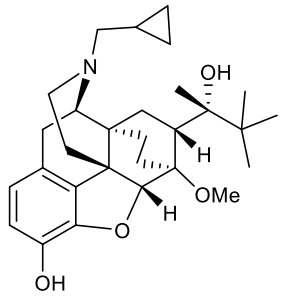
In conclusion, a strategy toward substituted 3-hydroxymethyl-5,5-difluoropiperidines, a new class of compounds with potential as building block in medicinal chemistry, was developed. The key step in the synthesis includes a cyclocondensation reaction of suitably substituted imines with 2,2-difluoroglutaric anhydride, which is easily available from ethyl bromodifluoroacetate in three steps. This reaction yielded mainly *trans*-substituted piperidinones, which were isolated after methylation to methyl piperidinone-3-carboxylates. The obtained methyl piperidinonecarboxylates were subsequently used as substrates for the synthesis of new difluorinated bifunctional building blocks. Hydroxymethylated difluoropiperidines were obtained in high yield by reduction of piperidinone-3-carboxylates using borane in dichloromethane.

3.2 Synthesis of 1-aminomethyl-1-fluorocycloalkane scaffolds

Cycloalkane units are abundantly present in natural products such as prostaglandins, steroids and pyrethroids, where they play a crucial role in the biological activity of these compounds.[147] (Aminomethyl)cyclohexane and -cyclopropane, in particular, are as a subunit present in two of the top selling pharmaceuticals in the United States, *i.e.*, Telaprevir **210a** and Buprenorphine **210b** as one of the active compounds in Suboxone®.[134]



210a
Telaprevir
Incivec®, Vertex
Antiviral



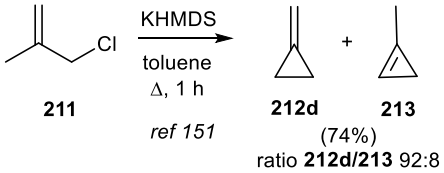
210b
Buprenorphine,
Suboxone®, Reckit Benckiser
Opioid agonist

As mentioned before (see 1. Introduction and Goals), replacement of one cycloalkane hydrogen atom by fluorine can dramatically alter the biological properties (conformation, pK_a, lipophilicity) of the cycloalkane unit and consequently of the entire structure. Fluorinated cycloalkanes in general are widely encountered in active substances for the treatment of asthma, diabetes, multiple sclerosis, psychiatric diseases and cancer,[148] as well as in insecticides[149] and herbicides.[150] In this work, the focus was directed toward the synthesis of 1-aminomethyl-1-fluorocycloalkanes as novel fluorinated building blocks. It is of crucial importance that newly prepared building blocks meet certain standards, such as being easily accessible, stable and potentially multifunctional to use in several syntheses. Furthermore, it is believed that these fluorinated compounds are suitable for use in the construction of libraries in medicinal research.

3.2.1 Synthesis of 1-aminomethyl-1-fluorocycloalkanes

In this section a convenient approach toward 1-aminomethyl-1-fluorocycloalkanes is described, starting from commercially available methylenecyclobutane, methylenecyclopentane and methylenecyclohexane. Only methylenecyclopropane **212d** is not commercially available and had to be synthesized starting from 3-chloro-2-methylpropene **211** and potassium bis(trimethylsilyl)amide (KHMDS) under vigorous reflux in toluene, according to a literature method,[151] in which

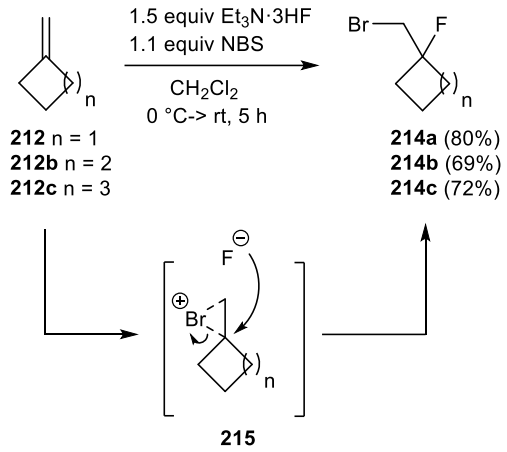
methylenecyclopropane **212d** was always obtained as major isomer in a mixture with 1-methylcyclopropene **213** (92:8) (Scheme 62).



Scheme 62

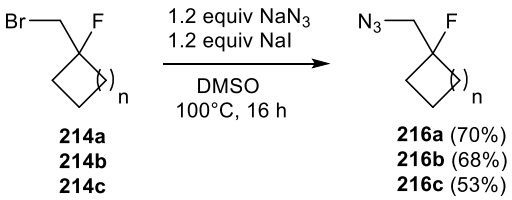
3.2.1.1 Synthesis of 1-aminomethyl-1-fluorocyclobutane, 1-aminomethyl-1-fluorocyclopentane and 1-aminomethyl-1-fluorocyclohexane[152]

Fluorine was introduced in the first step of the synthesis of 1-aminomethyl-1-fluorocycloalkanes by a bromofluorination addition across the exocyclic double bond of methylenecycloalkanes **212a-c** by treatment with triethylamine trihydrofluoride ($Et_3N{\cdot}3HF$) and *N*-bromosuccinimide (NBS) in dichloromethane. The bromofluorination reaction is generally recognized as a mild and useful method to introduce fluorine. The mechanism involves the electrophilic attack of a positive bromine species to give a bromonium ion **215** followed by attack of a nucleophilic fluorine ion at the most stabilized carbenium center (Scheme 63).[153] Primary alkyl-substituted alkenes often suffer from a lack of selectivity, due to low stabilizing abilities of the formed carbenium ions, resulting in a mixture of both the Markovnikov and the anti-Markovnikov product.[154] The regioselectivity of this addition is thus highly influenced by the nature of the alkene, although usually the addition of fluoride takes place at the most substituted carbon atom, leading to Markovnikov addition products.[153] For the four- to six-membered methylenecycloalkanes **212a-c**, the bromofluorination with 1.5 equivalents of triethylamine trihydrofluoride and 1.1 equivalents of *N*-bromosuccinimide led exclusively to 1-bromomethyl-1-fluorocycloalkane Markovnikov adducts **214a-c** in good yields (69-80%) after five hours (Scheme 63).



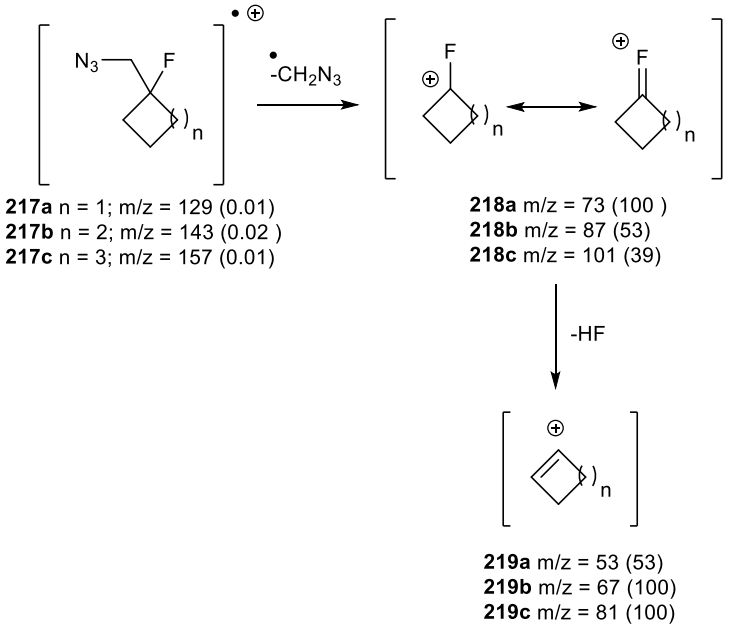
Scheme 63

Subsequently, nucleophilic substitution of bromine by azide in 1-bromomethyl-1-fluorocycloalkanes **214a-c** required activation by the *in situ* preparation of 1-iodomethyl-1-fluorocycloalkanes with sodium iodide, which are more susceptible substrates to a nucleophilic substitution reaction. Treatment of 1-bromomethyl-1-fluorocycloalkanes **214a-c** with 1.2 equivalents of sodium azide and 1.2 equivalents of sodium iodide in DMSO at 100°C yielded the fluorinated (azidomethyl)cycloalkanes **216a-c** (Scheme 64).



Scheme 64

Structural analyses of the fragmentation patterns (MS, EI) of the fluorinated bromomethyl- **214a-c** and (azidomethyl)cycloalkanes **216a-c** further established their structures. For example, the ionisation of the azidomethyl compounds **216a-c** leads to molecular ions **217a-c** (Scheme 65), followed by the expulsion of the azidomethyl moiety, thus providing stabilized 1-fluorocycloalkan-1-ylium ions **218a-c**. Subsequent elimination of hydrogen fluoride, leading toward the cycloalkenylium ions **219a-c** explains the second major peak in the mass spectrum. A similar fragmentation was also observed for the fluorinated (bromomethyl)cycloalkanes **214a-c.**



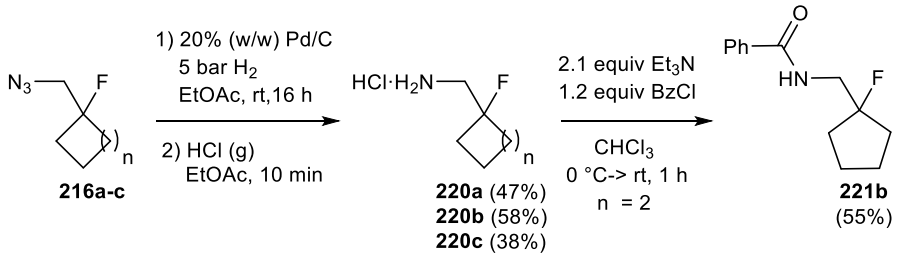
217a n = 1; m/z = 129 (0.01)
217b n = 2; m/z = 143 (0.02)
217c n = 3; m/z = 157 (0.01)

218a m/z = 73 (100)
218b m/z = 87 (53)
218c m/z = 101 (39)

219a m/z = 53 (53)
219b m/z = 67 (100)
219c m/z = 81 (100)

Scheme 65

Finally, due to the high solubility of (aminomethyl)cycloalkanes in water, a non-aqueous work up procedure was required for the reduction of 1-azidomethyl-1-fluorocyloalkanes **216a-c**. This reduction was achieved by applying a hydrogenation reaction in the presence of a catalytic amount of Pd/C (20% w/w) under H_2-pressure (5 bar) in ethyl acetate. 1-Aminomethyl-1-fluorocycloalkanes **220a-c** were precipitated as ammonium salts by bubbling dry HCl gas through the crude mixture, delivering the salts **220a-c** in acceptable yields (38-58%) (Scheme 66).



216a-c

220a (47%)
220b (58%)
220c (38%)

221b
(55%)

Scheme 66

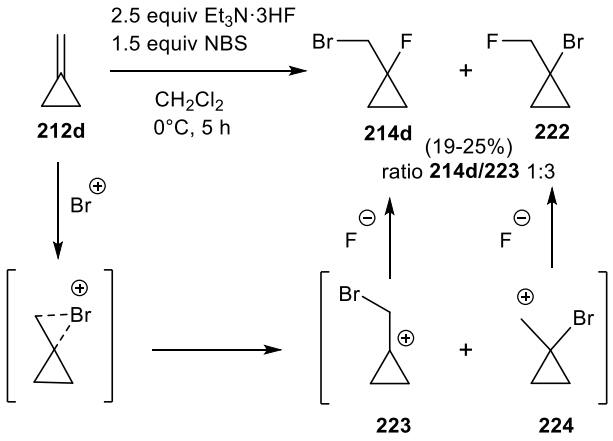
The synthetic availability of these 1-aminomethyl-1-fluorocycloalkanes **220a-c** was demonstrated by treatment of 1-aminomethyl-1-fluorocyclopentane **220b** with 2.1 equivalents of triethylamine in chloroform to liberate the free amine, which immediately reacted with benzoyl chloride to yield *N*-[(1-fluorocyclopentyl)methyl]benzamide **221b** in 55% (Scheme 66).

3.2.1.2 Synthesis of 1-aminomethyl-1-fluorocyclopropane

For methylenecyclopropane **212d**, however, the regioselectivity during the bromofluorination reaction was found to be quite different. After bromofluorination, both regioisomers **214d** and **222**

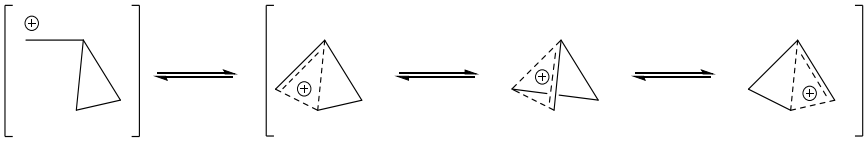
were isolated from a complex mixture in a 1:3 ratio, in a much lower yield (19-25%) as compared to the other cycloalkanes. Even when the reaction was kept at 0 °C for five hours and a larger excess of the used reagents, triethylamine trihydrofluoride (2.5 equivalents) and *N*-bromosuccinimide (1.5 equivalents) was added, no improvements in selectivity or yield could be obtained. In the literature, the bromofluorination of isobutene has been shown to lead exclusively toward the Markovnikov product, *i.e.*, 1-bromo-2-fluoro-2-methylpropane,[154] which excludes sterical hindrance as a determining factor for the different regioselectivity in the bromofluorination of methylenecyclopropane **212d**.[155]

As the bromofluorination is generally considered to follow an ionic mechanism,[153] the stability of the cyclopropyl carbenium ions, *i.e.*, 1-(bromomethyl)cyclopropyl cation **223** and 1-bromocycloprop-1-ylmethylcarbenium ion **224**, will probably play a crucial role in the regioselectivity of this reaction (Scheme 67).



Scheme 67

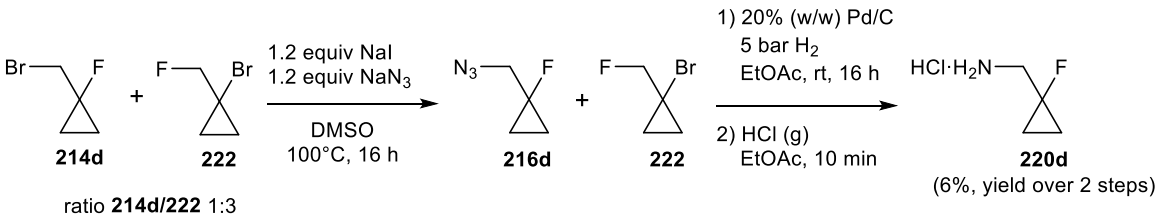
Numerous experimental and computational studies have been reported on the structure and energetics of the cyclopropylcarbinyl cation **225**,[156] however its structure has not yet been fully established.[156-157] Despite the fact that the cyclopropylcarbinyl carbenium ion is a primary cation, it is assumed that this ion is a relatively stable ion, in which the three-membered ring stabilizes the positively charged center.[158] This stability can be explained by an equilibrium which involves a set of σ-delocalized bicyclobutonium structures.[156-159] Most of the computational studies report a close proximity in energy of the bisected cyclopropylcarbinyl cation **225** and these bicyclobutonium structures **226** as minima, which results in an equilibrium between these two types of carbenium ions (Scheme 68).[156,159] This explains the stability of the 1-bromocyclopropylmethylcarbenium ion **224** and, as a consequence, the formation of the anti-Markovnikov product, 1-bromo-1-fluoromethylcyclopropane **222** (Scheme 67).



Scheme 68

In addition, 1-substituted cyclopropyl cations are only considered to be stabilized when the substituent is a strong π-donor (*i.e.*, NR_2, OR). For other substituents the barrier to ring opening is so small that it is unlikely that these cations will exist.[160] The formation of this cation **223**, which is attacked by a nucleophilic fluorine atom yielding the Markovnikov product, is reported here, but the low yield and the low regioselectivity point out the unstability of this cation. In the literature, only a few non-symmetrical addition reactions have been performed on methylenecyclopropane **212d**. For example, the reaction of methylenecyclopropane **212d** with HOBr[161] (NBS in H_2O) or PhSeBr[162] yielded, in agreement with our results, (mainly) the anti-Markovnikov products.[161-163]

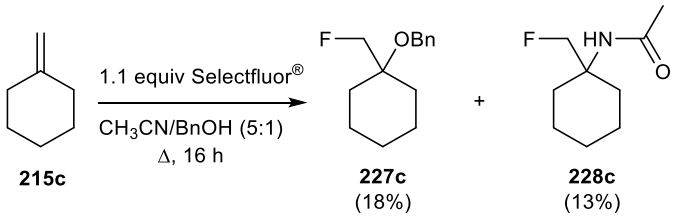
The crude mixture of cyclopropanes **214d** and **222** was first filtered over a silica plug and eluted with pentane. After evaporation of the eluens the mixture was distilled at atmospheric pressure, yielding several fractions with different regioisomeric ratios (**214d:222**), ranging from 1:6 to 2:1. Analogously to the other (bromomethyl)cycloalkanes **214a-c**, a mixture of bromofluorinated cyclopropanes **214d:222** (1:3) was treated with sodium azide and sodium iodide toward 1-azidomethyl-1-fluorocyclopropane **216d**. The only difference was that, after the workup, the solvent was distilled off at atmospheric pressure to prevent loss of the volatile azide **216d**. Without further purification, the mixture of 1-azidomethyl-1-fluorocyclopropane **216d** and 1-fluoromethyl-1-bromocyclopropane **222** was reduced under H_2-pressure (5 bar) in ethyl acetate, and the corresponding (aminomethyl)cyclopropane was precipitated as hydrochloric salt **220d** in 6% yield over two steps (Scheme 69).



Scheme 69

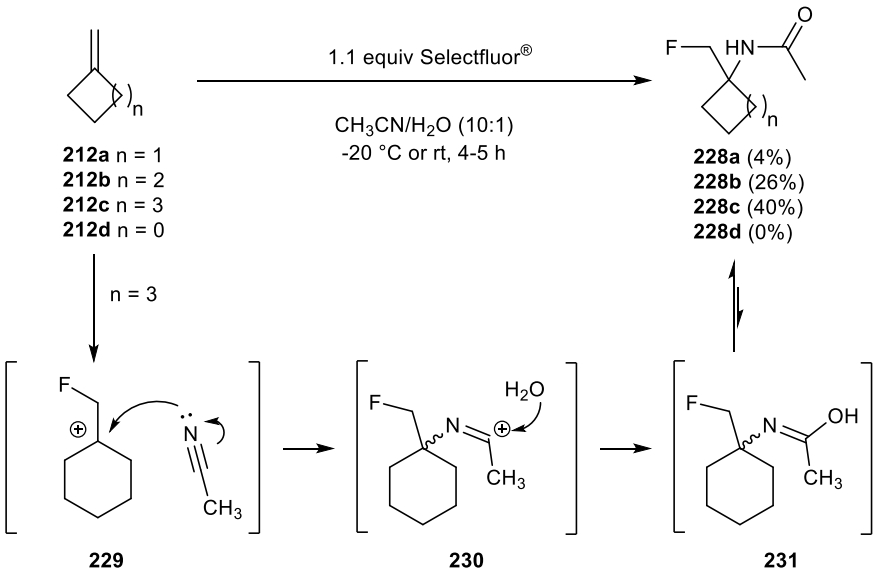
It should be mentioned that the risks associated with the presence of the azide moiety in these small molecules were never overlooked. As the C/N-ratio varied between 2.3 (7/3) and 1.3 (4/3), the safety limit of C/N ≥ 3 was always exceeded for all (azidomethyl)cycloalkanes **216a-d**. In that respect, reactions concerning the preparation or reduction of fluorinated (azidomethyl)cycloalkanes **216a-d** were limited to maximum one gram scale.

Regarding the regioselectivity shift of the cyclopropane unit, an inverted strategy, namely alkoxy/hydroxyfluorination, was evaluated in which fluorine played the role of the electrophile. This strategy was first tested on the higher cycloalkanes (butane, pentane, hexane) as these gave clean conversion for the bromofluorination. Treatment of methylenecyclohexane **215c** with 1.1 equivalents of Selectfluor® in a 5:1 mixture of acetonitrile/benzylalcohol gave rise to (1-fluoromethyl)cyclohexyl benzyl ether **227c** and *N*-[1-(fluoromethyl)cyclohexyl]acetamide **228c**, in 18% and 13% yield, respectively (Scheme 70).



Scheme 70

This unexpected acetamide **228** was the result of an aminofluorination across methylenecyclohexane **215c** and was formed by nucleophilic attack of acetonitrile on the carbenium ion **229** formed after electrophilic addition of fluorine. Addition of water to iminium **230** led to imidic acid **231** which immediately tautomerized to acetamide **228** (Scheme 71). With this encouraging result in mind, the scope of this aminofluorination was further investigated. When the reaction was performed in a 10:1 mixture acetonitrile/water the yield of acetamide **228c** could be increased to 40% at room temperature. Unfortunately the yield decreased significantly to 21% and 3% when smaller ring sizes were used (Scheme 71). Indeed, when these reaction conditions were applied on methylenecyclopropane **212d** at -20 °C no conversion to fluorinated *N*-(cyclopropyl)acetamide **228d** could be observed.



Scheme 71

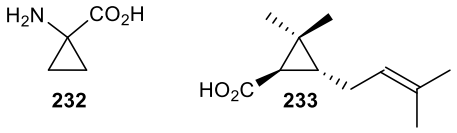
In conclusion, a convenient synthetic pathway toward new fluorinated building blocks was developed via an easy three-step procedure, starting from methylenecycloalkanes. The introduction of fluorine was achieved by regioselective bromofluorination of these olefins, except for methylenecyclopropane, which gave rise to a mixture of regioisomers. Substitution of bromide by azide led to the corresponding fluorinated (azidomethyl)cycloalkanes in good yields. Subsequent hydrogenation of these azides furnished 1-aminomethyl-1-fluorocycloalkanes, which were isolated as their stable hydrochloride salts. The latter fluorinated (aminomethyl)cycloalkanes can be considered as new building blocks in synthetic medicinal chemistry. Only the yields for the cyclopropane derivatives were rather disappointing. In that perspective, some alternative approaches were evaluated in order to obtain 1-aminomethyl-1-fluorocyclopropane.

3.2.2 Alternative approaches toward 1-aminomethyl-1-fluorocyclopropane

3.2.2.1 Synthesis of monofluorinated cyclopropanes in the literature

The cyclopropane unit is the smallest, and by consequence most constrained, cycloalkane, which constitutes the core of a wide variety of natural products and biomolecules, e.g. ACC **232** (1-aminocyclopropane-1-carboxylic acid) the biochemical precursor of ethylene, and *trans*-chrysanthemic acid **233**, an insecticide.[164] Incorporation of a cyclopropane ring to rigidify a structure can have a positive effect on the bioavailability, the selectivity, and the affinity of a bioactive molecule for biological receptors.[147] Moreover, the high ring strain of cyclopropanes can give birth to reactive substrates that can undergo various organic reactions.[165] With this in mind, it is obvious to see that fluorinated cyclopropanes which combine the characteristics of the cyclopropane ring and

the fluorine atom, could lead to important and relevant new scaffolds to synthesize a broad range of bioactive molecules.

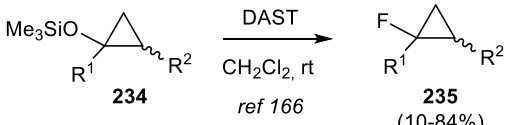


In general the preparation of monofluorinated cyclopropanes can be summarized by the following methods, namely, addition of carbenes to fluoroalkenes, addition of fluorocarbenes to alkenes, a MIRC reaction or the direct fluorination of a cyclopropane unit. As the suggested alternatives comprise the direct fluorination of cyclopropane rings, a short overview of similar methods is presented.

3.2.2.2 Direct fluorination methods in the literature

Only a few methods have been reported, so far, for the direct formation of the carbon-fluorine bond onto cyclopropanes. Early applied methods, using elemental fluorine lack selectivity, due to the extreme reactivity of the fluorine source and resulted in that matter in low yields.[166]

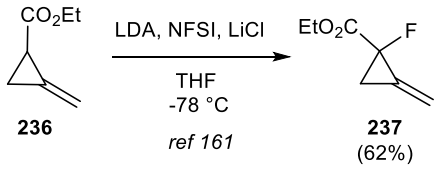
Direct nucleophilic fluorination of cyclopropyl silyl ethers **234** was described, using DAST as fluorinating agent. However, the reactivity of the cyclopropane ring was highly regulated by the electronic properties of the substituents present. In order to avoid ring fragmentation toward fluorinated allylic systems, the presence of an electron-donating group at the C1-position or an electron-withdrawing group at the C2-carbon was required to convert silyl ethers **234** toward the desired fluorocyclopropanes **235** (Scheme 72).[167]



R^1 = $CH_3(CH_2)_8$, Ph, 2-$MeOC_6H_4$
4-$MeOC_6H_4$, 1-Naph, 2-Naph
R^2 = H, CO_2Et

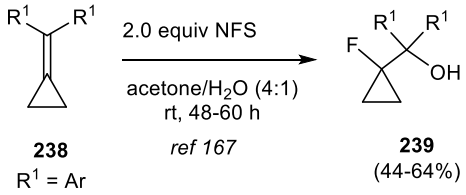
Scheme 72

N-Fluorobenzenesulfonimide (NFSI), as electrophilic fluorine source, was used for the preparation of fluoromethylenecyclopropane analogs of nucleosides. Deprotonation of ethyl 2-methylenecyclopropane-1-carboxylate **236** with lithium diisopropylamide (LDA) delivered the corresponding carbanion, which was trapped by an electrophilic fluorine, yielding the α-fluorinated ester **237** in 62% (Scheme 73).[162]



Scheme 73

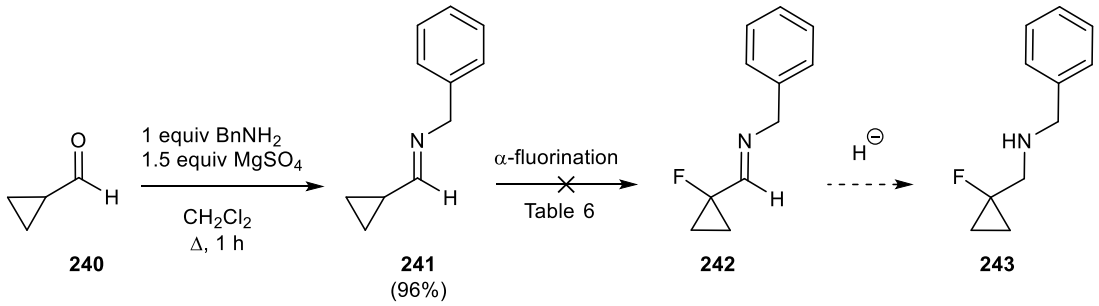
In a second electrophilic approach, the role of *N*-fluorosuccinimide (NFS) as halogen source in the halohydroxylation reaction of strained alkylidenecyclopropanes **238** was evaluated, providing easy access to (1-fluorocyclopropyl)alcohols **239** (Scheme 74).[168]



Scheme 74

3.2.2.3 Direct electrophilic fluorination of the cyclopropane ring

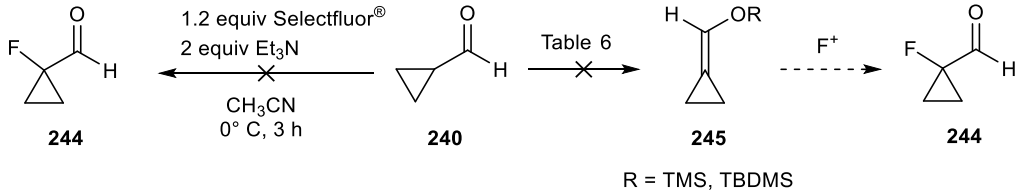
At the department of Sustainable Organic Chemistry and Technology, Ghent University, a general method for the preparation of α-fluorinated imines,[16] which can be applied as versatile substrates for the synthesis of β-fluorinated amines, has been developed. As illustrated in Scheme 75, our proposed strategy comprises the synthesis of *N*-(cyclopropylmethylidene)benzylamine **241** via imination of cyclopropanecarboxaldehyde **240** with benzylamine. Subsequently, fluorination at the α-position of aldimine **241**, followed by reduction toward the corresponding amine **242** should lead to the *N*-benzyl-protected (aminomethyl)cyclopropane **243**.



Scheme 75

Cyclopropanecarboxaldehyde **240** was smoothly transformed into *N*-(cyclopropylmethylidene)benzylamine **241** through a condensation reaction with benzylamine in the

presence of $MgSO_4$ in 96% yield within one hour. In the following step, the α-fluorination of *N*-(cyclopropylmethylidene)benzylamine **241** toward the corresponding fluorinated aldimine **242** was evaluated. Unfortunately, treatment of *N*-(cyclopropylmethylidene)benzylamine **241** with an electrophilic fluorine source under several reaction conditions only resulted in the decomposition of the cyclopropyl unit (Table 5, Entries 1-3). Also attempts to first prepare 1-fluorocyclopropane-1-carboxaldehyde **244** by direct introduction of fluorine in the α-position of cyclopropanecarboxaldehyde **240** (Table 5, Entry 4) or by first trapping aldehyde **240** as a silylated enol ether **245** (Table 6, Entries 5-6), did not lead to the desired products (Scheme 76).



244 **240** **245** **244**

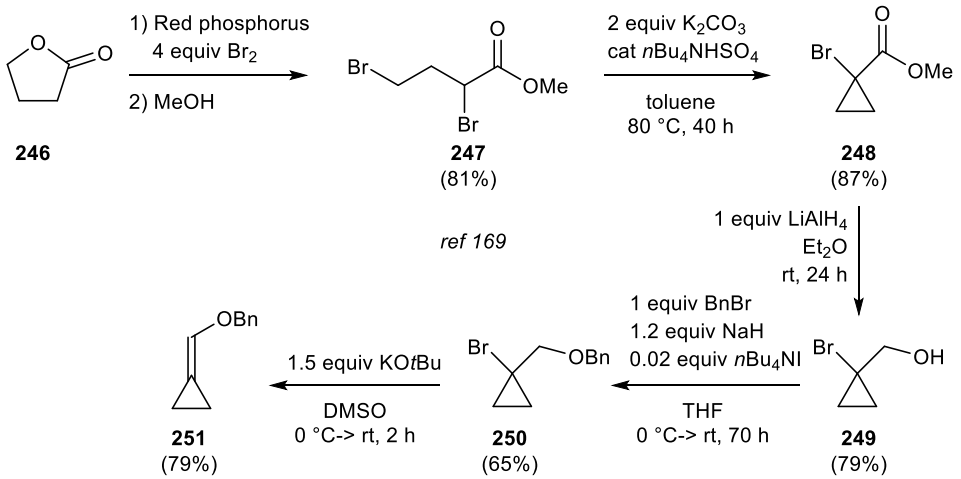
Scheme 76

Table 6. α-Fluorination of cyclopropanecarboxaldehyde 240 and cyclopropyl imine 241, and the formation of silylated enol ether 245.

Entry	Reaction conditions	Product	Result
1	1.2 equiv NFSI, 2 equiv K_2CO_3 Mol. siev., dry CH_3CN, 0 °C-> rt, 23 h	**242**	Decomposition cyclopropane ring
2	1.2 equiv NFSI, 2 equiv K_2CO_3 dry CH_3CN, 0 °C, 3 h	**242**	Decomposition cyclopropane ring
3	1.2 equiv Selectfluor®, 2 equiv K_2CO_3 dry CH_3CN, 0 °C, 3 h	**242**	Decomposition cyclopropane ring
4	1.5 equiv Selectfluor®, 2 equiv Et_3N CH_3CN, 0 °C, 3 h	**244**	Complex reaction mixture
5	1.2 equiv TMSCl, 1.2 equiv Et_3N dry CH_2Cl_2, 0 °C, 2 h	**245**	No product formed
6	1.2 equiv $TBDMSOSO_2CF_3$, 1.2 equiv DIPEA dry CH_2Cl_2, 0 °C ->rt, 2 h	**245**	No product formed

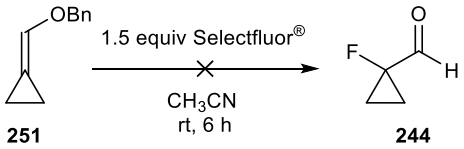
As fluorine is frequently introduced in the α-position of aldehydes and ketones by reaction of NFSI or Selectfluor® with the enol forms, the synthesis of cyclopropylidenemethyl ethers was further investigated. Benzyl cyclopropylidenemethyl ether **251** was prepared *via* a 5-step synthesis starting from γ-butyrolactone **246** according to literature procedures (Scheme 77).[169] Treatment of γ-

butyrolactone **246** with red phosphorus and bromine led to methyl 2,4-dibromobutanoate **247**. The formation of the cyclopropane ring toward **248** was achieved *via* a nucleophilic substitution reaction. Reduction of the ester moiety toward alcohol **249**, followed by etherification with benzylbromide and subsequent elimination of hydrogen bromide yielded benzyl cyclopropylidenemethyl ether **251**



Scheme 77

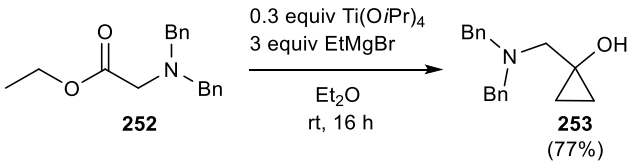
However, treatment of benzyl cyclopropylidenemethyl ether **251** with 1.5 equivalents of Selectfluor® did not result in the formation of any fluorinated product (Scheme 78).



Scheme 78

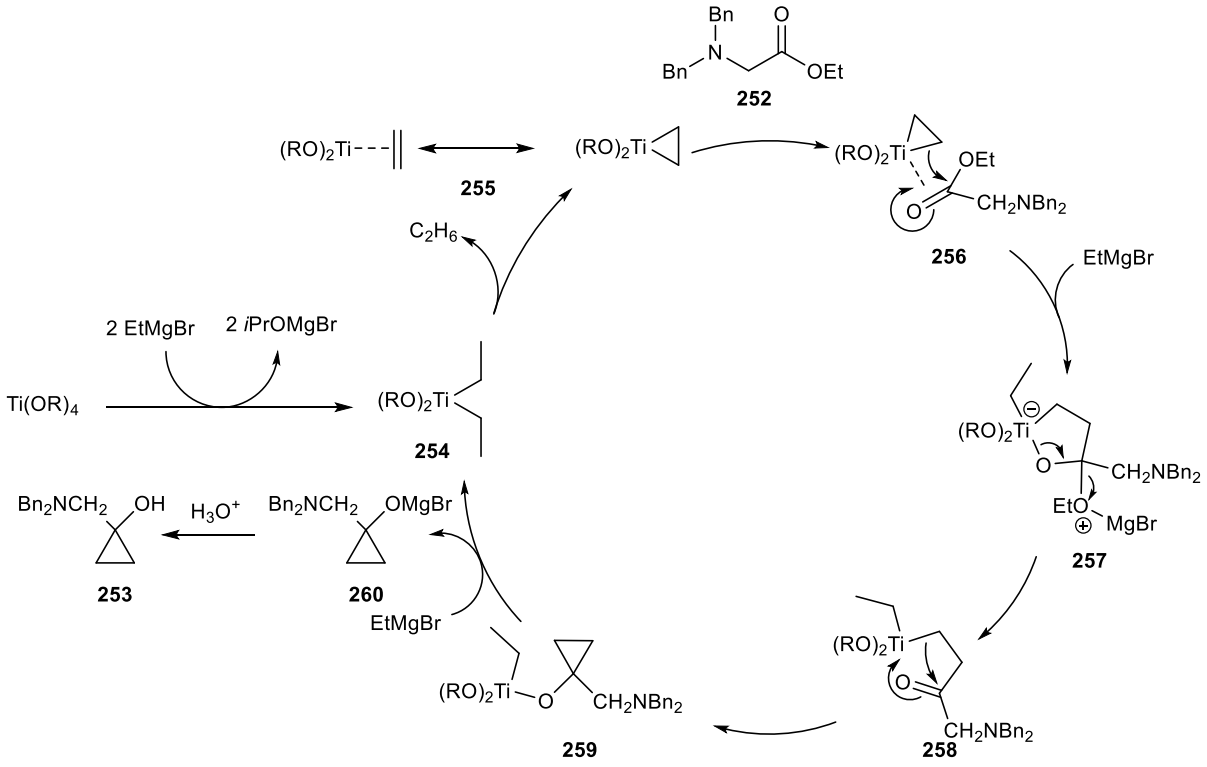
3.2.2.4 Direct nucleophilic fluorination of the cyclopropane ring

With these unsuccessful results in mind, the electrophilic approach toward 1-aminomethyl-1-fluorocyclopropane was abandoned and replaced by a nucleophilic approach. In a first step, ethyl *N,N*-dibenzylglycinate **252** reacted with ethylmagnesium bromide (EtMgBr) in the presence of a catalytic amount of titanium(IV)isopropoxide [Ti(O*i*Pr)$_4$] toward 1-(*N,N*-dibenzylaminomethyl)cyclopropane-1-ol **253** in 77% yield (Scheme 79).



Scheme 79

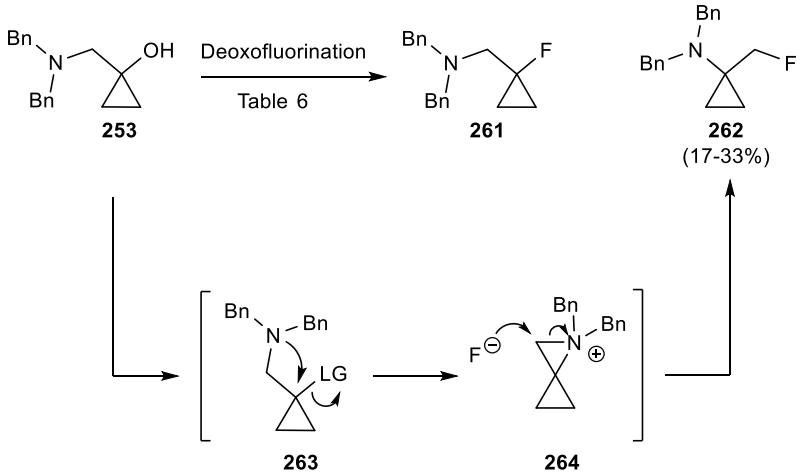
The Kulinkovich cyclopropanation is accepted to proceed according to the illustrated mechanism (Scheme 80).[170] Two equivalents of EtMgBr react with Ti(O*i*Pr)$_4$ to give the unstable diethyltitanium compound **254**, which undergoes β-hydride elimination with the loss of ethane to yield the substituted titanacyclopropane **255**, as active species. Titanacyclopropane **255** in the presence of ester **252** leads to titanacyclopropane-ester complex **256**. The carbonyl group of ester **252** was inserted into the titanium-carbon bond toward a oxatitanacyclopentane ate complex **257**. Subsequent rearrangement of oxatitanacyclopentane **257** to ketone **258** allowed cyclisation, resulting in the titanium cyclopropoxide **259**. The catalytic cycle was completed by alkylation of the latter titanium complex **259** with EtMgBr to regenerate the diethyltitanium derivative **254**. Hydrolysis of **260** during work up yielded cyclopropanol **253** (Scheme 80).



Scheme 80

Cyclopropanol **253** was submitted to a series of deoxofluorinating reagents in order to obtain 1-(*N,N*-dibenzylaminomethyl)-1-fluorocyclopropane **261** (Table 7). The formation of the desired fluorinated

cyclopropane **261** was not observed. Instead however, the regioisomer *N,N*-dibenzyl-1-(fluoromethyl)cyclopropylamine **262** was isolated as the major product in low yields (17-33%) (Scheme 81). This unintended rearrangement was caused by neighbouring group participation of the amino group. Before fluorine was introduced, the amino group interfered as nucleophile by expulsion of the *in situ* created leaving group in intermediate **263** toward bicyclic aziridinium ion **264**. Nucleophilic ring opening of the aziridinium intermediate **264** by a fluorine atom took place at the less sterically hindered position leading toward the rearranged aminocyclopropane **262**.



Scheme 81

Table 7. Deoxofluorination of 1-(*N,N*-dibenzylaminomethyl)cyclopropane-1-ol 253.

Entry	Reaction conditions	**262** (%)[a]
1	2 equiv DAST CH_2Cl_2, -78 °C->rt, 2 h	33
2	3 equiv Morph-DAST CH_2Cl_2, -78 °C->rt, 6 h	20
3	3 equiv Deoxofluor® CH_2Cl_2, -78 °C->rt, 16 h	18
4	1.5 equiv XtalFluor-E®, 1.5 equiv DBU CH_2Cl_2, rt, 24 h	17
5	1.5 equiv XtalFluor-M®, 1.5 equiv DBU CH_2Cl_2, rt, 24 h	23

[a] Isolated yields.

To conclude, in analogy with the few reported examples in the literature, the direct formation of a carbon-fluorine bond on a cyclopropyl moiety appeared challenging. The electrophilic fluorination of suitably substituted cyclopropanes only gave rise to the decomposition of the used substrates. Reaction of cyclopropanol **253**, on the other hand, with a nucleophilic fluorine source led to the rearranged *N,N*-dibenzyl-1-(fluoromethyl)cyclopropylamine **262** by neighbouring group participation of the tertiary amino group. The low selectivity and yields remain substantial obstacles toward the general use of this promising building block, although the preparation of 1-aminomethyl-1-fluorocyclopropane was achieved.

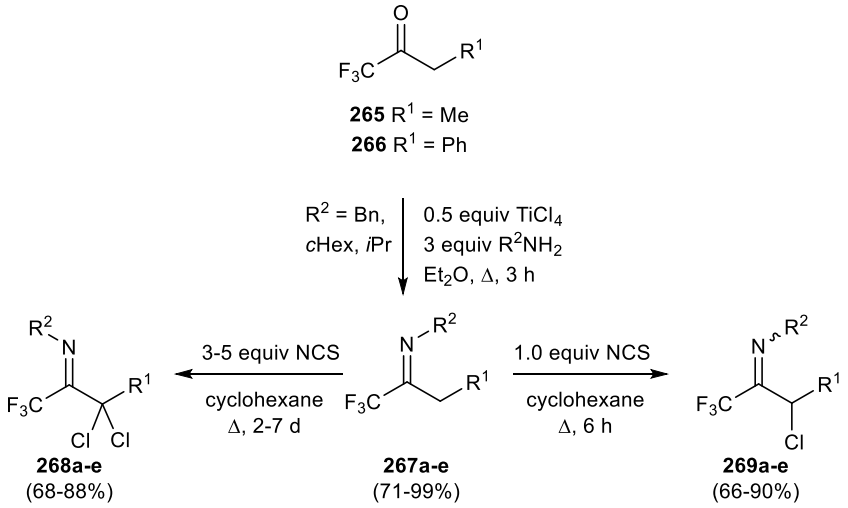
3.3 Synthesis and reactivity study of non-activated and activated *cis*-and *trans*-2-methyl/phenyl-3-(trifluoromethyl)aziridines

The aziridine moiety is generally considered as a highly reactive precursor for the synthesis of all kinds of nitrogen-containing compounds.[12a-c] When the pronounced reactivity of these three-membered rings is combined with the biological properties of a trifluoromethyl group, an interesting subclass of aziridines is touched. As a result, trifluoromethylated aziridines are employed as eligible substrates in the synthesis of diversely functionalized fluorinated building blocks. Over the years, the preparation and reactivity of 2-(trifluoromethyl)aziridines have already been extensively explored.[13b,15] However, the synthetic scope of stereoselective approaches toward 2-substituted 3-(trifluoromethyl)aziridines remain limited because most methods use precarious diazo compounds (ethyl diazoacetate or (trifluoromethyl)diazomethane) or require drastic circumstances.[14a-d,171] A second restricition in these methods is the requirement of the presence of a carbonyl substituent at the α-position of the reactive center of these reagents, resulting in a carbonyl unit in the C2-position of the trifluoromethylated aziridines. Therefore both a stereoselective synthetic pathway toward *cis*- and *trans*-2-substituted 3-(trifluoromethyl)aziridines as well as the reactivity of these aziridines was explored.

3.3.1 Stereoselective synthesis of 1-alkyl-2-methyl/phenyl-3-(trifluoromethyl)aziridines

In this section, a convenient approach toward *cis*- and *trans*-1-alkyl-2-methyl/phenyl-3-(trifluoromethyl)aziridines, starting from commercially available trifluoromethylated ketones, *i.e.*, 1,1,1-trifluorobutan-2-one **265** and 1,1,1-trifluoro-3-phenylpropan-2-one **266** (Scheme 82), is described. The corresponding trifluoromethylated imines **267a-e** were easily prepared in good yields (71-99%) through condensation of ketones **265** and **266** with three equivalents of the appropriate primary amine R^2NH_2 (R^2 = Bn, *c*Hex, *i*Pr) in the presence of 0.5 equivalents of titanium(IV) chloride ($TiCl_4$) in diethyl ether. Subsequent α-chlorination of imines **267a-e** was strongly concentration-dependent. The introduction of one chlorine atom proceeded smoothly with one equivalent of *N*-chlorosuccinimide (NCS) within a few hours (4-6 hours). The introduction of the second chlorine atom, on the other hand, demanded much longer reaction times (2-7 days), less solvent and the regular addition of fresh NCS to obtain a full conversion toward fluorinated dichloroimines **268a-e**. In this way, the synthesis of monochlorinated imines **269a-e** and dichlorinated imines **268a-e** was achieved in good yields (66-90%) (Scheme 82, Table 8). Despite the difficult introduction of the second chlorine atom, a small amount (< 5%) of dichlorinated product **268a-e** was observed during the formation of monochlorinated imines **269a-e** with one equivalent of NCS, and could not be avoided.

The E/Z-assignment of imines **269a-e** was determined from the chemical shifts in ^{19}F NMR ($CDCl_3$). (*E*)-CF_3-imines have in general a chemical shift of around -70 ppm.[172] As the major isomer of monochloroimines **269a-e** have shifts closely related to -70 ppm, these major isomers were assigned to the (*Z*)-imines, as the stereochemistry is switched by introduction of chlorine. If the chemical shift of the minor isomers were considered, these show a shift around -60 ppm which is in agreement with the obtained results for the dichlorinated imines **268a-e.**



Scheme 82

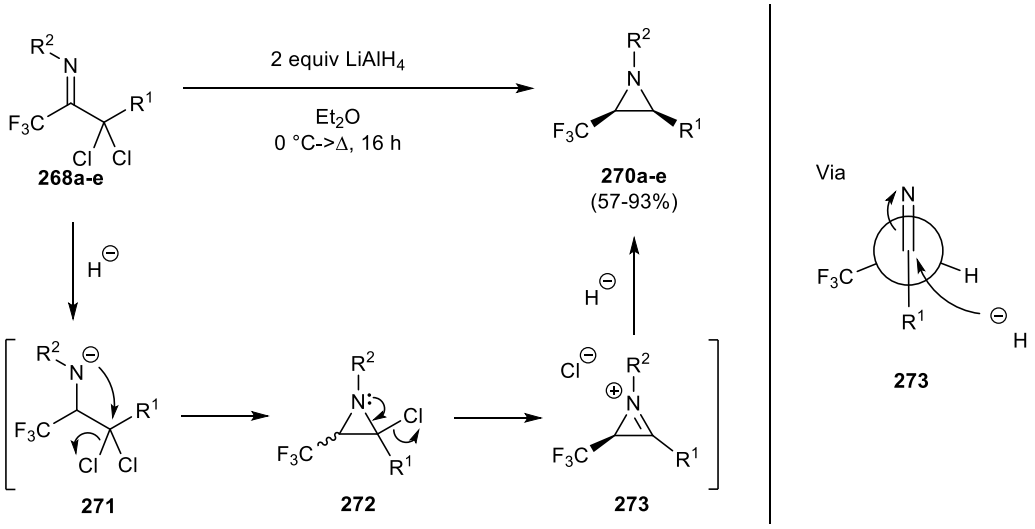
Table 8. α-Chlorination of imines 267a-e to dichloroimines 268a-e or monochloroimines 269a-e.

Compound	R^1	R^2	Yield (%)	Compound	R^1	R^2	Yield (%)	E/Z[c]
268a	Me	Bn	80[a]	**269a**	Me	Bn	78[a]	49:51
268b	Me	*c*Hex	79[b]	**269b**	Me	*c*Hex	90[b]	24:76
268c	Ph	Bn	74[a]	**269c**	Ph	Bn	84[b]	27:73
268d	Ph	*c*Hex	68[a]	**269d**	Ph	*c*Hex	89[b]	23:77
268e	Ph	*i*Pr	88[b]	**269e**	Ph	*i*Pr	66[b]	25:75

[a] Isolated yield. [b] Crude yield. [c] Based on ^{19}F NMR analysis ($CDCl_3$) of the crude mixture.

According to literature examples, for non-fluorinated aziridines, a hydride-induced ring closure of α-chlorinated imines toward 2-substituted 3-(trifluoromethyl)aziridines was evaluated.[173] Firstly, the reduction of α,α-dichlorinated imines **268a-e** with lithium aluminium hydride ($LiAlH_4$) was investigated. In analogy with their non-fluorinated derivatives,[174] imines **268a-e** were reduced using two equivalents of lithium aluminium hydride in diethyl ether under reflux toward *cis*-2-methyl/phenyl-3-(trifluoromethyl)aziridines **270a-e** as the major diastereomers in excellent yields (57-93%) and high diastereoselectivities (94-97:3-6) (Scheme 83, Table 9). The relative

stereochemistry of *cis*-aziridines **270a-e** could be deduced from the vicinal coupling constants between the C2- and C3-protons (J = 6.1-6.6 Hz) in ^{1}H NMR ($CDCl_3$), which is in accordance with literature data.[173j,175] This stereochemical outcome can be rationalized considering a mechanism in which, after imine reduction and intramolecular displacement of the first chlorine atom in dichloroimines **268** toward 2-chloroaziridines **272**, the subsequent formation of an 1-azirinium chloride intermediate **273** takes place by expulsion of the second chlorine atom. This highly reactive intermediate **273** will immediately be captured by the addition of another hydride ion coming in from the opposite side of the CF_3-directing group, *i.e.*, the least sterically hindered side, leading selectively toward *cis*-3-(trifluoromethyl)aziridines **270a-e**.[173j]



Scheme 83

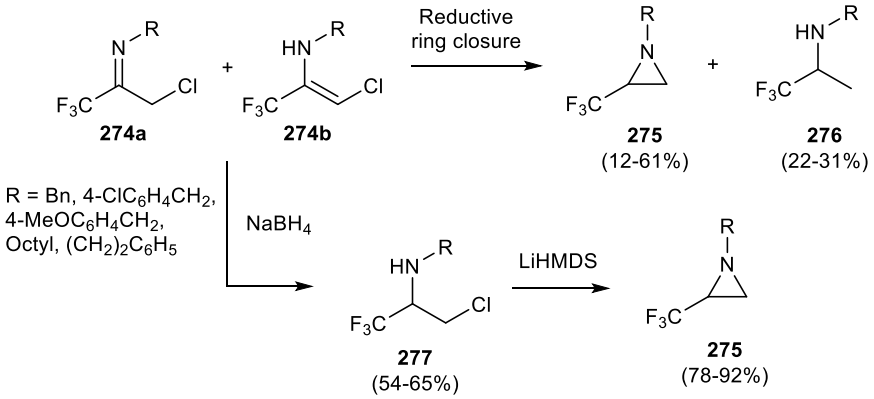
Table 9. Stereoselective synthesis of *cis*-3-(trifluoromethyl)aziridines 270.

Entry	Compound	R^1	R^2	Yield (%)[a]	Diastereomeric ratio *(cis/trans)*[b]
1	**270a**	Me	Bn	87	94:6
2	**270b**	Me	*c*Hex	65	96:4
3	**270c**	Ph	Bn	93	96:4
4	**270d**	Ph	*c*Hex	57	95:5
5	**270e**	Ph	*i*Pr	81	97:3

[a] Crude yield (purity > 85% based on GC). [b] Based on ^{1}H NMR ($CDCl_3$) or GC analysis of the crude mixture.

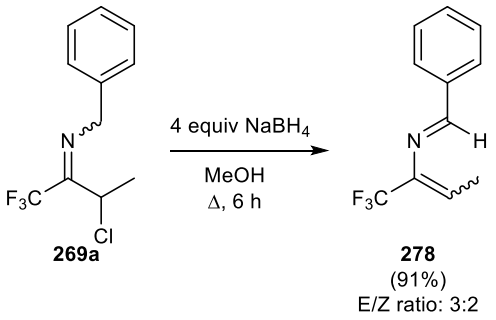
For the reduction of the monochlorinated imines **269a-e** a slightly different approach was intented, as a previous study on the synthesis of non-substituted 2-(trifluoromethyl)aziridines **275** revealed that immediate hydride-induced ring closure with lithium aluminium hydride ($LiAlH_4$) or lithium borohydride ($LiBH_4$) was troublesome and led to *N*-alkyl-1,1,1-trifluoropropan-2-amines **276** as side

products (22-31%) (Scheme 84).[176] This could be circumvented by reduction of imines **274a** and enamines **274b** with sodium borohydride ($NaBH_4$) to the corresponding β-chloroamines **277**, which were then ring closed upon treatment with lithium bis(trimethylsilyl)amide (LiHMDS) as a base (Scheme 84).



Scheme 84

However treatment of *N*-(3-chloro-1,1,1-trifluoro-2-butylidene)benzylamine **269a** with four molar equivalents of sodium borohydride in methanol under reflux led to elimination of hydrochloric acid and *in situ* isomerisation to the more stable 2-azadiene **278**, yielding a 3:2 mixture of *(2E)*- and (2*Z)*-*N*-(benzylidene)-1,1,1-trifluoro-2-but-2-eneamine **278** (Scheme 85).

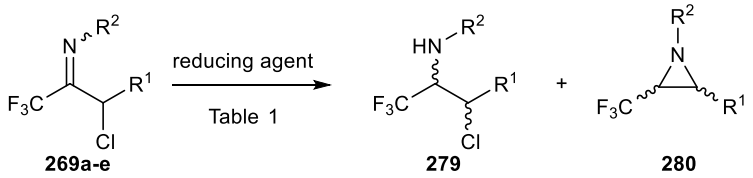


Scheme 85

When the reducing agent was changed from sodium borohydride to sodium cyanoborohydride ($NaCNBH_3$), this reaction gave rise to the desired β-chloroamines **279**, besides aziridines **280** in sometimes relative high conversion rates (10-93%) (Scheme 86, Table 10). These results clearly deviated from previous findings on the 1,1,1-trifluoroacetone imines **274a** (R^1 = H).[176] Therefore, the reduction of *N*-benzyl-substituted imine **274a** with sodium cyanoborohydride was performed and led exclusively to the formation of β-chloroamine **277** (Table 10, Entry 4), indicating that the R^1-substituent (Me or Ph) plays an important role on the ring-closure step. On the other hand, the use

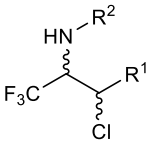
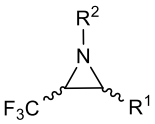
of acetic acid could be a drawback in this procedure, as trifluoromethylated aziridines undergo smooth ring opening upon acidic activation (see 3.3.2.1).

Simultaneously, the reactivity of monochlorinated imines **269a-e** with lithium aluminium hydride was explored. In this case, one equivalent of lithium aluminium hydride appeared to be sufficient to obtain full conversion toward aziridines **280** (Table 10, Entry 5). Thus, from this point on the focus was directed to the hydride-induced reductive cyclisation of monochlorinated imines **269a-e** toward aziridines **280**.



Scheme 86

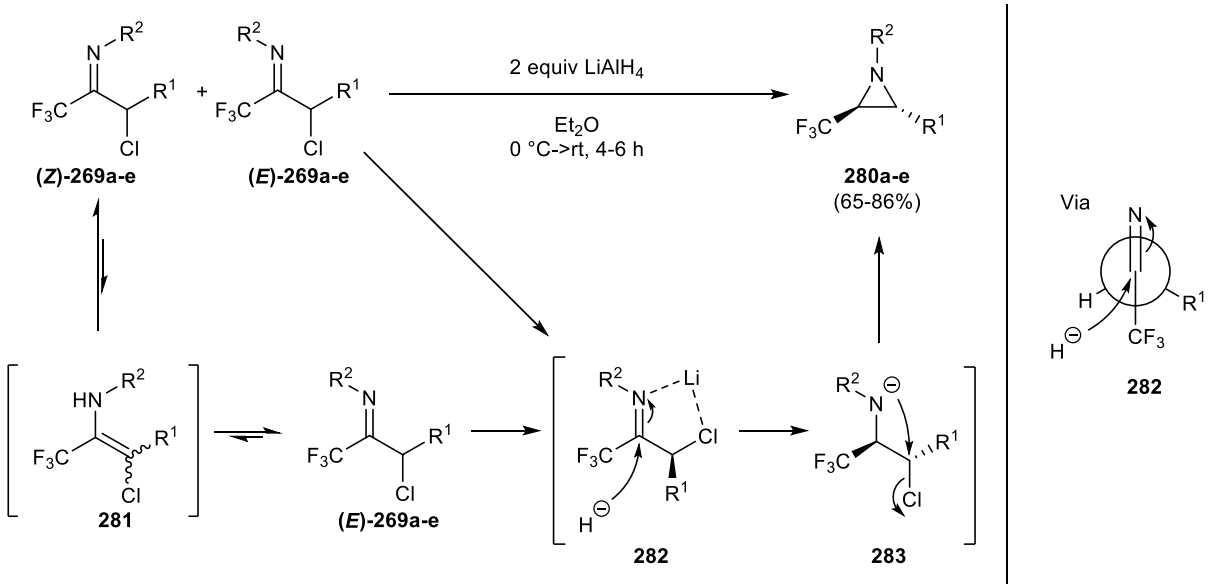
Table 10. Evaluation of reducing agents in the reduction of α-chloroimines 269 and 274a.

Entry	Reaction conditions	R^1	R^2	 **277** or **279** (%)	 **280** (%)
1	1.5 equiv $NaCNBH_3$, 1.0 equiv CH_3COOH MeOH, 0 °C->rt, 16 h	Me	*c*Hex	90[a]	10[a]
2	1.5 equiv $NaCNBH_3$, 1.0 equiv CH_3COOH MeOH, 0 °C->rt, 16 h	Ph	Bn	7[a]	93[a]
3	1.5 equiv $NaCNBH_3$, 1.0 equiv CH_3COOH MeOH, 0 °C->rt, 4 h	Ph	cHex	13[a]	87[a]
4	1.5 equiv $NaCNBH_3$, 1.0 equiv CH_3COOH MeOH, 0 °C->rt, 4 h	H	Bn	100[a]	0[a]
5	1 equiv $LiAlH_4$, Et_2O, 0 °C->Δ, 24 h	Ph	Bn	0	53[b]
6	2 equiv $LiAlH_4$, Et_2O, 0 °C->rt, 4 h	Ph	Bn	0	86[b]

[a] Based on ^{19}F NMR of the crude mixture ($CDCl_3$). [b] Isolated yield.

Optimisation of the reaction conditions led to an increase of the yield of the aziridine **280c** (R^1 = Ph, R^2 = Bn) to 86% by using two equivalents of lithium aluminium hydride at room temperature (Table 10, Entry 6). With this efficient method in hand, the synthetic and stereoselective scope of this reaction was further investigated by evaluating this procedure on other α-chloroimine derivatives

269a-e. The reduction of imines **269a-e** gave rise to *trans*-2-methyl/phenyl-3-(trifluoromethyl)aziridines **280a-e** as major isomers (Scheme 87). The relative stereochemistry of *trans*-aziridines **276a-e** could not be deduced from the vicinal coupling constants of the H2- and H3-protons as the aziridine signals were broadened due to fast nitrogen inversion. NMR-analysis (^{1}H and ^{13}C, $CDCl_3$) combined with other spectroscopic analysis (LC, GC, MS) of aziridines **280a-e** provided strong evidence to assume the *trans*-configuration, as these spectral data clearly differentiated from the earlier assigned *cis*-aziridines **270**. The diastereoselective outcome of this reaction can be explained considering complexation of lithium by nitrogen and chlorine in the (*E*)-isomer of imines **269a-e** toward a cyclic intermediate **282**.[177] The (*Z*)-isomers first had to undergo isomerisation *via* enamines **281** toward the (*E*)-isomers, followed by lithium-complex-induced diastereoselective hydride transfer to imine **282**. Under the influence of the R^1-substituent (R^1 = Me or Ph) the hydride ion will attack from the opposite side of the R^1-directing group, leading selectively to anion **283**. Free rotation around the C2-C3 bond toward an anti-periplanar geometry **283**, allowed ring closure *via* expulsion of chlorine through a S_N2 mechanism, resulting in *trans*-aziridines **280** (Scheme 87).



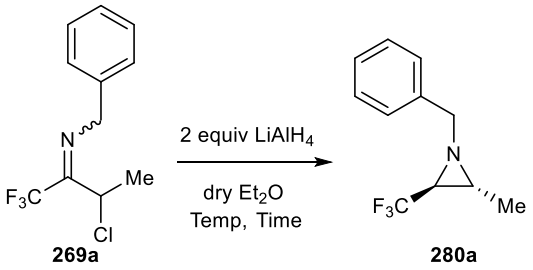
Scheme 87

Table 11. Stereoselective synthesis of *trans*-3-(trifluoromethyl)aziridines 280.

Entry	Compound	R^1	R^2	Yield (%)[a]	Diastereomeric ratio *(cis/trans)*[b]
1	**280a**	Me	Bn	79	7:93
2	**280b**	Me	*c*Hex	67	18:82
3	**280c**	Ph	Bn	86	17:83
4	**280d**	Ph	*c*Hex	82	22:78
5	**280e**	Ph	*i*Pr	65	6:94

[a] Crude yield (purity > 85% based on GC). [b] Based on ^{1}H NMR ($CDCl_3$) or GC analysis of the crude mixture.

Although the yields of *trans*-aziridines **280** (65-86%) were comparable with those of *cis*-aziridines **270**, the stereoselectivity was significantly lower (22-6:94-78) (Table 11). However, the diastereomeric ratio of aziridine **280a** could be enhanced considerably by changing the reaction temperature (Scheme 88, Table 12). By decreasing the temperature to -40 °C, an excellent diastereomeric ratio of 1:99 (*cis:trans*) was achieved (Table 12, Entry 4).



Scheme 88

Table 12. Evaluation of temperature on the diastereomeric ratio toward *trans*-aziridine 280a.

Entry	Temperature	Time	Yield (%)[a]	Diastereomeric ratio *(cis/trans)*[b]
1	0 °C -> Δ	16 h	70	12:88
2	0 °C -> rt	4 h	79	7:93
3	0 °C	4 h	63	3:97
4	-40 °C	5 h	78	1:99

[a] Crude yield (purity > 85% based on GC). [b] Based on GC analysis of the crude mixture.

Each diastereomer **270** and **280** was isolated in pure form by column chromatography on silica gel, before entering a thorough reactivity study.

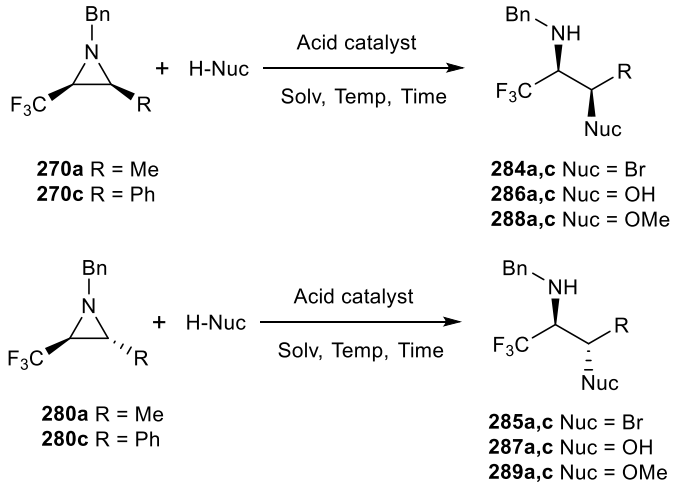
3.3.2 Ring-opening reactions of 1-alkyl-2-methyl/phenyl-3-(trifluoromethyl)aziridines

In a second part, the reactivity of the novel aziridines **270a,c** and **280a,c** was explored. It is commonly known that non-activated 1-alkylaziridines are not very prone to undergo ring opening,[178] and thus, prior to ring opening, 1-alkylaziridines are usually activated by adding a Lewis acid[179] or by quaternisation of the nitrogen atom.[180] On the other hand, Katagiri et al. demonstrated that for 2-(trifluoromethyl)aziridines the use of Lewis acids results in the complete recovery of 1-benzyl-2-(trifluoromethyl)aziridine, probably due to the low coordinating ability of the lone pair at nitrogen atom of trifluoromethylated aziridines.[13b,15b] Indeed, the inductive effect of the trifluoromethyl group renders the nitrogen atom less basic. Hence, the present study focused on *N*-protonation and *N*-alkylation instead in order to activate 2-methyl/phenyl-3-(trifluoromethyl)aziridines **270** and **280**.

3.3.2.1 Ring opening of 1-alkyl-2-methyl/phenyl-3-(trifluoromethyl)aziridines by acidic activation

In this section both ring-opening reactions with Brønsted acids as well as acid-catalyzed ring-opening reactions in the presence of nucleophiles were studied. Treatment of the *N*-protected *cis*-and *trans*-aziridines **270a,c** and **280a,c** with five equivalents of hydrogen bromide (48% in H_2O) in acetonitrile at room temperature gave smooth stereospecific ring opening toward the *syn*- and *anti*-β-bromoamines **284a,c** and **285a,c**, respectively (Scheme 89, Table 13) without the formation of β-amino alcohols as side products. β-Bromoamine **285c** spontaneously ring closed back to *trans*-aziridine **280c** upon dilution in acetonitrile, as only the starting substrate **280c** was observed on LC-MS analysis, while ^{1}H NMR and ^{19}F NMR analysis ($CDCl_3$) clearly indicated the formation of a new ring opened product **285c**. The high reactivity of bromoamine **285c** was further demostrated by dissolving **285c** in MeOH and *i*PrOH, resulting in the replacement of bromine by methanol and a mixture of the isopropanol substitution product with the ring-closed aziridine **280c**, respectively, even when a direct inlet MS technique was applied. If not solvated, bromoamine **285c** remained stable during storage in the freezer (-20 °C) for several months.

Acidic activation of *cis*- and *trans*-aziridines **270a,c** and **280a,c** with a catalytic amount of sulphuric acid (H_2SO_4) in a 1:1 mixture of acetonitrile and water or methanol at room temperature, led only to the complete recovery of starting materials. By increasing the reaction temperature to reflux, full conversion toward β-amino alcohols **286a,c** and **287a,c** and β-amino ethers **288a,c** and **289a,c** was attained within one hour in good yields (Scheme 89, Table 13).



Scheme 89

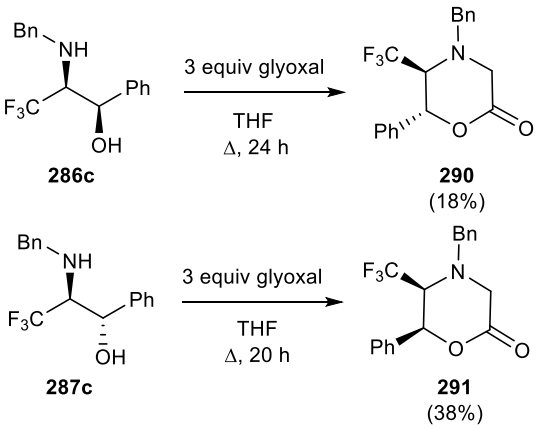
Table 13. Ring opening of *cis*-aziridines 270a,c and *trans*-aziridines 280a,c with hydrogen bromide or sulphuric acid.

Aziridine	R	HNuc	Acid catalyst	Solvent	Temp (°C)	Time (h)	Product	Yield (%)[a]
270a	Me	HBr[b]		CH_3CN	0 °C->rt	1 h	**284a**	88
270c	Ph	HBr[b]		CH_3CN	0 °C->rt	1 h	**284c**	82
270a	Me	H_2O	H_2SO_4	CH_3CN/H_2O (1:1)	Δ	1 h	**286a**	89
270c	Ph	H_2O	H_2SO_4	CH_3CN/H_2O (1:1)	Δ	1 h	**286c**	95
270a	Me	MeOH	H_2SO_4	CH_3CN/MeOH (1:1)	Δ	1 h	**288a**	50
270c	Ph	MeOH	H_2SO_4	CH_3CN/MeOH (1:1)	Δ	1 h	**288c**	75
Aziridine	R	HNuc	Acid catalyst	Solvent	Temp (°C)	Time (h)	Product	Yield (%)[a]
280a	Me	HBr[b]		CH_3CN	0 °C->rt	1 h	**285a**	86
280c	Ph	HBr[b]		CH_3CN	0 °C->rt	1 h	**285c**	82
280a	Me	H_2O	H_2SO_4	CH_3CN/H_2O (1:1)	Δ	1 h	**287a**	83
280c	Ph	H_2O	H_2SO_4	CH_3CN/H_2O (1:1)	Δ	1 h	**287c**	89
280a	Me	MeOH	H_2SO_4	CH_3CN/MeOH (1:1)	Δ	1 h	**289a**	52
280c	Ph	MeOH	H_2SO_4	CH_3CN/MeOH (1:1)	Δ	1 h	**289c**	78

[a] Isolated yields.[b] 5 equiv (48% in H_2O).

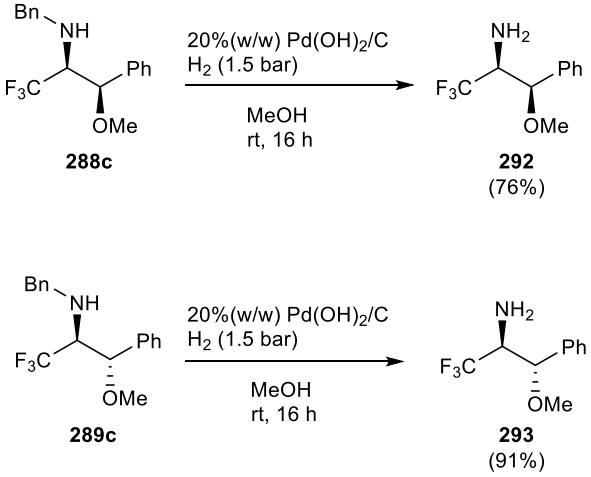
With this method in hand, the synthetic potential of *N*-benzylamino alcohols **286c** and **287c** and *N*-benzylamino ethers **288c** and **289c** as building blocks, was further evaluated (Scheme 90 and Scheme 91). In that respect, *trans*- and *cis*-4-benzyl-6-phenyl-5-(trifluoromethyl)morpholin-2-ones **290** and **291** were prepared starting from *syn*- and *anti*-2-benzylamino-3,3,3-trifluoro-1-phenylpropan-1-ol **286c** and **287c** upon treatment with three equivalents of glyoxal in tetrahydrofuran under reflux.[181] The relative stereochemistry as established in morpholinones **290** and **291** can be considered as an

indirect proof for the observed stereoselectivity in the S_N2 ring opening of the aziridine substrates **270** and **280**. This type of morpholin-2-ones can be of biological interest, for example as potential T-type Ca^{2+} channel blockers or tachykinin receptor antagonists.[182] Unfortunately, the isolated yields were quite low (18% and 38% after purification, respectively) (Scheme 90). Analysis of the crude reaction mixtures by ^{19}F NMR ($CDCl_3$) showed that the desired morpholin-2-ones **290** and **291** were only formed in 21% and 60%, respectively. This can be rationalized considering the reduced nucleophilic character of the nitrogen atom caused by the strong electron-withdrawing effect of the trifluoromethyl group, which impedes the imination of amine **286c** with glyoxal, as the first step in the mechanism toward morpholinones **290** and **291**.[13b,15b]



Scheme 90

On the other hand, this electronic effect enabled smooth debenzylation of *syn*- and *anti*-*N*-benzyl-1,1,1-trifluoro-3-methoxy-3-phenylpropan-2-amines **288c** and **289c** catalyzed by $Pd(OH)_2/C$ (20% w/w) under hydrogen atmosphere (1.5 bar) at room temperature, giving rise to *syn*- and *anti*-1,1,1-trifluoro-3-methoxy-3-phenylpropan-2-amines **292** and **293** in high yields (76-91%) (Scheme 91).



Scheme 91

3.3.2.2 Ring opening of 1- alkyl-2-methyl/phenyl-3-(trifluoromethyl)aziridines by alkyl activation

In a second part of the reactivity screening, activation through alkylation of the aziridine nitrogen was considered. At first, the ring opening of aziridines **270a,c** and **280c** with alkyl halides RX (R = Bn, Me; X = Br, I) toward β-halo amines was evaluated (Table 14). Unfortunately, reaction of *cis*-aziridine **270c** with one equivalent of benzyl bromide led to the complete recovery of the starting material (Table 14, Entry 1), even under neat conditions and at elevated temperatures (Table 14, Entry 2). In order to enhance the reactivity, benzyl iodide was deployed as alkyl halide, by the *in situ* formation with benzyl bromide and sodium iodide or by direct treatment with benzyl iodide, but these conditions gave rise to the recovery and decomposition of starting aziridine **270c**, respectively (Table 14, Entries 3-4). Alkyl activation by means of methyl iodide proved to be successful in the ring-opening reaction of 2-(trifluoromethyl)aziridines **275**.[13b] However, application of these conditions to the *cis*-2-substituted 3-(trifluoromethyl)aziridines **270a** and **270c** only resulted in complex reaction mixtures (Table 14, Entries 5-6). Additionally, also the ring-opening reaction of *trans*-aziridine **280c** with methyl iodide of *trans*-aziridine **280c** was evaluated, as the reactivity of *cis*- and *trans*-aziridines can be quite different in some transformations,[183] but also this approach gave rise to a complex reaction mixture (Table 14, Entry 7). The reasoning for this challenging alkyl-activated ring opening is probably two-sided. As a first effect the electron-withdrawing properties of the trifluoromethyl group strongly diminishes the nucleophilic character of the nitrogen atom. A second reason can be attributed to sterical hindrance caused by the R^1-substituents, shielding the nitrogen atom.

Table 14. Ring opening of *cis*-aziridines 270a,c and *trans*-aziridines 280c with alkyl halides.

Entry	Substrate	Reaction conditions	Results
1	**270c**	1 equiv BnBr, CH_3CN, rt, 24 h	Recovery of starting material
2	**270c**	1 equiv BnBr, 100°C, 24 h neat conditions	Recovery of starting material
3	**270c**	1 equiv BnBr, 1 equiv NaI, CH_3CN, Δ, 4 d	Recovery of starting material
4	**270c**	1 equiv BnI, CH_3CN, Δ, 24 h	Complex reaction mixture
5	**270c**	1 equiv MeI, CH_3CN, 100 °C 3 d, pressure vial	Complex reaction mixture
6	**270a**	1 equiv MeI, CH_3CN, 100 °C 3 d, pressure vial	Complex reaction mixture
7	**280c**	1 equiv MeI, CH_3CN, 100 °C 1 d, pressure vial	Complex reaction mixture

As an alternative to alkylation with alkyl halides, the strong methylating agent trimethyloxonium tetrafluoroborate (Me_3OBF_4) was selected. This reagent had already proven its potential in the methylation of other CF_3-containing azaheterocyclic compounds, such as 2-CF_3-aziridines[15b] and 2-CF_3-azetidines.[184] The non-nucleophilic character of the counterion BF_4^- made the isolation of the highly reactive *N*-methylaziridinium salts possible, allowing access to a broad range of β-substituted (trifluoromethyl)amines by simply selecting a suitable nucleophile.[15b,184]

Isolation of the aziridinium salts **294** and **295** after treatment of aziridines **270c** and **280c** in dichloromethane at 0 °C seemed, in this case, not to be possible. For that reason, the nucleophiles were added to the reaction mixture of aziridine **270c** or **280c** and 1.5 equivalents Me_3OBF_4 in dry acetonitrile after a one hour without prior isolation of the aziridinium salt (Scheme 92). When the ring-opening reaction was induced with two equivalents of benzylamine as a nucleophile, only 48% conversion was obtained (Table 15, Entry 1). In an effort to improve the conversion rate and from an environmental point of view, the methylation was evaluated by performing the reaction in four other different solvents. This solvent screening revealed that in diethyl ether, tetrahydrofuran and toluene no conversion at all could be obtained. The conversion and yield could be slightly enhanced by performing both the formation of aziridinium salts **294** and **295** and the subsequent ring opening reaction in dry acetonitrile (Table 15, Entry 5). By increasing the amount of Me_3OBF_4 to two

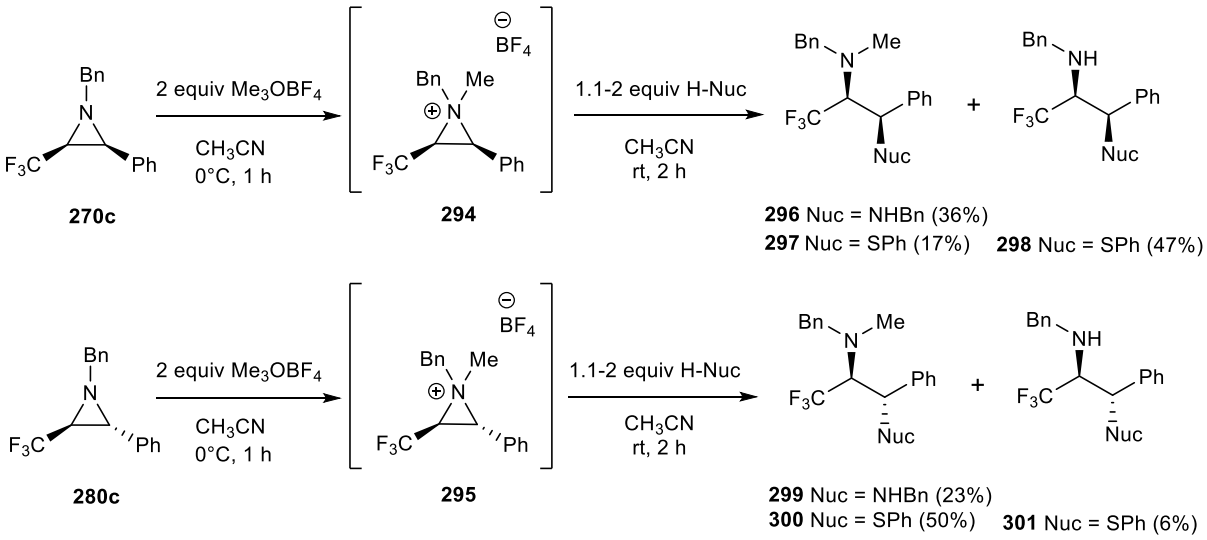
equivalents, full conversion of aziridines **270** and **280** was realized, although the yields were only slightly increased (from 23% to 36%). Both the *syn*- and *anti*-ring-opened diamines **296** and **299** were isolated, albeit in rather low yields, 36% and 23%, respectively (Scheme 92). The explanation for these low yields was found in the formation of several side products, mainly due to ring opening by H_2O or *N*-methyl-*N*-benzylamine.

Table 15. Solvent screening for the methylation of *cis*-(trifluoromethyl)aziridine 270c.

Entry	Solvent	Conversion (%)[c]	Yield (%)
1	CH_2Cl_2	48[a]	12[b]
2	Et_2O	0[a]	0
3	THF	0[a]	0
4	Toluene	0[a]	0
5	CH_3CN	64[a]	23[b]

[a] Based on ^{19}NMR-signals of the crude mixture ($CDCl_3$). [b] Isolated yield. [c] Reaction conditions: 1) 1 equiv aziridine **270c**, 1.5 equiv Me_3OBF_4, 1 h, 0 °C; 2) 2 equiv $BnNH_2$, rt, 2 h.

Actually, when thiophenol (PhSH) was deployed as a nucleophile, the ring opening of *cis*-1-benzyl-2-phenyl-3-(trifluoromethyl)aziridine **270c** led to *syn*-*N*-benzyl-1,1,1-trifluoro-3-phenyl-3-(phenylthio)propan-2-amine **298** as the main product (47%), besides the intended *syn*-*N*-benzyl-*N*-methyl-1,1,1-trifluoro-3-phenyl-3-(phenylthio)propan-2-amine **297** (17%). This peculiar result was only obtained when Me_3OBF_4 was present in the reaction mixture, as a blank reaction without this methylating agent resulted in the recovery of aziridine **270c**, even after addition of an excess of potassium carbonate (K_2CO_3). A possible explanation could be the acidic activation of aziridine **270c** by hydrogen fluoride, formed upon hydrolysis of the tetrafluoroborate anion (BF_4^-). However applying PhSH in the transformation of *trans*-1-benzyl-2-phenyl-3-(trifluoromethyl)aziridine **280c** with Me_3OBF_4 gave rise to *anti*-*N*-benzyl-*N*-methyl-1,1,1-trifluoro-3-phenyl-3-(phenylthio)propan-2-amine **300** (50%) as the major product, next to the corresponding non-methylated secondary amine **301**, but in quite small amounts (6%, purity > 83% based on ^{19}F NMR, $CDCl_3$). When using benzylamine as a nucleophile, these *N*-demethylated products were not observed (Scheme 92).



Scheme 92

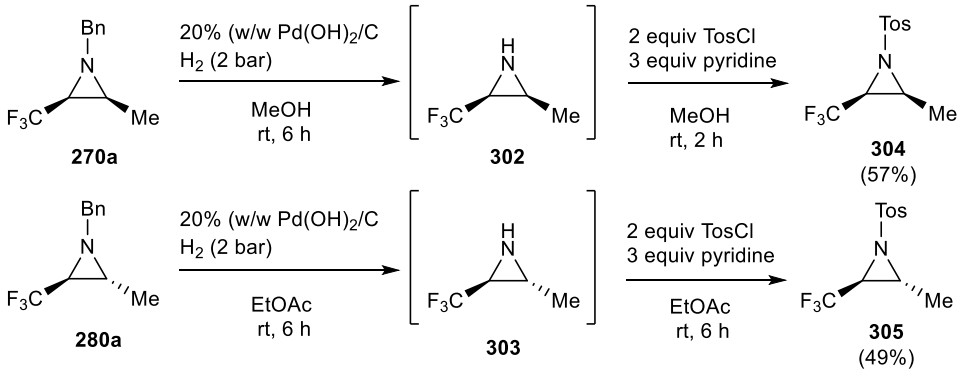
The stereocontrol of this nucleophile-induced ring opening of *cis*- and *trans*-aziridines implies a S_N2-mechanism, yielding the single *syn*- and *anti*-diastereomer, respectively. All ring-opening reactions, reported here, proceeded selectively through a nucleophilic attack at the C2-position, which is in analogy with literature reports on the ring opening of other trifluoromethylated aziridines.[2a,2c]

To conclude, a new, stereoselective synthetic pathway toward *cis*- and *trans*-1-alkyl-2-methyl/phenyl-3-(trifluoromethyl)azirdines was accomplished, starting from commercially available CF_3-ketones. Imination of these CF_3-ketones, followed by α-chlorination and hydride-induced ring closure gave rise to the stereoselective synthesis of *cis*- and *trans*-2-substituted 3-(trifluoromethyl)aziridines. Acidic activation of these trifluoromethylated aziridines smoothly led to a variety of regio- and stereospecific ring opening products using different nucleophiles such as bromide, water and methanol. The synthetic scope of the thus obtained trifluoromethylated building blocks was evaluated by the synthesis of 5-(trifluoromethyl)morpholin-2-ones and the removal of the *N*-benzyl group through hydrogenation toward free primary amines. Ring opening induced by aziridine *N*-alkylation was shown to be more sluggish and side products were formed, although also in this case the desired α-CF_3-amines could be isolated in acceptable yields. [13c,185] These stereo- and regiospecific ring-opening reactions provided access to a wide range of interesting trifluoromethylated functionalized β-amines, which can be further employed as versatile building blocks.

3.3.3 Synthesis of 1-tosyl-2-methyl-3-(trifluoromethyl)aziridines

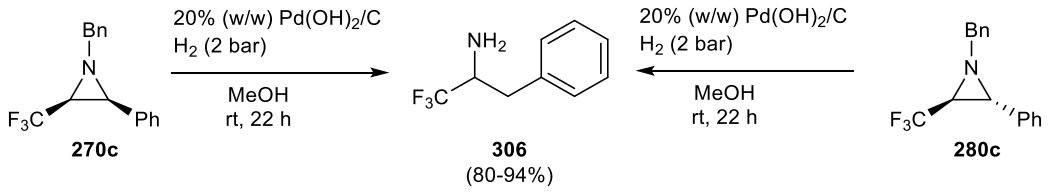
A drawback of the above described alkylation with Me_3OBF_4 (see 3.3.2.2) could be the difficult removal of the methyl unit as *N*-protective group in further transformations. In that objective, the synthesis of *N*-tosyl-protected trifluoromethylated aziridines was examined. It can be expected that these activated aziridines are very susceptible toward ring opening, without prior activation.

The synthesis of 1-tosyl-2-substituted 3-(trifluoromethyl)aziridines **304** and **305** was achieved from the corresponding non-activated *cis*- and *trans*-aziridines **270a** and **280a**, by initial removal of the *N*-benzyl group by hydrogenation over a catalytic amount of $Pd(OH)_2/C$ (20% w/w) under hydrogen atmosphere (2 bar) (Scheme 93). The thus formed free amines **302** and **303** were trapped by adding two equivalents of tosyl chloride (TosCl) in the presence of three equivalents of pyridine, yielding the *cis*- and *trans*-*N*-tosyl-protected 3-(trifluoromethyl)aziridines **304** and **305**, respectively, in good yields (49-57%). The relative stereochemistry of aziridines **304** and **305** could be deduced from the vicinal coupling constants between the C2- and C3-proton in ^1H NMR ($CDCl_3$). The *cis*-isomer was assigned to the compound with the largest coupling constant (J = 7.1 Hz), while the *trans*-isomer possessed a relatively small coupling constant (J = 3.9 Hz), which is in accordance with literature data.[183] This assignment proved that the transformation of the non-activated aziridines toward activated aziridines occurred without any change in relative configuration.



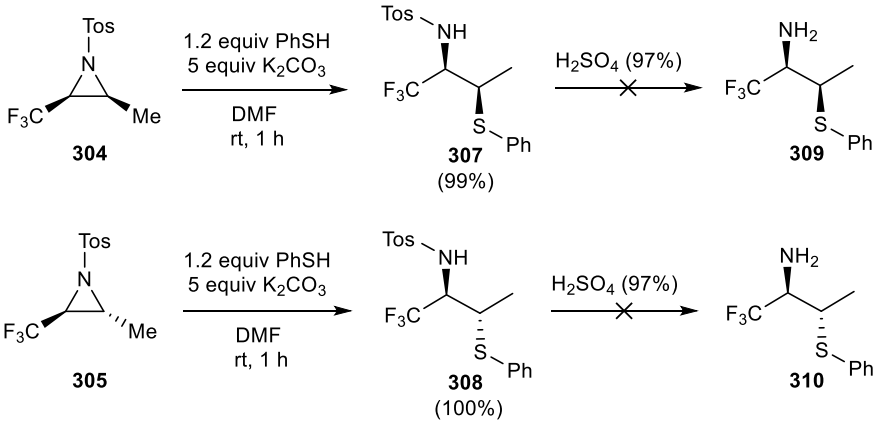
Scheme 93

Hydrogenation of *cis*- and *trans*-2-phenyl-3-trifluoromethyl aziridines **270c** and **280c** both gave rise to the aziridine ring-opened product, 1,1,1-trifluoro-3-phenylpropan-2-amine **306** in good to excellent yields (80-94%) (Scheme 94).



Scheme 94

As expected, these activated aziridines **304** and **305** are susceptible toward ring opening. This was demonstrated by the (near) quantitative (99-100%) ring opening with 1.2 equivalents of PhSH in *N,N*-dimethylformamide (DMF) to afford *syn*- and *anti*-*N*-tosyl-1,1,1-trifluoro-3-(phenylthio)butan-2-amines **307** and **308** without the need for initial aziridine activation toward aziridinium intermediates (Scheme 95).



Scheme 95

Recently, Katagiri et. al. reported the removal of a tosyl protecting group by treating trifluoromethylated amines with sulphuric acid.[13a] However, treatment of our substrates **307** and **308** in sulphuric acid at 0 °C gave rise to complex reaction mixtures. Alternatively, tosylamine **307** was heated in the presence of Mg in methanol, but no conversion could be achieved. Although, the recent development of a detosylation method for α-CF_3-amines,[13a] removal of the tosyl group for *N*-tosyl-1,1,1-trifluoro-3-(phenylthio)butan-2-amines **307** and **308** toward free amines **309** and **310** remains a challenge.

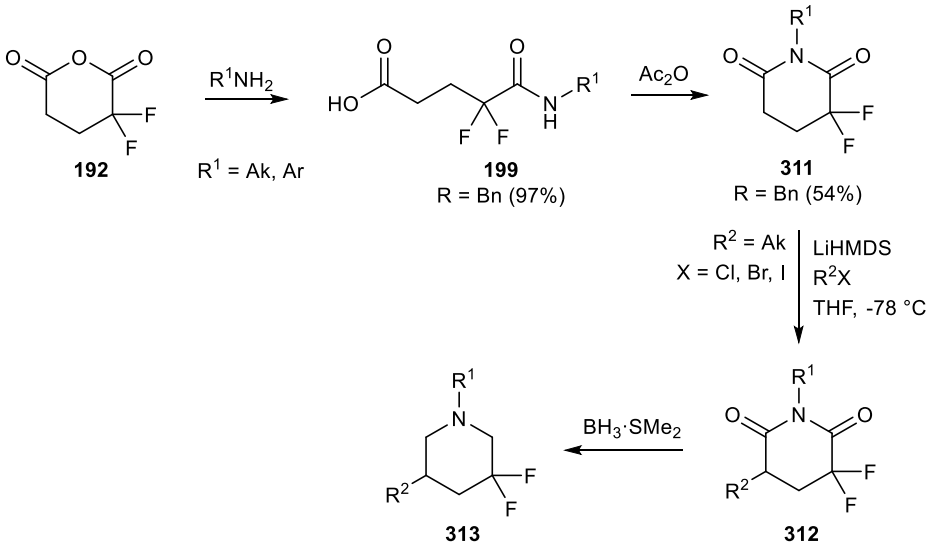
N-Tosylated 2-(trifluoromethyl)aziridines have already proven to be susceptible to deprotonation with organolithium bases in the C2-postion to produce the corresponding aziridinyl anions, allowing a coupling reaction with a diverse range of electrophiles (alkyl halides, carbonyl compounds).[186] The deprotonation of *cis*-*N*-tosylaziridine **304** was briefly touched in this work, but due to the high temperature-dependency of this reaction, no conclusive results were attained. Further elaboration of this reaction should allow access to a broad range of functionalized fluorinated building blocks.

In conclusion, a convenient transformation of the non-activated 3-(trifluoromethyl)aziridines into their activated analogues was established by replacing the *N*-benzyl protecting group with a *N*-tosyl group. The resulting aziridines were subjected to regio- and stereoselective ring opening by thiophenol in quantitative yields.

4 Perspectives

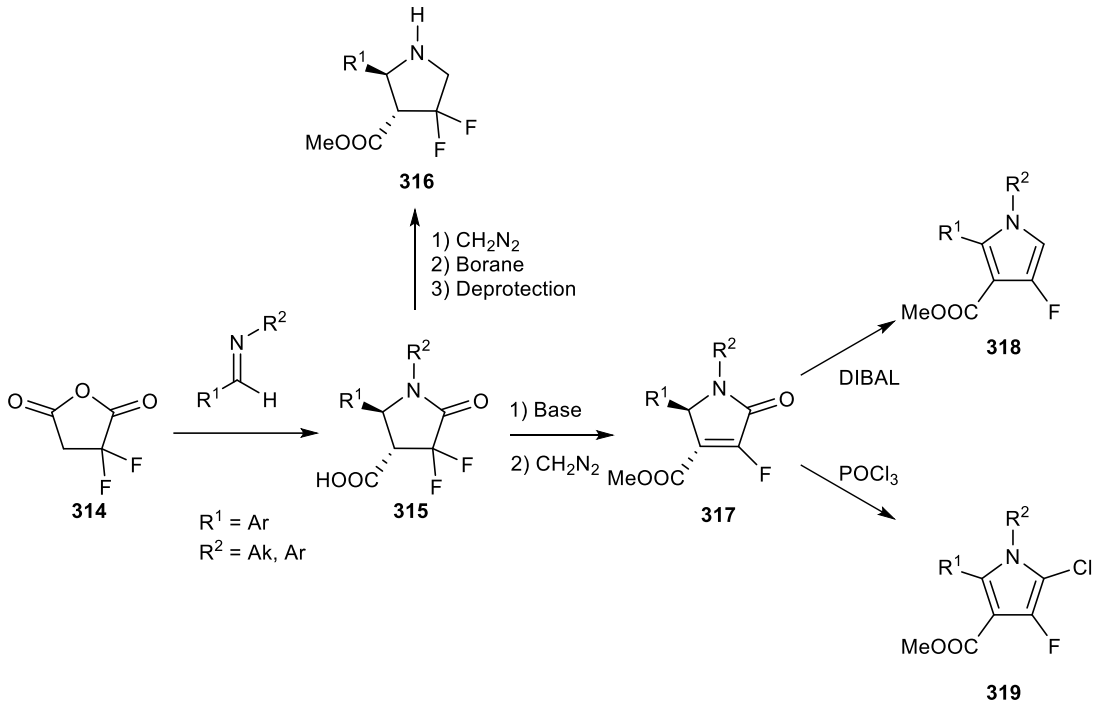
In this PhD-thesis, the application of 2,2-difluoroglutaric anhydride **192** as a valuable precursor in the synthesis of multifunctional piperidines was demonstrated. It could be of interest to further examine the synthetic scope of this highly reactive anhydride upon ring opening with a broad range of nucleophiles.

For example, primary amines have already proven to be suitable nucleophiles in the synthesis of fluorinated amides **199** (see 3.1.2.). These amides **199** could be ring closed again with acetic anhydride toward the corresponding fluorinated imides **311**, which is still an unexplored substrate in the synthesis of 5-functionalized 3,3-difluoropiperidines **313**. As a trial, the synthesis of 1-benzyl-3,3-difluoropiperidine-2,6-dione **311** was achieved in 54% yield. α-Deprotonation of imide **311** with a suitable base, followed by the addition of an electrophile could lead to 5-substituted 3,3-difluoroimides **312**. Subsequent reduction with an excess of borane could give rise to novel 5-substituted 3,3-difluorinated piperidines **313** (Scheme 96).



Scheme 96

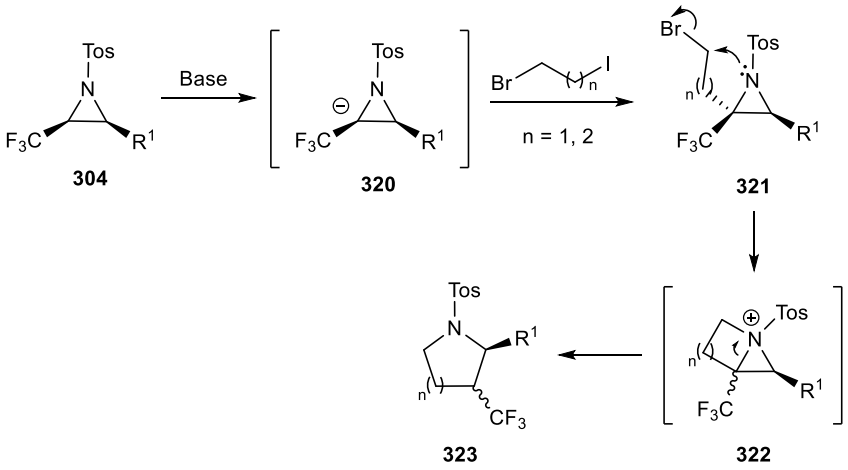
Closely related to this subject, the synthetic scope of 2,2-difluorosuccinic anhydride **314** could be examined. In analogy with the six-membered anhydride **192**, it can be expected that the reaction of succinic anhydride **314** with imines would give rise to *trans*-3,3-difluoropyrrolidones **315** as major products.[142] These fluorinated pyrrolidones **315** can be considered as interesting precursors for the synthesis of fluorinated β-amino acid derivatives **316** and 3-fluoropyrroles **318** and **319**. Analogous to transformations with the prepared piperidines from this work, methylation of pyrrolidones **315** followed by reduction and *N*-deprotection of should give rise to *trans*-pyrrolidines **316** (Scheme 97).



Scheme 97

Elimination of hydrogen fluoride by an excess of base and subsequent methylation with diazomethane of **315** should proceed fluently toward the conjugated **317**.[187] Treatment with diisobutylaluminium hydride (DIBAL) and phosphoryl chloride ($POCl_3$) could result in promising fluorinated pyrroles **318** and 5-chloro-4-fluoropyrroles **319**, respectively (Scheme 97).

As mentioned earlier in this work (see 3.3.3), the deprotonation of *cis*- and *trans*-2-methyl-1-tosyl-3-(trifluoromethyl)aziridines **304** and **305** could be further investigated. As illustrated for *cis*-aziridine **304,** reaction of the aziridinyl anion **320** against a broad range of electrophiles could give access to highly functionalized aziridines. When ω,ω'-dihaloalkanes are evaluated as electrophiles, a ring expansion toward novel trifluoromethylated azaheterocyclic compounds **323** could take place (Scheme 98).[186a]



Scheme 98

5 Experimental Part

5.1 General Methods

Flame-dried glassware was used for all non-aqueous reactions. Commercially available solvents and reagents were purchased from common chemical suppliers and used without further purification, unless stated otherwise.

Solvents

Diethyl ether (Et_2O), tetrahydrofuran (THF), benzene, toluene and xylene were distilled from sodium benzophenone ketyl or sodium, while dichloromethane (CH_2Cl_2) and acetonitrile (CH_3CN) were distilled from calcium hydride prior to use. Methanol (MeOH) was treated with magnesium metal and iodine, distilled and kept over molecular sieves. Petroleum ether refers to the 40-60 °C boiling fraction.

Column chromatography

The purification of the reaction mixtures was performed by column chromatography in a glass column with silica gel (Acros, particle size 35-70 µm, pore diameter ca. 6 nm). Solvent systems were determined *via* thin layer chromatography (TLC) on glass plates coated with silica gel (Merck, Kieselgel 60 F_{254}, precoated 0.25 mm) using standard visualisation techniques or agents: UV fluorescence (254 nm and 366 nm), colouring with iodine vapors or with potassium permanganate solution.

Gas chromatography

Gas chromatography/FID analysis was performed on an Agilent 6980 Series gas chromatograph, connected to a FID detector (H_2 gas), using an Alltech EC-5 capillary column (30 m x 0.25 mm) with a film thickness of 0.25 µm with helium as the carrier gas.

Liquid chromatography

Liquid chromatography analysis was performed by a reverse phase LC-column (Eclipse plus C18 column). The LC column has dimensions of 50 x 4.6 mm and has a particle size of 3.5 µm. Gradient elution was used (30% acetonitrile in water to 100% acetonitrile over 6 minutes).

Mass spectrometry

Low resolution mass spectra were recorded *via* injection on an Agilent 1100 Series LC/MSD type SL mass spectrometer with Electrospray ionisation geometry (ESI 70 eV) and using a Mass Selective

Detector (quadrupole). When crude reaction mixtures were analyzed, the mass spectrometer was preceded by a HPLC reversed phase column with a diode array UV/VIS detector.

Electron Impact (EI) mass spectra were obtained with an Agilent HP 5973 Series MSD mass spectrometer. The analyses of the electron impact mass spectra were preceded by a Agilent 6890A GC with an Agilent J&W HP-5MS (30 m x 0.25mm x 0.1 µm) column.

High resolution mass spectra were obtained with an Agilent Technologies 6210 Time-of-Flight Mass Spectrometer (TOFMS), equipped with ESI/APCI-multimode source.

NMR spectroscopy

High resolution ^{1}H NMR (300 or 400 MHz), ^{13}C NMR (75 or 100 MHz) and ^{19}F NMR (282 or 376 MHz) spectra were recorded on a Jeol Eclipse FT 300 NMR spectrometer or a Bruker Avance III Nanobay 400 MHz spectrometer at room temperature. Peak assignments were obtained with the aid of DEPT, APT, COSY and/or HSQC spectra. The compounds were diluted in deuterated solvents, quoted in parts per million (ppm) with tetramethylsilane (TMS) and trichlorofluoromethane ($CFCl_3$) as internal standards.

Infrared spectroscopy

Infrared spectra were recorded on a Perkin Elmer Spectrum BX FT-IR Spectrometer. All compounds were analyzed in neat form with an ATR (Attenuated Total Reflectance) accessory (ZnSe crystal). Only selected absorbances (ν_{max}/cm^{-1}) were reported.

Elemental analysis

Elementary analyses were obtained by means of a Perkin Elmer series II CHNS/O elementary analyzer 2400.

Melting point

Melting points of crystalline compounds were determined using a Büchi B-540 apparatus or a Kofler bench, type WME Heizbank of Wagner & Munz.

Microwave reactions

All microwave reactions were performed in a CEM *Focused Microwave™ Synthesis System*, Model Discover, with a continuous power output from 0 to 300 watt and a self-adjusting, single mode MW cavity. The reactions were performed in 10 mL thick-walled Pyrex reaction vessels, closed with a 'snap-on' septa cap and equipped with a small stirring bar. A ramp time of maximum five minutes was used whereby the temperature was increased from room temperature to the desired one. This temperature was maintained during the course of the reaction for the indicated time. The

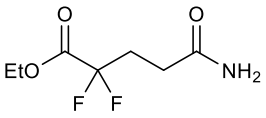
temperature control system used a non-contact infrared sensor to measure the temperature on the bottom of the vessel and was used in a feedback loop with the on-board computer to regulate the temperature from 25 to 250 °C by adjusting the power output (1 Watt increments). The pressure control*, IntelliVent™ Pressure Control system*, used an indirect measurement of the pressure by sensing changes in the external deflection of the septa on the top of the sealed pressure vessel. Stirring was performed by a rotating magnetic plate, located below the floor of the microwave cavity. When the reaction was done, cooling of the vial was performed by a stream of clean air onto the vial, which decreased the temperature of a 2 mL solution from approximately 150 °C to 40 °C in less than 120 seconds.

5.2 Synthetic Procedures

5.2.1 Synthesis of ethyl 4-carbamoyl-2,2-difluorobutanoate 194c

Copper (10.5 mmol, 2.1 equiv) was added to a solution of acrylamide **193c** (5.0 mmol, 1 equiv) and ethyl bromodifluoroacetate **61** (8.9 mmol, 1.8 equiv) in tetrahydrofuran (6 mL) and stirred at 50 °C. After 30 minutes tetramethylethylenediamine (2.5 mmol, 0.5 equiv) and acetic acid (4.5 mmol, 0.9 equiv) were added and the reaction was continued for another 30 minutes at 50 °C. The reaction was stopped by addition of saturated ammonium chloride (5 mL). The solids were filtered off over Celite® and washed with diethyl ether (2 x 5 mL). The combined organic phases were washed with ammonium chloride (2 x 10 mL), dried over $MgSO_4$ and concentrated *in vacuo.* The crude mixture was purified by column chromatography on silica gel to afford ethyl 4-carbamoyl-2,2-difluorobutanoate **194c** as a pure compound.

Ethyl 4-carbamoyl-2,2-difluorobutanoate 194c

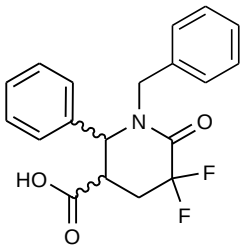


Colourless crystals: mp 57-62 °C. R_f 0.11 (petroleum ether/ ethyl acetate 4:1). Yield: 41%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.36 (3H, t, *J* = 7.2 Hz, $C\underline{H}_3CH_2$), 2.37-2.55 (4H, m, $CF_2(C\underline{H}_2)_2CONH_2$), 4.33 (2H, q, *J* = 7.2 Hz, $CH_3C\underline{H}_2O$), 5.41 (2H, br s, NH_2). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 12.1 ($\underline{C}H_3CH_2$), 25.7 ($\underline{C}H_2CONH_2$), 28.2 (t, *J* = 23.7 Hz, $\underline{C}H_2CF_2$), 63.5 ($CH_3\underline{C}H_2O$), 114.0 (t , *J* = 249.8 Hz, CF_2), 162.3 (t, *J* = 32.3 Hz, $CF_2\underline{C}O_2OEt$), 172.0 ($CONH_2$). **^{19}F NMR** (282 MHz, $CDCl_3$): δ -106.7 (t, *J* = 16.4 Hz, CF_2). **IR** (ATR, cm^{-1}): ν_{NH} 3356, 3190; $\nu_{C=O}$ 1758, 1657, 1632; ν_{max} 1432, 1284, 1201, 1100, 1077, 1046, 1013, 971, 777, 674, 624. **MS** (ES+): *m/z* (%): 196 (M+1, 100).

5.2.2 Synthesis of 1-benzyl-5,5-difluoro-6-oxo-2 arylpiperidine-3-carboxylic acids 196

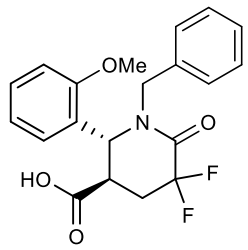
As a representative example, the synthesis of 1-benzyl-5,5-difluoro-6-oxo-2-phenylpiperidine-3-carboxylic acid **196a** is described. To a solution of *N*-(benzylidene)benzylamine **195a** (3.3 mmol, 1.0 equiv) in dry toluene (7 mL), 2,2-difluoroglutaric anhydride **192** (3.3 mmol, 1.0 equiv) was added. The reaction mixture was heated under reflux for six hours. After cooling, the reaction mixture was extracted with saturated sodium bicarbonate (3 x 10 mL) and the aqueous layer was acidified with 3M hydrochloric acid to pH = 1. The acidic aqueous layer was extracted with ethyl acetate (3 x 25 mL). The organic phase was dried over $MgSO_4$ and evaporated under reduced pressure, yielding the crude *trans*- and *cis*-1-benzyl-5,5-difluoro-6-oxo-2-phenylpiperidine-3-carboxylic acid **196a**.

1-Benzyl-5,5-difluoro-6-oxo-2-phenylpiperidine-3-carboxylic acid 196a



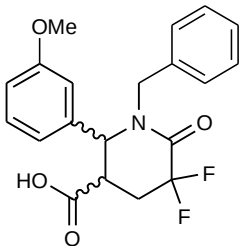
Colourless crystals. Yield 74%. R_f = 0.33. (petroleum ether/ethyl acetate 3:2). *Cis*-diastereomer: **^{1}H NMR** (300 MHz, $CDCl_3$): δ_{cis} 2.34-2.48 (2H, m, CH_2CF_2), 3.40 (1H, d, *J* = 14.9 Hz, NC$\underline{H}_a$H$_b$Ph), 4.44 (1H, d, *J* = 5.5 Hz, C$\underline{H}$CO$_2$H), 4.89 (1H, d, *J* = 5.0 Hz, NCH), 5.44 (1H, d, *J* = 14.9 Hz, NCH$_a$$\underline{H}_b$Ph), 7.04-7.41 (10H, m, 10 x CH_{Ar}), 10.58 (1H, s (br), CO_2H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 29.1 (t, *J* = 24.2 Hz, $\underline{C}H_2CF_2$), 43.6 (C$\underline{H}$CO$_2$H), 48.7 (NCH_2Ph), 60.4 (NCH), 112.0 (t, *J* = 245,8 Hz, CF_2), 127.2-129.5 (10 x CH_{Ar}), 135.0 ($C_{q,Ar}$), 136.8 ($C_{q,Ar}$), 162.1 (t, *J* = 30.0 Hz, C=O), 174.2 (CO_2H). **^{19}F NMR** (282 MHz, $CDCl_3$): δ -94.0 (1F, d x t, *J* = 25.0, 290.1 Hz, C$\underline{F}_a$F$_b$), -100.0 (1F, d, *J* = 290.1 Hz, CF$_a$$\underline{F}_b$). *Trans*-diastereomer: **^{1}H NMR** (300 MHz, $CDCl_3$): δ_{trans} 2.48-2.61 (2H, m, CH_2CF_2), 3.05-3.12 (1H, m, C$\underline{H}$CO$_2$H), 3.48 (1H, d, *J* = 14.3 Hz, NC$\underline{H}_a$H$_b$Ph), 4.80 (1H, d, *J* = 6.1 Hz, NCH), 5.36 (1H, d, *J* = 14.3 Hz, NCH$_a$$\underline{H}_b$Ph), 7.04-7.41 (10H, m, 10 x CH_{Ar}), 10.58 (1H, br s, CO_2H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 31.6 (t, *J* = 24.2 Hz, $\underline{C}H_2CF_2$), 44.0 ($\underline{C}HCO_2H$), 48.3 (NCH_2Ph), 61.0 (NCH), 111.5 (t, *J* = 224.6 Hz, CF_2), 127.2-129.5 (10 x CH_{Ar}), 162.2 (t, *J* = 30 Hz, C=O), 174.2 (CO_2H). **^{19}F NMR** (282 MHz, $CDCl_3$): δ -98.8 (2F, t, *J* = 13.2 Hz, CF_2). **IR** (ATR, cm^{-1}): ν_{OH} 3063; ν_{CO} 1736, 1638; ν_{max} 1271, 1143, 903, 695. **MS** (ES+): *m/z* (%): 346 (M+1, 100).

***Trans*-1-benzyl-4,4-difluoro-6-oxo-2-(2-methoxyphenyl)piperidine-3-carboxylic acid 196b**



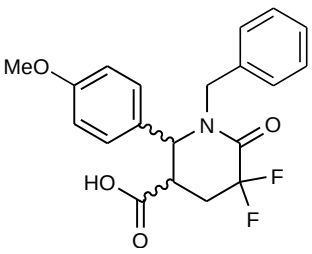
Colourless oil. Yield: 79%.**^{1}H NMR** (300 MHz, $CDCl_3$): 2.60-2.68 (2H, m, CH_2CF_2), 3.23 (1H, m, C$\underline{H}$CO$_2$H), 3.61 (1H, d, *J* = 14.9 Hz, NC$\underline{H}_a$CH$_b$), 3.76 (3H, s, OCH_3), 5.18 (1H, d, *J* = 3.9 Hz, NCH), 5.30 (1H, d, *J* = 14.3 Hz, NCH$_a$C$\underline{H}_b$), 6.28-7.38 (9H, m, 9 x CH_{Ar}), 10.63 (1H, br s, CO_2H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 31.3 (t, *J* = 24.2 Hz, $\underline{C}H_2CF_2$), 40.8 ($\underline{C}HCO_2H$), 49.0 (NCH_2Ph), 55.5 (OCH_3), 56.7 (NCH), 111.3 (CH_{Ar}), 111.6 (t, *J* = 243.5 Hz, CF_2), 121.0 (CH_{Ar}), 127.9-129.0 (7 x CH_{Ar}), 130.3 ($C_{q,Ar}$), 135.0 ($C_{q,Ar}$), 157.8 ($C_{q,Ar}$), 162.6 (t, *J* = 31.2 Hz, C=O), 176.0 (CO_2H). **^{19}F NMR** (282 MHz, $CDCl_3$): δ -100.4 (2F, d, *J* = 296.0 Hz, CF_2). **IR** (ATR, cm^{-1}): ν_{OH} 3028; ν_{CO} 1734, 1638; ν_{max} 1491, 1436, 1212, 1166, 1093, 750, 735. **MS** (ES+): *m/z* (%): 376 (M+1, 100).

1-Benzyl-5,5-difluoro-6-oxo-2-(3-methoxyphenyl)piperidine-3-carboxylic acid 196c



Colourless crystals.Yield: 67%. *Cis*-diastereomer: **^{1}H NMR** (300 MHz, $CDCl_3$): δ_{cis} 2.36-2.55 (2H, m, CH_2CF_2), 3.45 (1H, d, *J* = 14.9 Hz, NCH_aH_bPh), 3.72 (3H, s, OCH_3), 4.46 (1H, d, *J* = 5.5 Hz, $CHCO_2H$), 4.88 (1H, d, *J* = 5.0 Hz, NCH), 5.44 (1H, d, *J* = 14.9 Hz, NCH_aH_bPh), 6.65-7.37 (9H, m, 9 x CH_{Ar}), 9.88 (1H, br s, CO_2H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 29.2 (t, *J* = 24.2 Hz, CH_2CF_2), 43.6 ($CHCO_2H$), 48.7 (NCH_2Ph), 55.3 (OCH_3), 60.2 (NCH), 100.0 (t, *J* = 244.8 Hz, CF_2), 127.9 (2 x CH_{Ar}), 128.0 (2 x CH_{Ar}), 128.2 (CH_{Ar}), 128.6 (CH_{Ar}), 129.0 (CH_{Ar}), 121.0 (CH_{Ar}), 124.4 (CH_{Ar}), 130.8 ($C_{q,Ar}$), 135.0 ($C_{q,Ar}$), 157.9 ($C_{q,Ar}$), 163.6 (t, *J* = 31.2 Hz, C=O), 172.7 (CO_2H). **^{19}F NMR** (282 MHz, $CDCl_3$): δ -94.1 (1F, d x t, *J* = 23.4, 287.1 Hz, CF_aF_b), -102.4 (1F, d, *J* = 287.1 Hz, CF_aF_b). *Trans*-diastereomer: **^{1}H NMR** (300 MHz, $CDCl_3$): δ_{trans} 2.51-2.67 (2H, m, CH_2CF_2), 3.07-3.13 (1H, m, $CHCO_2H$), 3.48 (1H, d, *J* = 14.9 Hz, NCH_aH_bPh), 3.72 (3H, s, OCH_3), 4.80 (1H, d, *J* = 6.1 Hz, NCH), 5.35 (1H, d, *J* = 14.3 Hz, NCH_aH_bPh), 6.65-7.37 (9H, m, 9 x CH_{Ar}), 9.88 (1H, br s, CO_2H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 31.7 (t, *J* = 24.2 Hz, CH_2CF_2), 43.9 ($CHCO_2H$), 48.4 (NCH_2Ph), 55.4 (OCH_3), 60.7 (NCH), 111.3 (t, *J* = 224.6 Hz, CF_2), 113.0 (CH_{Ar}), 121.0 (CH_{Ar}), 127.9 (CH_{Ar}), 128.5 (2 x CH_{Ar}), 128.9 (2 x CH_{Ar}), 130.3 ($C_{q,Ar}$), 134.9 ($C_{q,Ar}$), 162.5 (t, *J* = 30 Hz, C=O), 176.0 (CO_2H). **^{19}F NMR** (282 MHz, $CDCl_3$): δ -99.7 (2F, t, *J* = 13.2, CF_2). **IR** (ATR, cm^{-1}): ν_{OH} 3029; ν_{CO} 1739, 1655; ν_{max} 1432, 1203, 698. **MS** (ES+): *m/z* (%): 376 (M+1, 100).

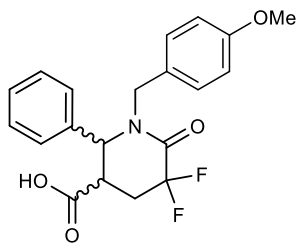
1-Benzyl-5,5-difluoro-6-oxo-2-(4-methoxyphenyl)piperidine-3-carboxylic acid 196d



Colourless crystals. Yield: 85%. R_f 0.21 (ethyl acetate/petroleum ether 1:1) *Cis*-diastereomer: **^{1}H NMR** (300 MHz, $CDCl_3$): δ_{cis} 2.39-2.50 (2H, m, CH_2CF_2), 3.41 (1H, d, *J* = 14.9 Hz, NCH_aH_bPh), 3.80 (3H, s, OCH_3), 4.49 (1H, d, *J* = 5.5 Hz, $CHCO_2H$), 4.84 (1H, d, *J* = 5.0 Hz, NCH), 5.45 (1H, d, *J* = 14.9 Hz, NCH_aH_bPh), 6.84-7.35 (9H, m, 9 x CH_{Ar}), 8.96 (1H, br s, CO_2H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 28.9 (t, *J* = 24.2 Hz, CH_2CF_2), 43.7 ($CHCO_2H$), 48.4 (NCH_2Ph), 55.4 (OCH_3), 60.7 (NCH), 111.9 (t, *J* = 238.8 Hz, CF_2), 114.6 (CH_{Ar}), 127.9-129.0 (8 x CH_{Ar}), 135.0 ($C_{q,Ar}$), 136.8 ($C_{q,Ar}$), 160.3 ($C_{q,Ar}$), 162.3 (t, *J* = 31.2 Hz, C=O), 177.2 (CO_2H). **^{19}F NMR** (282 MHz, $CDCl_3$): δ -94.3 (1F, d x d x d, *J* = 23.0, 27.0, 290.1 Hz, CF_aF_b), -102.5 (1F, d, *J* = 290.1 Hz, CF_aF_b). *Trans*-diastereomer: **^{1}H NMR** (300 MHz, $CDCl_3$): δ_{trans} 2.50-2.64 (2H, m, CH_2CF_2), 3.06-3.12 (1H, m, $CHCO_2H$), 3.49 (1H, d, *J* = 14.6 Hz, NCH_aH_bPh), 3.82 (3H, s, OCH_3), 4.71 (1H, d, *J* = 6.6 Hz, NCH), 5.36 (1H, d, *J* = 14.6 Hz, NCH_aH_bPh), 6.84-7.35 (9H, m, 9 x CH_{Ar}), 10.07 (1H, br s, CO_2H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ_{trans} 32.0 (t, *J* = 24.2 Hz, CH_2CF_2), 44.2 ($CHCO_2H$), 47.9 (NCH_2Ph), 55.4 (OCH_3), 60.4 (NCH), 111.4 (t, *J* = 243.5 Hz, CF_2), 114.7 (CH_{Ar}), 127.9-129.0 (8 x CH_{Ar}), 129.1 ($C_{q,Ar}$), 135.0 ($C_{q,Ar}$), 160.0 ($C_{q,Ar}$), 161.2 (t, *J* = 30 Hz, C=O), 174.8 (CO_2H). **^{19}F NMR** (282 MHz, $CDCl_3$): δ -99.3 (1F, d x d x d, *J* = 11.8, 18.7, 283.0 Hz, CF_aF_b), -102.4 (1F, d

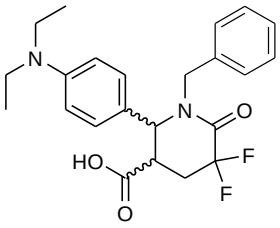
x t, *J* = 11.8, 283.0 Hz, $CF_a\underline{F}_b$). **IR** (ATR, cm^{-1}): ν_{OH} 2948; ν_{CO} 1731, 1632; ν_{max} 1250, 1188, 836, 743. **MS** (ES+): *m/z* (%): 376 (M+1, 100).

5,5-Difluoro-1-(4-methoxybenzyl)-6-oxo-2-phenylpiperidine-3-carboxylic acid 196e



Colourless crystals. Yield: 45%. *Cis*-diastereomer: **^{1}H NMR** (300 MHz, $CDCl_3$): δ_{cis} 2.36-2.71 (2H, m, CH_2CF_2), 3.36 (1H, d, *J* = 14.3 Hz, $C\underline{H}_aH_bPh$), 3.78 (3H, s, OCH_3), 4.42 (1H, d, *J* = 5.0 Hz, $C\underline{H}CO_2H$), 4.90 (1H, d, *J* = 5.0 Hz, NCH), 5.39 (1H, d, *J* = 14.3 Hz, $CH_a\underline{H}_bPh$), 6.78-7.59 (9H, m, 9 x CH_{Ar}), 10.3 (1H, br s, CO_2H). **^{19}F NMR** (282 MHz, $CDCl_3$): δ -94.3 (1F, d x t, *J* = 23.7, 291.4 Hz, $C\underline{F}_aF_b$), -102.6 (1F, d, *J* = 291.4 Hz, $CF_a\underline{F}_b$). *Trans*-diastereomer: **^{1}H NMR** (300 MHz, $CDCl_3$): δ_{trans} 2.36-2.71 (2H, m, CH_2CF_2), 3.10 (1H, ~q, *J* = 6.1 Hz, $C\underline{H}CO_2H$), 3.43 (1H, d, *J* = 14.9 Hz, $C\underline{H}_aH_bPh$), 3.78 (3H, s, OCH_3), 3.80 (1H, d, *J* = 14.3 Hz, $CH_a\underline{H}_bPh$), 4.82 (1H, d, *J* = 6.6 Hz, NCH), 5.32 (1H, d, *J* = 14.3 Hz, $CH_a\underline{H}_bPh$), 6.76-7.42 (9H, m, 9 x CH_{Ar}), 10.07 (1H, br s, CO_2H). **^{19}F NMR** (282 MHz, $CDCl_3$): δ -99.7 (1F, t, *J* = 13.2, 287.1 Hz, CF_2). **MS** (ES+): *m/z* (%): 376 (M+1, 100).

1-Benzyl-5,5-difluoro-6-oxo-2-(4-diethylaminophenyl)piperidine-3-carboxylic acid 196f

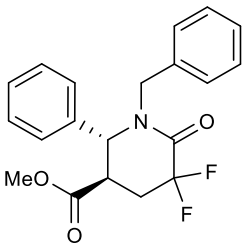


Orange crystals. R_f = 0.17 (ethyl acetate/petroleum ether 4:1). Yield = 87%. *Cis*-diastereomer: **^{1}H NMR** (300 MHz, $CDCl_3$): δ_{cis} 1.07 (6H, t, *J* = 7.2 Hz, $C\underline{H}_3CH_2N$), 2.37-2.51 (2H, m, CH_2CF_2), 3.26-3.36 (4H, m, $NC\underline{H}_2CH_3$), 3.51 (1H, d, *J* = 14.9 Hz, $NC\underline{H}_aH_bPh$), 4.48 (1H, d, *J* = 6.1 Hz, $C\underline{H}CO_2H$), 4.85 (1H, d, *J* = 5.0 Hz, NCH), 5.37 (1H, d, *J* = 14.3 Hz, $NCH_a\underline{H}_bPh$), 6.63 (2H, d, *J* = 7.2 Hz, CH_{Ar}), 6.97-7.37 (7H, m, 7 x CH_{Ar}), 8.79 (1H, br s, CO_2H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 12.0 ($\underline{C}H_3CH_2$) 30.0 ($\underline{C}H_2CF_2$), 44.6 ($\underline{C}HCO_2H$), 46.2 ($N\underline{C}H_2CH_3$), 48.5 (NCH_2Ph), 60.3 (NCH), 111.7 (t, *J* = 245.2 Hz, CF_2), 114.5 (CH_{Ar}), 127.8-129.2 (8 x CH_{Ar}), 135.5 ($C_{q,Ar}$), 146.5 ($C_{q,Ar}$), 162.3 (t, *J* = 30.0 Hz, C=O), 172.6 (CO_2H). **^{19}F NMR** (282 MHz, $CDCl_3$): δ -94.1 (1F, d x t, *J* = 23.0, 291.0 Hz, $C\underline{F}_aF_b$), -102.2 (1F, d, *J* = 291.0 Hz, $CF_a\underline{F}_b$). *Trans*-diastereomer: **^{1}H NMR** (300 MHz, $CDCl_3$): δ_{trans} 1.15 (6H, t, *J* = 6.9 Hz, $C\underline{H}_3CH_2N$), 2.51-2.63 (2H, m, CH_2CF_2), 3.00-3.07 (1H, m, $C\underline{H}CO_2H$), 3.26-3.36 (4H, m, $NC\underline{H}_2CH_3$), 3.59 (1H, d, *J* = 14.3 Hz, $NC\underline{H}_aH_bPh$), 4.72 (1H, d, *J* = 6.6 Hz, NCH), 5.27 (1H, d, *J* = 14.9 Hz, $NCH_a\underline{H}_bPh$), 6.73 (2H, d, *J* = 8.8 Hz, 2 x CH_{Ar}), 6.97-7.35 (7H, m, 7 x CH_{Ar}), 8.79 (1H, br s, CO_2H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 12.2 ($\underline{C}H_3CH_2$), 32.2 (t, *J* = 24.8 Hz, $\underline{C}H_2CF_2$), 44.6 ($\underline{C}HCO_2H$), 45.7 ($N\underline{C}H_2CH_3$), 48.0 (NCH_2Ph), 61.1 (NCH), 112.2 (t, *J* = 240.0 Hz, CF_2), 113.8 (CH_{Ar}), 127.8-129.2 (8 x CH_{Ar}), 135.5 ($C_{q,Ar}$), 146.0 ($C_{q,Ar}$), 162.1 (t, *J* = 30.0 Hz, C=O), 174.4 (CO_2H). **^{19}F NMR** (282 MHz, $CDCl_3$): δ -99.0 (1F, d x t, *J* = 14.5, 283.5 Hz, $C\underline{F}_aF_b$), -100.2 (1F, d x t, *J* = 13.2, 283.5 Hz, $CF_a\underline{F}_b$). **IR** (ATR, cm^{-1}): ν_{OH} 2968; ν_{CO} 1725, 1676; ν_{max} 1521, 1266, 1195, 1151, 1068, 733, 698. **MS** (ES+): *m/z* (%): 417 (M+1, 100).

5.2.3 Synthesis of *trans*-methyl 6-aryl-1-benzyl-3,3-difluoro-2-oxopiperidine-5-carboxylates 202

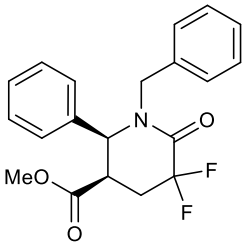
As a representative example, the synthesis of *trans*-methyl 1-benzyl-3,3-difluoro-2-oxo-6-phenyl-piperidine-5-carboxylate **202a** is described. To an ice-cooled solution of 1-benzyl-4,4-difluoro-6-oxo-2-phenylpiperidine-3-carboxylic acid **196a** (1.7 mmol, 1 equiv) in dry diethyl ether (10 mL), diazomethane (8.5 mmol, 5 equiv) in diethyl ether was carefully added at 0 °C and the reaction was then stirred overnight at room temperature. The solvent was evaporated *in vacuo* to yield a mixture of *trans*- and *cis*-isomers **202a**. These diastereomers were purified *via* column chromatography on silica gel and a subsequent recrystallisation in petroleum ether/diethyl ether (5:1) afforded *trans*-methyl 1-benzyl-3,3-difluoro-2-oxo-6-phenylpiperidine-5-carboxylate ***trans*-202a.**

***Trans*-methyl 1-benzyl-3,3-difluoro-2-oxo-6-phenylpiperidine-5-carboxylate *trans*-202a**



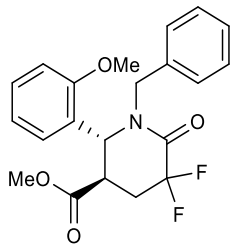
Colourless crystals: mp 139.0-140.5 °C. R_f = 0.16 (petroleum ether/ethyl acetate 4:1). Yield: 73%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 2.56 (2H, t x d, *J* = 6.6, 13.6 Hz, CH_2CF_2), 3.08 (1H, q, *J* = 6.6 Hz, $CHCO_2CH_3$), 3.49 (1H, d, *J* = 15.4 Hz, NCH_aH_bPh), 3.53 (3H, s, OCH_3), 4.84 (1H, d, *J* = 6.1 Hz, NCH), 5.41 (1H, d, *J* = 14.9 Hz, NCH_aH_bPh), 7.13-7.38 (10H, m, 10 x CH_{Ar}). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 31.9 (t, *J* = 24.2 Hz, CH_2CF_2), 44.0 (t, *J* = 5.2 Hz, $CHCO_2CH_3$), 48.1 (NCH_2Ph), 52.6 (OCH_3), 61.1 (NCH), 111.4 (t, *J* = 224.6 Hz, CF_2), 127.1 (2 x CH_{Ar}), 128.0 (CH_{Ar}), 128.7 (2 x CH_{Ar}), 128.9 (2 x CH_{Ar}), 129.0 (CH_{Ar}), 129.4 (2 x CH_{Ar}), 135.2 ($C_{q,Ar}$), 137.7 ($C_{q,Ar}$), 161.8 (t, *J* = 30 Hz, C=O), 170.6 (CO_2CH_3). **^{19}F NMR** (282 MHz, $CDCl_3$): δ -98.8 (1F, d x t, *J* = 13.2, 284.1 Hz, CF_aF_b), -100.0 (1F, d x t, *J* = 13.2, 284.1 Hz, CF_aF_b). **IR** (ATR, cm^{-1}): $\nu_{C=O}$ 1729, 1676; ν_{max} 1350, 1199, 1095, 746, 707. **MS** (ES+): *m/z* (%): 360 (M+1, 100). **Anal.** Calcd. for $C_{20}H_{19}F_2NO_3$: C, 66.84; H, 5.33; N, 3.90. Found: C, 66.66; H, 5.24; N, 3.95.

C*is*-methyl-1-benzyl-5,5-difluoro-6-oxo-2-phenylpiperidine-3-carboxylate *cis*-202a



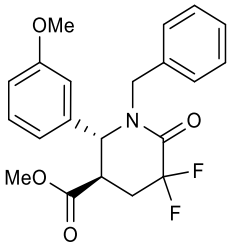
Not isolated as a single diastereomer. R_f = 0.16 (petroleum ether/ethyl acetate 4:1). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 2.45-2.53 (2H, m, CH_2CF_2), 3.41 (1H, d, *J* = 14.3 Hz, NCH_aH_bPh), 3.55 (3H, s, OCH_3), 4.49 (1H, d, *J* = 6.1 Hz, $CHCO_2CH_3$), 4.88 (1H, d, *J* = 5.5 Hz, NCH), 5.47 (1H, d, *J* = 14.9 Hz, NCH_aH_bPh), 7.08-7.44 (10H, m, 10 x CH_{Ar}). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 29.3 (t, *J* = 24.2 Hz, CH_2CF_2), 41.7 (d, *J* = 10.4 Hz, $CHCO_2CH_3$), 48.5 (NCH_2Ph), 52.3 (OCH_3), 60.5 (NCH), 112.0 (t, *J* = 241.1 Hz, CF_2), 127.6 (2 x CH_{Ar}), 128.2 (CH_{Ar}), 128.3 (2 x CH_{Ar}), 129.1 (2 x CH_{Ar}), 129.3 (2 x CH_{Ar}), 129.4 (CH_{Ar}), 134.0 ($C_{q,Ar}$), 137.7 ($C_{q,Ar}$), 161.9 (t, *J* = 30.0 Hz, C=O), 169.0 (CO_2CH_3). **^{19}F NMR** (282 MHz, $CDCl_3$): δ -94.3 (1F, d x d x d, *J* = 21.7, 28.3, 289.4 Hz, CF_aF_b), -100.0 (1F, d x t, *J* = 8.6, 289.4 Hz, CF_aF_b). **MS** (ES+): *m/z* (%): 360 (M+1, 100). **Anal.** Calcd. for $C_{21}H_{21}F_2NO_4$: C, 64.77; H, 5.44; N, 3.60. Found: C, 66.66; H, 5.24; N, 3.95.

***Trans*-methyl 1-benzyl-3,3-difluoro-2-oxo-6-(2-methoxyphenyl)piperidine-5-carboxylate *trans*-202b**



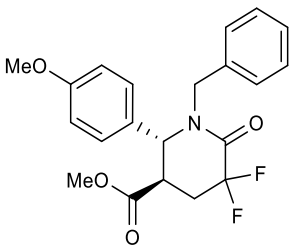
Colourless crystals: mp 118.3-120.3 °C. R_f = 0.20 (petroleum ether/ethyl acetate 3:1). Yield: 25%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 2.38-2.72 (2H, m, CH_2CF_2), 3.19 (1H, m, C<u>H</u>CO_2CH_3), 3.54 (3H, s, OCH_3), 3.58 (1H, d, *J* = 14.3 Hz, NC<u>H</u>$_a$H$_b$Ph), 3.77 (3H, s, OCH_3), 5.19 (1H, d, *J* = 4.4 Hz, NCH), 5.33 (1H, d, *J* = 14.3 Hz, NCH$_a$<u>H</u>$_b$Ph), 6.89-7.39 (9H, m, 9 x CH_{Ar}). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 31.6 (t, *J* = 24.2 Hz, <u>C</u>H_2CF_2), 41.0 (<u>C</u>HCO_2CH_3), 48.8 (NCH_2Ph), 52.5 (OCH_3), 55.4 (OCH_3), 57.0 (NCH), 111.5 (t, *J* = 244.6 Hz, CF_2), 111.2 (CH_{Ar}), 114.2 (CH_{Ar}), 121.0 (CH_{Ar}), 124.8 ($C_{q,Ar}$), 127.8 (CH_{Ar}), 128.0 ($C_{q,Ar}$), 128.5 (2 x CH_{Ar}), 129.0 (2 x CH_{Ar}), 130.1 (CH_{Ar}), 135.4 ($C_{q,Ar}$), 156.8 ($C_{q,Ar}$), 162.2 (t, *J* = 30Hz, C=O), 171.1 (<u>C</u>O_2CH_3). **^{19}F NMR** (282 MHz, $CDCl_3$): δ -97.2 (1F, d, *J* = 286.8 Hz, C<u>F</u>$_a$F$_b$), -100.4 (1F, d, *J* = 286.8 Hz, CF$_a$<u>F</u>$_b$). **IR** (ATR, cm^{-1}): $\nu_{C=O}$ 1742, 1685; ν_{max} 1600, 1487, 1456, 1362, 1239, 1197, 1101, 1101, 940, 756, 698. **MS** (ES+): *m/z* (%): 389 (M+1, 100). **Anal.** Calcd. for $C_{21}H_{21}F_2NO_4$: C, 64.77; H, 5.44; N, 3.60. Found: C, 64.38; H, 5.44; N, 3.63.

***Trans*-methyl 1-benzyl-3,3-difluoro-2-oxo-6-(3-methoxyphenyl)piperidine-5-carboxylate *trans*-202c**



Colourless crystals: mp 71.7-73.7 °C. R_f = 0.18 (petroleum ether/ethyl acetate 3:1). Yield: 40%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 2.57 (2H, t x d, *J* = 6.6, 13.6 Hz, CH_2CF_2), 3.09 (1H, q, *J* = 6.6 Hz, C<u>H</u>CO_2CH_3), 3.53 (1H, d, *J* = 14.3 Hz, NC<u>H</u>$_a$H$_b$Ph), 3.55 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 4.80 (1H, d, *J* = 6.1 Hz, NCH), 5.41 (1H, d, *J* = 14.9 Hz, NCH$_a$<u>H</u>$_b$Ph), 6.66-7.39 (9H, m, 9 x CH_{Ar}). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 32.0 (t, *J* = 24.2 Hz, <u>C</u>H_2CF_2), 44.4 (t, *J* = 4.6 Hz, <u>C</u>HCO_2CH_3), 48.1 (NCH_2Ph), 52.6 (OCH_3), 55.4 (OCH_3), 61.0 (NCH), 111.4 (t, *J* = 244.6 Hz, CF_2), 113.0 (CH_{Ar}), 114.2 (CH_{Ar}), 119.3 (CH_{Ar}), 128.1 (CH_{Ar}), 128.7 (2 x CH_{Ar}), 128.9 (2 x CH_{Ar}), 130.5 (CH_{Ar}), 135.3 ($C_{q,Ar}$), 139.4 ($C_{q,Ar}$), 160.4 ($C_{q,Ar}$), 161.8 (t, *J* = 30 Hz, C=O), 170.7 (<u>C</u>O_2CH_3). **^{19}F NMR** (282 MHz, $CDCl_3$): δ -98.9 (1F, d x t, *J* = 13.2, 284.1 Hz, C<u>F</u>$_a$F$_b$), -100.1 (1F, d x t, *J* = 13.2, 284.1 Hz, CF$_a$<u>F</u>$_b$). **IR** (ATR, cm^{-1}): $\nu_{C=O}$ 1745, 1672; ν_{max} 1600, 1364, 1284, 1210, 1096, 922, 792, 745, 701. **MS** (ES+): *m/z* (%): 390 (M+1, 100). **Anal.** Calcd. for $C_{21}H_{21}F_2NO_4$: C, 64.77; H, 5.44; N, 3.60. Found: C, 65.35; H, 5.47; N, 3.66.

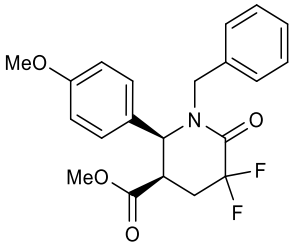
***Trans*-methyl 1-benzyl-3,3-difluoro-2-oxo-6-(4-methoxyphenyl)piperidine-5-carboxylate *trans*-202d**



Colourless crystals: mp 104.4-106.6 °C. R_f = 0.15 (petroleum ether/ethyl acetate 3:1). Yield: 13%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 2.43-2.64 (2H, m, CH_2CF_2), 3.04-3.11 (1H, m, C<u>H</u>CO_2CH_3), 3.49 (1H, d, *J* = 14.9 Hz, NC<u>H</u>$_a$H$_b$Ph), 3.54 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 4.73 (1H, d, *J* = 7.2 Hz, NCH), 5.40 (1H, d, *J* = 14.9 Hz, NCH$_a$<u>H</u>$_b$Ph), 6.90-7.31 (9H, m, 9 x CH_{Ar}). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 32.2 (t, *J* = 24.2 Hz, <u>C</u>H_2CF_2), 44.4 (t, *J* = 4.6 Hz, <u>C</u>HCO_2CH_3), 47.8 (NCH_2Ph), 52.6 (OCH_3), 55.4 (OCH_3), 60.7 (NCH), 111.5 (t, *J* = 243.5 Hz, CF_2), 114.7 (2 x CH_{Ar}), 128.0 (CH_{Ar}), 128.5 (2 x CH_{Ar}),

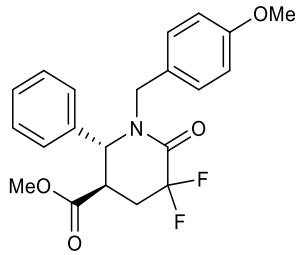
128.7 (2 x CH_{Ar}), 128.8 (2 x CH_{Ar}), 129.4 ($C_{q,Ar}$), 135.3 ($C_{q,Ar}$), 160.0 ($C_{q,Ar}$), 161.7 (t, *J* = 30 Hz, C=O), 170.8 ($\underline{C}O_2CH_3$). **^{19}F NMR** (282 MHz, $CDCl_3$): δ -98.9 (1F, d x t, *J* = 11.8, 282.8 Hz, $C\underline{F}_aF_b$), -100.6 (1F, d x t, *J* = 11.8, 282.8 Hz, $CF_a\underline{F}_b$). **IR** (ATR, cm^{-1}): $\nu_{C=O}$ 1747, 1667; ν_{max} 1610, 1515, 1426, 1284, 1251, 1146, 1023, 835, 747, 701. **MS** (ES+): *m/z* (%): 390 (M+1, 100). **Anal.** Calcd. for $C_{21}H_{21}F_2NO_4$: C, 64.77; H, 5.44; N, 3.60. Found: C, 64.84; H, 5.11; N, 3.59.

***Cis*-methyl 1-benzyl-3,3-difluoro-2-oxo-6-(4-methoxyphenyl)piperidine-5-carboxylate *cis*-202d**



R_f = 0.21 (petroleum ether/ethyl acetate 3:1).**^{1}H NMR** (300 MHz, $CDCl_3$): δ 2.49-2.68 (2H, m, CH_2CF_2), 3.35 (1H, d, *J* = 7.2 Hz, $C\underline{H}CO_2CH_3$), 3.41 (1H, d, *J* = 14.9 Hz, $NC\underline{H}_aH_bPh$), 3.56 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 4.82 (1H, d, *J* = 5.0 Hz, NCH), 5.47 (1H, d, *J* = 14.3 Hz, $NCH_a\underline{H}_bPh$), 6.89-7.35 (9H, m, 9 x CH_{Ar}). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 29.2 (t, *J* = 24.2 Hz, $\underline{C}H_2CF_2$), 41.8 (d, *J* = 10.4 Hz, $\underline{C}HCO_2CH_3$), 48.2 (NCH_2Ph), 52.3 (OCH_3), 55.4 (OCH_3), 59.8 (NCH), 111.9 (t, *J* = 242.9 Hz, CF_2), 114.6 (2 x CH_{Ar}), 125.6 (CH_{Ar}), 128.2 (2 x CH_{Ar}), 128.4 (2 x CH_{Ar}), 128.8 (2 x CH_{Ar}), 129.0 ($C_{q,Ar}$), 135.3 ($C_{q,Ar}$), 160.3 ($C_{q,Ar}$), 161.9 (t, *J* = 30 Hz, C=O), 169.1 ($\underline{C}O_2CH_3$). **^{19}F NMR** (282 MHz, $CDCl_3$): δ -94.4 (1F, d x d x d, *J* = 20.4, 28.9, 289.2 Hz, $C\underline{F}_aF_b$), -102.6 (1F, d x d, *J* = 5.3, 289.2 Hz, $CF_a\underline{F}_b$). **MS** (ES+): *m/z* (%): 390 (M+1, 100). **Anal.** Calcd. for $C_{21}H_{21}F_2NO_4$: C, 64.77; H, 5.44; N, 3.60. Found: C, 64.84; H, 5.11; N, 3.59.

***Trans*-methyl 1-(4-methoxybenzyl)-3,3-difluoro-2-oxo-6-phenylpiperidine-5-carboxylate *trans*-202e**

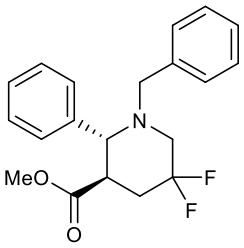


Colourless crystals: mp 118.5 °C. R_f = 0.21 (petroleum ether/ethyl acetate 3:1). Yield: 31%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 2.49-2.68 (2H, t x d, *J* = 6.6, 13.5 Hz, CH_2CF_2), 3.08 (1H, q, *J* = 6.6 Hz, $C\underline{H}CO_2CH_3$), 3.43 (1H, d, *J* = 14.9 Hz, $NC\underline{H}_aH_bPh$), 3.55 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 4.82 (1H, d, *J* = 6.6 Hz, NCH), 5.36 (1H, d, *J* = 14.3 Hz, $NCH_a\underline{H}_bPh$), 6.82 (2H, d, *J* = 8.8 Hz, 2 x CH_{Ar}), 7.04 (2H, d, *J* = 8.8 Hz, 2 x CH_{Ar}), 7.15 (2H, m, 2 x CH_{Ar}), 7.37-7.44 (3H, m, 3 x CH_{Ar}). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 32.0 (t, *J* = 24.2 Hz, $\underline{C}H_2CF_2$), 44.3 (d, *J* = 5.7 Hz, $\underline{C}HCO_2CH_3$), 47.3 (NCH_2Ph), 52.6 (OCH_3), 55.3 (OCH_3), 60.8 (NCH), 111.4 (t, *J* = 244.6 Hz, CF_2), 114.1 (2 x CH_{Ar}), 127.1 (2 x CH_{Ar}), 127.2 ($C_{q,Ar}$), 128.9 (CH_{Ar}), 129.4 (2 x CH_{Ar}), 130.3 (2 x CH_{Ar}), 137.8 ($C_{q,Ar}$), 159.4 ($C_{q,Ar}$), 161.7 (t, *J* = 30 Hz, C=O), 170.7 ($\underline{C}O_2CH_3$). **^{19}F NMR** (282 MHz, $CDCl_3$): δ -99.1 (1F, d x t, *J* = 13.2, 284.1 Hz, $C\underline{F}_aF_b$), -100.4 (1F, d x t, *J* = 13.2, 284.1 Hz, $CF_a\underline{F}_b$). **IR** (ATR, cm^{-1}): $\nu_{C=O}$ 1749, 1669; ν_{max} 1612, 1511, 1356, 1242, 1195, 1174, 1093, 1033, 941, 808, 758, 709. **MS** (ES+): *m/z* (%): 390 (M+1, 100). **Anal.** Calcd. for $C_{21}H_{21}F_2NO_4$: C, 64.77; H, 5.44; N, 3.60. Found: C, 64.54; H, 5.36; N, 3.42.

5.2.4 Synthesis of *trans*-methyl 1-benzyl-5,5-difluoro-2-phenylpiperidine-3-carboxylate 204a

To a solution of *trans*-methyl 1-benzyl-3,3-difluoro-2-oxo-6-phenylpiperidine-5-carboxylate ***trans*-202a** (0.3 mmol, 1 equiv) in anhydrous tetrahydrofuran (2 mL) was added BH_3·THF (2.8 mmol, 10 equiv). The reaction mixture was stirred under reflux for four hours and quenched by careful addition of water. The mixture was extracted with dichloromethane (3 x 2 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by column chromatography on silica gel to yield *trans*-methyl 1-benzyl-5,5-difluoro-2-phenylpiperidine-3-carboxylate **204a**.

***Trans*-methyl 1-benzyl-5,5-difluoro-2-phenylpiperidine-3-carboxylate 204a**

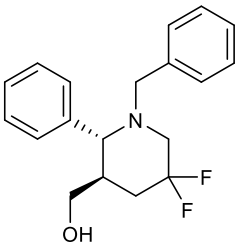


Colourless oil. Yield: 11%. R_f 0.44 (petroleum ether/ethyl acetate 2:1). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 2.14 (1H, d x t x d, *J* = 5.0, 12.9, 32.5 Hz, $C\underline{H}_aH_bCF_2$), 2.32-2.44 (2H, m, $CH_a\underline{H}_bCF_2$, $NC\underline{H}_aH_bCF_2$), 2.93 (1H, d, *J* = 13.2 Hz, $NC\underline{H}_aH_bPh$), 2.99-3.08 (1H, m, $C\underline{H}CO_2CH_3$), 3.14-3.23 (1H, m, $NCH_a\underline{H}_bCF_2$), 3.36 (3H, s, OCH_3), 3.47 (1H, d, *J* = 10.5 Hz, NCH), 3.76 (1H, d, *J* = 13.2 Hz, $NCH_a\underline{H}_bPh$), 7.22-7.42 (10H, m, 10 x CH_{Ar}). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 35.8 (t, *J* = 24.8 Hz, $CH\underline{C}H_2CF_2$), 48.7 (d, *J* = 10.4 Hz, $\underline{C}HCO_2CH_3$), 51.8 (OCH_3), 56.7 (d x d, *J* = 24.2, 31.2 Hz, $N\underline{C}H_2CF_2$), 58.3 (NCH_2Ph), 68.9 (NCH), 119.0 (d x d, *J* = 238.3, 242.9 Hz, CF_2), 127.3 (CH_{Ar}), 128.2 (2 x CH_{Ar}), 128.3 (CH_{Ar}), 128.47 (2 x CH_{Ar}), 128.52 (2 x CH_{Ar}), 128.8 (2 x CH_{Ar}), 137.6 ($C_{q,Ar}$), 139.5 ($C_{q,Ar}$), 172.6 (C=O). **^{19}F NMR** (282 MHz, $CDCl_3$): δ -99.4 (1F, d, *J* = -242.8 Hz, $C\underline{F}_aF_b$), -103.1 (1F, d x t x t, *J* = 10.5, 30.5, 242.8 Hz, $CF_a\underline{F}_b$). **MS** (ES+): *m/z* (%): 346 (M+1, 100).

5.2.5 Synthesis of *trans*-6-aryl-1-benzyl-3,3-difluoro-5-(hydroxymethyl)piperidines 205

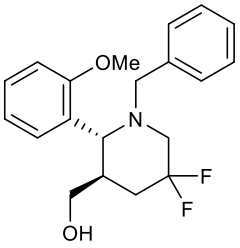
As a representative example, the synthesis of *trans*-6-aryl-1-benzyl-3,3-difluoro-5-(hydroxymethyl)piperidine **205a** is described. To a solution of *trans*-methyl 1-benzyl-3,3-difluoro-2-oxo-6-phenylpiperidine-5-carboxylate ***trans*-202a.** (0.3 mmol, 1 equiv) in dry dichloromethane (5 mL), BH_3·SMe_2 (1.5 mmol, 5 equiv) was added under N_2-atmosphere and the mixture was heated under reflux overnight. The reaction was quenched by careful addition of aqueous methanol (1:1) at 0 °C. The mixture was extracted with dichloromethane (3 x 10 mL), dried over $MgSO_4$ and evaporated under reduced pressure. The product was dissolved in MeOH (1 mL) and stirred overnight on Pd/C and filtered over Celite®. Final purification was performed by column chromatography on silica gel yielding *trans*-1-benzyl-3,3-difluoro-5-hydroxymethyl-6-phenylpiperidine **205a**.

***Trans*-1-benzyl-3,3-difluoro-5-hydroxymethyl-6-phenylpiperidine 205a**



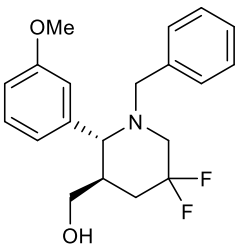
Colourless oil. Yield: 86%. R_f = 0.20 (petroleum ether/ethyl acetate 4:1). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.16 (1H, br s, OH), 1.91 (1H, d x t x d, *J* = 5.5, 13.0, 33.6 Hz, $CHC\underline{H}_aH_bCF_2$), 2.09-2.37 (3H, m, $CHCH_a\underline{H}_bCF_2$, $C\underline{H}CH_2CF_2$, $NC\underline{H}_aH_bCF_2$), 2.90 (1H, d, *J* = 13.8 Hz, $NC\underline{H}_aH_bPh$), 3.12-3.24 (3H, m, $NCH_a\underline{H}_bCF_2$, $C\underline{H}_aH_bOH$, $NC\underline{H}$), 3.33 (1H, d x d, *J* = 3.0, 10.7 Hz, $CH_a\underline{H}_bOH$), 3.74 (1H, d, *J* = 13.8 Hz, $NCH_a\underline{H}_bPh$), 7.20-7.46 (10H, m, 10 x CH_{Ar}). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 35.6 (d x d, *J* = 22.0, 31.7 Hz, $CH\underline{C}H_2CF_2$), 43.0 (d, *J* = 10.4 Hz, $\underline{C}HCH_2CF_2$), 56.8 (d x d, *J* = 6.9, 24.8 Hz, $N\underline{C}H_2CF_2$), 58.6 (NCH_2Ph), 63.7 (CH_2OH), 68.9 (NCHPh), 120.4 (t, *J* = 240.0 Hz, CF_2), 127.0 (CH_{Ar}), 128.0 (CH_{Ar}), 128.2 (2 x CH_{Ar}), 128.3 (2 x CH_{Ar}), 128.4 (2 x CH_{Ar}), 128.9 (2 x CH_{Ar}), 138.1 ($C_{q,Ar}$), 141.0 ($C_{q,Ar}$). **^{19}F NMR** (282 MHz, $CDCl_3$): δ -98.0 (1F, d, *J* = 239.4 Hz, $C\underline{F}_aF_b$), -103.2 (1F, d x t x t, *J* = 10.5, 30.9, 239.4 Hz, $CF_a\underline{F}_b$). **IR** (ATR, cm^{-1}): ν_{OH} 3387; ν_{max} 1452, 1310, 1133, 1060, 908, 763, 731, 699. **MS** (ES+): *m/z* (%): 317 (M+1, 100).

***Trans*-1-benzyl-3,3-difluoro-5-hydroxymethyl-6-(2-methoxyphenyl)piperidine 205b**



Colourless crystals: mp 117.0-119.0 °C. Yield: 75%. R_f = 0.19 (petroleum ether/ethyl acetate 4:1). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.96 (1H, br s, OH), 2.02-2.36 (4H, m, $C\underline{H}C\underline{H}_2CF_2$, $NC\underline{H}_aH_bCF_2$), 2.94 (1H, d, *J* = 13.8 Hz, $NC\underline{H}_aH_bPh$), 3.13-3.31 (3H, m, $NCH_a\underline{H}_bCF_2$, $C\underline{H}_2OH$), 3.72-3.80 (2H, m, $NCH_a\underline{H}_bPh$, $NC\underline{H}$), 3.89 (3H, s, OCH_3), 6.94 (1H, d, *J* = 7.7 Hz, CH_{Ar}), 7.05 (1H, t, *J* = 7.7 Hz, CH_{Ar}), 7.18-7.35 (6H, m, 6 x CH_{Ar}), 7.69 (1H, d x d, *J* = 1.7, 7.7 Hz, CH_{Ar}). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 35.6 (d x d, *J* = 22.0, 25.4 Hz, $CH\underline{C}H_2CF_2$), 43.7 (d, *J* = 9.2 Hz, $\underline{C}HCH_2CF_2$), 55.9 (OCH_3), 57.0 (d x d, *J* = 24.2, 32.3 Hz, $N\underline{C}H_2CF_2$), 58.6 (NCH_2Ph), 58.7 (NCH), 63.8 (CH_2OH), 110.7 (CH_{Ar}), 120.5 (t, *J* = 240.0 Hz, CF_2), 122.3 (CH_{Ar}), 127.0 (CH_{Ar}), 128.1 (CH_{Ar}), 128.3 (2 x CH_{Ar}), 128.5 (3 x CH_{Ar}), 129.1($C_{q,Ar}$), 138.0 ($C_{q,Ar}$), 157.3 ($C_{q,Ar}$). **^{19}F NMR** (282 MHz, $CDCl_3$): δ -97.8 (1F, d, *J* = 238.1 Hz, $C\underline{F}_aF_b$), -103.0 (1F, d x t x t, *J* = 10.5, 30.8, 238.1 Hz, $CF_a\underline{F}_b$). **IR** (ATR, cm^{-1}): ν_{OH} 3391; ν_{max} 1491, 1238, 1022, 1013, 753, 695. **MS** (ES+): *m/z* (%): 348 (M+1, 100). **Anal.** Calcd. for $C_{20}H_{23}F_2NO_2$: C, 69.15; H, 6.67; N, 4.03. Found: C, 68.72; H, 6.78; N, 3.83.

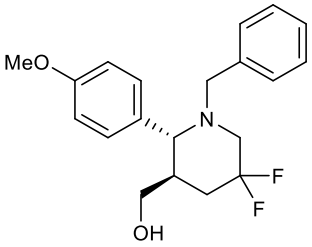
***Trans*-1-benzyl-3,3-difluoro-5-hydroxymethyl-6-(3-methoxyphenyl)piperidine 205c**



Colourless oil. Yield: 80%. R_f = 0.18 (petroleum ether/ethyl acetate 4:1). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.30 (1H, br s, OH), 1.89 (1H, d x t x d, *J* = 5.5, 13.0, 33.6 Hz, $CHC\underline{H}_aH_bCF_2$), 2.10-2.30 (3H, m, $CHCH_a\underline{H}_bCF_2$, $C\underline{H}CH_2CF_2$, $NC\underline{H}_aH_bCF_2$), 2.88 (1H, d, *J* = 13.2 Hz, $NC\underline{H}_aH_bPh$), 3.11-3.64 (4H, m, $NC\underline{H}_aH_bCF_2$, $C\underline{H}_2OH$, $NC\underline{H}$), 3.76 (1H, d, *J* = 13.2 Hz, $NCH_a\underline{H}_bPh$), 3.80 (3H, s, OCH_3), 6.83 (1H, d x d, *J* = 1.7, 8.3 Hz, CH_{Ar}), 7.00-7.03 (2H, m, 2 x CH_{Ar}), 7.17-7.30 (6H, m, 6 x CH_{Ar}). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 35.6 (d x d, *J* = 21.9, 25.4 Hz, $CH\underline{C}H_2CF_2$), 43.4 (d, *J* = 10.0 Hz, $C\underline{H}CH_2CF_2$), 55.2 (OCH_3), 56.9 (d x d, *J* =

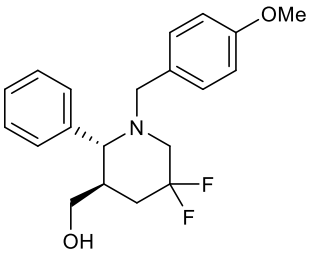
24.2, 31.2 Hz, N<u>C</u>H$_2$CF$_2$), 58.6 (NCH$_2$Ph), 63.7 (CH$_2$OH), 68.8 (NCH), 113.3 (CH$_{Ar}$), 113.4 (CH$_{Ar}$), 120.2 (t, *J* = 240.0 Hz, CF$_2$), 120.7 (CH$_{Ar}$), 127.0 (CH$_{Ar}$), 128.3 (2 x CH$_{Ar}$), 128.4 (2 x CH$_{Ar}$), 129.8 (CH$_{Ar}$), 138.2 (C$_{q,Ar}$), 142.6 (C$_{q,Ar}$), 160.0 (C$_{q,Ar}$). **^{19}F NMR** (282 MHz, CDCl$_3$): δ -98.0 (1F, d, *J* = 239.4 Hz, C<u>F</u>$_a$F$_b$), -103.1 (1F, d x t x t, *J* = 10.5, 32.9, 239.4 Hz, CF$_a$<u>F</u>$_b$). **IR** (ATR, cm^{-1}): ν$_{OH}$ 3422; ν$_{max}$ 1586, 1437, 1312, 1287, 1264, 1131, 1014, 973, 783, 754. **MS** (ES+): *m/z* (%): 348 (M+1, 100).

***Trans*-1-benzyl-3,3-difluoro-5-hydroxymethyl-6-(4-methoxyphenyl)piperidine 205d**



Colourless oil. Yield: 70%. R$_f$ = 0.14 (petroleum ether/ethyl acetate 4:1). **^{1}H NMR** (300 MHz, CDCl$_3$): δ 1.20 (1H, br s, OH), 1.89 (1H, d x t x d, *J* = 5.5, 13.1, 33.3 Hz, CHC<u>H</u>$_a$H$_b$CF$_2$), 2.07-2.36 (3H, m, CHCH$_a$<u>H</u>$_b$CF$_2$, C<u>H</u>CH$_2$CF$_2$, NC<u>H</u>$_a$H$_b$CF$_2$), 2.85 (1H, d, *J* = 13.8 Hz, NC<u>H</u>$_a$H$_b$Ph), 3.10-3.37 (4H, m, NC<u>H</u>$_a$H$_b$CF$_2$, C<u>H</u>$_2$OH, NC<u>H</u>), 3.75 (1H, d, *J* = 13.8 Hz, NCH$_a$<u>H</u>$_b$Ph), 3.79 (3H, s, OCH$_3$), 6.90 (2H, d x d, *J* = 1.7, 8.8 Hz, 2 x CH$_{Ar}$), 7.18-7.29 (5H, m, 5 x CH$_{Ar}$), 7.35 (2H, d, *J* = 8.8 Hz, 2 x CH$_{Ar}$). **^{13}C NMR** (75 MHz, CDCl$_3$): δ 35.6 (d x d, *J* = 22.0, 24.2 Hz, CH<u>C</u>H$_2$CF$_2$), 43.1 (d, *J* = 10.4 Hz, C<u>H</u>CH$_2$CF$_2$), 55.3 (OCH$_3$), 57.0 (d x d, *J* = 24.2, 31.2 Hz, N<u>C</u>H$_2$CF$_2$), 58.4 (NCH$_2$Ph), 63.8 (CH$_2$OH), 68.1 (NCH), 114.3 (2 x CH$_{Ar}$), 120.3 (t, *J* = 240.0 Hz, CF$_2$), 127.1 (CH$_{Ar}$), 128.4 (2 x CH$_{Ar}$), 128.5 (2 x CH$_{Ar}$), 129.3 (CH$_{Ar}$), 132.9 (C$_{q,Ar}$), 138.2 (C$_{q,Ar}$), 159.2 (C$_{q,Ar}$). **^{19}F NMR** (282 MHz, CDCl$_3$): δ -98.1 (1F, d, *J* = 239.2 Hz, C<u>F</u>$_a$F$_b$), -103.1 (1F, d x t x t, *J* = 10.5, 30.9, 239.2 Hz, CF$_a$<u>F</u>$_b$). **IR** (ATR, cm^{-1}): ν$_{OH}$ 3401; ν$_{max}$ 1610, 1511, 1297, 1242, 1133, 1060, 1014, 908, 829, 730, 689. **MS** (ES+): *m/z* (%): 348 (M+1, 100).

***Trans*-1-(4-methoxybenzyl)-3,3-difluoro-5-hydroxymethyl-6-phenylpiperidine 205e**

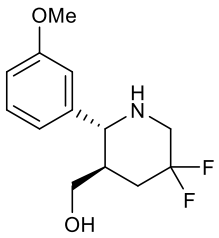


Colourless oil. Yield: 97%. R$_f$ = 0.16 (petroleum ether/ethyl acetate 4:1). **^{1}H NMR** (300 MHz, CDCl$_3$): δ 1.38 (1H, br s, OH), 1.90 (1H, d x t x d, *J* = 5.0, 13.2, 33.6 Hz, CHC<u>H</u>$_a$H$_b$CF$_2$), 2.08-2.36 (3H, m, CHCH$_a$<u>H</u>$_b$CF$_2$, C<u>H</u>CH$_2$CF$_2$, NC<u>H</u>$_a$H$_b$CF$_2$), 2.82 (1H, d, *J* = 13.2 Hz, NC<u>H</u>$_a$H$_b$Ph), 3.11-3.35 (4H, m, NC<u>H</u>$_a$H$_b$CF$_2$, C<u>H</u>$_2$OH, NC<u>H</u>), 3.66 (1H, d, *J* = 13.2 Hz, NCH$_a$<u>H</u>$_b$Ph), 3.79 (3H, s, OCH$_3$), 6.81 (2H, d, *J* = 8.8 Hz, 2 x CH$_{Ar}$), 7.13 (2H, d, *J* = 8.8 Hz, 2 x CH$_{Ar}$), 7.23-7.46 (5H, m, 5 x CH$_{Ar}$). **^{13}C NMR** (75 MHz, CDCl$_3$): δ 35.6 (d x d, *J* = 22.0, 24.2 Hz, CH<u>C</u>H$_2$CF$_2$), 43.1 (d, *J* = 10.4 Hz, C<u>H</u>CH$_2$CF$_2$), 55.2 (OCH$_3$), 56.7 (d x d, *J* = 24.2, 31.2 Hz, N<u>C</u>H$_2$CF$_2$), 57.9 (NCH$_2$Ph), 63.7 (CH$_2$OH), 68.7 (NCH), 113.7 (2 x CH$_{Ar}$), 120.3 (t, *J* = 240.0 Hz, CF$_2$), 127.9 (CH$_{Ar}$), 128.2 (2 x CH$_{Ar}$), 128.9 (2 x CH$_{Ar}$), 129.6 (2 x CH$_{Ar}$), 139.9 (C$_{q,Ar}$), 141.0 (C$_{q,Ar}$), 158.7 (C$_{q,Ar}$). **^{19}F NMR** (282 MHz, CDCl$_3$): δ -98.0 (1F, d, *J* = 239.4 Hz, C<u>F</u>$_a$F$_b$), -100.4 (1F, d x t x t, *J* = 10.5, 32.9, 239.4 Hz, CF$_a$<u>F</u>$_b$). **IR** (ATR, cm^{-1}): ν$_{OH}$ 3421; ν$_{max}$ 1611, 1510, 1301, 1248, 1132, 1060, 1012, 909, 818, 760, 732, 702. **MS** (ES+): *m/z* (%): 348 (M+1, 100).

5.2.6 Synthesis of *trans*-5,5-difluoro-3-hydroxymethyl-2-(3-methoxyphenyl)piperidine 209c

A solution of *trans*-1-benzyl-3,3-difluoro-5-hydroxymethyl-6-(3-methoxyphenyl)piperidine **205c** (0.1 mmol, 1 equiv) in methanol (1.5 mL) was stirred over a catalytic amount of $Pd(OH)_2$ (20% w/w) under H_2-atmosphere (4 bar) at room temperature. After two hours, the solids were filtered off over a filter plug and washed with methanol (2 x 1 mL). Evaporation of the solvent yielded *trans*-5,5-difluoro-3-hydroxymethyl-2-(3-methoxyphenyl)piperidine **209c**.

***Trans*-5,5-difluoro-3-hydroxymethyl-2-(3-methoxyphenyl)piperidine 209c**

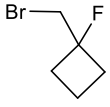


Yellow oil. Yield: 95%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.03-2.35 (3H, m, C<u>H</u>C<u>H</u>$_2$CF$_2$), 2.99 (1H, d x d, *J* = 13.3, 31.1 Hz, NC<u>H</u>$_a$H$_b$CF$_2$), 3.24-3.36 (5H, m, NCH$_a$<u>H</u>$_b$CF$_2$, C<u>H</u>$_2$O<u>H</u>, NC<u>H</u>), 3.87 (3H, s, OCH$_3$), 4.02 (1H, d, *J* = 9.9 Hz, NH), 6.81 (2H, d, *J* = 8.3 Hz, CH$_{Ar}$), 6.98 (1H, t x d, *J* = 0.9, 11.2 Hz, CH$_{Ar}$), 7.13 (1H, d x d x d, *J* = 1.5, 7.6, 8.3 Hz, CH$_{Ar}$), 7.36 (1H, d x d, *J* = 1.5, 7.6 Hz, CH$_{Ar}$). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 35.4 (d x d, *J* = 21.6, 24.9 Hz, CH<u>C</u>H$_2$CF$_2$), 41.9 (<u>C</u>HCH$_2$CF$_2$), 51.0 (d x d, *J* = 26.9, 30.5 Hz, N<u>C</u>H$_2$CF$_2$), 55.7 (OCH$_3$), 56.5 (NCH), 63.2 (CH$_2$OH), 111.0 (CH$_{Ar}$), 120.4 (d x d, *J* = 240.7, 244,9 Hz, CF$_2$), 121.6 (CH$_{Ar}$), 127.4 (C$_{q,Ar}$), 128.7 (CH$_{Ar}$), 129.2 (CH$_{Ar}$), 156.6 (C$_{q,Ar}$). **^{19}F NMR** (376 MHz, $CDCl_3$): δ -100.3 (1F, d, *J* = 241.6 Hz, C<u>F</u>$_a$F$_b$), -104.4 (1F, d x t, *J* = 32.3, 242.0 Hz, CF$_a$<u>F</u>$_b$). **IR** (ATR, cm^{-1}): ν$_{OH}$ 3325; ν$_{NH}$ 2936; ν$_{max}$ 1463, 1245, 1064, 1002, 907, 755, 727. **MS** (ES+): *m/z* (%): 258 (M+1, 100).

5.2.7 Synthesis of 1-bromomethyl-1 fluorocycloalkanes 214

As a representative example, the synthesis of 1-bromomethyl-1-fluorocyclopentane **214b** is described. An ice-cooled solution of methylenecyclopentane **212b** (24.2 mmol, 1 equiv) and triethylamine trihydrofluoride (36.4 mmol, 1.5 equiv) in dry dichloromethane (50 mL) was treated with *N*-bromosuccinimide (26.6 mmol, 1.1 equiv). After removal of the ice bath the reaction was continued for five hours at room temperature. The reaction mixture was poured into ice water (50 mL), made slightly basic with aqueous 28% ammonia and extracted with dichloromethane (3 x 30 mL). The combined extracts were washed with 0.1 M hydrochloric acid (3 x 20 mL) and saturated sodium bicarbonate solution (3 x 20 mL). After drying over $MgSO_4$ and evaporation of the solvent, the crude mixture was purified by distillation under reduced pressure, yielding 1-bromomethyl-1-fluorocyclopentane **214b** as pure compound.

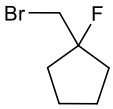
1-Bromomethyl-1-fluorocyclobutane 214a



Colourless oil: bp 32 °C (7.5 mmHg). Yield: 80%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.42-1.60 (1H, m, -CH$_2$C<u>H</u>$_a$H$_b$CH$_2$-), 1.80-1.94 (1H, m, -CH$_2$CH$_a$<u>H</u>$_b$CH$_2$-), 2.17-2.50 (4H, m, 2 x CH$_2$C<u>H</u>$_2$CF), 3.61 (2H, d, *J* = 22.0 Hz, CH$_2$Br). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 11.2 (d, *J* = 12.7 Hz, -CH$_2$<u>C</u>H$_2$CH$_2$-), 32.6 (d, *J* = 20.8 Hz, 2 x CH$_2$<u>C</u>H$_2$CF), 37.4 (d, *J* = 25.4 Hz, CH$_2$Br), 94.1 (d, *J* = 218. 1

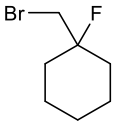
Hz). **^{19}F NMR** (282 MHz, $CDCl_3$): δ -132.2 to -131.8 (1F, m, CF). **IR** (ATR, cm^{-1}): ν_{max} 1272, 1074, 1055, 951, 659. **GC-MS** (EI) m/z (%): 166/168 (M^+, 0.4), 138/140 (78), 87 (62), 67 (10), 59 (100), 41 (10).

1-Bromomethyl-1-fluorocyclopentane 214b



Colourless oil: bp 46 °C (7.5 mmHg). Yield: 85%. **^{1}H NMR** (300MHz, $CDCl_3$): δ 1.63-2.14 (8H, m, -$(CH_2)_4$-), 3.59 (2H, d, *J* = 18.7 Hz, CH_2Br). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 24.5 (2 x CH_2), 37.0 (d, *J* = 24.2 Hz, 2 x $CH_2\underline{C}H_2CF$), 37.7 (d, *J* = 28.8 Hz, CH_2Br), 104.2 (d, *J* = 180.0 Hz, CF). **^{19}F NMR** (282 MHz, $CDCl_3$): δ -142.1 to -141.6 (1F, m, CF). **IR** ν_{max} 2964, 1433, 1340, 1256, 1213, 985, 839, 656. **GC-MS** (EI) m/z (%): 180/182 (M^+, 0.02), 101 (M+-Br, 15), 87 (100), 81 (43), 67 (56), 59 (10), 41 (19).

1-Bromomethyl-1-fluorocyclohexane 214c

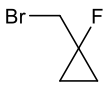


Colourless oil: bp 65 °C (7.5 mmHg). Yield 72%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.19-1.31 (1H, m -$(CH_2)_2C\underline{H}_aH_b(CH_2)_2$-), 1.42-1.70 (7H, m, -$(C\underline{H}_2)_2CH_a\underline{H}_bC\underline{H}_2CH_2$-), 1.91-1.99 (2H, m, $CH_2C\underline{H}_2CF$), 3.46 (2H, d, *J* = 18.2 Hz, CH_2Br). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 21.9 (d, *J* = 3.5 Hz, 2 x $\underline{C}H_2CH_2CF$), 25.1 (-$(CH_2)_2\underline{C}H_2(CH_2)_2$-), 33.8 (d, *J* = 21.9 Hz, 2 x $CH_2\underline{C}H_2CF$), 39.9 (d, *J* = 27.7 Hz, CH_2Br), 93.1 (d, *J* = 176.5 Hz, CF). **^{19}F NMR** (282 MHz, $CDCl_3$): δ -156.7 to 155.3 (1F, m, CF).[188] **IR** (ATR, cm^{-1}): ν_{max} 2936, 2864, 1446, 1138, 962, 826, 733, 660. **GC-MS** (EI) m/z (%): 194/196 (M^+, 3), 101 (100), 81 (100), 55 (12), 41 (12).

5.2.8 Synthesis of 1-bromomethyl-1-fluorocyclopropane 214d and 1-bromo-1-(fluoromethyl)cyclopropane 222

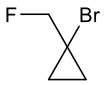
An ice-cooled solution of methylenecyclopropane **212d** (111 mmol, 1 equiv) and triethylamine trihydrofluoride (277 mmol, 2.5 equiv) in dry dichloromethane (100 mL) was treated with *N*-bromosuccinimide (167 mmol, 1.5 equiv) and the reaction was continued for five hours at the same temperature. The reaction mixture was poured into ice water (100 mL), made slightly basic with aqueous 28% ammonia, and was extracted with dichloromethane (3 x 60 mL). The combined extracts were washed with 0.1 M hydrochloric acid (3 x 40 mL) and saturated sodium bicarbonate solution (3 x 40 mL). After drying over $MgSO_4$ and evaporation of the solvent, the crude mixture was filtered over a short silica plug before distillation, yielding a 1:3 mixture 1-bromomethyl-1-fluorocyclopropane **214d** and 1-bromo-1-(fluoromethyl)cyclopropane **222.**

1-bromomethyl-1-fluorocyclopropane 214d



Colourless oil: bp 100-110 °C. Yield: 6%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 0.79-0.87 (2H, m, -$C\underline{H}_2CH_2$-), 1.27-1.38 (2H, m, -$CH_2C\underline{H}_2$-), 3.68 (2H, d, *J* = 20.9 Hz, CH_2Br). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 13.8 (d, *J* = 11.5 Hz, -$(CH_2)_2$-), 31.4 (CH_2Br), 82.6 (d, *J* = 169.6 Hz, CF). **^{19}F NMR** (282 MHz, $CDCl_3$): δ -183.6 to -183.4 (1F, m, CF).

1-bromo-1-(fluoromethyl)cyclopropane 222

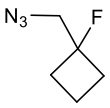


Colourless oil: bp 100-110 °C. Yield: 19%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.01-1.07 (2H, m, -$C\underline{H}_2CH_2$-), 1.20-1.26 (2H, m, -$CH_2C\underline{H}_2$-), 4.43 (2H, d, *J* = 47.9 Hz, CH_2F). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 14.3 (d, *J* = 4.6 Hz, -$(CH_2)_2$-), 37.1 (CBr), 89.6 (d, *J* = 176.5 Hz, CH_2F). **^{19}F NMR** (282 MHz, $CDCl_3$): δ -209.0 (1F, t x t, *J* = 4.0, 47.9 Hz, CF).

5.2.9 Synthesis of 1-azidomethyl-1-fluorocycloalkanes 216

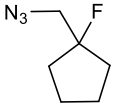
As a representative example, the synthesis of 1-azidomethyl-1-fluorocyclopentane **216b** is described. Sodium azide (6.6 mmol, 1.2 equiv) was added to a stirred solution of 1-bromomethyl-1-fluorocycloalkane **214b** (5.5 mmol, 1 equiv) and sodium iodide (6.6 mmol, 1.2 equiv) in anhydrous dimethyl sulfoxide (10 mL). The mixture was allowed to react for 16 hours at 100 °C. After cooling down the reaction mixture, water (15 mL) was added and the mixture was extracted with pentane (3 x 10 mL). The combined organic phases were washed with water (3 x 10 mL) and brine (2 x 10 mL). Drying over $MgSO_4$ and evaporation under reduced pressure yielded 1-azidomethyl-1-fluorocyclopentane **216b** without extra purification steps.

1-Azidomethyl-1-fluorocyclobutane 216a



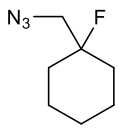
Yellow oil. Yield: 70%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.39-1.56 (1H, m, -$CH_2C\underline{H}_aH_bCH_2$-), 1.79-1.93 (1H, m, -$CH_2CH_a\underline{H}_bCH_2$-), 2.12-2.46 (4H, m, 2 x $CH_2C\underline{H}_2CF$), 3.43 (2H, d, *J* = 23.7 Hz, $C\underline{H}_2N_3$). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 11.4 (d, *J* = 13.9 Hz, -$CH_2\underline{C}H_2CH_2$-), 31.7 (d, *J* = 21.9 Hz, 2x $CH_2\underline{C}H_2CF$), 55.5 (d, *J* = 23.1 Hz, $\underline{C}H_2N_3$), 95.6 (d, *J* = 218. 1 Hz, CF). **^{19}F NMR** (282 MHz, $CDCl_3$): δ -133.9 to -133.5 (1F, m, CF). **IR** (ATR, cm^{-1}): ν_{N3} 2099; ν_{max} 1300, 915, 731. **GC-MS** (EI) m/z (%): 129 (M^+, 13), 101 (10), 86 (8), 73 (100), 59 (27), 53 (54), 46 (28), 41 (8).

1-Azidomethyl-1-fluorocyclopentane 216b.



Colourless oil. Yield: 68%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.60-2.07 (8H, m -$(CH_2)_4$-), 3.42 (2H, d, *J* = 20.9 Hz, CH_2N_3). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 24.1 (2 x CH_2), 35.9 (d, *J* = 24.2 Hz, 2x $CH_2\underline{C}H_2CF$), 57.1 (d, *J* = 25.4 Hz, $\underline{C}H_2N_3$), 106.1 (d, *J* = 177.7 Hz, CF). **^{19}F NMR** (282 MHz, $CDCl_3$): δ -145.7 to -145.1 (1F, m, CF). **IR** (ATR, cm^{-1}): ν_{N3} 2095; ν_{max} 1340, 1279, 1034, 923, 891. **GC-MS** (EI) m/z (%): 143 (M^+, 0.9), 87 (58), 67 (100), 59 (24), 41 (43).

1-Azidomethyl-1-fluorocyclohexane 216c.

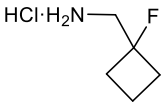


Colourless oil. Yield: 53%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.20-1.71 (8H, m, -$(CH_2)_4$-), 1.83-1.98 (2H, m, $CH_{2,cHex}$), 3.29 (2H, d, *J* = 19.2 Hz, CH_2N_3).[189] **^{13}C NMR** (75 MHz, $CDCl_3$) δ 21.6 (d, *J* = 3.5 Hz, 2 x $CH_{2,cHex}$), 25.2 ($CH_{2,cHex}$), 32.8 (d, *J* = 20.8 Hz, 2x $CH_2\underline{C}H_2CF$), 58.5 (d, *J* = 23.1 Hz, $\underline{C}H_2N_3$), 95.6 (d, *J* = 174.2 Hz, CF). **^{19}F NMR** (282 MHz, $CDCl_3$): δ -159.8 to -158.5 (1F, m, CF). **IR** (ATR, cm^{-1}): ν_{N3} 2094; ν_{max} 1447, 1307, 1275, 1257, 876, 728. **GC-MS** (EI) m/z (%): 157 (M^+, 0.4), 101 (39), 81 (100), 59 (11), 55 (13), 41 (12).

5.2.10 Synthesis of 1-aminomethyl-1-fluorocycloalkane hydrochlorides 220

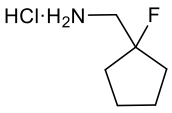
As a representative example, the synthesis of 1-aminomethyl-1-fluorocyclopentane hydrochloride **220b** is described. A solution of 1-azidomethyl-1-fluorocyclopentane **216b** (0.9 mmol, 1 equiv) and Pd/C (20% w/w) in ethyl acetate (3 mL) was stirred under H_2 pressure (5 bar) for 16 hours at room temperature. The mixture was then filtered over Celite® and the solids were washed with ethyl acetate (2 x 5 mL). After introduction of dry hydrochloric acid (g) the obtained crystals were filtered and washed with diethyl ether to obtain pure 1-aminomethyl-1-fluorcyclopentane hydrochloride **220b.**

1-Aminomethyl-1-fluorocyclobutane hydrochloride 220a



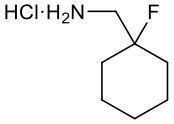
Colourless crystals. Yield: 47%. **^{1}H NMR** (300 MHz, D_2O): δ 1.33-1.51 (1H, m, -$CH_2C\underline{H}_aH_bCH_2$-), 1.64-1.80 (1H, m, -$CH_2CH_a\underline{H}_bCH_2$-), 2.00-2.38 (4H, m, 2 x $CH_2\underline{C}H_2CF$), 3.22 (2H, d, *J* = 22.6 Hz, CH_2N). **^{13}C NMR** (75 MHz, D_2O): δ 10.6 (d, *J* = 13.9 Hz, -$CH_2\underline{C}H_2CH_2$-), 30.1 (d, *J* = 20.8 Hz, 2 x $CH_2\underline{C}H_2CF$), 44.0 (d, *J* = 23.1 Hz, CH_2N), 94.3 (d, *J* = 213.5 Hz, CF). **^{19}F NMR** (282 MHz, D_2O): δ -137.7 to -137.2 (1F, m, CF). **IR** (ATR, cm^{-1}): ν_{NH} 2959; ν_{max} 2884, 1600, 1517, 1400, 1253, 1076, 943, 867, 720, 637.

1-Aminomethyl-1-fluorcyclopentane hydrochloride 220b



Colourless crystals. Yield: 58%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.61-2.18 (8H, m, -$(CH_2)_4$-), 3.29 (1H, d, *J* = 19.3 Hz, CH_2N), 8.65 (3H, br s, NH_3). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 24.0 (-$CH_2(\underline{C}H_2)_2CH_2$-), 36.2 (d, *J* = 23.1 Hz, 2 x $CH_2\underline{C}H_2CF$), 46.0 (d, *J* = 24.2 Hz, CH_2N), 103.5 (d, *J* = 176.5 Hz, CF). **^{19}F NMR** (282 MHz, $CDCl_3$): δ -148.2 to -147.6 (1F, m, CF). **IR** (ATR, cm^{-1}): ν_{NH} 2959; ν_{max} 2871, 1598, 1512, 1456, 1351, 1101, 978, 849.

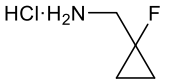
1-Aminomethyl-1-fluorocyclohexane hydrochloride 220c



Colourless crystals. Yield: 38%. **^{1}H NMR** (300 MHz, D_2O): δ 1.18-1.74 (10H, m, -$(CH_2)_5$-), 3.07 (2H, d, *J* = 20.9 Hz, CH_2N). **^{13}C NMR** (75 MHz, D_2O): δ 21.1 (2 x $CH_{2,cHex}$), 24.3 ($CH_{2,cHex}$), 32.1 (d, *J* = 20.8 Hz, 2 x $CH_2\underline{C}H_2CF$), 46.6 (d, *J* = 23.1 Hz, CH_2N), 94.5 (d,

J = 171.9 Hz, CF). **^{19}F NMR** (282 MHz, D_2O): δ -160.8 to -159.8 (1F, m, CF). **IR** (ATR, cm^{-1}): ν_{NH} 3020; ν_{max} 2955, 2851, 1595, 1501, 1116, 1003, 945, 827, 719.

1-Aminomethyl-1-fluorocyclopropane hydrochloride 220d

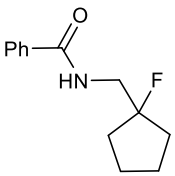


Colourless crystals. Yield: 6% (over 2 steps). **^{1}H NMR** (300 MHz, d_6-DMSO): δ 0.83-0.91 (2H, m, -C<u>H</u>$_2$CH$_2$-), 1.05-1.17 (2H, m, -CH$_2$C<u>H</u>$_2$-), 3.26 (2H, d, *J* = 23.1 Hz, CH_2N), 8.31 (3H, br s, NH_3). **^{13}C NMR** (75 MHz, d_6-DMSO): δ 9.9 (d, *J* = 10.4 Hz, -$(CH_2)_2$-), 43.1 (d, *J* = 21.9 Hz, CH_2N), 77.0 (d, *J* = 216.9 Hz, CF). **^{19}F NMR** (282 MHz, d_6-DMSO): δ -185.6 to -184.9 (1F, m, CF). **IR** (ATR, cm^{-1}): ν_{NH} 2906; ν_{max} 2993, 1599, 1520, 1417, 1256, 1021, 702.

5.2.11 Synthesis of *N*-[(1-fluorocyclopentyl)methyl]benzamide 221b

To a stirred solution of 1-aminomethyl-1-fluorocyclopentane hydrochloride (0.5 mmol, 1 equiv) in dry chloroform (2 mL) was added triethylamine (1.1 mmol, 2.1 equiv). After ten minutes the mixture was cooled to 0°C and benzoyl chloride (0.6 mmol, 1.2 equiv) was added. The reaction was stopped after one hour by adding water (1 mL). The aqueous phase was extracted with chloroform (3 x 1 mL) and the combined organic phases were washed with 0.1 M hydrochloric acid (2 x 1 mL) and saturated sodium bicarbonate (2 x 1 mL). After drying over $MgSO_4$ and evaporation of the solvent, the crude mixture was purified via column chromatography on silica gel yielding pure *N*-[(1-fluorocyclopentyl)methyl]benzamide **212b.**

***N*-[(1-Fluorocyclopentyl)methyl]benzamide 212b**



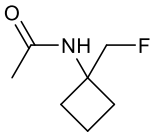
Colourless crystals: mp 97-99 °C. Yield: 55%. R_f 0.06 (petroleum ether/ethyl acetate 7:1). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.60-2.06 (8H, m, -$(CH_2)_4$-), 3.76 (2H, d x d, *J* = 5.5, 22.6 Hz, CH_2N), 6.64 (1H, br s, NH), 7.38-7.54 (3H, m, 3 x CH_{Ar}), 7.79 (2H, d, *J* = 7.7 Hz, 2 x CH_{Ar}). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 24.1 (2 x CH_2), 35.9 (d, *J* = 23.1 Hz, 2 x CH_2<u>C</u>H_2CF), 46.3 (d, *J* = 23.1 Hz, CH_2N), 107.0 (d, *J* = 174.2 Hz, CF), 127.1 (2 x CH_{Ar}), 128.7 (2 x CH_{Ar}), 131.7 (CH_{Ar}), 134.5 ($C_{q,Ar}$), 167.8 (C=O). **^{19}F NMR** (282 MHz, $CDCl_3$): δ -146.4 to -145.9 (1F, m). **IR** (ATR, cm^{-1}): ν_{NH} 3296; $\nu_{C=O}$ 1638; ν_{max} 2963, 2935, 1548, 1317, 1159, 1002, 803, 696, 664. **HRMS** (ES) calcd for $C_{13}H_{17}FNO$: 222.1289 $[M+H]^+$; Found: 222.1287.

5.2.12 Synthesis of *N*-[1-(fluoromethyl)cycloalkyl]acetamides 228

As a representative example, the synthesis of *N*-[1-(fluoromethyl)cyclobutyl]acetamide **228a** is described. Selectfluor® (8.1 mmol, 1.1 equiv) was added to a solution of methylenecyclobutane (7.4 mmol, 1 equiv) **212a** in acetonitrile (10 mL) and water (1 mL). After five hours the reaction was stopped by pouring the reaction mixture in water (10 mL), and the aqueous phase was extracted with ethyl acetate (3 x 15 mL). The combined organic phases were washed with water (10 mL) and brine

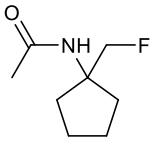
(10mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by recrystallisation in petroleum ether/diethyl ether (2:1) to obtain *N*-[1-(fluoromethyl)cyclobutyl]acetamide **228a** as a pure compound.

***N*-[1-(fluoromethyl)cyclobutyl]acetamide 228a**



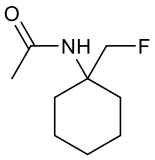
Colourless crystals: mp 66-68 °C. Yield: 3%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.75-2.03 (2H, m, -$CH_2C\underline{H_2}CH_2$-), 1.97 (3H, s, CH_3), 2.18-2.26 (4H, m, -$C\underline{H_2}CH_2C\underline{H_2}$-), 4.59 (2H, d, *J* = 47.9 Hz, CH_2F), 5.88 (1H, br s, NH). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 15.0 (-$CH_2\underline{C}H_2CH_2$-), 23.6 (CH_3), 29.2 (d, *J* = 6.9 Hz, -$\underline{C}H_2CH_2\underline{C}H_2$-), 56.4 (d, *J* = 18.5 Hz, C_qN), 84.5 (d, *J* = 171.9 Hz, CH_2F), 169.9 (C=O). **^{19}F NMR** (282 MHz, $CDCl_3$): δ -226.7 (d, *J* = 47.9 Hz, CH_2F). **IR** (ATR, cm^{-1}): ν_{NH} 3282; $\nu_{C=O}$ 1637; ν_{max} 1549, 1373, 1310, 955, 712, 611. **MS** (ES+): *m/z* (%): 146 (M+1, 100).

***N*-[1-(Fluoromethyl)cyclopentyl]acetamide 228b**



Colourless crystals: mp 84-88 °C. Yield: 26%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.61-1.95 (8H, m, -$(CH_2)_4$-), 1.96 (3H, s, CH_3), 4.51 (2H, d, *J* = 47.9 Hz, CH_2F), 5.66 (1H, br s, NH). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 23.9 (-$CH_2(\underline{C}H_2)_2CH_2$-), 24.2 ($CH_3$), 34.5 (d, *J* = 3.6 Hz, -$\underline{C}H_2(CH_2)_2\underline{C}H_2$-), 64.0 (d, *J* = 17.0 Hz, C_qN), 84.5 (d, *J* = 173.5 Hz, CH_2F), 170.3 (C=O). **^{19}F NMR** (282 MHz, $CDCl_3$): δ -221.9 (d, *J* = 47.9 Hz, CH_2F). **IR** (ATR, cm^{-1}): ν_{NH} 3278; $\nu_{C=O}$ 1634; ν_{max} 2955, 1547, 1372, 1309, 998, 724. **MS** (ES+): *m/z* (%): 160 (M+1, 100).

***N*-[1-(Fluoromethyl)cyclohexyl]acetamide 228c**

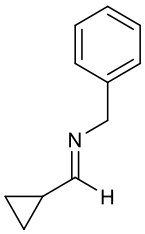


Colourless crystals: mp 98-104 °C. Yield: 26%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.26-1.64 (8H, m, 4 x $CH_{2,cHex}$), 1.99 (3H, s, CH_3), 2.04-2.12 (2H, m, $CH_{2,cHex}$), 4.55 (2H, d, *J* = 47.3 Hz, CH_2F), 5.11 (1H, br s, NH). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 21.0 (2 x $CH_{2,cHex}$), 24.0 (CH_3), 25.5 ($CH_{2,cHex}$), 30.5 (d, *J* = 4.6 Hz, 2 x $CH_{2,cHex}$), 56.7 (d, *J* = 17.3 Hz, C_qN), 85.6 (d, *J* = 173.1 Hz, CH_2F), 170.6 (C=O). **^{19}F NMR** (282 MHz, $CDCl_3$): δ -229.9 (d, *J* = 47.3 Hz, CH_2F). **IR** (ATR, cm^{-1}): ν_{NH} 3289; $\nu_{C=O}$ 1646; ν_{max} 1552, 1452, 1437, 1370, 1302, 1009, 724, 637. **MS** (ES+): *m/z* (%): 174 (M+1, 100).

5.2.13 Synthesis of *N*-(cyclopropylmethylidene)benzylamine 241

To a solution of benzylamine (2 mmol, 1 equiv) and $MgSO_4$ (3 mmol, 1.5 equiv) in dry dichloromethane (7 mL) was added cyclopropanecarboxaldehyde **240** (2 mmol, 1 equiv) and the reaction mixture was heated till reflux for one hour. Filtering off the solid residue and evaporation of the solvent under reduced pressure afforded *N*-(cyclopropylmethylidene)benzylamine **241**.

***N*-(Cyclopropylmethylidene)benzylamine 241**

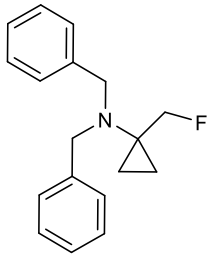


Colourless oil. Yield: 98%. **^{1}H NMR** (300 MHz, $CDCl_3$): 0.72 (2H, d x t , *J* = 4.4, 7.2 Hz, -C$\underline{H}_2$CH_2-), 0.87-0.93 (2H, m, -CH_2C$\underline{H}_2$-), 1.68-1.80 (1H, m, CH), 4.52 (2H, s, NCH_2Ph), 7.10 (1H, d, *J* = 7.7 Hz, CH_{Ar}), 7.23-7.36 (4H, m, 4 x CH_{Ar}). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 6.0 (-$(CH_2)_2$-), 16.4 (CH), 64.8 (NCH_2Ph), 126.9 (CH_{Ar}), 127.9 (2 x CH_{Ar}), 128.4 (2 x CH_{Ar}), 139.5 ($C_{q,Ar}$), 168.3 (C=N). **IR** (ATR, cm^{-1}): $\nu_{C=N}$ 1661; ν_{max} 2827, 1452, 1028, 933, 818, 733, 682.

5.2.14 Synthesis of *N,N*-dibenzyl-1-(fluoromethyl)cyclopropylamine 262

To a solution of 1-(*N,N*-dibenzylaminomethyl)cyclopropane-1-ol **253** (1.8 mmol, 1 equiv) in dry dichloromethane (20 mL) was added dropwise Morph-DAST (5.4 mmol, 3 equiv) at -78 °C, after which the temperature was allowed to slowly rise till room temperature. The reaction was quenched after six hours by careful addition of saturated sodium bicarbonate (10 mL) at 0 °C and the aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude mixture was purified via column chromatography on silica gel, yielding *N,N*-dibenzyl-1-(fluoromethyl)cyclopropylamine **262** as a pure compound.

***N,N*-Dibenzyl-1-(fluoromethyl)cyclopropanylamine 262**

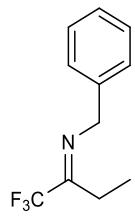


Yellow oil. Yield: 20%. **^{1}H NMR** (300 MHz, $CDCl_3$): 0.46-0.55 (4H, m, -($C\underline{H}_2$)$_2$-), 3.88 (4H, s, 2 x NCH_2Ph), 4.52 (2H, d, *J* = 49.4 Hz, CH_2F), 7.15-7.30 (10H, m, 10 x CH_{Ar}). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 13.9 (d, *J* = 6.9 Hz, -$(CH_2)_2$-), 43.1 (d, *J* = 20.85 Hz, C_q), 57.2 (2 x NCH_2Ph), 86.8 (d, *J* = 170.8 Hz, CF), 126.8 (2 x CH_{Ar}), 128.1 (4 x CH_{Ar}), 129.1 (4 x CH_{Ar}), 140.3 (2 x $C_{q,Ar}$). **^{19}F NMR** (282 MHz, $CDCl_3$): δ -210.1 (1F, t, *J* = 49.4 Hz, CF). **IR** (ATR, cm^{-1}): ν_{max} 2833, 1452, 1313, 1137, 1025, 979, 864, 746, 717, 694. **MS** (ES+): *m/z* (%): 270 (M+1, 100).

5.2.15 Synthesis of trifluoroimines 267

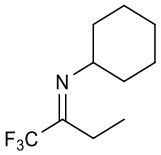
As a representative example, the synthesis of *N*-(1,1,1-trifluoro-2-butylidene)benzylamine **267a** is described. To an ice-cooled solution of 1,1,1-trifluorobutan-2-one **265** (7.9 mmol, 1 equiv) and benzylamine (23.8 mmol, 3 equiv) in anhydrous diethyl ether (30 mL), was added dropwise $TiCl_4$ (4.0 mmol, 0.5 equiv) in dry petroleum ether (10 mL) over a period of ten minutes. After stirring under reflux for three hours, the reaction mixture was filtered over a pad of Celite® and washed with diethyl ether (2 x 15 mL) Evaporation of the solvent under reduced pressure afforded *N*-(1,1,1-trifluoro-2-butylidene)benzylamine **267a**.

(*E*)-*N*-(1,1,1-Trifluoro-2-butylidene)benzylamine 267a



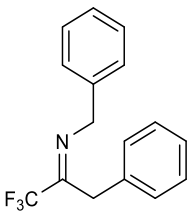
Yellow oil. Yield: 78%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.19 (3H, t, *J* = 7.7 Hz, CH_3), 2.54 (2H, q, *J* = 7.7 Hz, $C\underline{H}_2CH_3$), 4.73 (2H, s, NCH_2), 7.24-7.38 (5H, m, 5 x CH_{Ar}). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 10.6 (CH_3), 20.7 ($\underline{C}H_2CH_3$), 54.5 (NCH_2), 120.3 (q, *J* = 279.2 Hz, CF_3), 127.2 (CH_{Ar}), 127.6 (2 x CH_{Ar}), 128.7 (2 x CH_{Ar}), 138.3 ($C_{q,Ar}$), 161.6 (q, *J* = 31.2 Hz, C=N). **^{19}F NMR** (282 MHz, $CDCl_3$): δ -72.7 (3F, s, CF_3). **IR** (ATR, cm^{-1}): $\nu_{C=N}$ 1681; ν_{max} 1353, 1192, 1120, 1049, 933, 732, 696. **MS** (ES+): *m/z* (%): 216 (M+1, 100). **GC-MS** (EI) m/z (%): 215 (M^+, 7), 146 (14), 91 ($C_7H_7^+$, 100), 65 (8). **HRMS** (ES-TOF) calcd for $C_{11}H_{13}F_3N$ 216.0995 $[M + H]^+$, found 216.1000.

(*E*)-*N*-(1,1,1-Trifluoro-2-butylidene)cyclohexylamine 267b



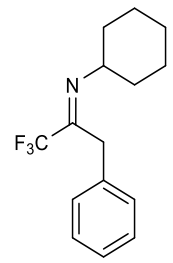
Colourless oil. Yield: 85%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.14-1.84 (13H, m, $(CH_2)_5$, CH_3), 2.42 (2H, q, *J* = 7.7 Hz, $C\underline{H}_2CH_3$), 3.48 (1H, m, CH). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 11.5 (CH_3), 19.9 ($\underline{C}H_2CH_3$), 24.2 (2 x CH_2), 25.4 (CH_2), 33.1 (2 x CH_2), 59.3 (NCH), 120.2 (q, *J* = 279.2 Hz, CF_3), 158.0 (q, *J* = 31.2 Hz, C=N). **^{19}F NMR** (282 MHz, $CDCl_3$): δ -72.6 (3F, s, CF_3). **IR** (ATR, cm^{-1}): $\nu_{C=N}$ 1679; ν_{max} 2932, 1451, 1344, 1192, 1151, 1117, 962. **GC-MS** (EI) m/z (%): 207 (M^+, 8), 192 (10), 178 (61), 164 (40), 138 (57), 126 (36), 83 (100), 67 (19), 55 (71), 41 (31). **HRMS** (ES-TOF) calcd for $C_{10}H_{17}F_3N$ 208.1308 $[M + H]^+$, found 208.1311.

(*E*)-*N*-(1,1,1-Trifluoro-3-phenylpropan-2-ylidene)benzylamine 267c



Yellow oil. Yield: 85%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 3.92 (2H, s, NCH_2), 4.70 (2H, s, NCH_2), 7.16-7.35 (10H, m, 10 x CH_{Ar}). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 33.6 (CH_2), 55.7 (NCH_2), 120.3 (q, *J* = 279.2 Hz, CF_3), 127.5 (2 x CH_{Ar}), 127.9 (2 x CH_{Ar}), 128.5 (2 x CH_{Ar}), 128.8 (2 x CH_{Ar}), 129.3 (2 x CH_{Ar}), 133.9 ($C_{q,Ar}$), 138.1 ($C_{q,Ar}$), 158.2 (q, *J* = 31.2 Hz, C=N). **^{19}F NMR** (282 MHz, $CDCl_3$): δ -72.0 (3F, s, CF_3). **IR** (ATR, cm^{-1}): $\nu_{C=N}$ 1681; ν_{max} 1496, 1454, 1354, 1336, 1195, 1176, 1124, 1090, 1072, 731, 714, 694. **MS** (ES+): *m/z* (%): 278 (M+1, 100). **GC-MS** (EI) m/z (%): 277 (M^+, 19), 199 (11), 186 (8), 167 (8), 91 (100), 65 (10). **HRMS** (ES-TOF) calcd for $C_{16}H_{15}F_3N$ 278.1151 $[M + H]^+$, found 278.1151.

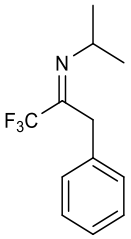
(*E*)-*N*-(1,1,1-Trifluoro-3-phenylpropan-2-ylidene)cyclohexylamine 267d



Orange oil. Yield: 71%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.15-1.31 (3H, m, 3 x CH_{cHex}), 1.46-1.82 (7H, m, 7 x CH_{cHex}), 3.52-3.61 (1H, m, NCH), 3.80 (2H, s, CH_2Ph), 7.13-7.36 (5H, m, 5 x CH_{Ar}). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 24.2 (2 x CH_2), 25.4 (CH_2), 32.8 (2 x CH_2), 32.9 (CH_2Ph), 60.4 (NCH), 120.0 (q, *J* = 279.2 Hz, CF_3), 127.0 (CH_{Ar}), 128.3 (2 x CH_{Ar}), 128.9 (2 x CH_{Ar}), 134.8 ($C_{q,Ar}$), 161.6 (q, *J* = 32.3 Hz, C=N). **^{19}F NMR** (282 MHz, $CDCl_3$): δ -73.6 (3F, s, CF_3). **IR** (ATR, cm^{-1}): $\nu_{C=N}$ 1677; ν_{max} 2931, 2857, 1453, 1332, 1175, 1122, 1093, 1032, 966, 735, 708, 694, 645. **GC-MS** (EI) m/z (%): 269 (M^+, 63), 226 (14), 200 (21),

191 (59), 178 (100), 118 (88), 91 (96), 83 (83), 67 (13), 55 (61), 41 (28). **HRMS** (ES-TOF) calcd for $C_{15}H_{19}F_3N$ 270.1464 $[M + H]^+$, found 270.1472.

(*E*)-*N*-(1,1,1-Trifluoro-3-phenylpropan-2-ylidene)isopropylamine 267e

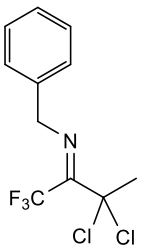


Orange oil. Yield: 95%. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.13 (6H, d, *J* = 6.2 Hz, $(C\underline{H}_3)_2CH$), 3.78 (2H, s, CH_2), 3.90 (1H, septet, *J* = 6.2 Hz, $(CH_3)_2C\underline{H}$), 7.14-7.33 (5H, m, 5 x CH_{Ar}). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 22.8 (2 x CH_3), 32.8 (CH_2), 52.0 (CHN), 120.0 (q, *J* = 279.4 Hz, CF_3), 127.0 (2 x CH_{Ar}), 128.2 (CH_{Ar}), 128.9 (2 x CH_{Ar}), 134.6 ($C_{q,Ar}$), 154.5 (q, *J* = 32.0 Hz, C=N). **^{19}F NMR** (376 MHz, $CDCl_3$): δ -72.2 (3F, s, CF_3). **IR** (ATR, cm^{-1}): $\nu_{C=N}$ 1681; ν_{max} 2974, 1496, 1455, 1333, 1176, 1129, 1065, 1030, 733, 702, 647. **GC-MS** (EI) m/z (%): 229 (M^+, 27), 214 (20), 172 (18), 160 (17), 151 (41), 118 (85), 91 (100), 65 (12), 43 (23).

5.2.16 Synthesis of (*E*)-3,3-dichloro-1,1,1-trifluoroimines 268

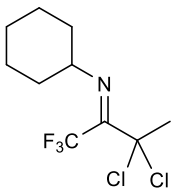
As a representative example, the synthesis of (*E*)-*N*-(3,3-dichloro-1,1,1-trifluoro-2-butylidene)benzylamine **268a** is described. To a solution of *N*-(1,1,1-trifluoro-2-butylidene)-benzylamine **267a** (4.7 mmol, 1 equiv) in cyclohexane (6 mL), was added *N*-chlorosuccinimide (14.0 mmol, 3 equiv) and was heated under reflux for two days. After cooling down the reaction mixture the solid residues were filtered off. Concentration under reduced pressure afforded the crude product. The crude mixtures of the dichlorinated products were purified by vacuum distillation or recrystallisation, yielding (*E*)-*N*-(3,3-dichloro-1,1,1-trifluoro-2-butylidene)benzylamine **268a**.

(*E*)-*N*-(3,3-Dichloro-1,1,1-trifluoro-2-butylidene)benzylamine 268a



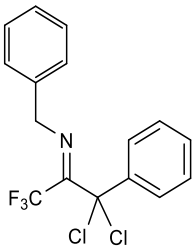
Colourless liquid: bp 60-63 °C (1.2 mmHg). Yield: 80%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 2.36 (3H, s, CH_3), 4.96 (2H, s, NCH_2), 7.30-7.40 (5H, m, 5 x CH_{Ar}). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 36.0 (CH_3), 55.9 (NCH_2), 81.9 (CCl_2), 117.1 (q, *J* = 290.8 Hz, CF_3), 127.7 (3 x CH_{Ar}), 128.8 (2 x CH_{Ar}), 137.7 ($C_{q,Ar}$), 152.8 (q, *J* = 28.8 Hz, C=N) .**^{19}F NMR** (282 MHz, $CDCl_3$): δ -59.9 (3F, s, CF_3) **IR** (ATR, cm^{-1}): $\nu_{C=N}$ 1671; ν_{max} 1290, 1198, 1166, 1136, 1003, 753, 732, 695, 661. **GC-MS** (EI) m/z (%): 283/285 (M^+, 3), 248 (3), 186 (5), 91 (100).

(*E*)-*N*-(3,3-Dichloro-1,1,1-trifluoro-2-butylidene)cyclohexylamine 268b



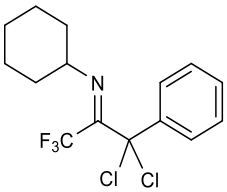
Colourless liquid: bp 41-44 °C (1.1 mmHg). Yield: 79%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.32-1.80 (10H, m, $(CH_2)_5$), 2.29 (3H, s, CH_3), 3.73-3.84 (1H, m, NCH). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 23.6 (2 x CH_2), 25.5 (CH_2), 33.0 (2 x CH_2), 36.0 (CH_3,), 60.8 (NCH), 82.0 (CCl_2), 117.1 (q, *J* = 290.8 Hz, CF_3), 149.9 (q, *J* = 27.7 Hz, C=N). **^{19}F NMR** (282 MHz, $CDCl_3$): δ -58.8 (3F, s, CF_3). **IR** (ATR, cm^{-1}): $\nu_{C=N}$ 1668; ν_{max} 2936, 2859, 1452, 1380, 1291, 1202, 1169, 1138, 997, 753, 662. **GC-MS** (EI) m/z (%): 275/277 (M^+, 0.5), 240/242 (44), 178 (11), 83 (100), 55 (33), 41 (13).

(*E*)-*N*-(1,1-Dichloro-3,3,3-trifluoro-1-phenylpropan-2-ylidene)benzylamine 268c



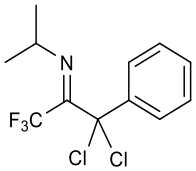
Colourless crystals: mp 54-58 °C (MeOH). Yield: 74%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 5.10 (2H, d, *J* = 1.5 Hz, NCH_2), 7.35-7.45 (8H, m, 8 x CH_{Ar}), 7.58-7.62 (2H, m, 2 x CH_{Ar}). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 55.6 (NCH_2), 88.3 (CCl_2), 116.9 (q, *J* = 291.5 Hz, CF_3), 126.1 (2 x CH_{Ar}), 127.4 (3 x CH_{Ar}), 128.7 (4 x CH_{Ar}), 129.7 (CH_{Ar}), 137.7 ($C_{q,Ar}$), 139.3 ($C_{q,Ar}$), 151.5 (q, *J* = 28.2 Hz, C=N). **^{19}F NMR** (282 MHz, $CDCl_3$): δ -58.9 (3F, s, CF_3). **IR** (ATR, cm^{-1}): $\nu_{C=N}$ 1667; ν_{max} 1492, 1374, 1265, 1178, 1159, 1143, 827, 753, 744, 713, 697, 638. **MS** (ES+): m/z 346/348 (M+1, 60). **HRMS** (ES-TOF) calcd for $C_{16}H_{13}Cl_2F_3N$ 346.0372 $[M + H]^+$, found 346.0377.

(*E*)-*N*-(1,1-Dichloro-3,3,3-trifluoro-1-phenylpropan-2-ylidene)cyclohexylamine 268d



Colourless crystals: mp 62-64 °C (EtOH). Yield: 68%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.32-1.84 (10H, m, $(CH_2)_5$), 3.85-3.96 (1H, m, NCH), 7.36-7.43 (3H, m, 3 x CH_{Ar}), 7.53-7.59 (2H, m, 2 x CH_{Ar}). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 23.5 (2 x CH_2), 25.5 (CH_2), 33.1 (2 x CH_2), 61.4 (NCH), 88.3 (CCl_2), 117.0 (q, *J* = 291.1 Hz, CF_3), 125.7 (2 x CH_{Ar}), 128.6 (2 x CH_{Ar}), 129.4 (CH_{Ar}), 139.6 ($C_{q,Ar}$), 148.5 (q, *J* = 27.7 Hz, C=N). **^{19}F NMR** (282 MHz, $CDCl_3$): δ -57.7 (3F, s, CF_3). **IR** (ATR, cm^{-1}): $\nu_{C=N}$ 1672; ν_{max} 2940, 2859, 1449, 1270, 1199, 1187, 1135, 1072, 808, 754, 716, 707, 692. **GC-MS** (EI) m/z (%): 337/339 (M^+, 1), 303/305 (9), 221 (19), 178 (22), 83 (100), 55 (42), 41 (13).

(*E*)-*N*-(1,1-Dichloro-3,3,3-trifluoro-1-phenylpropan-2-ylidene)isopropylamine 268e



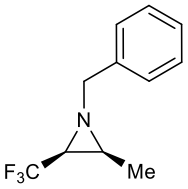
Colourless liquid. Yield: 88%. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.30 (6H, d, *J* = 6.0 Hz, $(C\underline{H}_3)_2CH$), 4.23 (1H, septet x d, *J* = 2.6, 6.0 Hz, NCH), 7.37-7.35 (3H, m, 3 x CH_{Ar}), 7.54-7.58 (2H, m, 2 x CH_{Ar}). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 23.4 ($(\underline{C}H_3)_2CH$), 53.9 (d, *J* = 2.2 Hz, NCH), 88.3 (CCl_2), 117.2 (q, *J* = 291.7 Hz, CF_3), 125.8 (2 x CH_{Ar}), 128.7 (2 x CH_{Ar}), 129.6 (CH_{Ar}), 139.7 ($C_{q,Ar}$), 148.6 (q, *J* = 27.9 Hz, C=N). **^{19}F NMR** (376 MHz, $CDCl_3$): δ -57.8 (3F, d, *J* = 1.8 Hz, CF_3). **IR** (ATR, cm^{-1}): $\nu_{C=N}$ 1674; ν_{max} 2980, 1449, 1366, 1264, 1198, 1140, 1068, 809, 752, 718, 692. **GC-MS** (EI) m/z (%): 337/339 (M^+, 1), 303 (9), 221 (19), 178 (22), 83 (100), 55 (42), 41 (13).

5.2.17 Synthesis of *cis*-1-alkyl-2-methyl/phenyl-3-(trifluoromethyl)aziridines 270

As a representative example, the synthesis of *cis*-1-benzyl-2-methyl-3-(trifluoromethyl)aziridine **270a** is described. To an ice-cooled solution of (*E*)-*N*-(3,3-dichloro-1,1,1-trifluoro-2-butylidene)benzylamine **268a** (3.5 mmol, 1.0 equiv) in dry diethyl ether (20 mL) was carefully added lithium aluminium hydride (7.0 mmol, 2.0 equiv). The cooling bath was removed and the mixture was stirred overnight under reflux. After cooling to ambient temperature, the reaction mixture was quenched by portion-wise addition of water at 0 °C. The formed salts were filtered off over a pad of

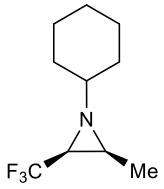
Celite® and were washed with diethyl ether (2 x 5 mL). The combined organic phases were washed with brine (15 mL), dried over K_2CO_3 and concentrated *in vacuo*. The crude mixture was purified by column chromatography on silica gel to yield *cis*-1-benzyl-2-methyl-3-(trifluoromethyl)aziridine **270a**.

***Cis*-1-benzyl-2-methyl-3-(trifluoromethyl)aziridine 270a**



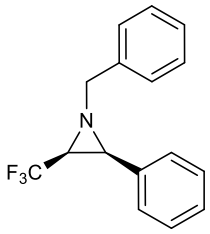
Colourless liquid. Yield 52%. R_f 0.01 (petroleum ether/diethyl ether 98:2). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.34 (3H, d, *J* = 5.0 Hz, CH_3), 1.91 (1H, ~quintet, *J* = 5.5 Hz, C<u>H</u>CH_3), 2.04 (1H, ~quintet, *J* = 6.6 Hz, $CHCF_3$), 3.59 (1H, d, *J* = 14.6 Hz, C<u>H</u>$_a$H$_b$Ph), 3.64 (1H, d, *J* = 14.6 Hz, CH_a<u>H</u>$_b$Ph), 7.28-7.38 (5H, m, 5 x CH_{Ar}). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 13.2 (CH_3), 38.8 (<u>C</u>HCH_3), 41.7 (q, *J* = 38.1 Hz, <u>C</u>HCF_3), 63.8 (CH_2), 125.0 (q, *J* = 273.5 Hz, CF_3), 127.4 (CH_{Ar}), 127.9 (2 x CH_{Ar}), 128.5 (2 x CH_{Ar}), 137.7 ($C_{q,Ar}$). **^{19}F NMR** (282 MHz, $CDCl_3$): δ -64.2 (3F, d, *J* = 6.6 Hz, CF_3). **IR** (ATR, cm^{-1}): ν_{max} 2937, 1454, 1440, 1401, 1291, 1137, 1095, 1046, 1029, 875, 843, 733, 696. **MS** (ES+): m/z 216 (M+1, 100). **GC-MS** (EI) m/z (%): 215 (M^+, 13), 200 (M^+-CH_3, 12), 124 (91), 91 ($C_7H_7^+$, 100), 65 (11), 51 (4), 41 (2). **HRMS** (ES-TOF) calcd for $C_{11}H_{13}F_3N$ 216.0995 $[M + H]^+$, found 216.1002.

***Cis*-1-cyclohexyl-2-methyl-3-(trifluoromethyl)aziridine 270b**



Colourless oil. Yield: 29%. R_f 0.03 (petroleum ether/diethyl ether 99:1). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 1.10-1.57 (6H, m, 6 x CH_{cHex}), 1.31 (3H, d x q, *J* = 1.3, 5.9 Hz, CH_3), 1.57-1.62 (1H, m, CH_{cHex}), 1.74-1.85 (5H, m, 4 x CH_{cHex}, C<u>H</u>CH_3), 1.88 (1H, ~quintet, *J* = 6.5 Hz, C<u>H</u>CF_3). **^{13}C NMR** (125 MHz, $CDCl_3$): δ 13.7 (CH_3), 24.5 (CH_2), 24.6 (CH_2), 25.8 (CH_2), 31.8 (CH_2), 32.2 (CH_2), 37.5 (<u>C</u>HCH_3), 41.2 (q, *J* = 38.1 Hz, <u>C</u>HCF_3), 68.9 (NCH_{cHex}), 125.0 (q, *J* = 273.6 Hz, CF_3). **^{19}F NMR** (376 MHz, $CDCl_3$): δ -64.7 (3F, d, *J* = 6.3 Hz, CF_3). **IR** (ATR, cm^{-1}): ν_{max} 2929, 2856, 2360, 1292, 1146, 735. **GC-MS** (EI) m/z (%): 207 (M^+, 7), 192 (M^+-CH_3, 32), 178 (13), 164 (82), 126 (100), 106 (19), 83 (31), 67 (26), 55 (58), 41 (26). **HRMS** (ES-TOF) calcd for $C_{10}H_{17}F_3N$ 208.1308 $[M + H]^+$, found 208.1312.

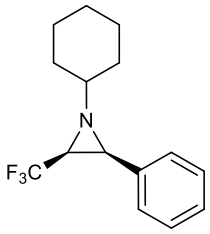
***Cis*-1-benzyl-2-phenyl-3-(trifluoromethyl)aziridine 270c**



Yellow oil. Yield: 79%. R_f 0.10 (petroleum ether/diethyl ether 99:1). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 2.74 (1H, ~quintet, *J* = 6.1 Hz, $CHCF_3$), 3.06 (1H, d, *J* = 6.6 Hz, CHPh), 3.71 (1H, d, *J* = 13.2 Hz, NC<u>H</u>$_a$H$_b$), 3.92 (1H, d, *J* = 13.2 Hz, NCH$_a$<u>H</u>$_b$), 7.24-7.43 (10H, m, 10 x CH_{Ar}). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 44.1 (q, *J* = 38.1 Hz, <u>C</u>HCF_3), 45.0 (CHPh), 63.9 (NCH_2Ph), 124.4 (q, *J* = 275.8 Hz, CF_3), 127.7 (CH_{Ar}), 127.8 (CH_{Ar}), 127.9 (2 x CH_{Ar}), 128.2 (2 x CH_{Ar}), 128.5 (2 x CH_{Ar}), 128.7 (2 x CH_{Ar}), 134.3 ($C_{q,Ar}$), 137.4 ($C_{q,Ar}$). **^{19}F NMR** (282 MHz, $CDCl_3$): δ -65.4 (3F, d, *J* = 5.3 Hz, CF_3). **IR** (ATR, cm^{-1}): ν_{max} 3064, 1497, 1448, 1384, 1295, 1181, 1136, 1074, 887, 739, 697. **MS** (ES+): m/z 278 (M+1, 100). **GC-MS** (EI) m/z (%): 277 (M^+, 33),

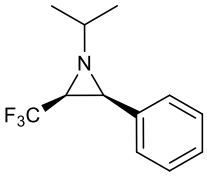
186 (M^+-CH_2Ph, 100), 159 (90), 109 (39), 91 ($C_7H_7^+$, 42), 77 (5), 65 (8), 51 (4). **HRMS** (ES-TOF) calcd for $C_{16}H_{15}F_3N$ 278.1157 $[M + H]^+$, found 278.1163.

***Cis*-1-cyclohexyl-2-phenyl-3-(trifluoromethyl)aziridine 270d**



Colourless crystals: mp 42-47 °C. Yield: 50%. R_f 0.16 (petroleum ether/diethyl ether 99:1). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.16-1.38 (4H, m, 4 x CH_{cHex}), 1.49-1.66 (3H, m, 3 x CH_{cHex}), 1.78-1.92 (4H, m, 4 x CH_{cHex}), 2.27 (1H, ~quintet, *J* = 6.1 Hz, $CHCF_3$), 2.91 (1H, d, *J* = 6.1 Hz, CHPh), 7.26-7.41 (5H, m, 5 x CH_{Ar}). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 24.2 (CH_2), 24.3 (CH_2), 25.9 (CH_2), 31.7 (CH_2), 32.2 (CH_2), 43.4 (q, *J* = 38.1 Hz, $CHCF_3$), 44.1 (CHPh), 68.1 (NCH_{cHex}), 124.4 (q, *J* = 274.6 Hz, CF_3), 127.5 (CH_{Ar}), 127.8 (2 x CH_{Ar}), 128.1 (2 x CH_{Ar}), 135.1 ($C_{q,Ar}$). **^{19}F NMR** (282 MHz, $CDCl_3$): δ -66.1 (3F, d, *J* = 6.6 Hz, CF_3). **IR** (ATR, cm^{-1}): ν_{max} 2932, 1458, 1443, 1372, 1294, 1182, 1151, 1138, 1115, 901, 747, 700, 691. **MS** (ES+): m/z 270 (M+1, 100). **HRMS** (ES-TOF) calcd for $C_{15}H_{19}F_3N$ 270.1464 $[M + H]^+$, found 270.1471.

***Cis*-1-isopropyl-2-phenyl-3-(trifluoromethyl)aziridine 270e**

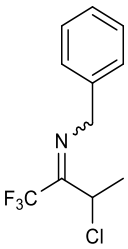


Yellow oil. Yield: 75%. R_f 0.11 (petroleum ether/diethyl ether 99:1). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.25 (6H, d, *J* = 6.3 Hz, $(C\underline{H}_3)_2CH$), 1.86 (1H, septet, *J* = 6.3 Hz, $NC\underline{H}(CH_3)_2$), 2.25 (1H, ~quintet, *J* = 6.1 Hz, $CHCF_3$), 2.90 (1 H, d, *J* = 6.3 Hz, CHPh), 7.23-7.33 (3H, m, 3 x CH_{Ar}), 7.38-7.42 (2H, m, 2 x CH_{Ar}). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.5 ($(\underline{C}H_3)CH(CH_3)$), 21.9 ($(CH_3)CH(\underline{C}H_3)$), 43.9 (q, *J* = 38.1 Hz, $\underline{C}HCF_3$), 44.5 (CHPh), 61.1 ($N\underline{C}H(CH_3)_2$), 124.3 (q, *J* = 274.2 Hz, CF_3), 127.4 (CH_{Ar}), 127.7 (2 x CH_{Ar}), 128.1 (2 x CH_{Ar}), 134.8 ($C_{q,Ar}$). **^{19}F NMR** (376 MHz, $CDCl_3$): δ -65.6 (3F, d, *J* = 5.6 Hz, CF_3). **IR** (ATR, cm^{-1}): ν_{max} 2970, 2359, 1446, 1384, 1343, 1295, 1191, 1129, 1088, 981, 898, 772, 742, 700, 692. **GC-MS** (EI) m/z (%): 228/229 (M^+, 89), 186 (M^+-*i*Pr, 84), 159 (100), 118 (19), 109 (43), 89 (13), 77 (6), 51 (4), 43 (5). **HRMS** (ES-TOF) calcd for $C_{12}H_{15}F_3N$ 230.1151 $[M + H]^+$, found 230.1160.

5.2.18 Synthesis of 3-chloro-1,1,1-trifluoroimines 269

As a representative example, the synthesis of *N*-(3-chloro-1,1,1-trifluoro-2-butylidene)benzylamine **269a** is described. To a solution of *N*-(1,1,1-trifluoro-2-butylidene)benzylamine **267a** (4.7 mmol, 1.0 equiv) in cyclohexane (10 mL) was added *N*-chlorosuccinimide (4.7 mmol, 1.0 equiv), and the resulting mixture was stirred for six hours under reflux. After cooling down the reaction mixture, the solid residues were filtered off. Concentration under reduced pressure afforded *N*-(3-chloro-1,1,1-trifluoro-2-butylidene)benzylamine **269a**, which was used without further purification (purity >90%, ^{19}F NMR).

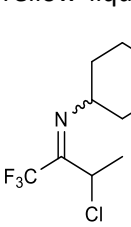
***N*-(3-Chloro-1,1,1-trifluoro-2-butylidene)benzylamine 269a**



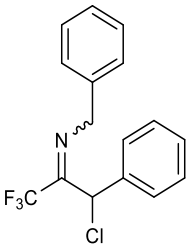
Yellow oil. Yield: 78%. Isomer ratio E/Z 49:51. **^{1}H NMR** (300 MHz, $CDCl_3$): $\delta_{MINOR\text{-}isomer}$ 1.74 (3H, d, *J* = 6.6 Hz, CH_3), 4.84 (1H, q, *J* = 6.6 Hz, CHCl), 4.92 (2H, s, NCH_2), 7.27-7.40 (5H, m, 5 x CH_{Ar}); $\delta_{MAJOR\text{-}isomer}$ 1.84 (3H, d x d, *J* = 1.1, 7.2 Hz, CH_3), 4.96 (2H, d, *J* = 1.1 Hz, NCH_2), 4.97 (1H, q, *J* = 7.2 Hz, CHCl), 7.27-7.40 (5H, m, 5 x CH_{Ar}). **^{13}C NMR** (75 MHz, $CDCl_3$): $\delta_{MINOR\text{-}isomer}$ 21.0 (CH_3), 53.5 (CHCl), 56.1 (NCH_2), 119.6 (q, *J* = 280.4 Hz, CF_3), 127.4, 127.6, 127.7, 128.7 or 128.9 (CH_{Ar}), 138.7 ($C_{q,\ Ar}$), 155.0 (q, *J* = 27.7 Hz, C=N); $\delta_{MAJOR\text{-}isomer}$ 21.2 (CH_3), 45.6 (CHCl), 54.8 (NCH_2), 117.3 (q, *J* = 290.8 Hz, CF_3), 127.4, 127.6, 127.7, 128.7 or 128.9 (CH_{Ar}), 137.6 ($C_{q,Ar}$), 156.0 (q, *J* = 31.2 Hz, C=N). **^{19}F NMR** (282 MHz, $CDCl_3$): δ -64.4 (3F, s, $CF_{3\ MINOR}$); -69.6 (3F, s, $CF_{3\ MAJOR}$). **IR** (ATR, cm^{-1}): $\nu_{C=N}$ 1670; ν_{max} 1454, 1343, 1297, 1275, 1187, 1128, 1030, 949, 732, 696. **GC-MS** (EI) m/z (%): 249/251 (M^+, 6), 214 (4), 91 (100), 65 (6).

***N*-(3-Chloro-1,1,1-trifluoro-2-butylidene)cyclohexylamine 269b**

Yellow liquid. Yield: 72%. Isomer ratio E/Z 24:76. **^{1}H NMR** (300 MHz, $CDCl_3$): $\delta_{MINOR\text{-}isomer}$ 1.25-1.86 (10H, m, $(CH_2)_5$), 1.67 (3H, d, *J* = 6.6 Hz, CH_3), 3.69-3.79 (1H, m, NCH), 4.76 (1H, q, *J* = 6.6 Hz, CHCl); $\delta_{MAJOR\text{-}isomer}$ 1.25-1.86 (10H, m, $(CH_2)_5$), 1.77 (3H, d, *J* = 7.2 Hz, NCH_3), 3.77-3.86 (1H, m, NCH), 4.90 (1H, q, *J* = 7.2 Hz, CHCl). **^{13}C NMR** (75 MHz, $CDCl_3$): $\delta_{MINOR\text{-}isomer}$ 21.1 (CH_3), 25.4 (2 x CH_2), 25.6 (CH_2), 32.4 (CH_2), 33.3 (CH_2), 53.5 (CHN), 61.2 (CHCl), 119.6 (q, *J* = 280.4 Hz, CF_3), 151.8 (q, *J* = 27.7 Hz, C=N); $\delta_{MAJOR\text{-}isomer}$ 21.8 (CH_3), 23.8 (CH_2), 24.1 (2 x CH_2), 33.0 (CH_2), 33.3 (CH_2), 45.1 (d, *J* = 10.4 Hz, CHN), 60.0 (CHCl), 117.4 (q, *J* = 290.8 Hz, CF_3), 153.2 (q, *J* = 31.2 Hz, C=N). **^{19}F NMR** (282 MHz, $CDCl_3$): δ -64.4 (3F, s, $CF_{3\ MINOR}$); -69.2 (3F, s, $CF_{3\ MAJOR}$). **IR** (ATR, cm^{-1}): $\nu_{C=N}$ 1667; ν_{max} 2934, 2859, 1450, 1298, 1275, 1182, 1139, 1126, 1022, 970, 684. **GC-MS** (EI) m/z (%): 241/243 (M^+,0.5), 206 (100), 83 (36), 55 (26), 41 (10).

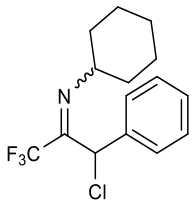


***N*-(3-Chloro-1,1,1-trifluoro-3-phenylprop-2-ylidene)benzylamine 269c**



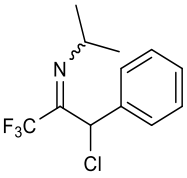
Yellow oil. Yield: 84%. Isomer ratio E/Z 27:73. **^{1}H NMR** (300 MHz, $CDCl_3$): $\delta_{MINOR\text{-}isomer}$ 4.95 (2H, m, NCH_2), 5.84 (1H, s, CHCl), 7.18-7.45 (10H, m, 10 x CH_{Ar}); $\delta_{MAJOR\text{-}isomer}$ 4.60 (2H, d x d, *J* = 1.4, 16.3 Hz, $NC\underline{H}_aH_b$), 4.87 (2H, d x d, *J* = 1.4, 16.3 Hz, $NCH_a\underline{H}_b$), 6.00 (1H, s, CHCl), 7.18-7.45 (10H, m, 10 x CH_{Ar}). **^{13}C NMR** (75 MHz, $CDCl_3$): $\delta_{MINOR\text{-}isomer}$ 56.3 (NCH_2), 61.1 (CHCl), 117.1 (q, *J* = 291.3 Hz, CF_3), 127.5 (2 x CH_{Ar}), 128.0 (2 x CH_{Ar}), 128.6 (2 x CH_{Ar}), 128.7 (2 x CH_{Ar}), 128.8 (2 x CH_{Ar}), 135.5 ($C_{q,Ar}$), 138.0 ($C_{q,Ar}$), 153.8 (q, *J* = 27.6 Hz, C=N); $\delta_{MAJOR\text{-}isomer}$ 51.8 (CHCl), 55.9 (NCH_2), 119.4 (q, *J* = 279.9 Hz, CF_3), 126.5 (2 x CH_{Ar}), 127.4 (2 x CH_{Ar}), 127.7 (2 x CH_{Ar}), 128.6 (2 x CH_{Ar}), 129.1 (2 x CH_{Ar}), 134.2 ($C_{q,Ar}$), 137.3 ($C_{q,Ar}$), 154.5 (q, *J* = 32.7 Hz, C=N). **^{19}F NMR** (282 MHz, $CDCl_3$): δ -62.3 (3F, s, $CF_{3\ MINOR}$); -70.5 (3F, s, $CF_{3\ MAJOR}$). **IR** (ATR, cm^{-1}): $\nu_{C=N}$ 1682; ν_{max} 1496, 1454, 1337, 1277, 1193, 1178, 1128, 1093, 1070, 732, 694. **GC-MS** (EI) m/z (%): 311/313 (M^+, 2), 276 (M^+-Cl, 25), 198 (6), 178 (7), 125 (20), 91 (100), 65 (8).

***N*-(3-Chloro-1,1,1-trifluoro-3-phenylprop-2-ylidene)cyclohexylamine 269d**



Colourless oil. Yield: 89%. Isomer ratio E/Z 23:77. **^{1}H NMR** (300 MHz, $CDCl_3$): $\delta_{MINOR\text{-}isomer}$ 1.21-1.85 (10H, m, $(CH_2)_5$), 3.67-3.77 (1H, m, NCH), 5.77 (1H, s, CHCl), 7.31-7.46 (5H, m, 5 x CH_{Ar}); $\delta_{MAJOR\text{-}isomer}$ 1.21-1.85 (10H, m, $(CH_2)_5$), 3.73-3.85 (1H, m, NCH), 5.92 (1H, s, CHCl), 7.31-7.46 (5H, m, 5 x CH_{Ar}). **^{13}C NMR** (75 MHz, $CDCl_3$): $\delta_{MINOR\text{-}isomer}$ 23.8, 23.9, 25.4, 25.5, 31.7, 32.4 or 33.3 (5 x CH_2), 61.1 (CHCl), 61.6 (CHN), 117.2 (q, *J* = 291.9 Hz, CF_3), 126.4, 127.8, 128.6, 128.8 (5 x CH_{Ar}), 135.9 ($C_{q,Ar}$), 150.7 (q, *J* = 27.7 Hz, C=N); $\delta_{MAJOR\text{-}isomer}$ 23.8, 23.9, 25.4, 25.5, 31.7, 32.4 or 33.3 (5 x CH_2), 51.2 (CHCl), 60.6 (CHN), 119.5 (q, *J* = 280.4 Hz, CF_3), 126.4, 127.8, 128.6, 128.8 (5 x CH_{Ar}), 135.2 ($C_{q,Ar}$), 152.4 (q, *J* = 32.3 Hz, C=N). **^{19}F NMR** (282 MHz, $CDCl_3$): δ -61.9 (3F, s, $CF_{3\ MINOR}$); -70.5 (3F, s, $CF_{3\ MAJOR}$). **IR** (ATR, cm^{-1}): $\nu_{C=N}$ 1679; ν_{max} 2933, 2857, 1449, 1277, 1190, 1142, 1125, 1095, 730, 713, 693. **GC-MS** (EI) m/z (%): 303/305 (M^+, 3), 268 (35), 178 (19), 125 (13), 83 (100), 55 (42), 41 (13).

***N*-(3-Chloro-1,1,1-trifluoro-3-phenylprop-2-ylidene)isopropylamine 269e**



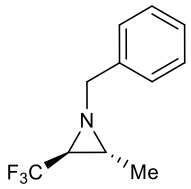
Yellow oil. Yield: 66%. Isomer ratio E/Z 25:75. **^{1}H NMR** (400 MHz, $CDCl_3$): $\delta_{MINOR\text{-}isomer}$ 1.22 (3H, d, *J* = 6.1 Hz, $(C\underline{H}_3)CH(CH_3)$), 1.26 (3H, d, *J* = 6.1 Hz, $(CH_3)CH(C\underline{H}_3)$), 4.11 (1H, septet x d, *J* = 2.5, 6.1 Hz, $NC\underline{H}(CH_3)_2$), 5.74 (1H, s, CHCl), 7.25-7.41 (5H, m, 5 x CH_{Ar}); $\delta_{MAJOR\text{-}isomer}$ 0.88 (3H, d, *J* = 6.1 Hz, $(C\underline{H}_3)CH(CH_3)$), 1.16 (3H, d, *J* = 6.1 Hz, $(CH_3)CH(C\underline{H}_3)$), 4.01 (1H, septet, *J* = 6.1 Hz, $NC\underline{H}(CH_3)_2$), 5.85 (1H, s, CHCl), 7.25-7.41 (5H, m, 5 x CH_{Ar}). **^{13}C NMR** (100 MHz, $CDCl_3$): $\delta_{MINOR\text{-}isomer}$ 21.7 and 22.5 ($(\underline{C}H_3)_2CH$), 53.5 (CHN), 61.1 (CHCl), 117.3 (q, *J* = 291.4 Hz, CF_3), 125.7 (2 x CH_{Ar}), 127.0 (CH_{Ar}), 128.7 (2 x CH_{Ar}), 135.8 ($C_{q,Ar}$), 150.7 (q, *J* = 27.1 Hz, C=N); $\delta_{MAJOR\text{-}isomer}$ 22.7 and 23.6 ($(\underline{C}H_3)_2CH$), 51.2 (CHN), 52.3 (CHCl), 119.6 (q, *J* = 280.0 Hz, CF_3), 126.3 (2 x CH_{Ar}), 127.7 (CH_{Ar}), 128.6 (2 x CH_{Ar}), 135.0 ($C_{q,Ar}$), 152.1 (q, *J* = 32.0 Hz, C=N). **^{19}F NMR** (376 MHz, $CDCl_3$): δ -61.5 (3F, s, $CF_{3\ MINOR}$); -70.3 (3F, s, $CF_{3\ MAJOR}$). **IR** (ATR, cm^{-1}): $\nu_{C=N}$ 1681; ν_{max} 2978, 2935, 1450, 1364, 1276, 1189, 1130, 1038, 939, 712, 694. **GC-MS** (EI) m/z (%): 263/265 (M^+, 8), 228 (72), 186 (31), 151 (14), 138 (51), 125 (100), 117 (25), 91 (21), 43 (51).

5.2.19 Synthesis of *trans*-1-alkyl-2-methyl/phenyl-3-(trifluoromethyl)aziridines 280

As a representative example, the synthesis of *trans*-1-benzyl-2-methyl-3-(trifluoromethyl)aziridine **280a** is described. To an ice-cooled solution of *N*-(3-chloro-1,1,1-trifluoro-2-butylidene)benzylamine **269a** (4.0 mmol, 1.0 equiv) in dry diethyl ether (20mL) was carefully added $LiAlH_4$ (8.0 mmol, 2.0 equiv). The cooling bath was removed and the mixture was stirred for six hours at room temperature. The reaction was quenched by portion-wise addition of water at 0 °C. The formed salts were filtered off over Celite® and were washed with diethyl ether (2 x 5 mL). The combined organic phases were washed with brine (15mL), dried over K_2CO_3 and concentrated *in vacuo*. The crude

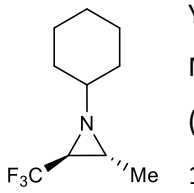
mixture was purified by column chromatography on silica gel to yield *trans*-1-benzyl-2-methyl-3-(trifluoromethyl)aziridine **280a.**

***Trans*-1-benzyl-2-methyl-3-(trifluoromethyl)aziridine 280a**



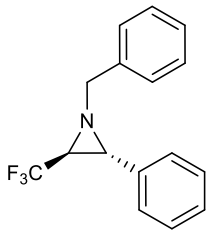
Yellow oil. Yield 48%. R_f 0.07 (petroleum ether/diethyl ether 99:1). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.40 (3H, d, *J* = 6.0 Hz, CH_3), 2.02 (1H, br s, $CHCF_3$), 2.57 (1H, br s, $C\underline{H}CH_3$), 3.73 (1H, d, *J* = 14.0 Hz, $NC\underline{H}_aH_bPh$), 3.85 (1H, d, *J* = 14.0 Hz, $NCH_a\underline{H}_bPh$), 7.30-7.45 (5H, m, 5 x CH_{Ar}). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 10.2 (CH_3), 35.2 ($\underline{C}HCH_3$), 43.7 (q, *J* = 39.0 Hz, $\underline{C}HCF_3$), 54.4 (NCH_2Ph), 124.3 (q, *J* = 269.9 Hz, CF_3), 127.2 (CH_{Ar}), 127.8 (2 x CH_{Ar}), 128.5 (2 x CH_{Ar}), 138.5 ($C_{q,Ar}$). **^{19}F NMR** (376 MHz, $CDCl_3$): δ -70.7 (3F, d, *J* = 5.0 Hz, CF_3). **IR** (ATR, cm^{-1}): ν_{max} 2930, 1140, 1352, 1283, 1139, 1122, 1088, 847, 731, 696, 694. **GC-MS** (EI) m/z (%): 214/215 (M^+, 15), 200 (15), 124 (M^+-CH_2Ph, 91), 91 ($C_7H_7^+$, 100), 65 (10), 51 (4), 41 (2). **HRMS** (ES-TOF) calcd for $C_{11}H_{13}F_3N$ 216.0995 $[M + H]^+$, found 216.1005.

***Trans*-1-cyclohexyl-2-methyl-3-(trifluoromethyl)aziridine 280b**



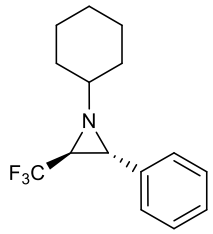
Yellow oil. Yield: 54%. R_f 0.06 (petroleum ether/diethyl ether 99:1). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.14-1.29 (3H, m, 3 x CH_{cHex}), 1.33 (3H, d, *J* = 6.0 Hz, CH_3), 1.36-1.47 (2H, m, 2 x CH_{cHex}), 1.59-1.64 (1H, m, CH_{cHex}), 1.70-1.85 (5H, m, $CHCF_3$, 4 x CH_{cHex}), 1.90-2.00 (1H, m, NCH_{cHex}), 2.42 (1H, br s, $C\underline{H}CH_3$). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 10.1 (CH_3), 24.4 (CH_2), 24.8 (CH_2), 25.8 (CH_2), 32.6 (CH_2), 33.1 (CH_2), 35.0 (q, *J* = 2.2 Hz, $\underline{C}HCH_3$), 42.1 (q, *J* = 38.9 Hz, $\underline{C}HCF_3$), 58.8 (NCH_{cHex}), 124.4 (q, *J* = 272.5 Hz, CF_3). **^{19}F NMR** (376 MHz, $CDCl_3$): δ -70.8 (3F, d, *J* = 5.3 Hz, CF_3). **IR** (ATR, cm^{-1}): ν_{max} 2931, 2858, 1449, 1283, 1256, 1139, 1123, 1090, 878, 844, 684. **GC-MS** (EI) m/z (%): 207 (M^+, 10), 192 (M^+-CH_3, 29), 178 (12), 164 (100), 126 (92), 106 (19), 82 (34), 67 (30), 55 (61), 41 (31). **HRMS** (ES-TOF) calcd for $C_{10}H_{17}F_3N$ 208.1308 $[M + H]^+$, found 208.1310.

***Trans*-1-benzyl-2-phenyl-3-(trifluoromethyl)aziridine 280c**



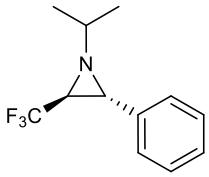
Yellow oil. Yield: 50%. R_f 0.08 (petroleum ether/diethyl ether 99:1). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.78 (1H, br s, $CHCF_3$), 3.24 (1H, br s, $NC\underline{H}_aH_b$), 3.51 (1H, br s, $NCH_a\underline{H}_b$), 3.67 (1H, br s, CHPh), 7.14-7.43 (10H, m, 10 x CH_{Ar}). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 41.6 (q, *J* = 39.3 Hz, $\underline{C}HCF_3$), 43.6 (CHPh), 55.3 (NCH_2Ph), 124.3 (q, *J* = 274.1 Hz, CF_3), 127.2 (2 x CH_{Ar}), 128.0 (CH_{Ar}), 128.3 (3 x CH_{Ar}), 128.5 (3 x CH_{Ar}), 130.1 (CH_{Ar}), 131.0 ($C_{q,Ar}$), 138.0 ($C_{q,Ar}$). **^{19}F NMR** (376 MHz, $CDCl_3$): δ -70.7 (3F, s, CF_3). **IR** (ATR, cm^{-1}): ν_{max} 3031, 1455, 1282, 1189, 1139, 1107, 852, 732, 696. **GC-MS** (EI) m/z (%): 277 (M^+, 33), 186 (M^+-CH_2Ph, 100), 172 (9), 159 (78), 109 (32), 91 ($C_7H_7^+$, 45), 77 (9), 65 (7), 51 (5). **HRMS** (ES-TOF) calcd for $C_{16}H_{15}F_3N$ 278.1157 $[M + H]^+$, found 278.1154.

***Trans*-1-cyclohexyl-2-phenyl-3-(trifluoromethyl)aziridine 280d**



Colourless crystals: mp 98-100 °C. Yield: 48%. R_f 0.05 (petroleum ether/diethyl ether 100:1). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.10-1.20 (3H, m, 3 x CH_{cHex}), 1.33-1.83 (8H, m, 8 x CH_{cHex}), 2.72 (1H, br s, $CHCF_3$), 3.54 (1H, br s, CHPh), 7.28-7.40 (5H, m, 5 x CH_{Ar}). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 24.1 (CH_2), 24.5 (CH_2), 25.8 (CH_2), 32.0 (CH_2), 32.5 (CH_2), 40.0 (br s, $\underline{C}HCF_3$), 43.1 (CHPh), 58.0 (NCH_{cHex}), 124.4 (q, *J* = 273.5 Hz, CF_3), 128.3 (5 x CH_{Ar}), 129.9 ($C_{q,Ar}$). **^{19}F NMR** (376 MHz, $CDCl_3$): δ -71.0 (3F, s, CF_3). **IR** (ATR, cm^{-1}): ν_{max} 2936, 2857, 1459, 1282, 1254, 1184, 1158, 1141, 1112, 1084, 865, 740, 700, 686. **GC-MS** (EI) m/z (%): 269 (M^+, 71), 226 (33), 186 (M^+-*c*Hex, 100), 172 (16), 159 (31), 118 (17), 109 (18), 91 ($C_7H_7^+$, 16), 83 (24), 55 (31), 41 (14). **HRMS** (ES-TOF) calcd for $C_{15}H_{19}F_3N$ 270.1464 $[M + H]^+$, found 270.1476.

***Trans*-1-isopropyl-2-phenyl-3-(trifluoromethyl)aziridine 280e**

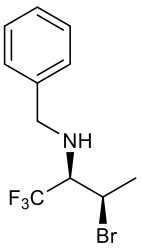


Yellow oil. Yield: 45%. R_f 0.06 (petroleum ether/diethyl ether 99:1). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.84 (3H, br s, $(C\underline{H}_3)CH(CH_3)$), 1.15 (3H, d, *J* = 6.3 Hz, $(CH_3)CH(C\underline{H}_3)$), 2.0 (1H, br s, $NC\underline{H}(CH_3)_2$), 2.67-2.75 (1H, m, $CHCF_3$), 3.56 (1 H, br s, CHPh), 7.29-7.38 (5H, m, 5 x CH_{Ar}). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.5 ($(\underline{C}H_3)CH(CH_3)$), 22.3 ($(CH_3)CH(\underline{C}H_3)$), 40.4 (br signal, $\underline{C}HCF_3$), 43.6 (CHPh), 50.6 ($N\underline{C}H(CH_3)_2$), 124.4 (q, *J* = 273.5 Hz, CF_3), 128.4 (3 x CH_{Ar}), 128.5 (CH_{Ar}), 130.0 (CH_{Ar}), 131.0 ($C_{q,Ar}$). **^{19}F NMR** (376 MHz, $CDCl_3$): δ -71.0 (3F, s, CF_3). **IR** (ATR, cm^{-1}): ν_{max} 2972, 1461, 1442, 1344, 1283, 1256, 1193, 1130, 1084, 997, 868, 840, 762, 730, 698, 685. **GC-MS** (EI) m/z (%): 229 (M^+, 90), 186 (M^+-*i*Pr, 87), 159 (100), 118 (23), 109 (43), 91 ($C_7H_7^+$, 17), 77 (8), 51 (7), 41 (8). **HRMS** (ES-TOF) calcd for $C_{12}H_{15}F_3N$ 230.1151 $[M + H]^+$, found 230.1150.

5.2.20 *Synthesis of syn-* and *anti*-β-bromoamines 284 and 285

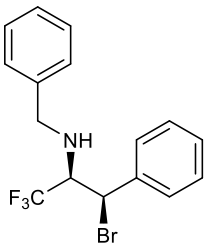
As a representative example, the synthesis of *syn*-*N*-benzyl-3-bromo-1,1,1-trifluorobutan-2-amine **284a** is described. To an ice-cooled solution of *cis*-1-benzyl-2-methyl-3-(trifluoromethyl)aziridine **270a** (0.5 mmol, 1.0 equiv) in acetonitrile (0.6 mL) was added hydrogen bromide (2.5 mmol, 5.0 equiv, 48% in water). The cooling bath was removed and the mixture was stirred for one hour at room temperature. The reaction mixture was poured in diethyl ether (2 mL) and neutralized with saturated sodium bicarbonate at 0 °C. The aqueous layer was extracted with diethyl ether (3 x 10 mL), dried over K_2CO_3 and concentrated *in vacuo,* affording pure *syn*-*N*-benzyl-3-bromo-1,1,1-trifluorobutan-2-amine **284a** without extra purification steps (purity >93%, ^{19}F NMR).

***Syn-N*-benzyl-3-bromo-1,1,1-trifluorobutan-2-amine 284a**



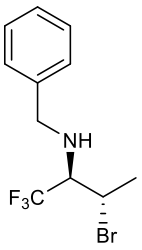
Yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.75 (3H, d, *J* = 6.8 Hz, CH_3), 1.98 (1H, br s, NH), 3.01-3.11 (1H, m, $CHCF_3$), 3.92 (1H, d x d, *J* = 5.1, 13.1 Hz, $NC\underline{H}_aH_b$), 4.09 (1H, d x d, *J* = 3.3, 13.1 Hz, $NCH_a\underline{H}_b$), 4.48 (1H, q x d, *J* = 2.6, 6.8 Hz, CHBr), 7.27-7.40 (5H, m, 5 x CH_{Ar}). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 24.1 (CH_3), 46.4 (q, *J* = 2.6 Hz, $\underline{C}$HBr), 51.7 (NCH_2Ph), 62.3 (q, *J* = 26.8 Hz, $\underline{C}HCF_3$), 125.6 (q, *J* = 287.5 Hz, CF_3), 127.5 (CH_{Ar}), 128.46 (2 x CH_{Ar}), 128.52 (2 x CH_{Ar}), 139.1 ($C_{q,Ar}$). **^{19}F NMR** (376 MHz, $CDCl_3$): δ -70.5 (3F, d, *J* = 6.9 Hz, CF_3). **IR** (ATR, cm^{-1}): ν_{NH} 2924; ν_{max} 2868, 1466, 1454, 1264, 1150, 1128, 1077, 958, 846, 745, 714, 698. **MS** (ES+): m/z 296/298 (M+1, 100). **HRMS** (ES-TOF) calcd for $C_{11}H_{14}BrF_3N$ 296.0256 $[M + H]^+$, found 296.0262.

***Syn-N*-benzyl-3-bromo-1,1,1-trifluoro-3-phenylpropan-2-amine 284c**



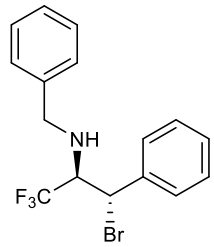
Orange oil. Yield: 82%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.21 (1H, br s, NH), 3.47-3.56 (1H, m, $CHCF_3$), 3.92 (1H, d, *J* = 12.9 Hz, $NC\underline{H}_aH_b$), 4.13 (1H, d, *J* = 12.9 Hz, $NCH_a\underline{H}_b$), 5.35 (1H, d, *J* = 3.7 Hz, CHBr), 7.29-7.47 (8H, m, 8 x CH_{Ar}), 7.58-7.64 (2H, m, 2 x CH_{Ar}). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 51.7 (q, *J* = 2.4 Hz, CHBr), 52.1 (NCH_2Ph), 64.3 (q, *J* = 26.6 Hz, $\underline{C}HCF_3$), 125.3 (q, *J* = 287.8 Hz, CF_3), 127.3 (CH_{Ar}), 128.27 (2 x CH_{Ar}), 128.33 (2 x CH_{Ar}), 128.36 (2 x CH_{Ar}), 128.41 (2 x CH_{Ar}), 128.7 (CH_{Ar}), 138.8 ($C_{q,Ar}$), 139.0 ($C_{q,Ar}$). **^{19}F NMR** (376 MHz, $CDCl_3$): δ -70.4 (3F, d, *J* = 6.9 Hz, CF_3). **IR** (ATR, cm^{-1}): ν_{NH} 3031; ν_{max} 1454, 1251, 1202, 1144, 1118, 1078, 1029, 820, 766, 744, 694, 626. **MS** (ES+): m/z 358/360 (M+1, 100). **HRMS** (ES-TOF) calcd for $C_{16}H_{16}BrF_3N$ 358.0413 $[M + H]^+$, found 358.0424.

***Anti-N*-benzyl-3-bromo-1,1,1-trifluorobutan-2-amine 285a**



Colourless oil. Yield 86%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.72 (3H, d x q, *J* = 0.9, 7.0 Hz, CH_3), 1.75 (1H, br s, NH), 3.49 (1H, ~quintet x d, *J* = 2.9, 7.5 Hz, $CHCF_3$), 3.95 (1H, d x d, *J* = 5.8, 12.9 Hz, $NC\underline{H}_aH_b$), 4.09 (1H, d x d, *J* = 5.8, 12.9 Hz, $NCH_a\underline{H}_b$), 4.48 (1H, q x d, *J* = 2.9, 7.0 Hz, CHBr), 7.26-7.43 (5H, m, 5 x CH_{Ar}). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 20.5-20.6 (m, CH_3), 45.7 (q, *J* = 1.8 Hz, CHBr), 53.4 (NCH_2Ph), 64.1 (q, *J* = 26.7 Hz, $\underline{C}HCF_3$), 125.4 (q, *J* = 286.2 Hz, CF_3), 127.5 (CH_{Ar}), 128.47 (2 x CH_{Ar}), 128.50 (2 x CH_{Ar}), 139.0 ($C_{q,Ar}$). **^{19}F NMR** (376 MHz, $CDCl_3$): δ -70.5 (3F, d, *J* = 7.5 Hz, CF_3). **IR** (ATR, cm^{-1}): ν_{NH} 2927; ν_{max} 2856, 1473, 1454, 1330, 1252, 1138, 1092, 1029, 744, 698. **MS** (ES+): m/z 296/298 (M+1, 100). **HRMS** (ES-TOF) calcd for $C_{11}H_{14}BrF_3N$ 296.0256 $[M + H]^+$, found 296.0270.

***Anti*-*N*-benzyl-3-bromo-1,1,1-trifluoro-3-phenylpropan-2-amine 285c**

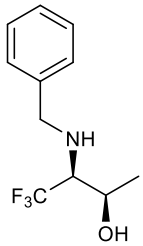


Yellow oil. Yield: 82%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.81 (1H, br s, NH), 3.73-3.82 (1H, m, $CHCF_3$), 3.92 (1H, d, *J* = 13.0 Hz, $NC\underline{H}_aH_b$), 4.08 (1H, d, *J* = 13.0 Hz, $NCH_a\underline{H}_b$), 5.24 (1H, d, *J* = 4.5 Hz, CHBr), 7.27-7.49 (10H, m, 10 x CH_{Ar}). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 49.1-49.2 (m, CHBr), 53.1 (NCH_2Ph), 65.2 (q, *J* = 26.2 Hz, $\underline{C}HCF_3$), 125.3 (q, *J* = 286.9 Hz, CF_3), 127.4 (CH_{Ar}), 128.4 (6 x CH_{Ar}), 128.9 (3 x CH_{Ar}), 136.8 ($C_{q,Ar}$), 139.0 ($C_{q,Ar}$). **^{19}F NMR** (376 MHz, $CDCl_3$): δ -70.1 (3F, d, *J* = 7.0 Hz, CF_3). **IR** (ATR, cm^{-1}): ν_{NH} 3031; ν_{max} 2926, 1471, 1454, 1339, 1249, 1152, 1120, 1029, 733, 696, 659.

5.2.21 Synthesis of *syn*- and *anti*-benzylamino alcohols 286 and 287

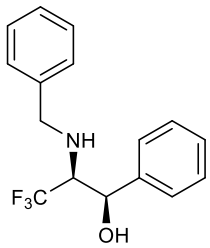
As a representative example, the synthesis of *syn*-3-benzylamino-4,4,4-trifluorobutan-2-ol **286a** is described. To an ice-cooled solution of *cis*-1-benzyl-2-methyl-3-(trifluoromethyl)aziridine **270a** (0.5 mmol, 1.0 equiv) in acetonitrile (0.5 mL) and water (0.5 mL) were added four drops of sulphuric acid. The mixture was stirred for one hour under reflux conditions, and after cooling down the reaction mixture was neutralized with saturated sodium bicarbonate and extracted with ethyl acetate (3 x 5 mL). The combined organic phases were washed with brine (2 x 5 mL), dried over K_2CO_3 and concentrated *in vacuo,* yielding *syn*-3-benzylamino-4,4,4-trifluorobutan-2-ol **286a** without the need for extra purification steps (purity >95%, ^{19}F NMR).

***Syn*-3-benzylamino-4,4,4-trifluorobutan-2-ol 286a**



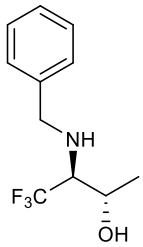
Orange oil. Yield: 89%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.27 (3H, d x q, *J* = 1.0, 6.0 Hz, CH_3), 1.81 (1H, br s, NH), 2.87 (1H, q x d, *J* = 6.0, 7.7 Hz, $CHCF_3$), 2.90 (1H, br s, OH), 3.86 (1H, d, *J* = 12.7 Hz, $NC\underline{H}_aH_b$), 3.89 (1H, ~quintet, *J* = 6.0 Hz, $C\underline{H}OH$), 4.13 (1H, d, *J* = 12.7 Hz, $NCH_a\underline{H}_b$), 7.27-7.37 (5H, m, 5 x CH_{Ar}). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 20.3 (CH_3), 52.6 (NCH_2Ph), 63.6 (q, *J* = 25.5 Hz, $\underline{C}HCF_3$), 64.7 (q, *J* = 7.8 Hz, CHOH), 126.7 (q, *J* = 285.8 Hz, CF_3), 127.6 (CH_{Ar}), 128.5 (2 x CH_{Ar}), 128.6 (2 x CH_{Ar}), 139.1 ($C_{q,Ar}$). **^{19}F NMR** (376 MHz, $CDCl_3$): δ -70.9 (3F, d, *J* = 7.7 Hz, CF_3). **IR** (ATR, cm^{-1}): ν_{NH} 3066; ν_{OH} 3366; ν_{max} 1454, 1376, 1261, 1132, 1072, 886, 869, 743, 716, 698. **MS** (ES+): m/z 234 (M+1, 100). **HRMS** (ES-TOF) calcd for $C_{11}H_{15}F_3NO$ 234.1100 $[M + H]^+$, found 234.1103.

***Syn*-2-benzylamino-3,3,3-trifluoro-1-phenylpropan-1-ol 286c**



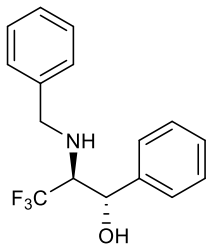
Colourless crystals: mp 66-70 °C. Yield: 95%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.02 (1H, br s, NH), 3.66 (1H, q x d, *J* = 4.8, 7.6 Hz, $CHCF_3$), 3.34 (1H, br s, OH), 3.70 (1H, d, *J* = 12.9 Hz, NCH_aH_b), 3.92 (1H, d, *J* = 12.9 Hz, NCH_aH_b), 4.87 (1H, d, *J* = 4.8 Hz, CHOH), 7.14-7.18 (2H, m, 2 x CH_{Ar}), 7.23-7.39 (8H, m, 8 x CH_{Ar}). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 52.5 (NCH_2), 63.9 (q, *J* = 25.7 Hz, $CHCF_3$), 70.2 (q, *J* = 2.2 Hz, CHOH), 126.26 (q, *J* = 285.3 Hz, CF_3), 126.30 (2 x CH_{Ar}), 127.4 (CH_{Ar}), 128.0 (CH_{Ar}), 128.3 (2 x CH_{Ar}), 128.4 (2 x CH_{Ar}), 128.5 (2 x CH_{Ar}), 138.7 ($C_{q,Ar}$), 140.8 ($C_{q,Ar}$). **^{19}F NMR** (376 MHz, $CDCl_3$): δ -71.2 (3F, d, *J* = 7.6 Hz, CF_3). **IR** (ATR, cm^{-1}): ν_{OH} 3216; ν_{NH} 3318; ν_{max} 1494, 1476, 1454, 1371, 1352, 1272, 1229, 1195, 1152, 1129, 1103, 932, 863, 846, 748, 706, 698, 660. **MS** (ES+): m/z 296 (M+1, 100). **HRMS** (ES-TOF) calcd for $C_{16}H_{17}F_3NO$ 296.1257 $[M + H]^+$, found 296.1268.

***Anti*-3-benzylamino-4,4,4-trifluorobutan-2-ol 287a**



Colourless crystals: mp 39-41 °C. Yield: 83%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.16 (3H, d x q, *J* = 1.1, 6.5 Hz, CH_3), 1.64 (1H, br s, NH), 2.61 (1H, br s, OH), 3.28 (1H, q x d, *J* = 4.2, 7.9 Hz, $CHCF_3$), 3.83 (1H, d, *J* = 12.8 Hz, NCH_aH_b), 3.97-4.07 (1H, m, CHOH), 4.12 (1H, d, *J* = 12.8 Hz, NCH_aH_b), 7.28-7.38 (5H, m, 5 x CH_{Ar}). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 17.9 (q, *J* = 1.2 Hz, CH_3), 52.6 (NCH_2), 62.5 (q, *J* = 25.8 Hz, $CHCF_3$), 64.6 (q, *J* = 2.1 Hz, CHOH), 126.5 (q, *J* = 285.7 Hz, CF_3), 127.6 (CH_{Ar}), 128.4 (2 x CH_{Ar}), 128.6 (2 x CH_{Ar}), 139.0 ($C_{q,Ar}$). **^{19}F NMR** (376 MHz, $CDCl_3$): δ -70.2 (3F, d, *J* = 7.9 Hz, CF_3). **IR** (ATR, cm^{-1}): ν_{NH} 3276; ν_{OH} 3168; ν_{max} 2360, 2340, 1455, 1389, 1269, 1229, 1163, 1140, 1124, 1092, 1070, 1058, 1018, 962, 927, 895, 853, 752, 698. **MS** (ES+): m/z 234 (M+1, 100). **HRMS** (ES-TOF) calcd for $C_{11}H_{15}F_3NO$ 234.1100 $[M + H]^+$, found 234.1104.

***Anti*-2-benzylamino-3,3,3-trifluoro-1-phenylpropan-1-ol 287c**

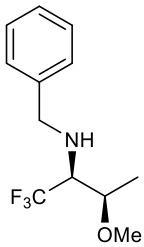


Colourless oil. Yield: 89%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.53 (1H, br s, NH), 3.23 (1H, d, *J* = 7.3 Hz, OH), 3.46 (1H, q x d, *J* = 5.4, 7.5 Hz, $CHCF_3$), 3.74 (1H, d, *J* = 13.0 Hz, NCH_aH_b), 3.99 (1H, d, *J* = 13.0 Hz, NCH_aH_b), 4.88 (1H, d x d, *J* = 5.4, 7.3 Hz, CHOH), 7.19-7.36 (10H, m, 10 x CH_{Ar}). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 52.3 (NCH_2Ph), 63.2 (q, *J* = 25.8 Hz, $CHCF_3$), 71.3 (q, *J* = 2.2 Hz, CHOH), 126.0 (q, *J* = 285.3 Hz, CF_3), 126.9 (2 x CH_{Ar}), 127.5 (CH_{Ar}), 128.32 (2 x CH_{Ar}), 128.34 (CH_{Ar}), 128.4 (2 x CH_{Ar}), 128.6 (2 x CH_{Ar}), 138.9 ($C_{q,Ar}$), 139.2 ($C_{q,Ar}$). **^{19}F NMR** (376 MHz, $CDCl_3$): δ -69.6 (3F, d, *J* = 7.5 Hz, CF_3). **IR** (ATR, cm^{-1}): ν_{OH} 3360; ν_{NH} 3032; ν_{max} 1495, 1454, 1376, 1347, 1256, 1153, 1122, 1081, 1041, 1028, 876, 735, 697. **MS** (ES+): m/z 296 (M+1, 100). **HRMS** (ES-TOF) calcd for $C_{16}H_{17}F_3NO$ 296.1257 $[M + H]^+$, found 296.1262.

5.2.22 Synthesis of *syn*- and *anti*-amino ethers 288 and 289

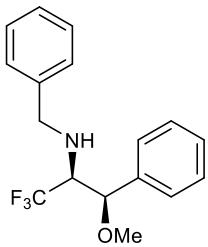
As a representative example, the synthesis of *syn*-*N*-benzyl-1,1,1-trifluoro-3-methoxybutan-2-amine **288a** is described. To an ice-cooled solution of *cis*-1-benzyl-2-methyl-3-(trifluoromethyl)aziridine **270a** (0.5 mmol, 1.0 equiv) in acetonitrile (0.5 mL) and methanol (0.5 mL) were added four drops of sulphuric acid. The mixture was stirred for one hour under reflux conditions, and after cooling down the reaction mixture was neutralized with saturated sodium bicarbonate and extracted with ethyl acetate (3 x 5 mL). The combined organic phases were washed with brine (2 x 5 mL), dried over K_2CO_3 and concentrated *in vacuo*. The crude mixture was purified by column chromatography over silica to yield pure *syn*-*N*-benzyl-1,1,1-trifluoro-3-methoxybutan-2-amine **288a.**

***Syn*-*N*-benzyl-1,1,1-trifluoro-3-methoxybutan-2-amine 288a**



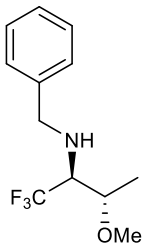
Yellow oil. Yield: 50%. R_f 0.17 (petroleum ether/diethyl ether 98:2). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.21 (3H, d, *J* = 6.3 Hz, $CHC\underline{H}_3$), 2.00 (1H, br s, NH), 2.89 (1H, q x d, *J* = 2.9, 7.7 Hz, $CHCF_3$), 3.31 (3H, s, OCH_3), 3.61 (1H, q x d, *J* = 2.9, 6.3 Hz, $C\underline{H}OCH_3$), 3.85 (1H, d, *J* = 13.2 Hz, $NC\underline{H}_aH_b$), 4.06 (1H, d, *J* = 13.2 Hz, $NCH_a\underline{H}_b$), 7.22-7.38 (5H, m, 5 x CH_{Ar}). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 16.5 (CH_3), 52.4 (NCH_2), 56.8 (OCH_3), 62.3 (q, *J* = 25.9 Hz, $\underline{C}HCF_3$), 74.3 (q, *J* = 2.3 Hz, $\underline{C}HOCH_3$), 126.6 (q, *J* = 286.2 Hz, CF_3), 127.2 (CH_{Ar}), 128.36 (2 x CH_{Ar}), 128.42 (2 x CH_{Ar}), 139.8 ($C_{q,Ar}$). **^{19}F NMR** (376 MHz, $CDCl_3$): δ -71.1 (3F, d, *J* = 7.7 Hz, CF_3). **IR** (ATR, cm^{-1}): ν_{NH} 3370; ν_{max} 2934, 1467, 1454, 1374, 1263, 1195, 1151, 1129, 1097, 1051, 849, 743, 719, 698. **MS** (ES+): m/z 248 (M+1, 100). **HRMS** (ES-TOF) calcd for $C_{12}H_{17}F_3NO$ 248.1257 $[M + H]^+$, found 248.1263.

***Syn*-*N*-benzyl-1,1,1-trifluoro-3-methoxy-3-phenylpropan-2-amine 288c**



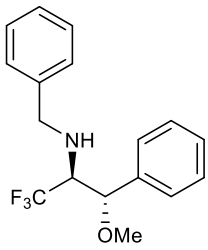
Colourless oil. Yield: 75%. R_f 0.12 (petroleum ether /diethyl ether 98:2). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.18 (1H, br s, NH), 3.13 (1H, m, $CHCF_3$), 3.30 (3H, s, OCH_3), 3.61 (1H, d, *J* = 13.0 Hz, $NC\underline{H}_aH_b$), 3.78 (1H, d, *J* = 13.0 Hz, $NCH_a\underline{H}_b$), 4.52 (1H, d, *J* = 3.0 Hz, $C\underline{H}OCH_3$), 7.02-7.07 (2H, m, 2 x CH_{Ar}), 7.17-7.21 (3H, m, 3 x CH_{Ar}), 7.31-7.42 (5H, m, 5 x CH_{Ar}). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 52.4 (NCH_2), 57.4 (OCH_3), 63.6 (q, *J* = 26.1 Hz, $\underline{C}HCF_3$), 80.1 (q, *J* = 2.4 Hz, $\underline{C}HOCH_3$), 126.2 (q, *J* = 285.9 Hz, CF_3), 126.9 (2 x CH_{Ar}), 127.0 (CH_{Ar}), 128.1 (CH_{Ar}), 128.2 (4 x CH_{Ar}), 128.4 (2 x CH_{Ar}), 138.5 ($C_{q,Ar}$), 139.6 ($C_{q,Ar}$). **^{19}F NMR** (376 MHz, $CDCl_3$): δ -71.5 (3F, d, *J* = 7.8 Hz, CF_3). **IR** (ATR, cm^{-1}): ν_{NH} 3370; ν_{max} 2936, 2889, 1454, 1259, 1202, 1122, 1102, 1076, 1028, 820, 742, 697. **MS** (ES+): m/z 310 (M+1, 100). **HRMS** (ES-TOF) calcd for $C_{17}H_{19}F_3NO$ 310.1413 $[M + H]^+$, found 310.1419.

***Anti-N*-benzyl-1,1,1-trifluoro-3-methoxybutan-2-amine 289a**



Yellow oil. Yield: 52%. R_f 0.08 (petroleum ether/diethyl ether 98:2). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.27 (3H, d x q, *J* = 0.9, 6.4 Hz, CHC$\underline{H}_3$), 1.71 (1H, br s, NH), 3.21 (3H, s, OCH_3), 3.30 (1H, q x d, *J* = 3.8, 7.9 Hz, $CHCF_3$), 3.60 (1H, q x d, *J* = 3.8, 6.4 Hz, C$\underline{H}OCH_3$), 3.87 (1H, d, *J* = 13.3 Hz, NC$\underline{H}_a$H$_b$), 4.02 (1H, d, *J* = 13.3 Hz, NCH$_a\underline{H}_b$), 7.23-7.37 (5H, m, 5 x CH_{Ar}). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.8 (q, *J* = 1.4 Hz, CH_3), 52.6 (NCH_2), 56.7 (OCH_3), 60.1 (q, *J* = 25.9 Hz, $\underline{C}HCF_3$), 75.2 (q, *J* = 2.2 Hz, $\underline{C}HOCH_3$), 126.3 (q, *J* = 284.0 Hz, CF_3), 127.3 (CH_{Ar}), 128.4 (2 x CH_{Ar}), 128.5 (2 x CH_{Ar}), 139.6 ($C_{q,Ar}$). **^{19}F NMR** (376 MHz, $CDCl_3$): δ -70.5 (3F, d, *J* = 7.9 Hz, CF_3). **IR** (ATR, cm^{-1}): ν_{NH} 3351; ν_{max} 2933, 1454, 1383, 1257, 1139, 1089, 1044, 1029, 848, 739, 698. **MS** (ES+): m/z 248 (M+1, 100). **HRMS** (ES-TOF) calcd for $C_{12}H_{17}F_3NO$ 248.1257 $[M + H]^+$, found 248.1265.

***Anti-N*-benzyl-1,1,1-trifluoro-3-methoxy-3-phenylpropan-2-amine 289c**

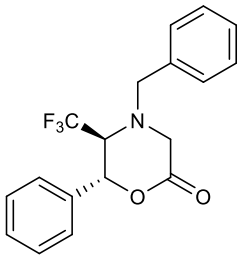


Yellow crystals: mp 40-42 °C. Yield: 78%. R_f 0.12 (petroleum ether/diethyl ether 98:2). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.32 (1H, br s, NH), 3.22 (3H, s, OCH_3), 3.39 (1H, m, $CHCF_3$), 3.68 (1H, d, *J* = 13.4 Hz, NC$\underline{H}_a$H$_b$), 3.86 (1H, d, *J* = 13.4 Hz, NCH$_a\underline{H}_b$), 4.36 (1H, d, *J* = 6.3 Hz, C$\underline{H}OCH_3$), 7.04-7.08 (2H, m, 2 x CH_{Ar}), 7.15-7.25 (3H, m, 3 x CH_{Ar}), 7.28-7.41 (5H, m, 5 x CH_{Ar}). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 52.8 (NCH_2), 57.1 (OCH_3), 62.9 (q, *J* = 26.1 Hz, $\underline{C}HCF_3$), 82.5 (q, *J* = 1.5 Hz, $\underline{C}HOCH_3$), 126.2 (q, *J* = 284.3 Hz, CF_3), 127.1 (CH_{Ar}), 127.9 (2 x CH_{Ar}), 128.2 (2 x CH_{Ar}), 128.3 (2 x CH_{Ar}), 128.5 (2 x CH_{Ar}), 128.6 (CH_{Ar}), 137.1 ($C_{q,Ar}$), 139.3 ($C_{q,Ar}$). **^{19}F NMR** (376 MHz, $CDCl_3$): δ -70.8 (3F, d, *J* = 7.2 Hz, CF_3). **IR** (ATR, cm^{-1}): ν_{NH} 3346; ν_{max} 2943, 1468, 1456, 1436, 1381, 1354, 1336, 1261, 1188, 1159, 1149, 1128, 1110, 1092, 1076, 955, 827, 756, 699, 679. **MS** (ES+): m/z 310 (M+1, 100). **HRMS** (ES-TOF) calcd for $C_{17}H_{19}F_3NO$ 310.1413 $[M + H]^+$, found 310.1417. **Anal.** Calcd. for $C_{17}H_{18}F_3NO$: C: 66.01; H: 5.87; N: 4.53. Found: C: 66.22; H: 5.71; N: 4.54.

5.2.23 Synthesis of *trans*- and *cis*-4-benzyl-6-phenyl-5-(trifluoromethyl)morpholin-2-ones 290 and 291

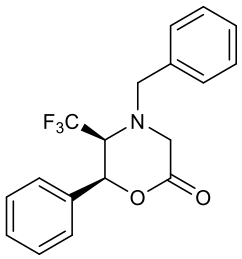
As a representative example, the synthesis of *trans*-4-benzyl-6-phenyl-5-(trifluoromethyl)morpholin-2-one **290** is described. To a stirred solution of *syn*-2-benzylamino-3,3,3-trifluoro-1-phenylpropan-1-ol **286c** (0.2 mmol, 1 equiv) in tetrahydrofuran (0.6 mL) was added glyoxal (0.6 mmol, 3 equiv, 40% in water) and the resulting mixture was heated under reflux for 24 hours. After cooling down, the reaction mixture was poured in water (3 mL) and extracted with diethyl ether (3 x 5 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel to yield *trans*-4-benzyl-6-phenyl-5-(trifluoromethyl)morpholin-2-one **290**.

***Trans*-4-benzyl-6-phenyl-5-(trifluoromethyl)morpholin-2-one 290**



Colourless crystals: mp 88-93 °C. Yield: 18%. R_f 0.27 (petroleum ether/diethyl ether 4:1). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.51 (1H, q x d, *J* = 3.7, 7.9 Hz, $CHCF_3$), 3.61 (1H, d x q, *J* = 1.6, 18.0 Hz, NCH_aH_bPh), 3.75 (1H, d x q, 1.6, 18.0 Hz, NCH_aH_bPh), 3.86 (1H, d, *J* = 13.3 Hz, $NCH_aH_bC{=}O$), 3.90 (1H, d, *J* = 13.3 Hz, $NCH_aH_bC{=}O$), 5.62 (1H, d, *J* = 3.7 Hz, OCH), 6.98-7.03 (2H, m, 2 x CH_{Ar}), 7.19-7.31 (5H, m, 5 x CH_{Ar}), 7.40-7.45 (3H, m, 3 x CH_{Ar}). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 49.3 (NCH_2Ph), 59.7 ($NCH_2C{=}O$), 61.4 (q, *J* = 26.5 Hz, $CHCF_3$), 77.6 (OCH), 126.0 (q, *J* = 289.8 Hz, CF_3), 126.2 (2 x CH_{Ar}), 128.1 (CH_{Ar}), 128.7 (2 x CH_{Ar}), 128.8 (2 x CH_{Ar}), 128.9 (2 x CH_{Ar}), 129.0 (CH_{Ar}), 135.8 ($C_{q,Ar}$), 137.3 ($C_{q,Ar}$), 167.2 (C=O). **^{19}F NMR** (376 MHz, $CDCl_3$): δ -68.8 (3F, d, *J* = 7.9 Hz, CF_3). **IR** (ATR, cm^{-1}): $\nu_{C=O}$ 1763; ν_{max} 2923, 1456, 1308, 1272, 1258, 1241, 1225, 1183, 1167, 1128, 1100, 1014, 862, 764, 736, 697. **MS** (ES+): m/z 336 (M+1, 100). **HRMS** (ES-TOF) calcd for $C_{18}H_{17}F_3NO_2$ 336.1206 $[M + H]^+$, found 336.1222.

***Cis*-4-benzyl-6-phenyl-5-(trifluoromethyl)morpholin-2-one 291**

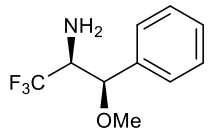


Colourless crystals: mp 157-163 °C. Yield: 38%. R_f 0.08 (petroleum ether/diethyl ether 4:1). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.70 (1H, q x d, *J* = 3.7, 8.0 Hz, $CHCF_3$), 3.71-3.74 (2H, m, NCH_2Ph), 4.00 (1H, d, *J* = 13.4 Hz, $NCH_aH_bC{=}O$), 4.08 (1H, d, *J* = 13.4 Hz, $NCH_aH_bC{=}O$), 5.80-5.84 (1H, m, OCH), 7.30-7.43 (10H, m, 10 x CH_{Ar}). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 49.4 (NCH_2Ph), 59.5 (d, *J* = 1.5 Hz, $NCH_2C{=}O$), 60.7 (q, *J* = 24.9 Hz, $CHCF_3$), 79.2 (OCH), 125.568 (2 x CH_{Ar}), 125.573 (q, *J* = 291.5 Hz, CF_3), 128.3 (CH_{Ar}), 128.5 (2 x CH_{Ar}), 128.65 (CH_{Ar}), 128.72 (2 x CH_{Ar}), 128.9 (2 x CH_{Ar}), 133.7 ($C_{q,Ar}$), 135.8 ($C_{q,Ar}$), 166.8 (C=O). **^{19}F NMR** (376 MHz, $CDCl_3$): δ -62.8 (3F, d, *J* = 7.9 Hz, CF_3). **IR** (ATR, cm^{-1}): $\nu_{C=O}$ 1739; ν_{max} 2958, 1454, 1405, 1367, 1320, 1268, 1246, 1170, 1147, 1126, 1095, 1064, 871, 743, 734, 699. **MS** (ES+): m/z 336 (M+1, 100). **HRMS** (ES-TOF) calcd for $C_{18}H_{17}F_3NO_2$ 336.1206 $[M + H]^+$, found 336.1202.

5.2.24 Synthesis of *syn*- and *anti*-1,1,1-trifluoro-3-methoxy-3-phenylpropan-2-amines 292 and 293

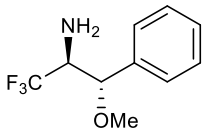
As a representative example, the synthesis of *syn*-1,1,1-trifluoro-3-methoxy-3-phenylpropan-2-amine **292** is described. Hydrogen gas was bubbled through a stirred solution of *syn*-*N*-benzyl-1,1,1-trifluoro-3-methoxy-3-phenylpropan-2-amine **288c** (0.1 mmol, 1 equiv) and $Pd(OH)_2/C$ (20%w/w) in methanol (1 mL) for 16 hours. After filtering off the solids and evaporation of the solvent, pure *syn*-*N*-benzyl-1,1,1-trifluoro-3-methoxy-3-phenylpropan-2-amine **292** was obtained (purity >90%, ^{19}F NMR).

***Syn-N*-benzyl-1,1,1-trifluoro-3-methoxy-3-phenylpropan-2-amine 292**



Colourless crystals. Yield: 76%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.20 (2H, br s, NH_2), 3.29-3.38 (1H, m, $CHCF_3$), 3.31 (3H, s, OCH_3), 4.51 (1H, d, *J* = 3.2 Hz, C<u>H</u>OCH_3), 7.32-7.43 (5H, m, 5 x CH_{Ar}). **^{19}F NMR** (376 MHz, $CDCl_3$): δ -74.3 (3F, br s, CF_3). **IR** (ATR, cm^{-1}): ν_{NH} 3401; ν_{max} 2934, 1259, 1152, 1123, 1102, 1076, 760, 702, 623. **MS** (ES+): m/z 220 (M+1, 100). **HRMS** (ES-TOF) calcd for $C_{10}H_{13}F_3NO$ 220.0944 $[M + H]^+$, found 220.0940.

***Anti*-1,1,1-trifluoro-3-methoxy-3-phenylpropan-2-amine 293**

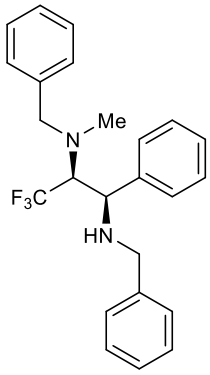


Yellow oil. Yield: 91%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.60 (2H, br s, NH_2), 3.25 (3H, s, OCH_3), 3.60 (1H, q x d, *J* = 5.9, 7.5 Hz, $CHCF_3$), 4.38 (1H, d, *J* = 5.9 Hz, C<u>H</u>OCH_3), 7.33-7.43 (5H, m, 5 x CH_{Ar}). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 57.0 (OCH_3), 58.1 (q, *J* = 27.3 Hz, <u>C</u>HCF_3), 82.0 (q, *J* = 1.5 Hz, <u>C</u>$HOCH_3$), 125.6 (q, *J* = 282.0 Hz, CF_3), 127.9 (2 x CH_{Ar}), 128.6 (2 x CH_{Ar}), 128.7 (CH_{Ar}), 136.5 ($C_{q,Ar}$). **^{19}F NMR** (376 MHz, $CDCl_3$): δ -73.4 (3F, d, *J* = 7.5 Hz, CF_3). **IR** (ATR, cm^{-1}): ν_{NH} 3392; ν_{max} 2945, 2086, 1260, 1185, 1137, 1090, 759, 698. **MS** (ES+): m/z 220 (M+1, 100). **HRMS** (ES-TOF) calcd for $C_{10}H_{13}F_3NO$ 220.0944 $[M + H]^+$, found 220.0941.

5.2.25 Synthesis of *syn*- and *anti*-N^1,N^3-dibenzyl-3,3,3-trifluoro-N^3-methyl-1-phenylpropane-1,2-diamine 296 and 299

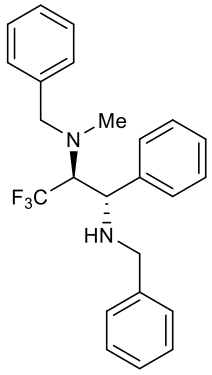
As a representative example, the synthesis of *syn*-N^1,N^3-dibenzyl-3,3,3-trifluoro-N^3-methyl-1-phenylpropane-1,2-diamine **296** is described. To a stirred solution of c*is*-1-benzyl-2-phenyl-3-(trifluoromethyl)aziridine **270c** (0.4 mmol, 1 equiv) in dry acetonitrile (1 mL) was added trimethyloxonium tetrafluoroborate (0.8 mmol, 2 equiv) at 0 °C. The reaction mixture was kept at this temperature for one hour and benzylamine (0.8 mmol, 2 equiv) was added. After stirring for two hours at room temperature, the reaction mixture was quenched by careful addition of water (2 mL) and extracted with diethyl ether (3 x 5 mL). The combined organic phases were washed with brine (5 mL), dried over K_2CO_3 and concentrated *in vacuo*. The crude mixture was purified by column chromatography on silica gel yielding *syn*-N^1,N^3-dibenzyl-3,3,3-trifluoro-N^3-methyl-1-phenylpropane-1,2-diamine **296**.

***Syn*-N^1,N^3-dibenzyl-3,3,3-trifluoro-N^3-methyl-1-phenylpropane-1,2-diamine 296**



Yellow oil. Yield: 36%. R_f 0.12 (petroleum ether/diethyl ether 95:5). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.28 (3H, br s, NCH_3), 3.06 (1H, br s, NH), 3.38 (1H, d, *J* = 13.4 Hz, $N^1C\underline{H}_aH_b$), 3.38-3.50 (1H, m, $CHCF_3$), 3.66 (1H, d, *J* = 13.4 Hz, $N^1CH_a\underline{H}_b$), 3.88 (1H, d, *J* = 13.5 Hz, $N^3C\underline{H}_aH_b$), 3.85 (1H, d, *J* = 10.0 Hz, CHPh), 3.94 (1H, d, *J* = 13.5 Hz, $N^3CH_a\underline{H}_b$), 7.16-7.44 (15H, m, 15 x CH_{Ar}). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 36.1 (CH_3), 50.4 (N^1CH_2), 58.9 (N^3CH_2), 59.8 (CHPh), 70.3 (q, *J* = 22.9 Hz, $\underline{C}HCF_3$), 126.8 (q, *J* = 293.9 Hz, CF_3), 127.1 (CH_{Ar}), 127.4 (CH_{Ar}), 128.0 (CH_{Ar}), 128.3 (2 x CH_{Ar}), 128.4 (2 x CH_{Ar}), 128.45 (2 x CH_{Ar}), 128.53 (2 x CH_{Ar}), 128.7 (2 x CH_{Ar}), 129.0 (2 x CH_{Ar}), 138.8 ($C_{q,Ar}$), 139.0 ($C_{q,Ar}$), 139.9 ($C_{q,Ar}$). **^{19}F NMR** (376 MHz, $CDCl_3$): δ -61.7 (3F, d, *J* = 8.0 Hz, CF_3). **IR** (ATR, cm^{-1}): ν_{NH} 3313; ν_{max} 2857, 1453, 1244, 1165, 1116, 1079, 1026, 742, 696. **MS** (ES+): m/z 399 (M+1, 100). **HRMS** (ES-TOF) calcd for $C_{24}H_{26}F_3N_2$ 399.2043 $[M + H]^+$, found 399.1904.

***Anti*-N^1,N^3-dibenzyl-3,3,3-trifluoro-N^3-methyl-1-phenylpropane-1,2-diamine 299**



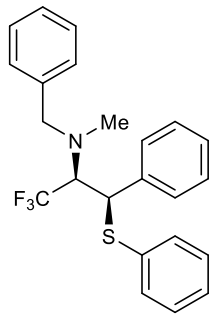
Colourless crystals: mp 67-69 °C. Yield: 23%. R_f 0.13 (petroleum ether/diethyl ether 95:5). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.17 (3H, q, *J* = 1.6 Hz, NCH_3), 3.39-3.46 (1H, m, $CHCF_3$), 3.46 (1H, d, *J* = 13.2 Hz, $N^1C\underline{H}_aH_b$), 3.62 (2H, br d, *J* = 13.6 Hz, $N^1CH_a\underline{H}_b$ and $N^3C\underline{H}_aH_b$), 3.72 (1H, d, *J* = 13.9 Hz, $N^3CH_a\underline{H}_b$), 4.01 (1H, d, *J* = 9.5 Hz, CHPh), 6.59 (2H, d, *J* = 6.6 Hz, 2 x CH_{Ar}), 7.04-7.41 (13H, m, 13 x CH_{Ar}). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 36.1 (CH_3), 51.2 (N^1CH_2), 60.8 (N^3CH_2), 60.9 (CHPh), 69.4 (q, *J* = 23.2 Hz, $\underline{C}HCF_3$), 126.8 (CH_{Ar}), 126.9 (CH_{Ar}), 127.4 (CH_{Ar}), 127.85 (q, *J* = 294.0 Hz, CF_3), 127.91 (2 x CH_{Ar}), 128.0 (2 x CH_{Ar}), 128.1 (2 x CH_{Ar}), 128.2 (2 x CH_{Ar}), 128.3 (2 x CH_{Ar}), 128.4 (2 x CH_{Ar}), 138.8 ($C_{q,Ar}$), 140.0 ($C_{q,Ar}$), 141.3 ($C_{q,Ar}$). **^{19}F NMR** (376 MHz, $CDCl_3$): δ -62.6 (3F, d, *J* = 8.1 Hz, CF_3). **IR** (ATR, cm^{-1}): ν_{NH} 3029; ν_{max} 2848, 1453, 1248, 1139, 1119, 1062, 750, 731, 700. **MS** (ES+): m/z 399 (M+1, 100). **HRMS** (ES-TOF) calcd for $C_{24}H_{26}F_3N_2$ 399.2043 $[M + H]^+$, found 399.2041.

5.2.26 Synthesis of *syn*- and *anti*-*N*-benzyl-*N*-methyl-3-phenyl-3-phenylthio-1,1,1-trifluoropropane-2-amines 297 and 300 and *syn*- *and anti*-*N*-benzyl-3-phenyl-3-phenylthio-1,1,1-trifluoropropane-2-amines 298 and 301

As a representative example, the synthesis of *syn*-*N*-benzyl-*N*-methyl-3-phenyl-3-phenylthio-1,1,1-trifluoropropane-2-amine **297** is described. To a stirred solution of *cis*-1-benzyl-2-phenyl-3-(trifluoromethyl)aziridine **270c** (0.4 mmol, 1 equiv) in dry acetonitrile (1 mL) was added trimethyloxonium tetrafluoroborate (0.8 mmol, 2 equiv) at 0 °C. The reaction mixture was kept at this temperature for one hour and thiophenol (0.5 mmol, 1.2 equiv) was added. After stirring for two hours at room temperature, the reaction was quenched by careful addition of water (2 mL) and

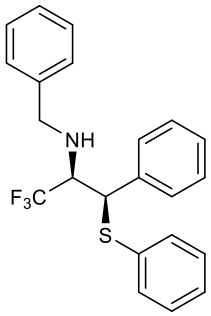
extracted with diethyl ether (3 x 5 mL). The combined organic phases were washed with brine (5 mL), dried over K_2CO_3 and concentrated *in vacuo*. The crude mixture was purified by column chromatography on silica gel yielding *syn*-*N*-benzyl-*N*-methyl-3-phenyl-3-phenylthio-1,1,1-trifluoropropane-2-amine **297**.

***Syn*-*N*-benzyl-*N*-methyl-3-phenyl-3-phenylthio-1,1,1-trifluoropropane-2-amine 297**



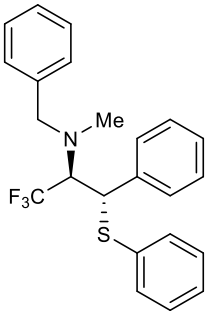
Colourless crystals: mp 111-115 °C. Yield : 17%. R_f 0.25 (petroleum ether/diethyl ether 200:1). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.55 (3H, q, *J* = 1.7 Hz, NCH_3), 3.77 (1H, d x q, *J* = 7.3, 10.8 Hz, $CHCF_3$), 3.99 (1H, d, *J* = 13.6 Hz, $NC\underline{H}_aH_b$), 4.12 (1H, d, *J* = 13.6 Hz, $NCH_a\underline{H}_b$), 4.65 (1H, d, *J* = 10.8 Hz, SCH), 7.01-7.15 (10H, m, 10 x CH_{Ar}), 7.29-7.40 (3H, m, 3 x CH_{Ar}), 7.54-7.59 (2H, m, 2 x CH_{Ar}). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 36.2 (CH_3), 54.3 (SCH), 60.5 (NCH_2), 68.6 (q, *J* = 23.3 Hz, $\underline{C}HCF_3$), 126.9 (q, *J* = 291.7 Hz, CF_3), 127.3 (2 x CH_{Ar}), 127.5 (CH_{Ar}), 127.9 (2 x CH_{Ar}), 128.3 (2 x CH_{Ar}), 128.4 (2 x CH_{Ar}), 128.8 (2 x CH_{Ar}), 129.0 (2 x CH_{Ar}), 133.7 ($C_{q,Ar}$), 134.4 (2 x CH_{Ar}), 137.0 ($C_{q,Ar}$), 138.8 ($C_{q,Ar}$). **^{19}F NMR** (376 MHz, $CDCl_3$): δ -62.9 (3F, d, *J* = 7.3 Hz, CF_3). **IR** (ATR, cm^{-1}): ν_{max} 2884, 1438, 1362, 1234, 1175, 1106, 1064, 885, 852, 750, 731, 689. **MS** (ES+): m/z 402 (M+1, 100). **HRMS** (ES-TOF) calcd for $C_{23}H_{23}F_3NS$ 402.1498 $[M + H]^+$, found 402.1494.

***Syn*-*N*-benzyl-3-phenyl-3-phenylthio-1,1,1-trifluoropropane-2-amine 298**



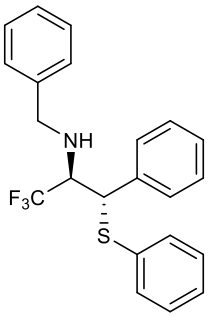
Colourless crystals: mp 59-61 °C. Yield: 47%. R_f 0.11 (petroleum ether/diethyl ether 200:1). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.14 (1H, br s, NH), 3.48-3.60 (1H, m, $CHCF_3$), 3.87 (1H, d, *J* = 12.9 Hz, $NC\underline{H}_aH_b$), 4.08 (1H, d, *J* = 12.9 Hz, $NCH_a\underline{H}_b$), 4.44 (1H, d, *J* = 5.8 Hz, SCH), 7.13-7.33 (15H, m, 15 x CH_{Ar}). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 52.7 (NCH_2), 54.8 (SCH), 63.6 (q, *J* = 26.3 Hz, $\underline{C}HCF_3$), 126.2 (q, *J* = 286.8 Hz, CF_3), 127.4 (CH_{Ar}), 127.6 (2 x CH_{Ar}), 128.36 (2 x CH_{Ar}), 128.42 (2 x CH_{Ar}), 128.46 (2 x CH_{Ar}), 128.49 (2 x CH_{Ar}), 128.9 (2 x CH_{Ar}), 132.8 (2 x CH_{Ar}), 134.0 ($C_{q,Ar}$), 139.2 ($C_{q,Ar}$), 140.0 ($C_{q,Ar}$). **^{19}F NMR** (376 MHz, $CDCl_3$): δ -70.4 (3F, d, *J* = 7.1 Hz, CF_3). **IR** (ATR, cm^{-1}): ν_{NH} 3353; ν_{max} 2920, 1456, 1357, 1243, 1175, 1155, 1110, 1086, 851, 745, 734, 698, 690. **MS** (ES+): m/z 388 (M+1, 100). **HRMS** (ES-TOF) calcd for $C_{22}H_{21}F_3NS$ 388.1341 $[M + H]^+$, found 388.1344.

***Anti-N*-benzyl-*N*-methyl-3-phenyl-3-phenylthio-1,1,1-trifluoropropane-2-amine 300**



Colourless Oil. Yield: 50%. R_f 0.26 (petroleum ether/diethyl ether 200:1). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.11 (3H, q, *J* = 1.7 Hz, NCH_3), 3.66-3.82 (3H, m, NCH_2 and $CHCF_3$), 4.41 (1H, d, *J* = 8.9 Hz, SCH), 6.75-6.81 (2H, m, 2 x CH_{Ar}), 7.12-7.24 (13H, m, 13 x CH_{Ar}). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 36.2 (CH_3), 52.9 (SCH), 60.8 (NCH_2), 68.6 (q, *J* = 24.7 Hz, $\underline{C}HCF_3$), 126.9 (CH_{Ar}), 127.1 (CH_{Ar}), 127.2 (q, *J* = 296.5 Hz, CF_3), 127.9 (CH_{Ar}), 128.04 (2 x CH_{Ar}), 128.07 (2 x CH_{Ar}), 128.3 (2 x CH_{Ar}), 128.7 (2 x CH_{Ar}), 128.8 (2 x CH_{Ar}), 133.5 ($C_{q,Ar}$), 133.7 (2 x CH_{Ar}), 138.7 ($C_{q,Ar}$), 139.7 ($C_{q,Ar}$). **^{19}F NMR** (376 MHz, $CDCl_3$): δ -62.8 (3F, d, *J* = 8.0 Hz, CF_3). **IR** (ATR, cm^{-1}): ν_{max} 2812, 1454, 1246, 1161, 1145, 1108, 1057, 1021, 744, 692. **MS** (ES+): m/z 402 (M+1, 100). **HRMS** (ES-TOF) calcd for $C_{23}H_{23}F_3NS$ 402.1498 $[M + H]^+$, found 402.1496.

***Anti-N*-benzyl-3-phenyl-3-phenylthio-1,1,1-trifluoropropane-2-amine 301**

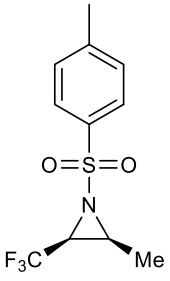


Yield: 6%. Yellow oil. Yield: 6%. R_f 0.13 (petroleum ether/diethyl ether 200:1). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.64 (1H, br s, NH), 3.59-3.70 (1H, m, $CHCF_3$), 3.93 (1H, d x d, *J* = 4.8, 13.3 Hz, $NC\underline{H}_aH_b$), 4.10 (1H, d, *J* = 13.3 Hz, $NCH_a\underline{H}_b$), 4.60 (1H, d, *J* = 3.3 Hz, SCH), 7.14-7.47 (15H, m, 15 x CH_{Ar}). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 51.9 (NCH_2), 52.3 (SCH), 61.3 (q, *J* = 26.0 Hz, $\underline{C}HCF_3$), 124.9 (q, *J* = 286.2 Hz, CF_3), 126.3 (CH_{Ar}), 126.4 (CH_{Ar}), 127.0 (CH_{Ar}), 127.3 (2 x CH_{Ar}), 127.4 (4 x CH_{Ar}), 128.0 (2 x CH_{Ar}), 128.3 (2 x CH_{Ar}), 130.7 (2 x CH_{Ar}), 133.8 ($C_{q,Ar}$), 135.7 ($C_{q,Ar}$), 138.5 ($C_{q,Ar}$). **^{19}F NMR** (376 MHz, $CDCl_3$): δ -69.9 (3F, d, *J* = 7.6 Hz, CF_3). **IR** (ATR, cm^{-1}): ν_{NH} 3360; ν_{max} 2920, 1453, 1251, 1120, 743, 699. **MS** (ES+): m/z 388 (M+1, 100). **HRMS** (ES-TOF) calcd for $C_{22}H_{21}F_3NS$ 388.1341 $[M + H]^+$, found 388.1339.

5.2.27 Synthesis of *cis*-2-methyl-1-tosyl-3-(trifluoromethyl)aziridine 304

To a solution of *cis*-1-benzyl-2-methyl-3-(trifluoromethyl)aziridine **270a** (0.2 mmol, 1 equiv) was added $Pd(OH)_2/C$ (20% w/w) in methanol (1 mL). This solution was stirred for six hours at room temperature under hydrogen atmosphere (2 bar). After filtering off the catalyst over a filter plug, pyridine (0.6 mmol, 3 equiv) and tosyl chloride (0.4 mmol, 2 equiv) were added at 0 °C. The reaction was stopped after stirring for two hours at room temperature by addition of water (5 mL) and diethyl ether (5 mL), The aqueous layer was extracted with diethyl ether (3 x 5 mL) and the combined organic phases were washed with 1M hydrochloric acid (8 mL), saturated bicarbonate (8 mL) and brine (8 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by column chromatography on silica gel yielding *cis*-2-methyl-1-tosyl-3-(trifluoromethyl)aziridine **304**.

***Cis*-2-methyl-1-tosyl-3-(trifluoromethyl)aziridine 304**

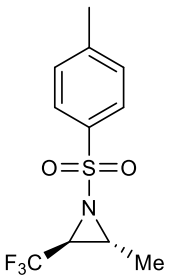


Colourless crystals: mp: 72-77 °C. Yield: 57%. R_f 0.27 (petroleum ether/diethyl ether 9:1). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.41 (3H, d x q, *J* = 1.1, 5.9 Hz, $CHC\underline{H}_3$), 2.46 (3H, s, $PhCH_3$), 3.06-3.15 (1H, m, $CHCF_3$), 3.18 (1H, d x q, *J* = 5.9 Hz, 7.1 Hz, $C\underline{H}CH_3$), 7.37 (2H, d, *J* = 8.2 Hz, 2 x CH_{Ar}), 7.83 (2H, d, *J* = 8.2 Hz, 2 x CH_{Ar}). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 12.0 ($CH\underline{C}H_3$), 21.7 ($PhCH_3$), 38.2 ($\underline{C}HCH_3$), 41.3 (q, *J* = 40.1 Hz, $\underline{C}HCF_3$), 122.8 (q, *J* = 275.0 Hz, CF_3), 128.0 (2 x CH_{Ar}), 129.3 (2 x CH_{Ar}), 134.0 ($C_{q,Ar}$), 145.4 ($C_{q,Ar}$). **^{19}F NMR** (376 MHz, $CDCl_3$): δ -65.4 (3F, d, *J* = 5.8 Hz, CF_3). **IR** (ATR, cm^{-1}): ν_{max} 2923, 1598, 1438, 1400, 1332, 1285, 1156, 1141, 1090, 1048, 1032, 892, 836, 820, 742, 673. **MS** (ES+): m/z 280 (M+1, 100), 297 ($M+NH_4$, 85). **HRMS** (ES-TOF) calcd for $C_{11}H_{13}F_3NO_2S$ 280.0614 $[M + H]^+$, found 280.0614.

5.2.28 Synthesis of *trans*-2-methyl-1-tosyl-3-(trifluoromethyl)aziridine 305

To a solution of *trans*-1-benzyl-2-methyl-3-(trifluoromethyl)aziridine **280a** (0.2 mmol, 1 equiv) was added $Pd(OH)_2/C$ (20% w/w) in ethyl acetate (1.5 mL). This solution was stirred for six hours at room temperature under hydrogen atmosphere (2 bar). After filtering off the catalyst over a filter plug, pyridine (0.6 mmol, 3 equiv) and tosyl chloride (0.4 mmol, 2 equiv) were added at 0 °C. The reaction was stopped after stirring for six hours at room temperature by addition of water (5 mL) and diethyl ether (5 mL), and extracted with diethyl ether (3 x 5 mL). The combined organic phases were washed with 1M hydrochloric acid (8 mL), saturated bicarbonate (8 mL) and brine (8 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by column chromatography on silica gel yielding *trans*-2-methyl-1-tosyl-3-(trifluoromethyl)aziridine **305**.

***Trans*-2-methyl-1-tosyl-3-(trifluoromethyl)aziridine 305**

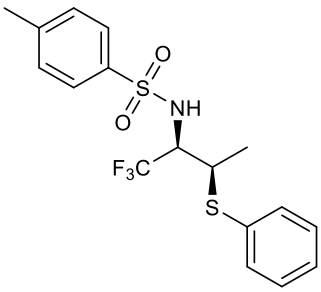


Colourless oil. Yield: 49%. R_f 0.15 (petroleum ether/diethyl ether 95:5). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.79 (3H, d, *J* = 6.0 Hz, $CHC\underline{H}_3$), 2.43 (3H, s, $PhCH_3$), 3.05 (1H, q x d, *J* = 3.9, 6.0 Hz, $C\underline{H}CH_3$), 3.32 (1H, q x d, *J* = 3.9, 5.0 Hz, $CHCF_3$), 7.31-7.34 (2H, m, 2 x CH_{Ar}), 7.81-7.85 (2H, m, 2 x CH_{Ar}). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 12.9 ($CH\underline{C}H_3$), 21.7 ($PhCH_3$), 42.4 (q, *J* = 2.3 Hz, $\underline{C}HCH_3$), 43.9 (q, *J* = 40.9 Hz, $\underline{C}HCF_3$), 122.2 (q, *J* = 273.3 Hz, CF_3), 127.6 (2 x CH_{Ar}), 129.8 (2 x CH_{Ar}), 136.5 ($C_{q,Ar}$), 144.9 ($C_{q,Ar}$). **^{19}F NMR** (376 MHz, $CDCl_3$): δ -71.6 (3F, d, *J* = 5.0 Hz, CF_3). **IR** (ATR, cm^{-1}): ν_{max} 2926, 1447, 1342, 1333, 1281, 1241, 1154, 1124, 1090, 1033, 1006, 914, 846, 820, 813, 710, 691, 681. **MS** (ES+): m/z 280 (M+1, 100). **HRMS** (ES-TOF) calcd for $C_{11}H_{13}F_3NO_2S$ 280.0614 $[M + H]^+$, found 280.0620.

5.2.29 Synthesis of *syn*- and *anti*-*N*-tosyl-3-phenylthio-1,1,1-trifluorobutane-2-amine 307 and 308

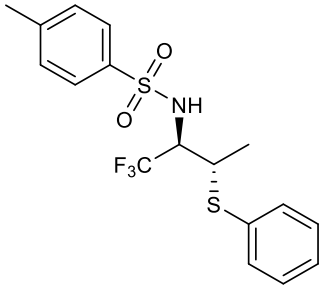
As a representative example, the synthesis of *syn*-*N*-tosyl-3-phenylthio-1,1,1-trifluorobutane-2-amine **303** is described. To a solution of *cis*-2-methyl-1-tosyl-3-(trifluoromethyl)aziridine **304** (0.7 mmol, 1 equiv) and potassium carbonate (3.5 mmol, 5 equiv) in *N,N*-dimethylformamide (5 mL) was added thiophenol (0.8 mmol, 1.2 equiv). This suspension was stirred for one hour at room temperature. The reaction was stopped by addition of water (10 mL) and extracted with diethyl ether (5 x 10 mL). The combined organic phases were washed with brine (2 x 15 mL), dried over $MgSO_4$ and concentrated *in vacuo* to yield *syn*-*N*-tosyl-3-phenylthio-1,1,1-trifluorobutane-2-amine **307** (purity >97%, ^{19}F NMR).

***Syn*-*N*-tosyl-3-phenylthio-1,1,1-trifluorobutane-2-amine 307**



Colourless crystals: mp 82-86 °C. Yield 99%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.38 (3H, d, *J* = 7.2 Hz, CHC<u>H</u>$_3$), 2.41 (3H, s, PhC<u>H</u>$_3$), 3.60 (1H, q x d, *J* = 2.6, 7.2 Hz, C<u>H</u>CH$_3$), 4.09 (1H, d x q x d, *J* = 2.6, 7.7, 9.7 Hz, CHCF$_3$), 5.49 (1H, d, *J* = 9.7 Hz, NH), 7.22-7.33 (5H, m, 5 x CH$_{Ar}$), 7.38-7.44 (2H, m, 2 x CH$_{Ar}$), 7.71-7.75 (2H, m, 2 x CH$_{Ar}$). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 19.7 (CH<u>C</u>H$_3$), 21.6 (PhCH$_3$), 43.8 (<u>C</u>HCH$_3$), 58.7 (q, *J* = 30.1 Hz, <u>C</u>HCF$_3$), 124.0 (q, *J* = 283.6 Hz, CF$_3$), 127.0 (2 x CH$_{Ar}$), 128.1 (CH$_{Ar}$), 129.1 (2 x CH$_{Ar}$), 129.6 (2 x CH$_{Ar}$), 132.6 (C$_{q,Ar}$), 133.2 (2 x CH$_{Ar}$), 137.7 (C$_{q,Ar}$), 143.9 (C$_{q,Ar}$). **^{19}F NMR** (376 MHz, $CDCl_3$): δ -71.7 (3F, d, *J* = 7.7 Hz, CF$_3$). **IR** (ATR, cm^{-1}): ν$_{NH}$ 3252; ν$_{max}$ 2921, 1450, 1394, 1332, 1287, 1265, 1228, 1184, 1168, 1152, 1088, 1051, 915, 814, 742, 688, 662. **MS** (ES+): m/z 407 (M+NH$_4$, 100). **HRMS** (ES-TOF) calcd for $C_{17}H_{19}F_3NO_2S_2$ 390.0804 $[M + H]^+$, found 390.0803.

***Anti*-*N*-tosyl-3-phenylthio-1,1,1-trifluorobutane-2-amine 308**

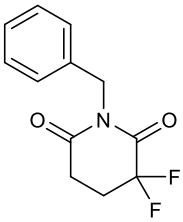


Colourless crystals: mp 166-169 °C. Yield: 100%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.35 (3H, d x d, *J* = 0.9, 7.2 Hz, CHC<u>H</u>$_3$), 2.42 (3H, s, PhC<u>H</u>$_3$), 3.52 (1H, q x d, *J* = 2.8, 7.2 Hz, C<u>H</u>CH$_3$), 4.18 (1H, d x q x d, *J* = 2.8, 7.7, 9.7 Hz, CHCF$_3$), 5.36 (1H, d, *J* = 9.7 Hz, NH), 7.19-7.52 (8H, m, 8 x CH$_{Ar}$), 7.75-7.79 (2H, m, 2 x CH$_{Ar}$). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 16.2 (CH<u>C</u>H$_3$), 21.6 (PhCH$_3$), 44.3 (<u>C</u>HCH$_3$), 57.5 (q, *J* = 29.5 Hz, <u>C</u>HCF$_3$), 124.3 (q, *J* = 284.4 Hz, CF$_3$), 127.1 (2 x CH$_{Ar}$), 128.1 (CH$_{Ar}$), 129.3 (2 x CH$_{Ar}$), 129.6 (2 x CH$_{Ar}$), 132.6 (2 x CH$_{Ar}$), 133.4 (C$_{q,Ar}$), 137.8 (C$_{q,Ar}$), 143.8 (C$_{q,Ar}$). **^{19}F NMR** (376 MHz, $CDCl_3$): δ -71.2 (3F, d, *J* = 7.7 Hz, CF$_3$). **IR** (ATR, cm^{-1}): ν$_{NH}$ 3290; ν$_{max}$ 2977, 1441, 1363, 1329, 1261, 1183, 1152, 1136, 1093, 1056, 1000, 908, 755, 676, 666. **MS** (ES+): m/z 407 (M+NH$_4$, 100). **HRMS** (ES-TOF) calcd for $C_{17}H_{19}F_3NO_2S_2$ 390.0804 $[M + H]^+$, found 390.0798.

5.2.30 Synthesis of 1-benzyl-3,3-difluoropiperidine-2,6-dione 311

To an ice-cooled solution of 2,2-difluoroglutaric anhydride **192** (1 mmol, 1 equiv) in dry tetrahydrofuran (5 mL) was added benzylamine (1 mmol, 1 equiv) and the reaction was stirred for one hour at room temperature. Evaporation of the solvent afforded 5-benzylamino-4,4-difluoro-5-oxopentanoic acid **199**, which was treated with acetic anhydride (5 mL) in the presence of triethyl amine (1.4 mmol, 1.4 equiv). After one hour the reaction was stopped by evaporation of the solvent, water was added (5 mL) and the aqueous phase was extracted with ethyl acetate (3 x 5 mL). The combined organic phases were washed with 1M hydrochloric acid (2 x 5 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by column chromatography yielding 1-benzyl-3,3-difluoropiperidine-2,6-dione **311** as a pure compound.

1-Benzyl-3,3-difluoropiperidine-2,6-dione 311

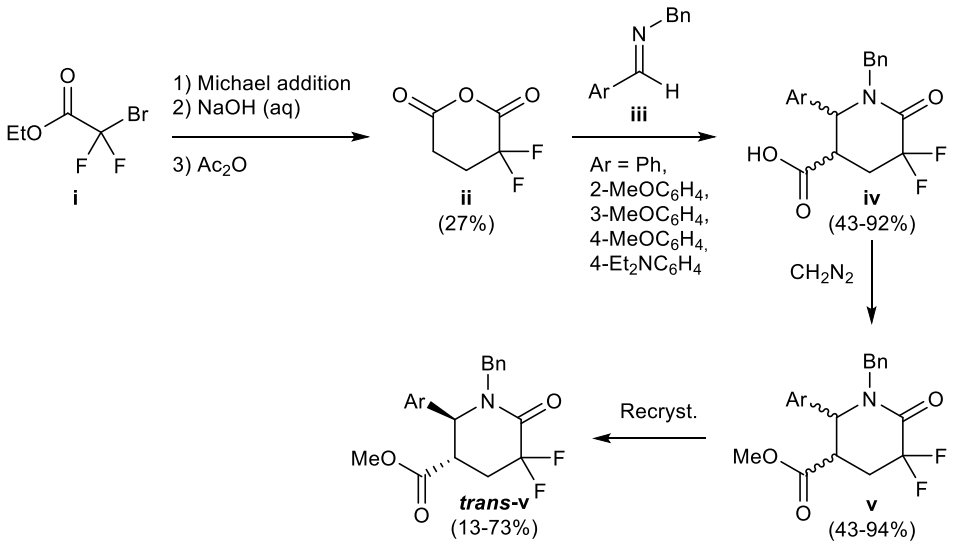


Orange oil. Yield: 54%. R_f 0.13 (petroleum ether/ethyl acetate 9/1). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.36 (2H, ~septet, *J* = 6.9 Hz, CH_2CF_2), 2.85 (2H, *J* = 6.9 Hz, CH_2C=O), 4.92 (NCH_2Ph), 7.21-7.35 (5H, m, 5 x CH_{Ar}). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 27.1 (t, *J* = 23.4 Hz, $\underline{C}H_2CF_2$), 28.7 (t, *J* = 5.1 Hz, $C\underline{H}_2C$=O), 43.8 (NCH_2Ph), 111.6 (t, *J* = 246.3 Hz, CF_2), 128.0 (CH_{Ar}), 128.6 (2 x CH_{Ar}), 128.8 (2 x CH_{Ar}), 135.8 ($C_{q,Ar}$), 162.9 (t, *J* = 32.4 Hz, $CF_2\underline{C}$=O), 169.1 ($CH_2\underline{C}$=O). **^{19}F NMR** (376 MHz, $CDCl_3$): δ -106.0 (2F, t, *J* = 13.8 Hz, CF_2). **IR** (ATR, cm^{-1}): $\nu_{C=O}$ 1751, 1695; ν_{max} 2922, 1355, 1331, 1313, 1278, 1213, 1172, 1152, 1093, 1088, 1081, 1001, 950, 910, 752, 731, 716, 699. **MS** (ES+): m/z 257 ($M+NH_4$, 100). **GC-MS** (EI) m/z (%): 239 (100), 211 (67), 82 (10), 146 (35), 132 (23), 118 (18), 104 (51), 91 (96), 77 (26), 65 (10), 51 (7), 42 (7).

6 Summary

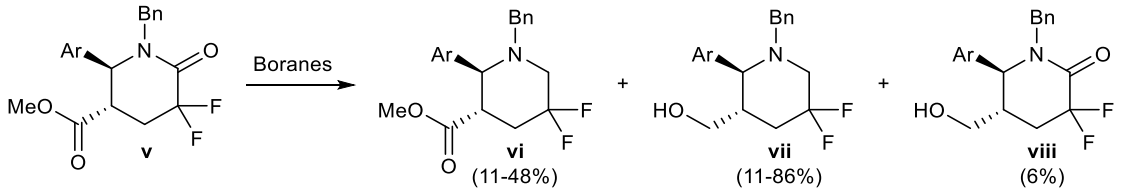
Over the years a broad range of applications with fluorinated compounds have been developed in as well inorganic as organic chemistry fields. Recently, the organofluorine chemistry started flourishing with the development of safe and selective fluorine-containing reagents. Another important factor was the growing awareness of the potential changes in chemical and biological properties caused by introduction of fluorine in bioactive compounds. These unique properties of fluorine as a substituent in organic chemistry explain the success of organofluorine chemistry and have resulted in the need for new fluorinated building blocks for pharmaceuticals and agrochemicals with enhanced activity and selectivity. For those reasons, in this PhD-thesis several synthetic approaches toward new, potentially bioactive fluorinated carbo- and heterocyclic building blocks were developed.

A first part of this PhD-work deals with the synthesis of 3-functionalized 5,5-difluoropiperidines, in particular 3-alkoxycarbonyl- and 3-hydroxymethylpiperidines, as these piperidines are of interest as fluorinated nipecotic acid derivatives and polyfunctional fluorinated building blocks, respectively. Starting from ethyl bromodifluoroacetate **i**, the synthesis of 2,2-difluoroglutaric anhydride **ii** was achieved via a copper-mediated 1,4-addition, hydrolysis and ring closure step. This key intermediate **ii** reacted with diversely substituted imines **iii**, in which only electron-rich benzaldehyde-derived imines were converted to 1-benzyl-2-aryl-5,5-difluoropiperidin-6-one-3-carboxylic acids **iv**. Subsequent esterification of carboxylic acids **iv** toward methyl 1-benzyl-2-aryl-5,5-difluoropiperidin-6-one-3-carboxylates **v** allowed for smooth purification and the isolation of *trans*-methyl 1-benzyl-2-aryl-5,5-difluoropiperidin-6-one-3-carboxylates **v** by recrystallisation as the major isomers.

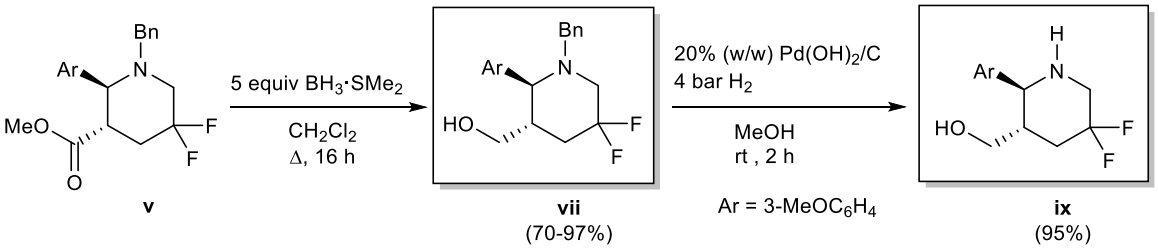


During various reduction attempts to selectively reduce the amide functionality in the presence of the ester moiety within methyl piperidinone-3-carboxylates **v** toward methyl 5,5-difluoropiperidine

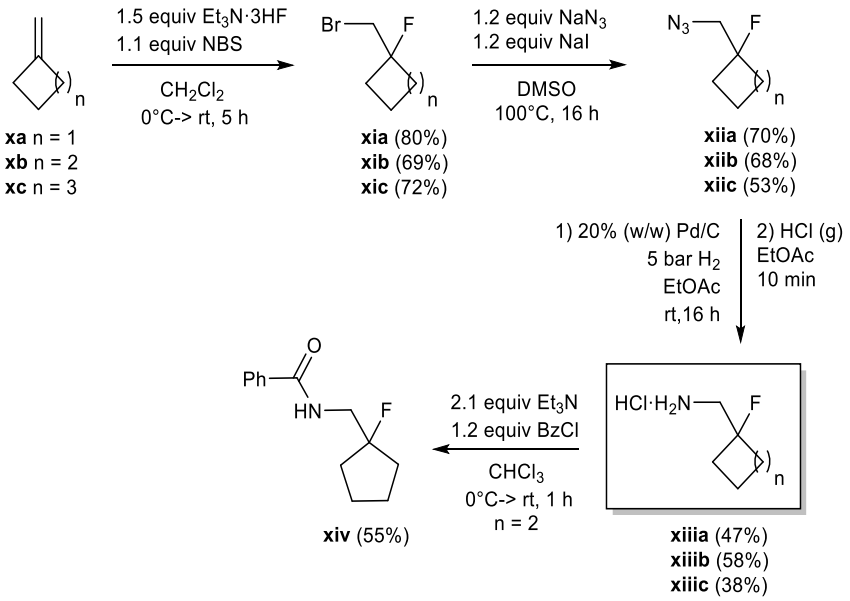
carboxylates **vi**, reduction of the ester moiety could not be avoided, resulting in the formation of hydroxymethylated piperidines **vii** and hydroxymethylated piperidinones **viii** as side products.



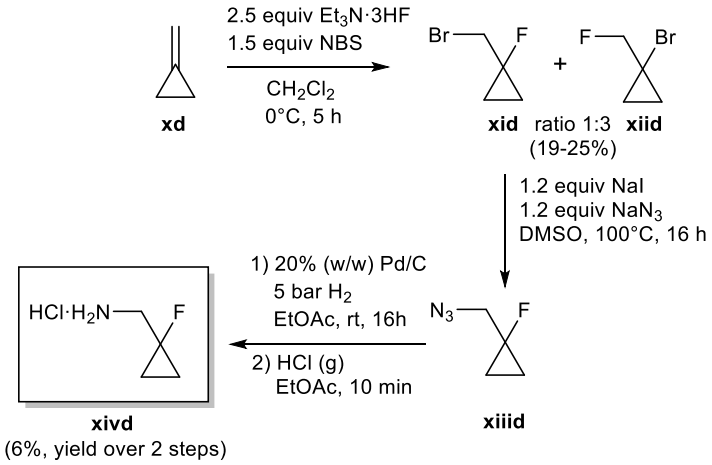
Out of these efforts, a convenient protocol, utilizing an excess of borane, for the reduction of methyl piperidinone-3-carboxylate **v** toward 3-(hydroxymethyl)piperidines **vii** could be extracted. The *N*-benzyl-protected amine in 3-(hydroxymethyl)piperidines **vii** was easily liberated by a $Pd(OH)_2$/C-catalyzed hydrogenation reaction under H_2-atmospere, resulting in *trans*-5,5-difluoro-3-hydroxymethyl-2-aryl-substituted piperidines **ix**, as a novel multifunctional fluorinated building block.



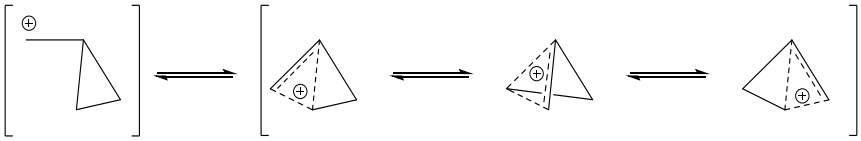
In a second part, a straightforward synthetic pathway toward 1-aminomethyl-1-fluorocycloalkane scaffolds is described. The synthesis was initialized by regioselective bromofluorination from readily available methylenecycloalkanes **xa-c** toward the corresponding Markovnikov adducts, *i.e.*, 1-bromomethyl-1-fluorocycloalkanes **xia-c**. Replacement of bromine was achieved by a nucleophilic substitution with sodium azide in the presence of sodium iodide, resulting in 1-azidomethyl-1-fluorocycloalkanes **xiia-c** under reflux. Azide reduction by hydrogenation over a catalytic amount of Pd/C afforded the corresponding amines **xiiia-c**, which were precipitated as hydrochloric acid salts by bubbling dry HCl gas through the crude mixture. The synthetic value of fluorinated (aminomethyl)cycloalkane **xiiib** was demonstrated by treatment with benzoyl chloride yielding *N*-[(1-fluorocyclopentyl)methyl]benzamide **xiv**, after liberation of the free amine in alkaline medium.



However, when this procedure was applied to the three-membered methylenecyclopropane **xd** the regioselectivity and the yield of the bromofluorination was dramatically lowered, leading to the formation of both the Markovnikov product **xid** and anti-Markovnikov product **xiid** in a 1:3 ratio. Fluorinated (azidomethyl)cyclopropane **xiiid** was isolated after treatment with sodium azide and sodium iodide to give bromine by azide displacement. Subsequent hydrogenation over Pd/C under H_2-atmosphere and precipitation as hydrochloric acid salt led to 1-aminomethyl-1-fluorocyclopropane **xivd**, albeit in only 6% yield.

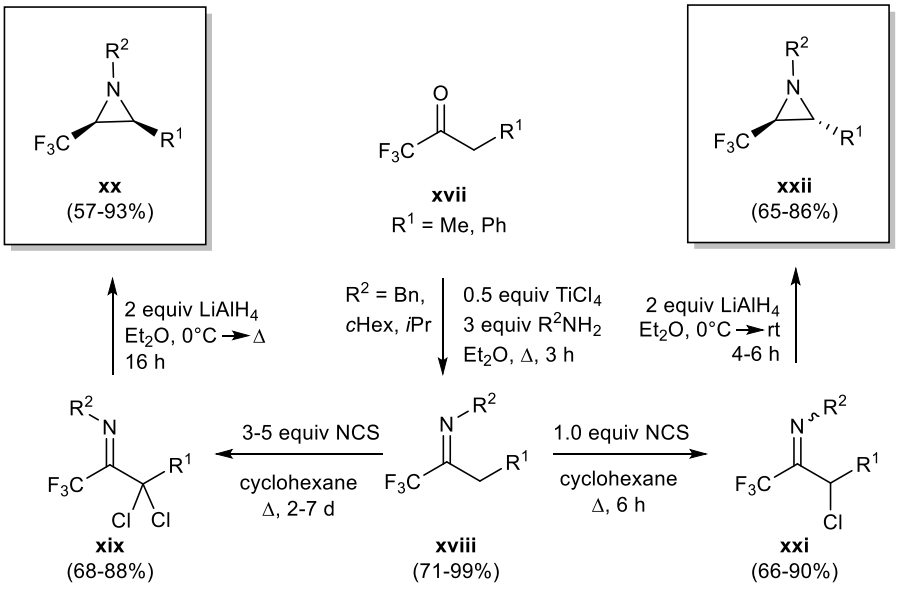


The change in regioselectivity of the cyclopropane derivative compared to the other cycloalkanes could be explained by the interference of a relatively stable cyclopropylcarbinyl carbenium ion **xv**. The stability of this primary cation **xv** can be argued by an equilibrium which involves a set of σ-delocalized bicyclobutonium structures **xvi**.



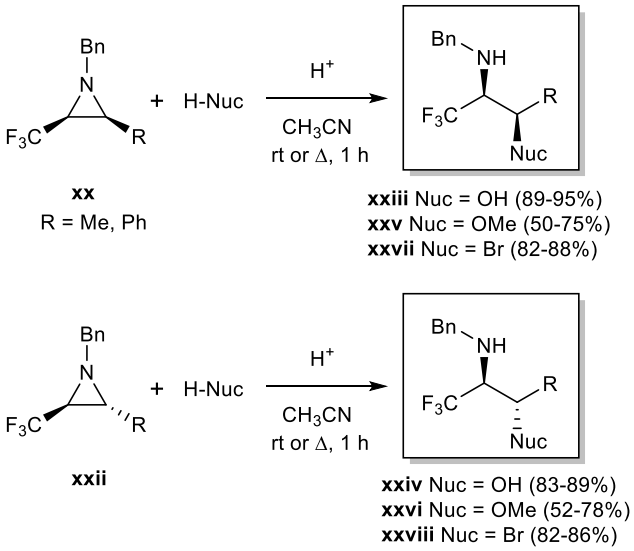
xv **xvi**

In a final part of this PhD-thesis, the stereoselective synthesis and reactivity of *cis*- and *trans*-2-substituted-3-(trifluoromethyl)aziridines was explored. Aziridines are interesting precursors for the synthesis of a wide variety of functionalized nitrogen-containing building blocks due to their high ring-strain. Fluorinated aziridines combine the pronounced reactivity of three-membered azaheterocyles with the biological properties of fluorine. α-(Trifluoromethyl)aziridines **xx** and **xxii** were acquired via imination, α-chlorination and hydride-induced ring closure of commercially available trifluoromethylated ketones **xvii**, *i.e.* 1,1,1-trifluorobutan-2-one and 1,1,1-trifluoro-3-phenylpropan-2-one. Stereoselectivity was introduced by controlling the number of chlorine atoms in the α-position of the trifluoromethylated imines **xviii**. Treatment of dichlorinated imines with $LiAlH_4$ resulted in the formation of *cis*-3-(trifluoromethyl)aziridines **xx** as major isomers in excellent diastereomeric ratios (94-97:3-6) *via* an azirinium intermediate, which was reduced by a second hydride by attack from the least hindered side. On the other hand, the reductive ring-closing reaction of monochlorinated imines **xxi** led to *trans*-(trifluoromethyl)aziridines **xxii** as major isomers in slightly lower diastereomeric ratios (22-6:94-78) in comparison with the dichlorinated imines **xix**. This shift in stereoselectivity can be rationalised by considering complexation of lithium by nitrogen and chlorine toward a cyclic intermediate, followed by diastereoselective hydride transfer to imines **xxi**.

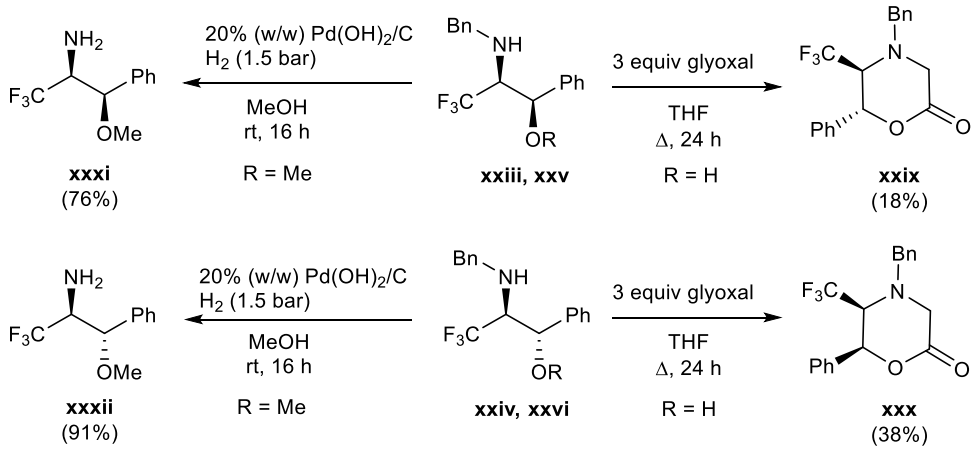


With these stereoselective approaches in hand, the reactivity profile of trifluoromethylated aziridines **xx** and **xxii** was investigated. Ring opening of *cis*- and *trans*-aziridines **xx** and **xxii** under acidic

activation with water, methanol and hydrogen bromide gave fluently rise to *syn*- and *anti*-β-amino alcohols **xxiii** and **xxiv**, β-amino ethers **xxv** and **xxvi** and β-bromo amines **xxvii** and **xxviii**, respectively.

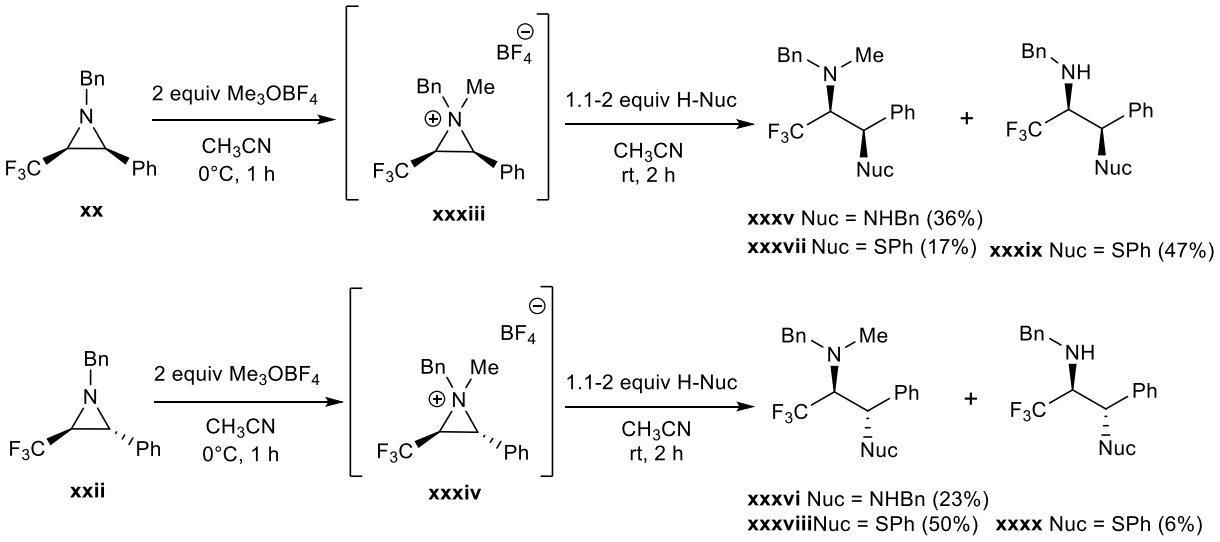


The stereocontrol of nucleophile-induced ring opening of *cis*- and *trans*-aziridines **xx** and **xii** implies a S_N2-mechanism, yielding the single *syn*- and *anti*-diastereomer, respectively. The nucleophilic ring opening of aziridines **xx** and **xxii** occurred in a regiospecific way at the C2-position, which is in accordance with ring-opening reactions of analogous compounds. Additionally, the synthetic potential of β-amino alcohols **xxiii** and **xxiv** and β-amino ethers **xxv** and **xxvi** was further evaluated by reaction with glyoxal toward *trans*- and *cis*-morpholinones **xxix** and **xxx** and hydrogenation over $Pd(OH)_2/C$ toward the primary amines **xxxi** and **xxxii**.

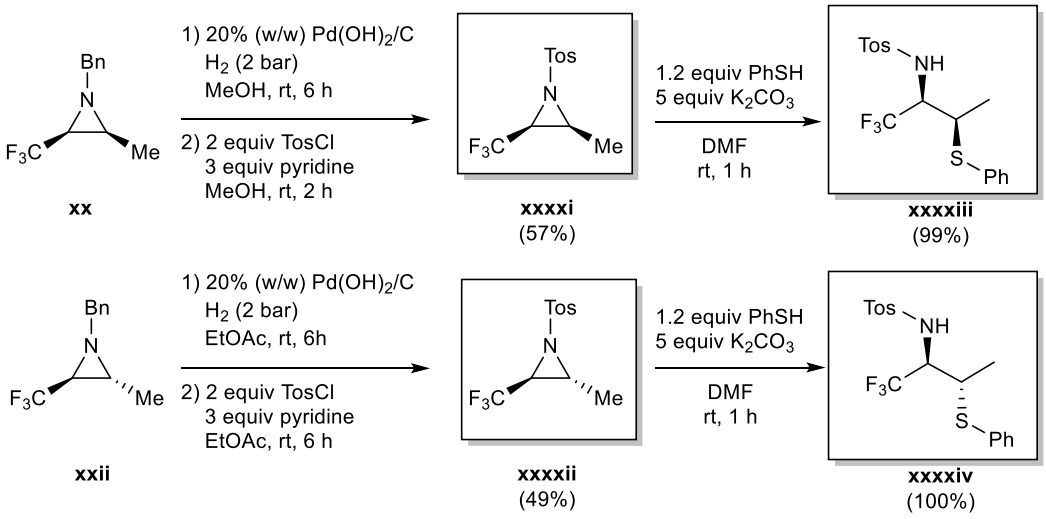


As an alternative for acid-induced ring opening reactions with nucleophiles, activation *via N*-alkylation was evaluated. Treatment of 2-phenyl-substituted aziridines with Me_3OBF_4 yielded the corresponding fluorinated tertiary methylamines **xxxv**, **xxxvi** and **xxxvii, xxxviii** upon ring opening

with benzylamine and thiophenol, although in quite low yields (17-50%). Actually, the ring opening of *cis*-1-benzyl-2-phenyl-3-(trifluoromethyl)aziridine **xx** with thiophenol led to *syn*-*N*-benzyl-1,1,1-trifluoro-3-phenyl-3-(phenylthio)propan-2-amine **xxxix** as the main product (47%).



N-Benzyl-protected non-activated aziridines were smoothly transformed to the corresponding *N*-tosyl activated aziridines by deprotection under hydrogenative reaction conditions and subsequent trapping of the free amines with tosylchloride. The reactivity of these activated aziridines **xxxxi** and **xxxxii** was demonstrated by the near quantitave ring opening with thiophenol without prior activation of the nitrogen atom.



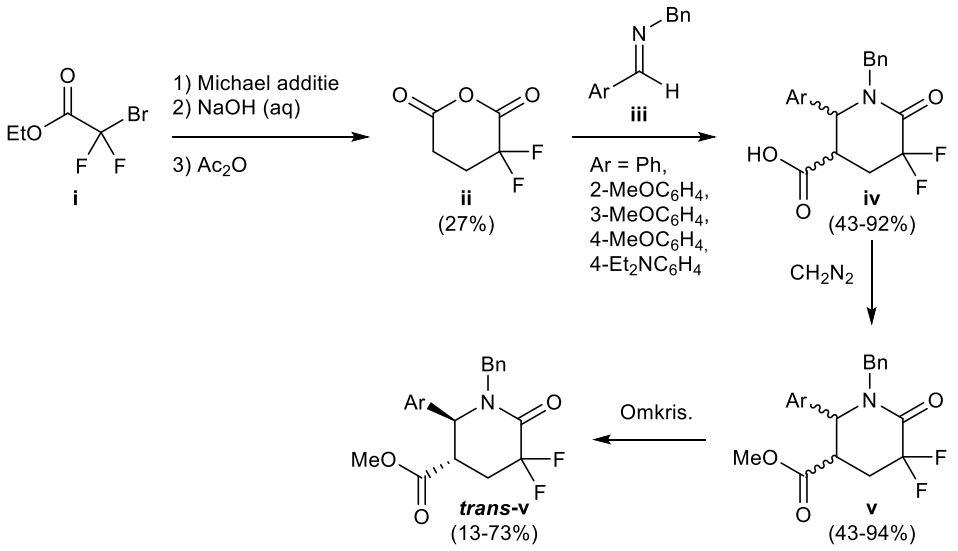
In conclusion, this PhD-work resulted in the successful preparation of diversely fluorinated carbo- and heterocyclic compounds, by starting from commercially available fluorinated compounds or by direct fluorine introduction on cyclic compounds. Furthermore, the synthetic potential of these

compounds as valuable synthons in organic chemistry has been demonstrated, proving their availability as fluorinated building blocks for the preparation of new pharmaceuticals and agrochemicals.

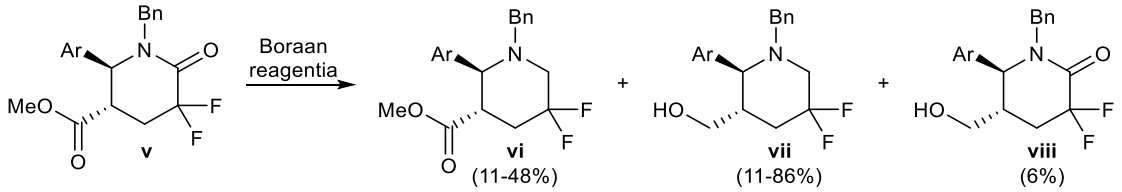
7 Samenvatting

Over de jaren heen werd er, zowel op het vlak van de anorganische chemie als van de organische chemie, een breed gamma aan toepassingen met gefluoreerde verbindingen ontwikkeld, bijvoorbeeld fluoride in tandpasta en de Teflon polymeer coating. Het domein van de organofluorchemie bloeide recent sterk op met de ontwikkeling van veilige, selectieve en handelbare fluorreagentia. Een tweede belangrijke factor hierin was het groeiende besef van de chemische en fysische veranderingen die de invoering van fluor in bioactieve verbindingen teweeg brengt. Deze unieke eigenschappen van fluor verklaren het grote succes van de organofluorchemie en de constante behoefte aan nieuwe, specifiek gefluoreerde bouwstenen voor de ontwikkeling van geneesmiddelen en agrochemische producten met verhoogde activiteit en selectiviteit. Daarom werden in dit doctoraatsonderzoek verscheidene synthesewegen ontwikkeld naar nieuwe potentieel bioactieve gefluoreerde carbo- en heterocyclische bouwstenen.

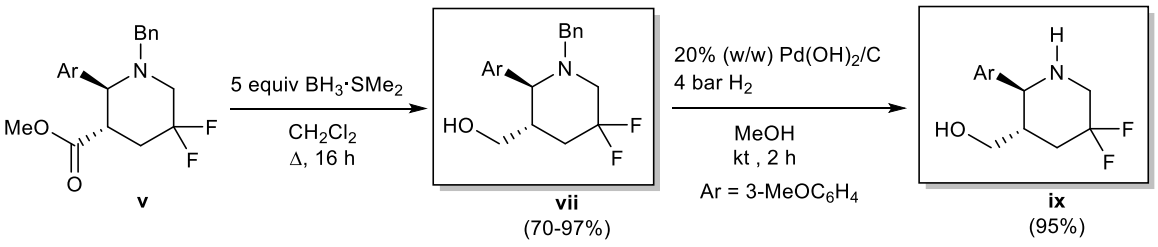
In een eerste deel van dit werk werd de synthese van 3-gefunctionaliseerde 5,5-difluorpiperidinen behandeld, meer specifiek, 3-alkoxycarbonyl- en 3-(hydroxymethyl)piperidinen, daar deze piperidinen interessante gefluoreerde derivaten vormen van het bioactieve piperidine-3-carbonzuur en kunnen aangewend worden als polygefunctionaliseerde bouwstenen. De synthese van het sleutelintermediair 2,2-difluorglutaarzuuranhydride **ii** werd gerealiseerd vertrekkend van ethyl broomdifluoracetaat **i**, via een koper-gemedieerde 1,4-additie, gevolgd door hydrolyse en ringsluiting met azijnzuuranhydride. 2,2-Difluorglutaarzuuranhydride **ii** reageerde met zeer sterk uiteenlopend gesubstitueerde iminen **iii**, waarbij enkel de elektronenrijke iminen afgeleid van benzaldehyde omzetting gaven tot 1-benzyl-2-aryl-5,5-difluorpiperidin-6-on-3-carbonzuur **iv**. Vervolgens werden deze gefluoreerde carbonzuren **iv** onderworpen aan een veresteringsreactie, hetgeen een vlotte zuivering en scheiding van *trans*-methyl-1-benzyl-2-aryl-5,5-difluoropiperidin-6-on-3-carboxylaten **v** als hoofdisomeer via omkristallisatie mogelijk maakte.



Tijdens de evaluatie van de selectieve reductie van de amide-functionaliteit in methylpiperidinon-3-carboxylaat **v**, in de aanwezigheid van een estergroep, kon de overreductie van de estergroep niet vermeden worden. Dit resulteerde in de vorming van (hydroxymethyl)piperidinen **vii** en (hydroxymethyl)piperidinonen **viii** als bijproducten.

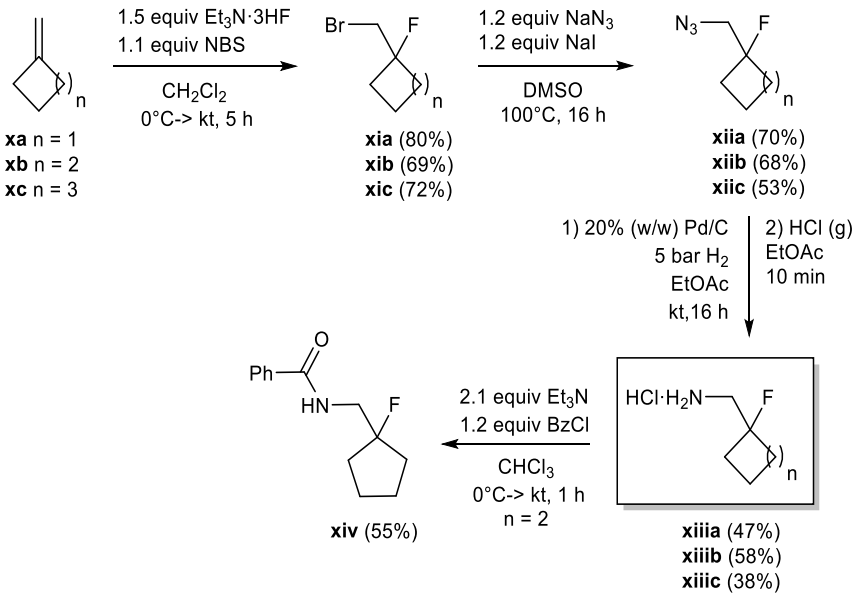


Uit deze pogingen kon wel een geschikte procedure gehaald worden, waarbij een overmaat aan boraanreagens de reductie van methylpiperidinon-3-carboxylaat **v** naar 3-(hydroxymethyl)piperidinen **vii** drijft. De finale ontscherming van het amine in piperidinen **vii** werd vlot gerealiseerd via een $Pd(OH)_2/C$ gekatalyseerde hydrogenatie onder H_2-atmosfeer, wat resulteerde in *trans*-5,5-difluor-3-hydroxymethyl-2-aryl gesubstitueerde piperidinen **ix**, die van nut zijn als nieuwe polygefunctionaliseerde bouwstenen.

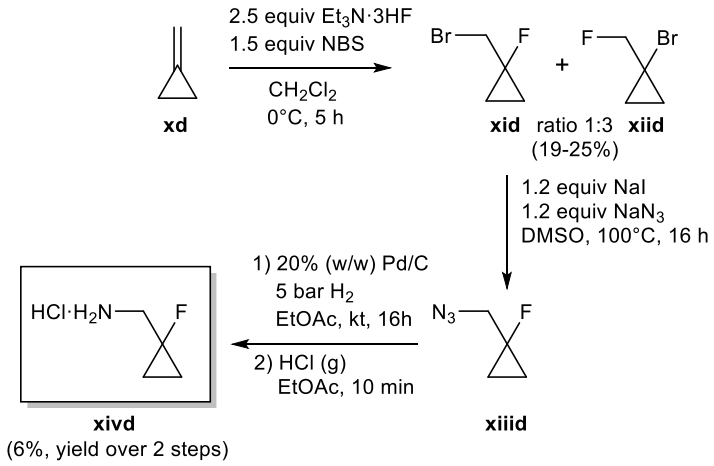


In een tweede deel van dit werk werd de rechtstreekse synthese van 1-aminomethyl-1-fluorcycloalkanen beschreven. Deze methode werd geïnitialiseerd door een regioselectieve broomfluoreringsreactie, vertrekkende van eenvoudig beschikbare methyleencycloakanen **xa-c**, die

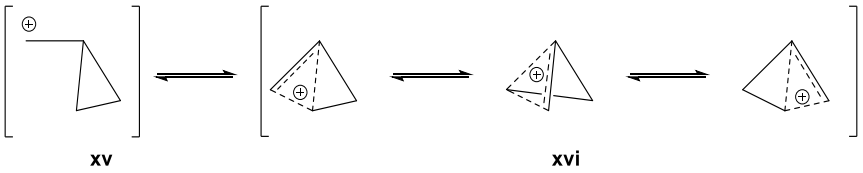
werden omgezet naar de overeenkomstige Markovnivkov reactieproducten, zijnde 1-broommethyl-1-fluorcycloakanen **xia-c**. Vervanging van het broomatoom door een azidegroep tot 1-azidomethyl-1-fluorcycloalkanen **xiia-c** werd bekomen via een nucleofiele substitutie onder verhitting in de aanwezigheid van natriumazide en natriumiodide. Reductie van de azidegroep via hydrogenatie over een katalytische hoeveelheid Pd/C onder H_2-atmosfeer gaf aanleiding tot 1-aminomethyl-1-fluorcycloalkanen **xiiia-c**. Deze aminen werden onmiddellijk neergeslagen als de overeenkomstige ammoniumchloriden door de doorborreling van droog HCl-gas door het ruwe reactiemengsel. De synthetische waarde van deze nieuwe bouwstenen werd aangetoond door omzetting van methylamine **xiiib** tot gefluoreerde amide **xiv** met benzoylchloride in alkalische milieu.



Wanneer de broomfluoreringsreactie werd toegepast op het cyclopropaanderivaat, methyleencyclopropaan **xd**, werd echter een aanzienlijke verandering in de regioselectiviteit en een daling van het bekomen rendement waargenomen. Deze reactie gaf aanleiding tot de vorming van zowel het Markovnikovproduct **xid** als het anti-Markovnikovproduct **xiid** in een 1:3 verhouding. 1-Aminomethyl-1-fluorcyclopropaan werd eveneens neergeslaan als het HCl-zout na de substitutie van broom door azide, gevolgd door een hydrogenatie over Pd/C, met een rendement van 6% over twee stappen.

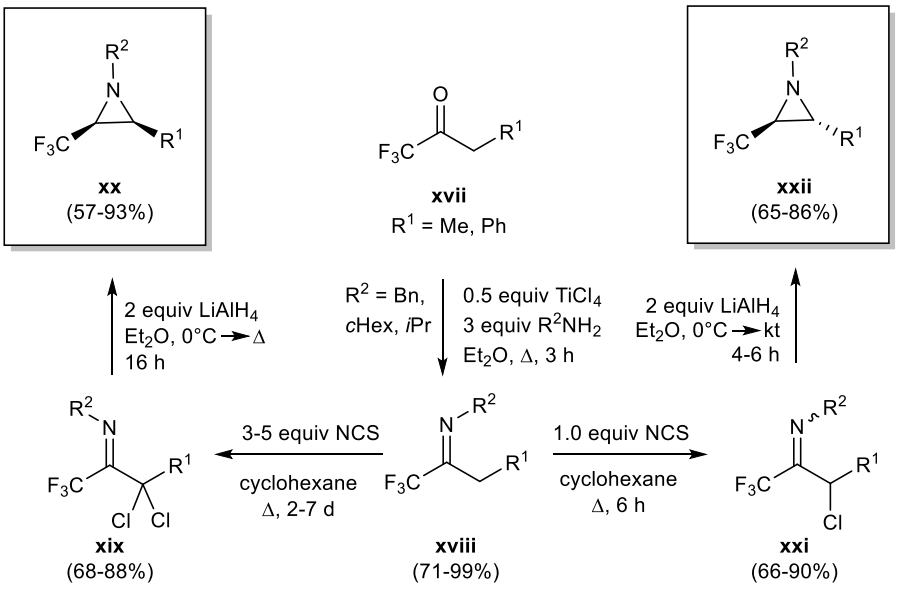


De verandering in regioselectiviteit tijdens de broomfluoreringsreactie met methyleencyclopropaan **xd** ten opzichte van de grotere cycloalkaanringen kon worden verklaard door de tussenkomst van het relatief stabiele cyclopropylcarbinylcarbeniumion **xv**. Dit primaire ion staat in evenwicht met een set van σ-gedelokaliseerde bicyclobutoniumstructuren **xvi**, waardoor het mogelijk wordt om de positieve lading te spreiden over de gehele structuur.

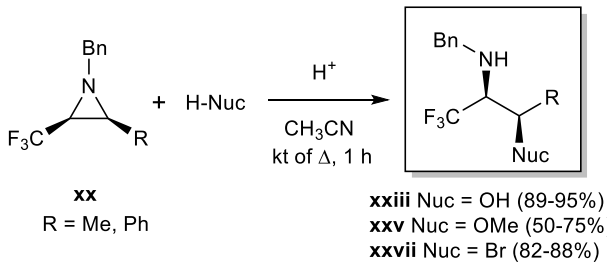


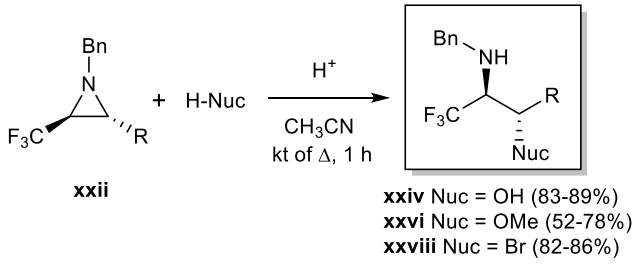
In een laatste deel van dit werk werd een stereoselectieve route tot de synthese van *cis*- en *trans*-3-(trifluormethyl)aziridinen uitgewerkt, waarna het reactiviteitsprofiel van deze aziridinen uitgebreid onderzocht werd. Aziridinen zijn door hun grote ringspanning de ideale precursoren voor de synthese van een breed gamma aan stikstofhoudende bouwstenen. Gefluoreerde aziridinen combineren de uitgesproken reactiviteit van deze drieringen met de biologische eigenschappen verbonden aan fluor. (Trifluormethyl)aziridinen **xx** en **xxii** werden bekomen door de iminering, α-chlorering en hydride-geïnduceerde ringsluiting van commercieel beschikbaar trifluormethylketonen **xvii**, namelijk 1,1,1-trifluorbutan-2-on en 1,1,1-trifluor-3-fenylpropan-2-on. De stereoselectiviteit in deze methode werd gecontroleerd door het aantal chlooratomen die ingevoerd werden in de α-plaats van getrifluormethyleerde iminen **xviii**. Behandeling van de digechloreerde iminen **xix** met $LiAlH_4$ leidde tot de vorming van (trifluormethyl)aziridinen **xx**, met de *cis*-vorm als hoofdisomeer in uitstekende diastereomere verhoudingen (94-97:3-6). Deze stereoselectiviteit kon verklaard worden door de *in situ* vorming van een aziriniumintermediair, dat door de uitstoot van het tweede chlooratoom gevormd wordt. Dit intermediair werd verder gereduceerd door de aanval van een tweede hydride ion langs de minst gehinderde zijde, wat resulteerde in de vorming van *cis*-aziridinen.

Indien deze reductieve ringsluitingsreactie werd toegepast op monochlooriminen **xxi** gaf deze aanleiding tot de *trans*-(trifluormethyl)aziridinen **xxii** als hoofdisomeer. De verklaring voor deze verandering in stereoselectiviteit werd gevonden in de complexatie van lithium met het stikstof- en chlooratoom tot een cyclisch intermediair, hetgeen de diastereoselectieve introductie van het hydride impliceert.



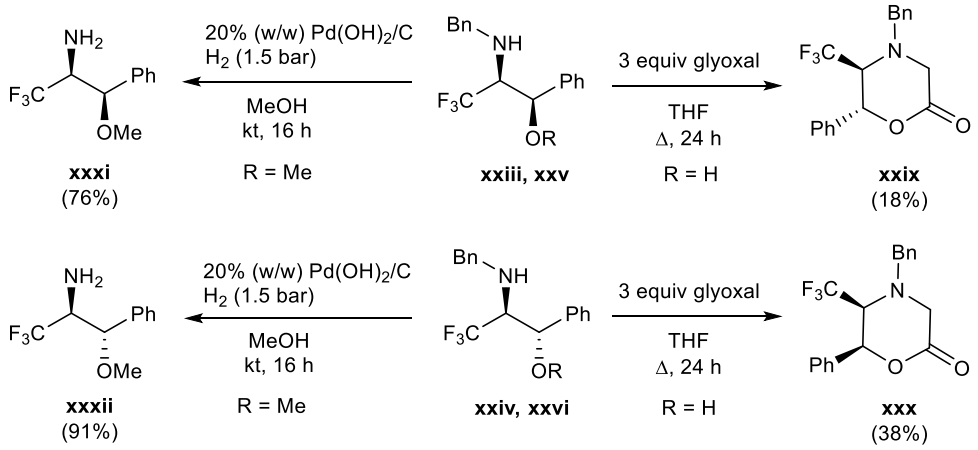
Met deze eenvoudige, stereoselectieve procedure voorhanden, werd het reactiviteitsprofiel van getrifluormethyleerde aziridinen **xx** en **xxii** van naderbij bekeken. Door middel van zuuractivatie werden zowel de *cis*- als *trans*-aziridinen **xx** en **xxii** zeer vlot omgezet tot hun overeenkomstige β-aminoalcoholen **xxiiii** en **xxiv**, β-aminoëthers **xxv** en **xxvi** en β-broomaminen **xxvii** en **xxviii**, met respectievelijk water, methanol en waterstofbromide.



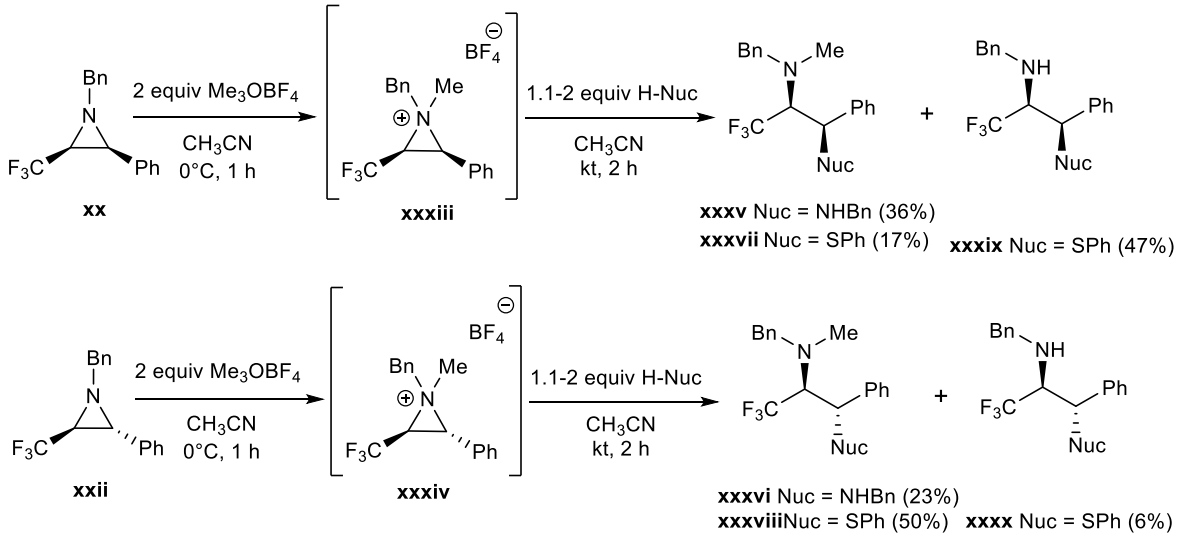


De stereocontrole, die gepaard gaat met de nucleofiele ringopening van *cis*- en *trans*-aziridinen **xx** en **xxii,** duidt op een S_N2 mechanisme, waarbij enkel het *syn*-, respectievelijk het *anti*-diastereomeer gevormd wordt. Naar analogie met ringopeningsreacties van andere α-(trifluormethyl)aziridinen, openen ook de hier gesynthetiseerde aziridinen **xx** en **xxii** specifiek op de C2-plaats.

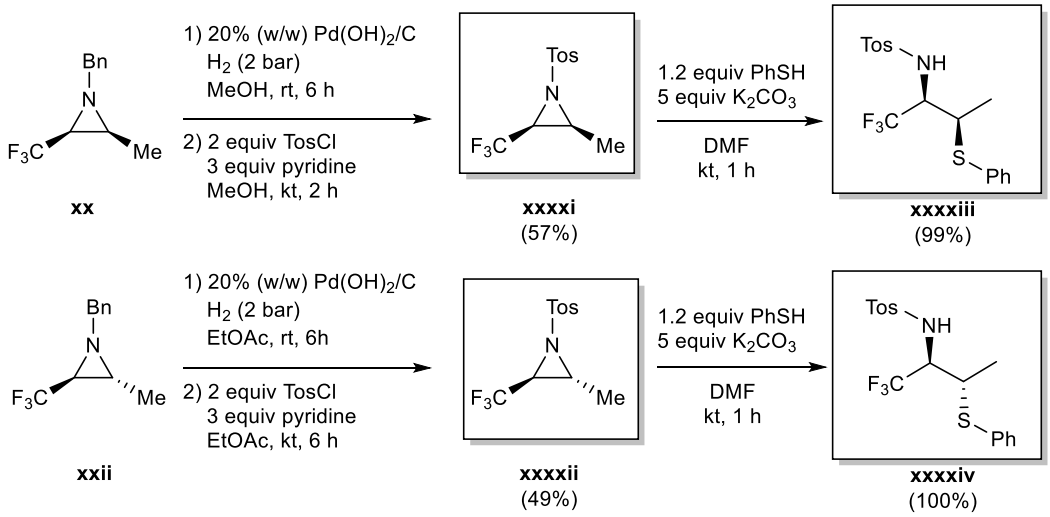
Het synthetisch potentieel van deze nieuwe gefluoreerde bouwstenen werd kort geëvalueerd door de reactie van β-aminoalcoholen **xxiii** en **xxiv** met glyoxal tot *trans*- en *cis*-morfolinonen **xxix** en **xxx** en door de hydrogenatie van β-aminoëthers **xxv** en **xxvi** over $Pd(OH)_2/C$ tot de primaire aminen **xxxi** en **xxxii**.



Als een alternatief voor zuurgeactiveerde ringopeningsreacties werd de activatie door *N*-alkylering van het aziridinestikstofatoom onderzocht. Reactie van 2-fenylgesubstitueerde aziridinen met Me_3OBF_4 leverde de overeenkomstige tertiaire methylaminen **xxxv**, **xxxvi** en **xxxvii**, **xxxviii** op in eerder lage rendementen (17-50%) na ringopening met respectievelijk benzylamine en thiofenol. In het geval thiofenol als nucleofiel werd aangewend in de reactie met cis-aziridine **xx** werd onverwacht het niet-gemethyleerde *syn*-*N*-benzyl-1,1,1-trifluor-3-fenyl-3-(fenylthio)propaan-2-amine **xxxix** bekomen als hoofdproduct (47%).



N-Benzyl beschermde, niet-geactiveerde aziridinen werden vlot omgezet tot hun overeenkomstige *N*-tosyl geactiveerde analogen door ontscherming van het stikstofatoom via hydrogenatie waarna de vrije aminen onmiddellijk in reactie werden gebracht met tosylchloride. De reactiviteit van deze geactiveerde aziridinen **xxxxi** en **xxxxii** werd aangetoond door de quasi kwantitatieve ringopening met thiofenol, zonder dat een voorafgaande activatie van het stikstofatoom nodig was.



Tot slot kan besloten worden dat dit doctoraatswerk geleid heeft tot de synthese van zowel monogefluoreerde, digefluoreerde, als trifluorgemethyleerde nieuwe carbo- en heterocyclische verbindingen. In de hier ontwikkelde procedures werd er gebruikt gemaakt van zowel commercieel beschikbare gefluoreerde substraten als van de directe invoering van fluor op het ringsysteem. Verder werd het synthetisch potentieel van deze nieuwe verbindingen, als waardevolle synthons in de organische chemie, onderzocht. Hieruit kon hun beschikbaarheid als potentiële gefluoreerde bouwstenen voor nieuwe farmaceutische en agrochemische producten aangetoond worden.

8 References

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1. Moens, Matthias; D'hooghe, Matthias; De Kimpe, Norbert. 'Selective synthesis of *cis*- and *trans*-2-methyl/phenyl-3-(trifluoromethyl)aziridines and their regio- and stereospecific ring opening.' *The Journal of Organic Chemistry* **2014**, *79*, 5558.

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Conferences *(active participation)*

1. 14th Belgian Organic Synthesis Symposium, July 13-18, 2014, Louvain-la-Neuve (Belgium).
   Moens, Matthias; D'hooghe, Matthias; De Kimpe, Norbert. 'Selective synthesis of *cis*- and *trans*-2-methyl/phenyl-3-(trifluoromethyl)aziridines and their regio- and stereospecific ring opening.' Abstract p. poster 211. (poster)

2. 16th Sigma-Aldrich Organic Synthesis Meeting, December 6-7, 2012, Spa (Belgium).
   Moens, Matthias; Verniest, Guido; De Schrijver, Matthias; ten Holte, Peter; Thuring, Jan-Willem; Deroose, Frederik; De Kimpe, Norbert. 'Synthesis of 2-aryl-3-hydroxymethyl-5,5-difluoropiperidines.' Abstract p. poster 46. (poster)

Conferences *(passive participation)*

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3. 'Tales and Careers in Organic Synthesis', September 19-20, 2013, Ghent (Belgium).
4. 13th Belgian Organic Synthesis Symposium, July 15-20, 2012, Leuven (Belgium).
5. 15th Sigma-Aldrich Organic Synthesis Meeting, December 1-2, 2011, Spa (Belgium).
6. 14th Sigma-Aldrich Organic Synthesis Meeting, December 2-3, 2010, Spa (Belgium).