Fluorine leaves nobody indifferent; it enflames emotions be that affections or aversions.
As a substituent, it is rarely boring, always good for a surprise,
but often completely unpredictable.

- M. Schlosser, 1998

Members of the jury

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ir. Tamara Meiresonne

Synthesis of strained cyclic amino acid derivatives and fluorinated 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:

Synthese van gespannen cyclische aminozuurderivaten en gefluoreerde heterocyclische verbindingen

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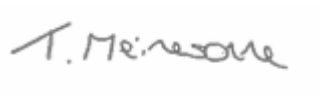

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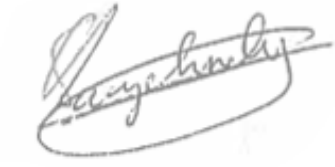

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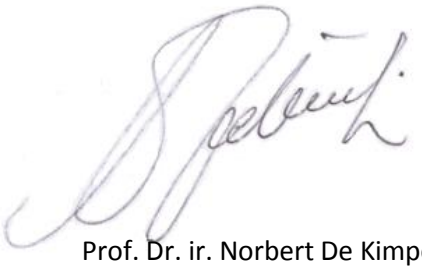

Prof. Dr. ir. Norbert De Kimpe

Woord vooraf

'*Je hebt er lang naar uitgekeken, maar het is toch een beetje raar. Want de afgelopen weken waren de laatste met elkaar*.' Dit liedje zong ik samen met mijn klasgenootjes op het einde van het zesde leerjaar. Ook nu, na zes jaar doctoreren, is de tijd opnieuw gekomen om afscheid te nemen. En ook nu heb ik weken- en maandenlang uitgekeken naar dit moment, met het besef dat dit tegelijk het einde betekent van mijn tijd aan de vakgroep. Maar afscheid nemen kan ik niet zonder de mensen te bedanken die mij de afgelopen zes jaar geholpen hebben om dit werk te maken tot wat het is.

Eerst en vooral wil ik mijn promotor, Prof. Norbert De Kimpe bedanken. Ik ben heel erg dankbaar dat u mij de kans heeft gegeven om een doctoraat te starten als assistent aan de vakgroep. Dit zorgde voor een combinatie die ik altijd erg leuk heb gevonden en met veel plezier heb gedaan. Bedankt voor het vertrouwen en de goede begeleiding en om mij te blijven motiveren om het beste van mijzelf te geven.

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I would also like to thank the members of the jury: Prof. Dr. Alberto Brandi, Prof. Dr. ir. Kourosch Abbaspour Tehrani, Prof. Dr. ir. Matthias D'hooghe, Prof. Dr. ir. Bruno De Meulenaer and Prof. Dr. ir. Guy Smagghe, for your time and efforts and the critical reading of my manuscript.

Het is al in veel 'woorden vooraf' aan bod gekomen, maar de sfeer in ons labo is echt ongelofelijk. (Ex-) collega's, jullie zorgden ervoor dat ik elke dag met plezier kwam werken. Ik zal de vele Koepuurfeestjes, congresfeestjes, SynBioC Summer activities en andere feestjes zeker missen! Ook het komen en gaan van mensen hoort er bij in ons labo. Ik heb in deze zes jaar dan ook veel collega's zien vertrekken, maar vooral na het vertrek van mijn jaargenoten was het labo niet echt meer hetzelfde.

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Mijn lieve Koen, wat ben ik blij dat je de keuze van je laboplaats hebt laten afhangen van de positie van de rotavapor. Jij hebt de afgelopen jaren meer voor mij betekend dan je je kan voorstellen en niet alleen omdat je de perfecte labogenoot benaderde. Of benadert de perfecte labogenoot jou? Jij bent veruit het meest waardevolle dat ik heb overgehouden aan mijn tijd hier en ik ben doodgelukkig dat ik dat voor jou kan, wat jij voor mij doet als je lacht.

Tamara Meiresonne

September 2015

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List of abbreviations

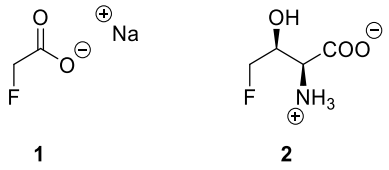
[^{18}F]FDG:	2-[^{18}F]-2-deoxy-D-glucose
2-Me-THF:	2-methyltetrahydrofuran
Ac:	acetyl
ACBC:	aminocyclobutanecarboxylic acid
Ala:	alanine
ATR:	Attenuated Total Reflectance
α-ACC:	1-aminocyclopropanecarboxylic acid
Bn:	benzyl
Boc:	*tert*-butoxycarbonyl
Bz:	benzoyl
β-ACC:	2-aminocyclopropanecarboxylic acid
CAN:	cerium ammonium nitrate
Cbz:	benzyloxycarbonyl
CV:	column volume
DAST:	diethylaminosulfur trifluoride
DCC:	*N*,*N*'-dicyclohexylcarbodiimide
DCY:	decay corrected yield
de:	diastereomeric excess
DIBAL:	diisobutylaluminiumhydride
DIPEA:	diisopropylethylamine
DMAP:	4-(dimethylamino)pyridine
DMF:	*N*,*N*-dimethylformamide
DMSO:	dimethyl sulfoxide
DPPA:	diphenylphosphoryl azide
dr:	diastereomeric ratio

EDC:	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee:	enantiomeric excess
equiv:	equivalent(s)
Gly:	glycine
HBTU:	2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HMPA:	hexamethylphosphoramide
KHMDS:	potassium bis(trimethylsilyl)amide
kt:	kamertemperatuur
LC:	liquid chromatography
LDA:	lithium diisopropylamide
LiHMDS:	lithium bis(trimethylsilyl)amide
LiTMP:	lithium tetramethylpiperidide
mGluR4:	metabotropic glutamate receptor subtype 4
MIRC:	Michael Induced Ring Closure
MorphDAST:	morpholinosulfur trifluoride
MS:	molecular sieves
Ms:	methanesulfonyl
MW:	microwave
NBS:	*N*-bromosuccinimide
NMDA:	*N*-methyl-D-aspartate
NaHMDS:	sodium bis(trimethylsilyl)amide
Ns:	4-nitrobenzenesulfonyl
Nu, NuH or Nu^-:	nucleophile
on:	overnight
PET:	Positron Emission Tomography
Phth:	phthalimido

PivCl:	pivaloyl chloride
PLE:	Pig Liver Esterase
PMB:	4-methoxybenzyl
PMP:	4-methoxyphenyl
r.t.:	room temperature
S_NV:	nucleophilic vinylic substitution
TBAF:	tetra-*n*-butylammonium fluoride
TBAI:	tetra-*n*-butylammonium iodide
TBDMS:	*tert*-butyldimethylsilyl
Tf:	trifluoromethanesulfonyl (triflyl)
THF:	tetrahydrofuran
TLC:	thin layer chromatography
TMAF:	tetramethylammonium fluoride
TMS:	trimethylsilyl (in silyl compounds) or tetramethylsilane (in NMR)
trans-[^{18}F]FACBC:	*trans*-1-amino-3-[^{18}F]cyclobutane-1-carboxylic acid
Ts:	*p*-toluenesulfonyl

1 Introduction and goals

Although fluorine is the most abundant halogen atom in the earth's crust, only 13 natural products incorporating fluorine have been discovered so far.[1] The first fluorinated natural product to be discovered was fluoroacetate **1**, isolated from *Dichapetalum cymosum*, also known as Gifblaar or Poison leaf (Figure 1). The name of this South African shrub indicates its toxicity, which is due to the high levels of fluoroacetate **1** in its leafs. The only amino acid among the 13 fluorinated natural products is 4-fluorothreonine **2** which is produced in the actinomycete *Streptomyces cattleya* (Figure 1).[2]



1 **2**

Figure 1

The introduction of fluorine in organic compounds is very popular in medicinal chemistry. This can be attributed to its unique chemical, biological and physical properties.[3] The high electronegativity of fluorine ($\chi_{pauling}$ = 4) and the excellent overlap between the 2s and 2p orbitals of fluorine with the corresponding orbitals of carbon lead to a highly polarized, very strong and short carbon-fluorine bond. In addition, this bond has a low polarizability, which often leads to an increase in lipophilicity of fluorinated compounds, especially in the case of aromatic fluorination and fluorination adjacent to atoms with π-bonds. Since the lipophilicity of a compound has a profound effect on its passive transport in the body, this is a very important property of orally administered drugs. Another result of the electron-withdrawing character of fluorine is the pronounced effect of fluorine substitution on the acidity of adjacent functional groups. This in turn is an important feature in the solubility and bioavailability of pharmaceuticals. Furthermore, the introduction of fluorine in molecules can enhance their metabolic stability. As such, metabolically labile sites can be blocked by the introduction of fluorine. Another important feature of fluorine substitution is its effect on the conformation of molecules. Because of the fact that the van der Waals radius of fluorine (1.47 Å) is situated in between that of hydrogen (1.20 Å) and oxygen (1.57 Å), the replacement of one of these two elements by fluorine does not have a pronounced effect on steric grounds. However, the electronic properties of fluorine can lead to a conformational change in fluorinated molecules. For example, 1,2-difluoroethane **3** adopts a gauche conformation due to the stabilizing effect of hyperconjugative (σ -> σ*) interactions.

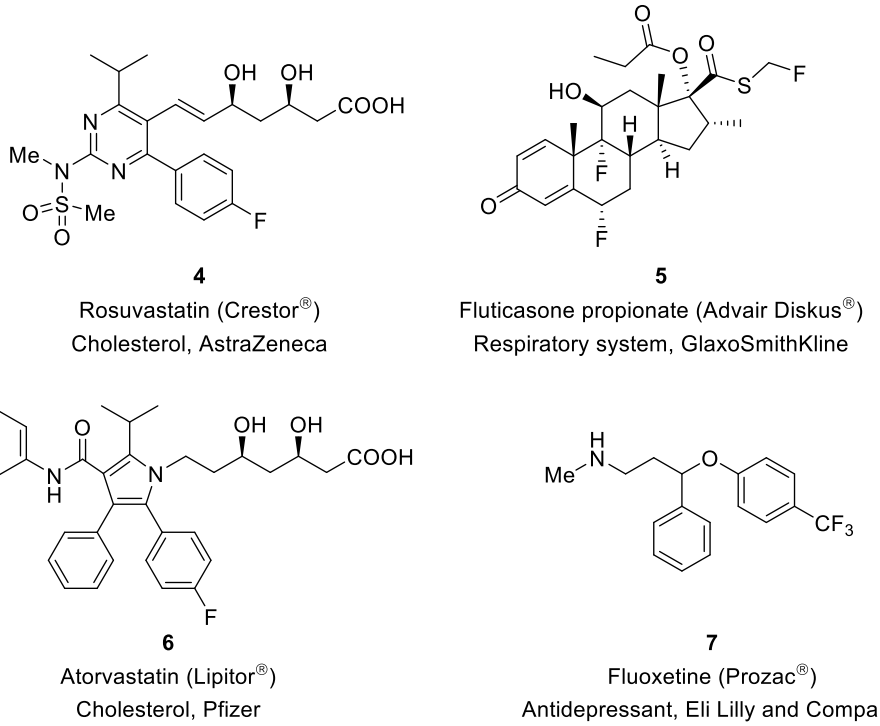
3
Gauche
0 kJ/mol*

3
Anti
1.8 kJ/mol*

*relative energies

Figure 2

These unique properties of fluorine have led to an increasing number of fluorinated pharmaceuticals, with 2% of fluorine-containing drugs in 1970 and about 25% of fluorinated drugs nowadays.[4] In 2013, seven of the 30 best-selling drugs incorporated at least one fluorine atom in their structure. The cholesterol-lowering drug Crestor® (rosuvastatin) **4** occupied the fourth place in this list and Advair Diskus® (a combination drug of fluticasone propionate **5** and salmeterol), which is used for the treatment of asthma, was the sixth best-selling drug in 2013 (Figure 3). In 2011, the cholesterol lowering drug Lipitor® (atorvastatin) **6** was the best-selling drug worldwide. Another important example of a fluorinated drug is the well-known antidepressant Prozac® (fluoxetine) **7**.



4
Rosuvastatin (Crestor®)
Cholesterol, AstraZeneca

5
Fluticasone propionate (Advair Diskus®)
Respiratory system, GlaxoSmithKline

6
Atorvastatin (Lipitor®)
Cholesterol, Pfizer

7
Fluoxetine (Prozac®)
Antidepressant, Eli Lilly and Company

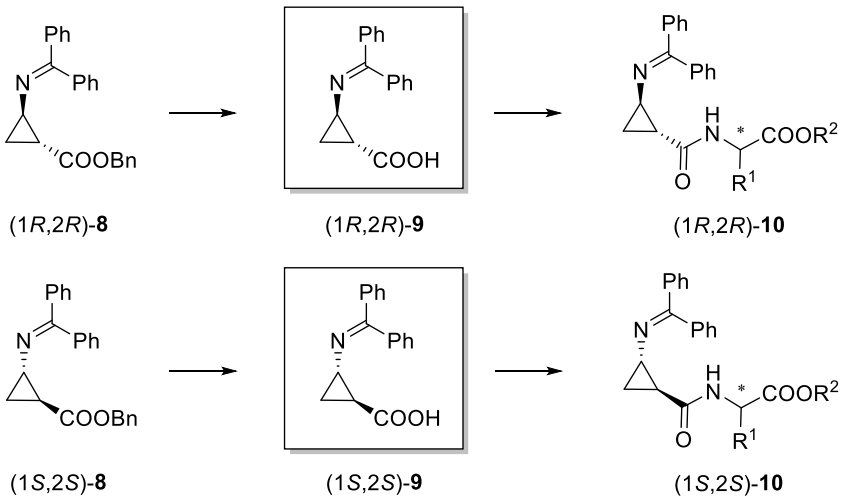
Figure 3

The above-mentioned drugs are members of the class of 'small molecule' drugs, with a molecular weight generally less than 500 Da. The biggest advantage of these drugs is that they can be administered orally.

However, some disadvantages are associated with this class of drugs, for example a reduced target selectivity, which can lead to the occurrence of side-effects. Another class of drugs comprises the biopharmaceuticals, such as proteins. The biggest advantage of this class is their high site-specificity due to the higher amount of interactions with the appropriate receptors. However, due to the high molecular weight of these compounds, oral administration is not possible and these drugs need to be administered by injection, which is probably the major drawback of this type of drugs. Another disadvantage is their low metabolic stability. Nevertheless, biopharmaceuticals are also represented in the list of top-selling blockbuster drugs in 2013, with four protein drugs in the top 10. For example, adalimumab (Humira®), an anti-inflammatory drug, is a monoclonal antibody consisting of 1330 amino acids and was listed as the third best-selling drug in 2013.

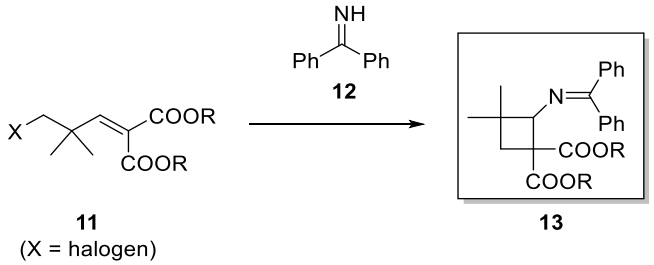
Peptides can be mentioned as a third class of pharmaceuticals, with a molecular weight situated between that of 'small molecule' drugs and biopharmaceuticals.[5] An example of a synthetic therapeutic peptide is exenatide (Byetta®), which is used for the treatment of diabetes mellitus type 2. The biggest drawback of peptides is their limited metabolic stability since they are readily degraded by proteolytic enzymes. In order to reduce the biodegradation of peptides, different strategies have been developed. For example, since the β-peptide bond is stable toward proteases,[6] it is useful to consider β-amino acids as building blocks for more stable peptides.[7] Furthermore, the use of conformationally restricted β-amino acids increases the conformational stability and rigidity of peptides.[8] Thus, less β-amino acid residues are required for the formation of secondary structures, as compared to α-amino acids.[9] The use of fluorine in peptide chemistry is also an emerging area[10] and the influence of fluorine substitution on the formation of secondary structures has been described.[11] One of the main limitations for the synthesis of fluorinated peptides is now the accessibility of the appropriate building blocks, namely fluorinated amino acids.

The first part of this PhD thesis will focus on the synthesis of carbocyclic β-amino acid analogues, as new building blocks for β-peptides. In previous research at our department, the synthesis of various analogues of β-aminocyclopropanecarboxylic acid has already been developed.[12] The synthesis of one enantiomer of *trans*-2-(diphenylmethylideneamino)cyclopropanecarboxylate (1*R*,2*R*)-**8** starting from (*S*)-β-benzyl *N*-(*tert*-butoxycarbonyl)aspartate has already been developed in a previous Master thesis.[13] In this work, this synthesis will be optimized and the synthesis of the other enantiomer (1*S*,2*S*)-**8** is envisaged, as well as the saponification of both enantiomers **8** toward the corresponding carboxylic acids **9**. Furthermore, coupling of these cyclopropanecarboxylic acids **9** with amino acids should lead to dipeptides **10** (Scheme 1).



Scheme 1

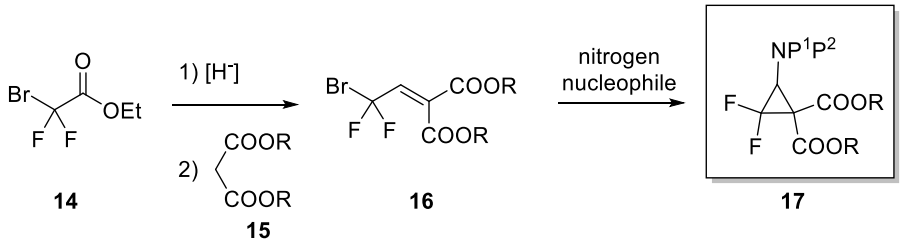
2-Aminocyclobutanecarboxylates are another class of conformationally restricted β-amino acids. In a previous Master thesis,[13] the synthesis of dialkyl β-aminocyclobutane-1,1-dicarboxylates **13** was described *via* a Michael Induced Ring Closure (MIRC) reaction. In that reaction, Michael-type addition of diphenylmethylideneamine **12** across halogenated propylidenemalonates **11** is followed by intramolecular substitution of the leaving group X, leading to ring closure. However, this reaction suffered from low yields (28-38%) and therefore, in this PhD thesis, it will be tried to optimize the synthesis of β-aminocyclobutanecarboxylates **13** (Scheme 2).



Scheme 2

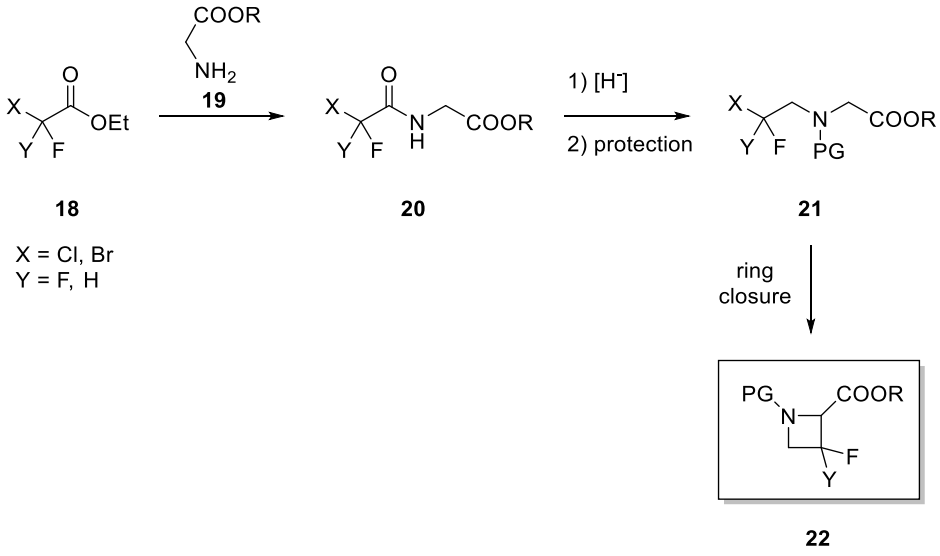
In the second part of this PhD thesis, the focus will lie on the synthesis of fluorinated conformationally restricted amino acids. As a first example, the synthesis of fluorinated 2-aminocyclopropanecarboxylates **17** will be attempted. This would be the first example of the synthesis of ring fluorinated β-aminocyclopropanecarboxylates. In analogy with the synthesis of cyclobutanes **13**, the synthesis of cyclopropanes **17** is envisaged *via* the MIRC reaction starting from the appropriate fluorinated Michael acceptors **16** and various nitrogen nucleophiles. The synthesis of ethylidenemalonates **16** should proceed starting from ethyl bromodifluoroacetate **14** *via* reduction toward the corresponding aldehyde and

subsequent Knoevenagel condensation with malonates **15** (Scheme 3). Having fluorinated β-ACC derivatives **17** hopefully in hand, their reactivity will be studied.



Scheme 3

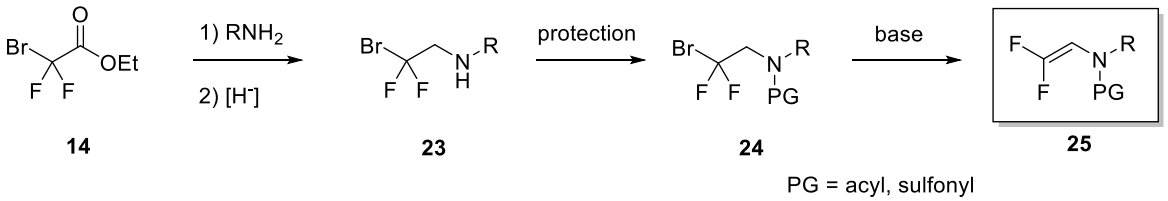
As a second class of fluorinated conformationally restricted amino acids, the synthesis of mono- and difluorinated azetidine-2-carboxylates **22** will be attempted. Based on the work of Couty, which describes the synthesis of azetidine-2-carboxylates,[14] the synthesis of azetidines **22** is envisaged *via* the base-induced ring closure of fluorinated *N*-protected amino esters **21**. Precursors **21** should be accessible *via* the condensation of amino esters **19** with fluorinated building blocks **18** leading to amides **20**, followed by selective reduction of the amide bond and protection of the amine function. In case of the monofluorinated azetidines, the stereoselectivity of the ring closure will also be evaluated (Scheme 4).



Scheme 4

The third part of this PhD thesis will be devoted to the synthesis of fluorinated heterocycles, because there is a profound interest from medicinal chemistry in this type of compounds. The use of fluorinated building blocks in the synthesis of fluorinated heterocyclic compounds avoids the need for a late-stage fluorination step, which often has a low functional group compatibility. In this work, the synthesis of a new building

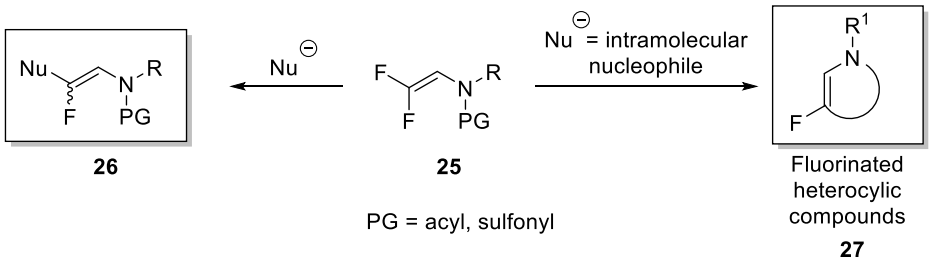
block **25** is envisaged, followed by its application in the synthesis of fluorinated heterocycles. Transformation of ethyl bromodifluoroacetate **14** into amines **23** has already been described in the literature.[15] Protection of the amine could give compounds **24**, which should be transformed into enamides **25** (PG = acyl, sulfonyl) upon treatment with base (Scheme 5).



14 **23** **24** **25**

Scheme 5

The presence of two fluorine atoms at the β-carbon atom of enamides **25**, in combination with an electron-withdrawing acyl or sulfonyl group (PG) at nitrogen, could lead to a highly polarized double bond and an electron-deficient difluorinated carbon atom. If this effect could predominate the electron-donating effect of the enamide nitrogen atom, enamides **25** would be an example of electrophilic enamides readily reacting with nucleophiles. Thus, when having enamides **25** in hand, their reactivity toward nucleophiles will be investigated, possibly leading to the formation of fluorinated enamides **26**. By incorporating the nucleophile in the same molecule as the enamide moiety, this method should give rise to the formation of fluorinated heterocycles **27** (Scheme 6).

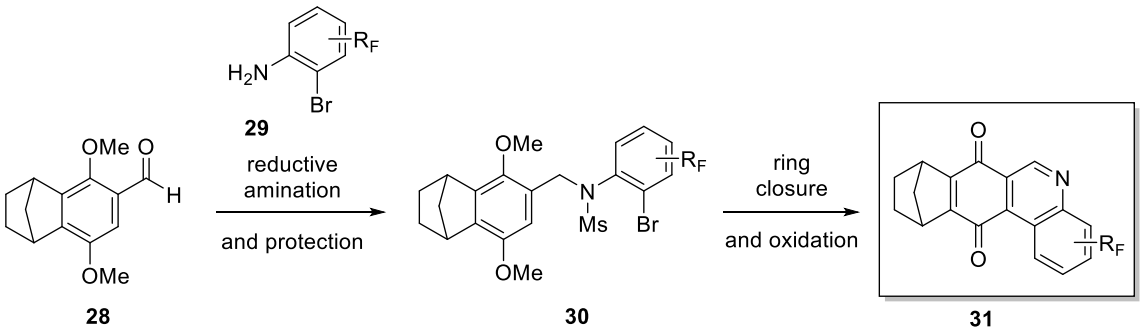


26 **25** **27**

Scheme 6

In the last part of this PhD thesis, the synthesis of fluorinated 8,9,10,11-tetrahydro-8,11-methanobenzo[*j*]-phenanthridine-7,12-diones **31** is envisioned (Scheme 7). Non-fluorinated derivatives of **31** have already been synthesized in our research group and they have been tested for activity against *Mycobacterium tuberculosis*. However, these compounds showed a low specificity since they are also active against gram positive bacteria. Therefore, the synthesis of fluorinated derivatives **31** will be attempted starting from aldehyde **28**, *via* sequential reductive amination, mesylation, ring closure and oxidation steps. These

fluorinated 8,9,10,11-tetrahydro-8,11-methanobenzo[*j*]phenanthridine-7,12-diones **31** will also be tested for activity against *M. tuberculosis.*



Scheme 7

2 Literature overview

In recent decades, much attention has been devoted to the synthesis of fluorinated amino acids, as can be seen in a number of reviews that have been published in this area.[16] However, there has been no general representation on the synthesis of small-membered ring-containing fluorinated amino acids. So, the objective of this literature overview is to give a short summary of the synthetic routes toward amino acid derivatives with a cyclopropane, cyclobutane, aziridine or azetidine core, containing one or more fluorine atoms directly attached to the carbo- or heterocyclic ring. Carbo- or heterocyclic amino acids incorporating the fluorine atoms in a trifluoromethyl group or on a side chain will not be discussed here, just like the higher homologues, i.e. amino acids containing a five- or six-membered ring as a core structure and oxa- and thiaheterocyclic compounds.

2.1 Synthesis of ring fluorinated 1-amino- and 2-aminocyclopropanecarboxylic acid derivatives

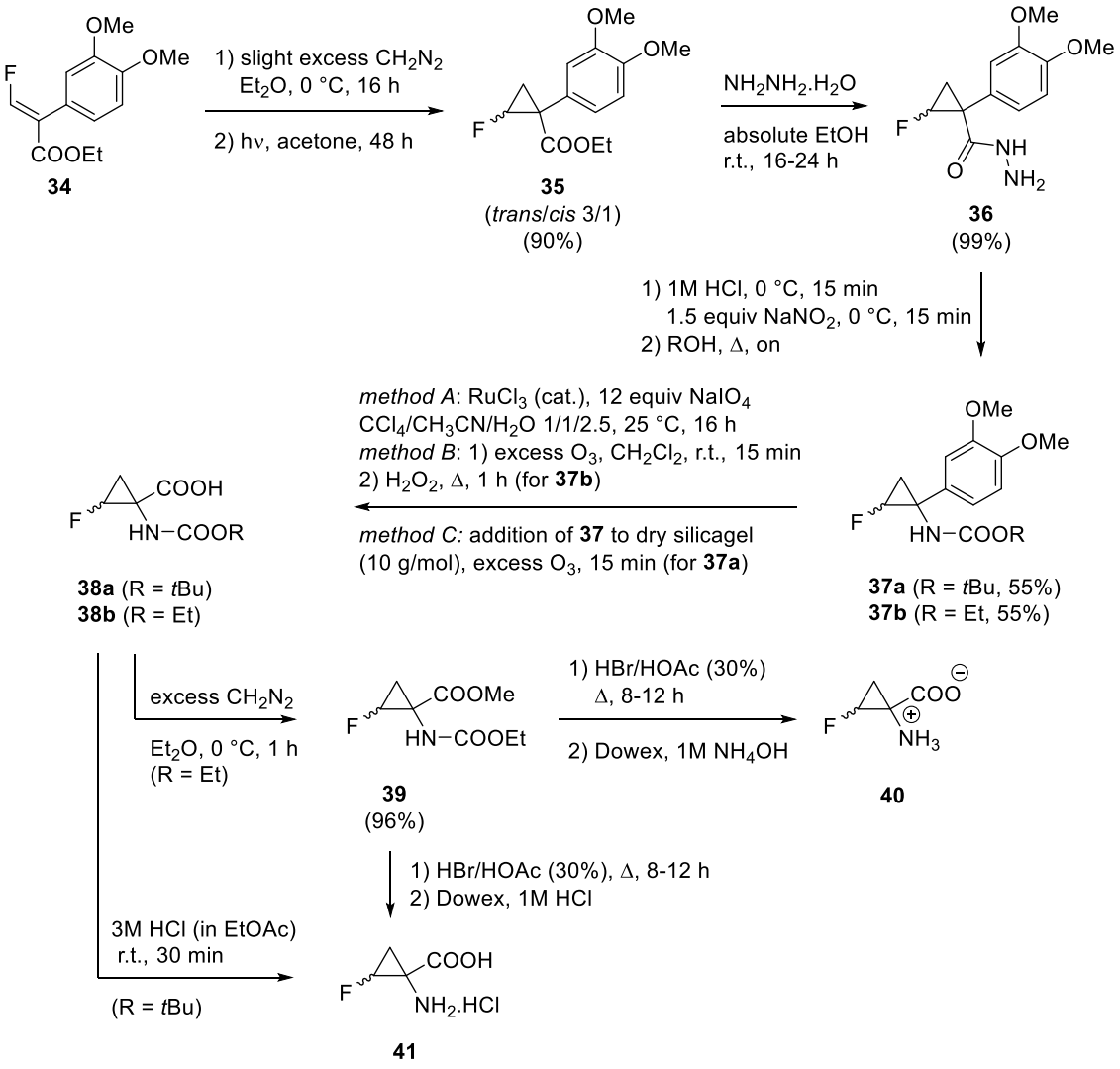
1-Aminocyclopropanecarboxylic acid (α-ACC), the precursor of the plant hormone ethylene, and 2-aminocyclopropanecarboxylic acid (β-ACC) are the two carbocyclic amino acids possessing the most severe ring strain. In the first part of this literature overview, the synthesis of ring fluorinated analogues of α-ACC **32** and β-ACC **33** will be discussed (Figure 4).

32 **33**

Figure 4

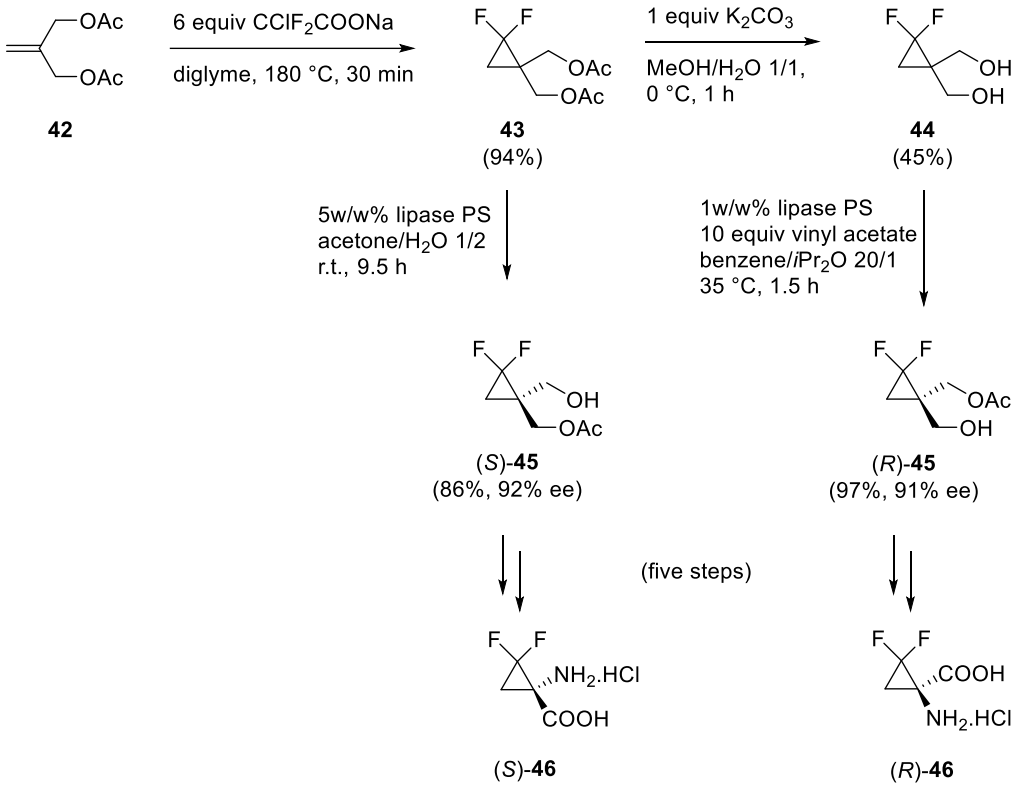
The first synthesis of a ring fluorinated 1-aminocyclopropanecarboxylic acid was reported in 1997 (Scheme 8).[17] In the first step of this reaction sequence, treatment of acrylate **34**[18] with diazomethane (CH_2N_2) afforded the corresponding pyrazoline, which underwent photochemical expulsion of dinitrogen, leading to the formation of cyclopropanes **35** (*trans*/*cis* 3/1). Subsequently, this diastereomeric mixture **35** was converted into hydrazides **36** in excellent yield by treatment with hydrazine monohydrate in ethanol. Curtius rearrangement of hydrazines **36** toward carbamates **37** was performed by addition of $NaNO_2$ in the presence of HCl, followed by heating at reflux temperature using the corresponding alcohol

as solvent. In the next step, the oxidation of the aromatic moiety of cyclopropanes **37** was studied. A first method (method A) comprised the oxidation by means of RuO_4, prepared *in situ* from $RuCl_3$, in the presence of $NaIO_4$ as a co-oxidant. However, ozonolysis followed by an oxidative work-up in H_2O_2 proved to be a more suitable route toward acids **38b** (R = Et, method B). For the synthesis of *tert*-butyl esters **38a**, ozonolysis over dry silica gel gave the best results (method C). No yields were reported for this oxidation step. In a last step, removal of the Boc-protecting group of carbamates **38a** proceeded smoothly in the presence of 3M HCl in EtOAc to afford fluorinated ACC derivatives **41**, as a mixture of two isomers. In case of derivatives **38b**, the carboxylic acids were first converted into the corresponding methyl esters **39** by treatment with CH_2N_2. Hydrolysis of carbamates **39** was achieved in a solution of HBr in HOAc under reflux conditions, affording the corresponding hydrobromic acids which were subjected to ion exchange chromatography over Dowex® using 1M HCl as the eluent, leading to hydrochloric acids **41**, or using NH_4OH as the eluent, which led to the formation of the free amino acids **40**. No yields were reported for this last step. The *trans*-isomer *trans*-**41** was obtained in pure form applying the same reaction sequence on hydrazide *trans*-**36**, which precipitated upon concentration of the solution after conversion of esters **35** into hydrazides **36**. 1-Aminocyclopropanecarboxylic acid (α-ACC) is a potent glycine agonist on the *N*-methyl-D-aspartate (NMDA) receptor ion chanel,[19] a very important receptor involved in the process of learning and memory.[20] The activity of 1-amino-2-fluorocyclopropanecarboxylic acid **40** was also tested in this regard, and it proved to be comparable to α-ACC itself.



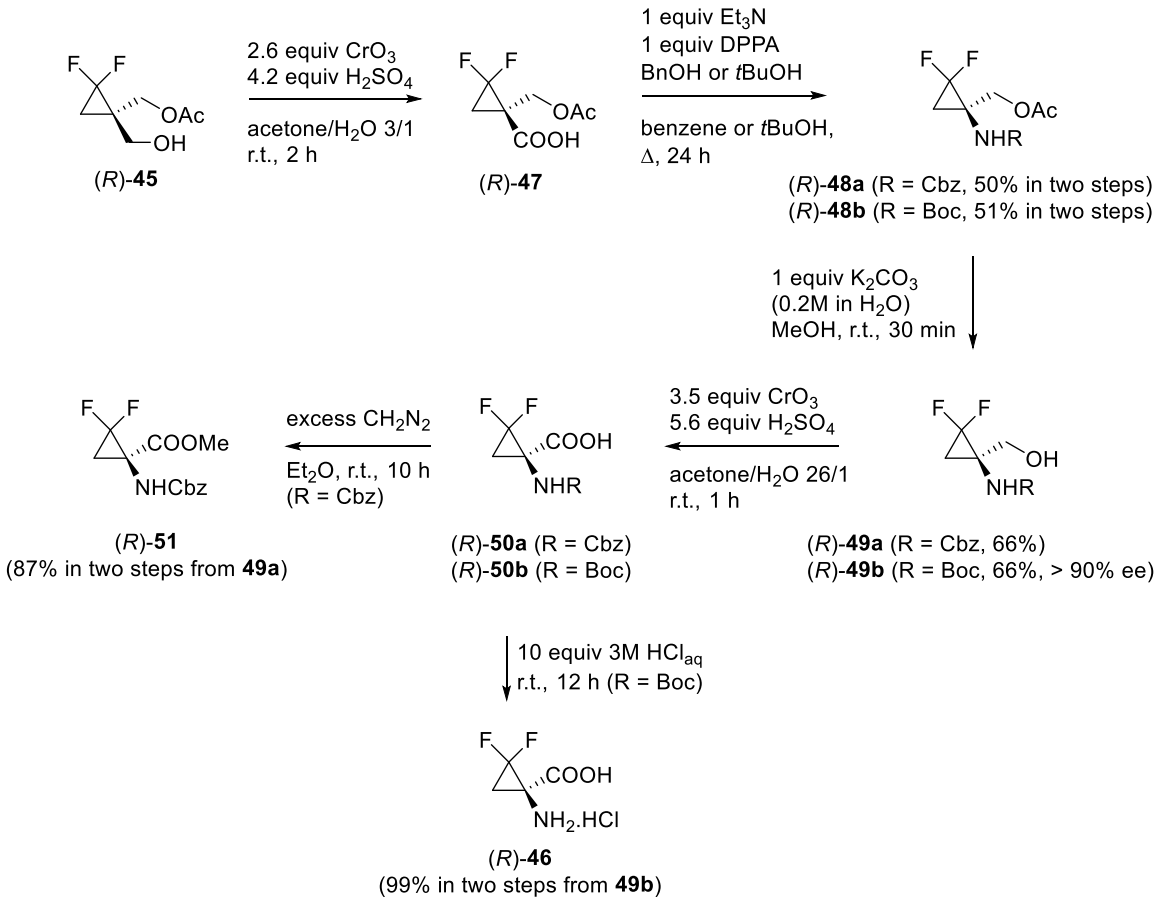
Scheme 8[17]

An enantioselective synthetic pathway toward *gem*-difluorinated 1-aminocyclopropanecarboxylic acids (*S*)-**46** and (*R*)-**46** has also been developed, starting from diacetoxy alkene **42** (Scheme 9, Scheme 10).[21] Cyclopropanation of alkene **42** by addition of difluorocarbene, derived from sodium chlorodifluoroacetate, led to the formation of fluorinated cyclopropane **43**, which was hydrolyzed toward diol **44** using potassium carbonate in a methanol/water mixture (1/1). A lipase-catalysed (Amano PS from *Pseudomonas cepacia*) desymmetrization of prochiral precursors **43** and **44** led to the formation of monoacetates (*S*)-**45** and (*R*)-**45**, respectively, which were converted into 2,2-difluoro-1-aminocyclopropanecarboxylic acids (*S*)-**46** and (*R*)-**46** in five steps (Scheme 9).



Scheme 9[21]

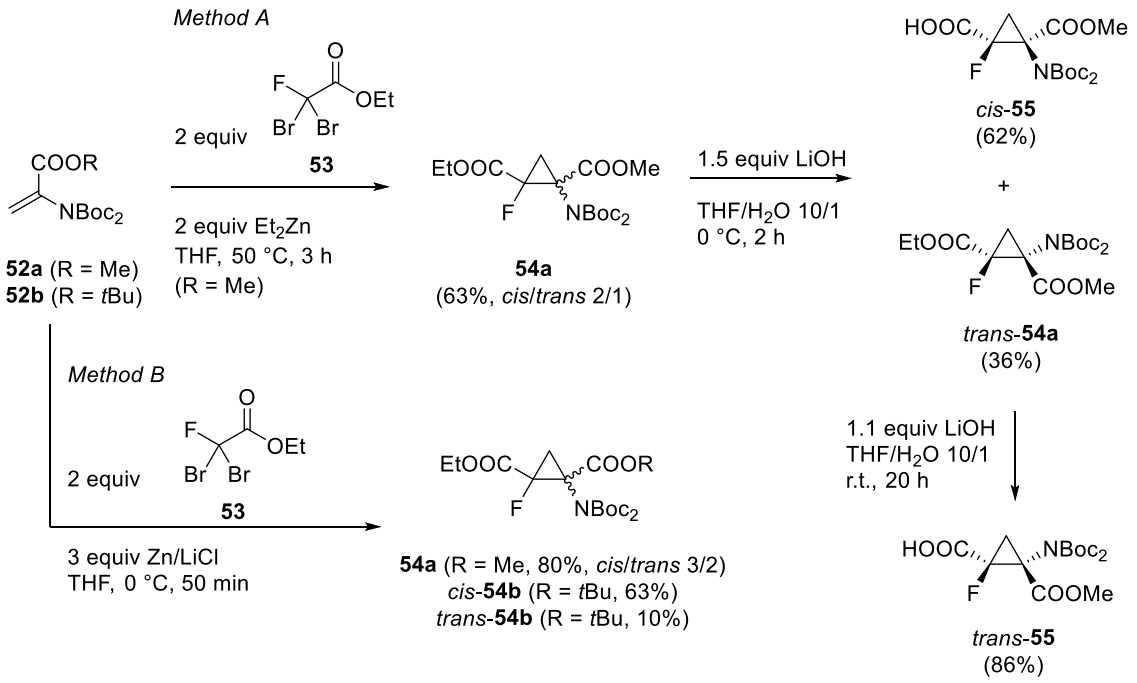
The synthesis of carboxylic acid (*R*)-**46** from monoacetate (*R*)-**45** is presented in detail in Scheme 10. Jones oxidation of alcohol (*R*)-**45** toward carboxylic acid (*R*)-**47**, followed by Curtius rearrangement using diphenylphosphoryl azide (DPPA) in the presence of benzyl alcohol or *tert*-butanol afforded carbamates (*R*)-**48a** and (*R*)-**48b**. Removal of the acetate protecting group was achieved by stirring carbamates (*R*)-**48** in MeOH in the presence of K_2CO_3 for 30 minutes at room temperature and subsequent Jones oxidation afforded carboxylic acids (*R*)-**50a** and (*R*)-**50b**. While the Cbz-protecting group in compound (*R*)-**50a** could not be removed under various reaction conditions, deprotection of compound (*R*)-**50b** could be achieved upon stirring in an aqueous solution of HCl, leading to cleavage of the Boc group and the formation of the envisaged hydrochloric salt (*R*)-**46**. Carboxylic acid (*R*)-**50a** were converted into the corresponding methyl ester (*R*)-**51** by treatment with an excess of diazomethane.



Scheme 10[21]

Besides the synthesis of the above-mentioned mono- and difluorinated 1-aminocyclopropanecarboxylic acids, some examples of fluorinated derivatives of α-ACC containing extra functional groups have also been described. In the diastereoselective synthesis of novel fluorinated glutamic acid analogues **56**-**61**, cyclopropane-1,2-dicarboxylates *cis*-**55** and *trans*-**55** were obtained as intermediates (Scheme 11, Scheme 12).[22] A Michael Induced Ring Closure (MIRC) reaction using *N*-Boc-protected methyl 2-aminoacrylate **52a** and the Reformatsky reagent derived from ethyl dibromofluoroacetate **53**, prepared using Et_2Zn (Method A), led to the formation of cyclopropanes **54a** as a mixture of two diastereomers (*cis*/*trans* 2/1). Alternatively, cyclopropanes **54a** could also be prepared using Zn in the precense of LiCl in a total yield of 80%, but with a lower diastereoselectivity (*cis*/*trans* 3/2).[23] In the preparation of the corresponding *tert*-butyl esters **54b**, a higher diastereomeric ratio (*cis*/*trans* 8/2) was observed, due to presence of the bulky *tert*-butyl group. The two diastereomers *cis*-**54b** and *trans*-**54b** were isolated in 63% and 10% yield, respectively. Subsequently, using the mixture of diesters **54a** (*cis*/*trans* 2/1), a regio- and diastereoselective saponification of the ethyl ester of diester *cis*-**54a** using LiOH at 0 °C afforded a mixture

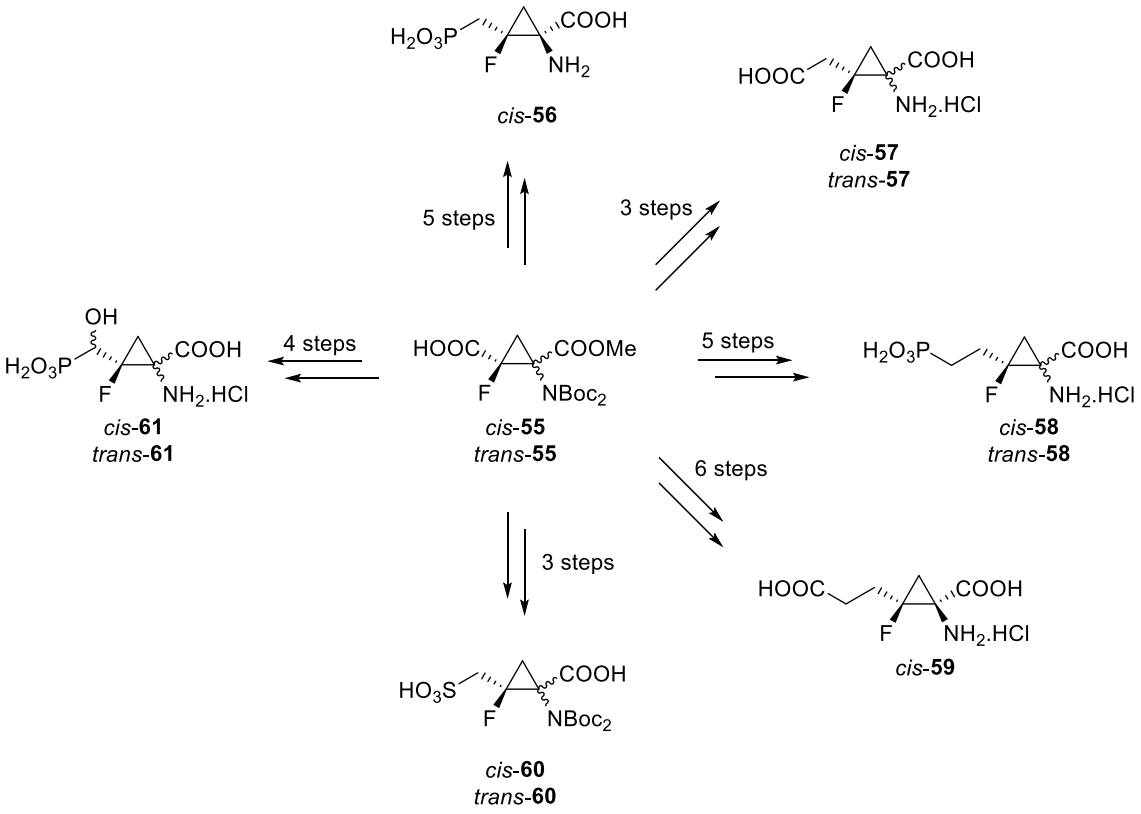
of carboxylic acid *cis*-**55** and ethyl ester *trans*-**54a**, which could be separated *via* acid/base extraction. In a next step, the regioselective saponification of diester *trans*-**54a** toward carboxylic acid *trans*-**55** was achieved with LiOH at room temperature.



Scheme 11[22]

Cyclopropanecarboxylates *cis*-**55** and *trans*-**55** were then converted into a variety of fluorinated cyclopropyl-containing glutamic acid analogues **56**-**61** (Scheme 12). Phosphonic acid *cis*-**56** was prepared *via* a sequential reduction, mesylation, iodination and Arbuzov condensation, followed by a complete deprotection in the last step. This reaction sequence could not be applied for the synthesis of the corresponding *trans*-**56**. Reduction of *cis*-**55** and *trans*-**55** toward the corresponding alcohol, followed by a Mitsunobu reaction with 2-hydroxy-2-methylpropanenitrile and hydrolysis furnished dicarboxylates *cis*-**57** and *trans*-**57**. Furthermore, the homologated derivatives *cis*-**58**, *trans*-**58** and *cis*-**59** were prepared by transformation of the carboxylic acid of *cis*-**55** or *trans*-**55** into the corresponding aldehydes, followed by a Horner-Wadsworth-Emmons condensation, hydrogenation of the alkenes and a subsequent deprotection/hydrolysis step. Sulfonic acids *cis*-**60** and *trans*-**60** were also prepared *via* the corresponding alcohols of compounds *cis*-**55** and *trans*-**55**, followed by a Mitsunobu reaction using thioacetic acid as the nucleophile and a subsequent one pot oxidation and hydrolysis step. Finally, branched phosphonic acids *cis*-**61** and *trans*-**61** were prepared by the addition of diethyl phosphite across the corresponding aldehydes of compounds *cis*-**55** and *trans*-**55**, followed by hydrolysis of the protecting groups.

Subsequently, these compounds were tested as agonists of metabotropic glutamate receptor subtype 4 (mGluR4), revealing a potency of phosphonic acid *cis*-**56** which is ten times higher than that of glutamate. Furthermore, phosphonic acid *cis*-**56** proved to be seven times more potent than the non-fluorinated analogue.



Scheme 12[22]

Furthermore, cyclopropanecarboxylates *cis*-**55** and *trans*-**55** were used as building blocks for the synthesis of various fluorinated cyclopropyl amino acid analogues, more specifically methionine **62**, leucine **63**, lysine **64** and arginine *cis*-**65** analogues (Figure 5).[24]

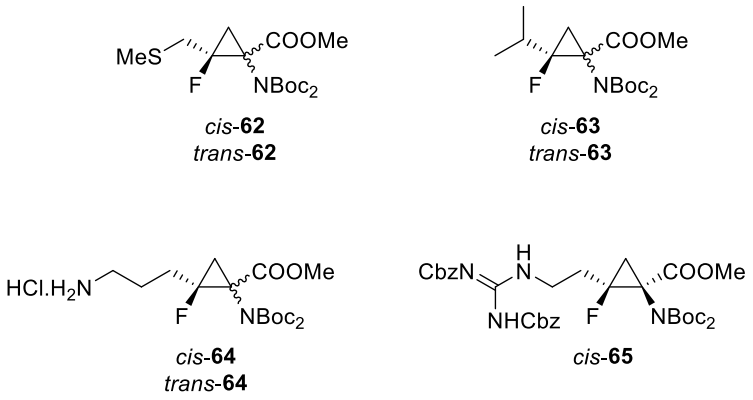
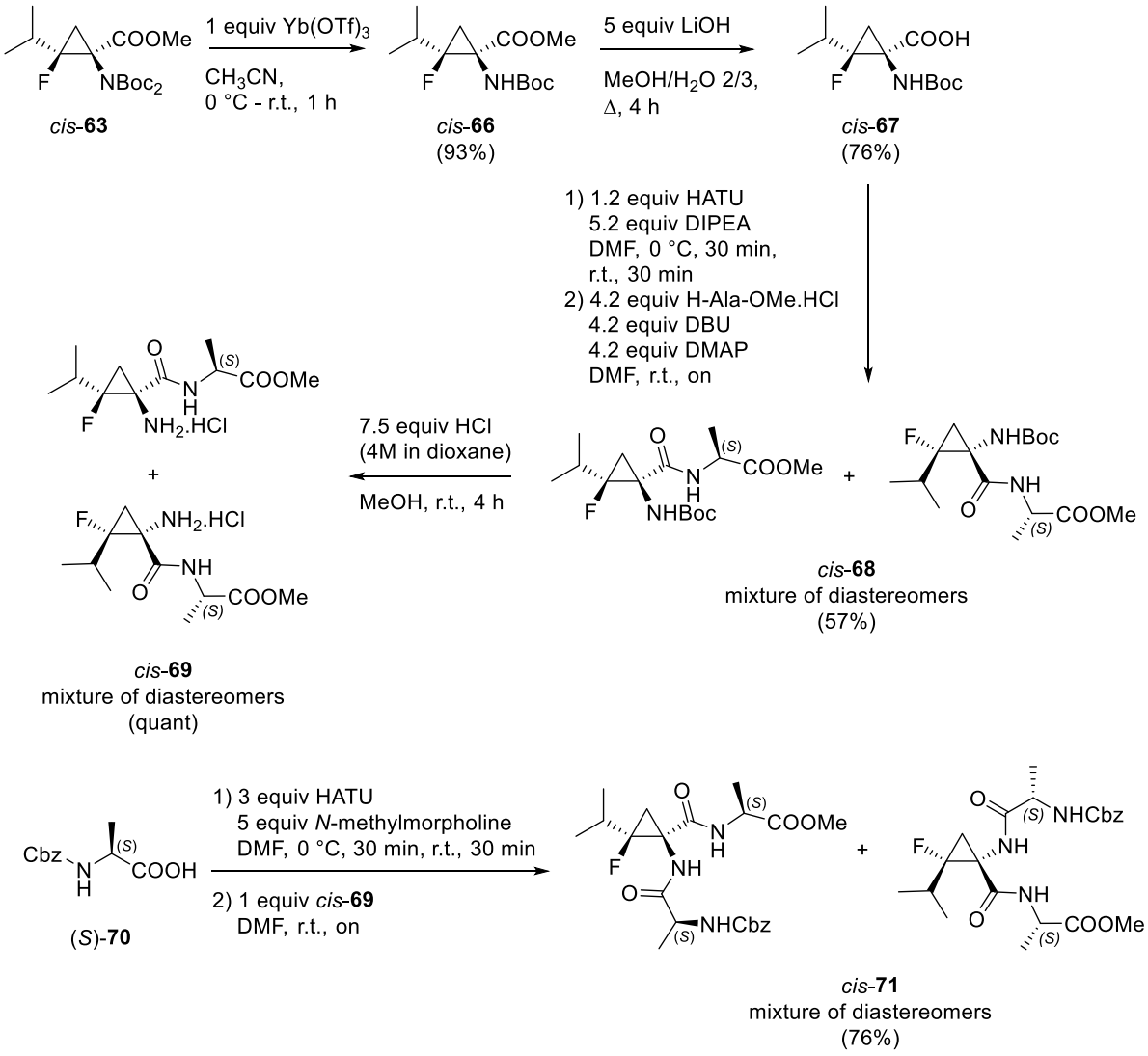


Figure 5[24]

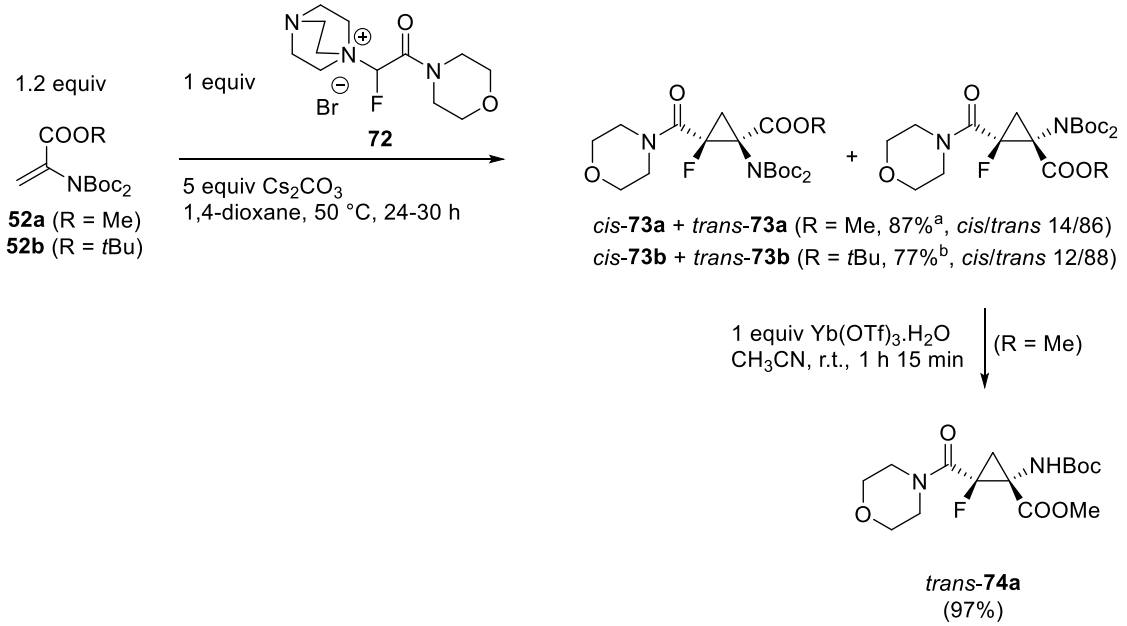
Additionally, the incorporation of fluorinated ACC derivative *cis*-**63** in a tripeptide was reported. This was the first example of a tripeptide incorporating a fluorinated cyclopropane amino acid analogue (Scheme 13).[24] To this end, protected amino acid derivative *cis*-**63** was converted into the mono *N*-Boc protected carboxylic acid *cis*-**67** in two steps, by a selective monodeprotection of the amine using $Yb(OTf)_3$ followed by hydrolysis of the ester to give the corresponding carboxylic acid. In the next step, a standard peptide-coupling reaction was employed for the synthesis of dipeptide *cis*-**68** which was obtained as a mixture of diastereomers in 57% yield. Removal of the resulting Boc group in dipeptide *cis*-**68** was achieved by treatment with HCl in dioxane and MeOH, leading to hydrochloric salt *cis*-**69** in quantitative yield. In a last step, coupling of this dipeptide *cis*-**69** with Cbz-Ala-OH **70** was achieved, again using a standard peptide-coupling technique, leading to the unprecedented fluorinated cyclopropyl-containing tripeptide *cis*-**71** in 76% yield, as a mixture of diastereomers.



Scheme 13[24]

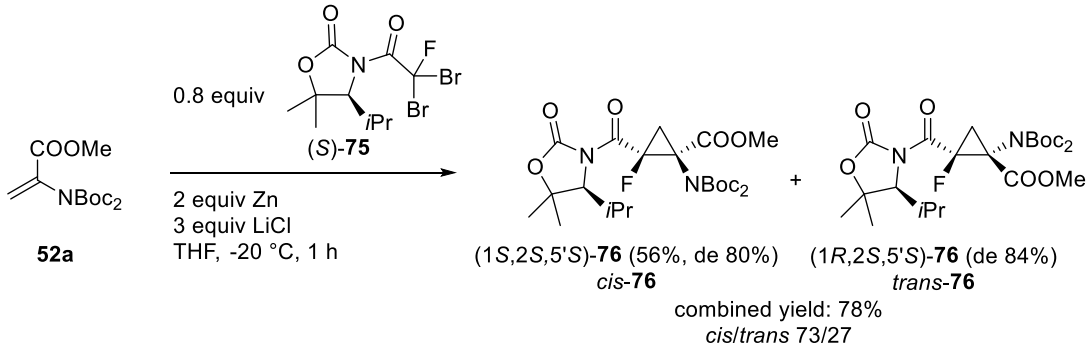
Monofluorinated ACC derivatives **73** were also synthesized in a diastereoselective way using quaternary ammonium salt **72** in a MIRC reaction with Michael acceptors **52** (Scheme 14).[25] This reaction, which probably proceeds *via* a two-step mechanism, afforded a mixture of two isomers *cis*-**73** and *trans*-**73** with good diastereoselectivity. In case of the methyl ester **73a**, the two isomers were separated and were obtained in a total yield of 87% (separate yields were not mentioned), while the *tert*-butyl derivatives **73b** were inseparable and a combined yield of 77% was reported. The cyclopropanation of methyl acrylate **52a** could also be effectuated in a one-pot reaction, by treatment of acrylate **52a** with DABCO and 2-bromo-2-fluoro-1-morpholinoethan-1-one in the presence of Cs_2CO_3. The two isomers *cis*-**73a** and *trans*-**73a** were obtained with a similar diastereoselectivity (*cis*/*trans* 12/88) and were isolated in 8% and 59% yield, respectively. Selective removal of one of the Boc protecting groups of cyclopropane *trans*-**73a** was

effectuated using $Yb(OTf)_3.H_2O$ in dry acetonitrile leading to the formation of ACC derivative *trans*-**74a** which was isolated in an excellent yield of 97%.[25]



Scheme 14[25] [a] Sum of the yields of the isolated isomers *cis*-**73a** and *trans*-**73a**.
[b] Combined yield, the isomers *cis*-**73b** and *trans*-**73b** could not be separated *via* column chromatography.

Furthermore, the enantioselective version of the synthetic route toward 1-amino-2-fluorocyclopropanecarboxylates was developed, again *via* a Reformatsky reaction using the combination of Zn and LiCl as metalating reagents for the cyclopropanation (Scheme 15).[26] As a chiral auxiliary, dibromofluoroacetylated oxazolidinone (*S*)-**75** was employed. The reaction proceeded smoothly, leading to a mixture of two diastereomers *cis*-**76** and *trans*-**76** with a good *cis*/*trans* ratio of 73/27 and a good combined yield of 78%. The major isomer *cis*-**76** was isolated in 56% yield and showed a diastereomeric excess of 80%.



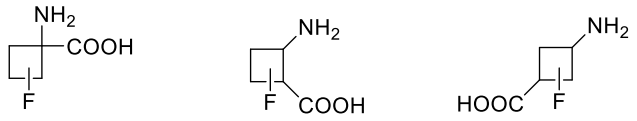
Scheme 15[26]

Additionally, some examples of trifluoromethylated 1- or 2-aminocyclopropanecarboxylic acid derivatives have been reported.[27] But as mentioned before, these examples will not be discussed in detail since this exceeds the scope of this literature overview.

In conclusion, various mono- and difluorinated derivatives of 1-aminocyclopropanecarboxylic acid have been reported, while the synthesis of ring fluorinated 2-aminocyclopropanecarboxylic acid derivatives has been limited to cyclopropanes **55**, which can be seen as α-ACC-derivatives with an extra carboxylic acid functionality at C2. This is probably due to the inherent instability of β-ACC caused by its 1,2-donor-acceptor substituted cyclopropane structure. Therefore, a suitable protecting group at nitrogen is essential to avoid spontaneous ring opening of the cyclopropane core, which complicates the synthesis of β-ACC derivatives.

2.2 Synthesis of ring fluorinated 1-amino- and 2-aminocyclobutanecarboxylic acid derivatives

In the second part of this literature overview, the synthesis of the higher carbocyclic homologues, cyclobutanes incorporating an amino acid functionality, will be discussed. This section is divided in two different parts, more specifically the synthesis of ring fluorinated 1-aminocyclobutanecarboxylic acid analogues **77** and ring fluorinated 2-aminocyclobutanecarboxylic acids analogues **78** (Figure 6). Since no relevant references were found concerning the synthesis of fluorinated 3-aminocyclobutanecarboxylic acid derivatives **79**, these will not be discussed in this section.



77 **78** **79**

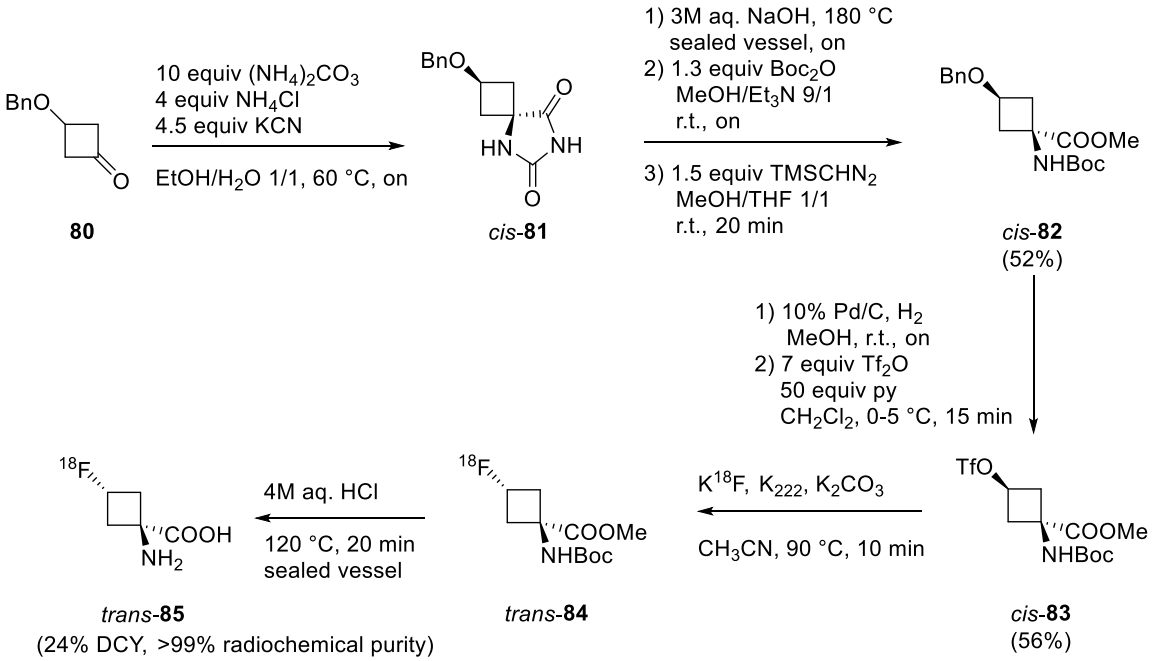
Figure 6

2.2.1 Ring fluorinated 1-aminocyclobutanecarboxylic acid derivatives

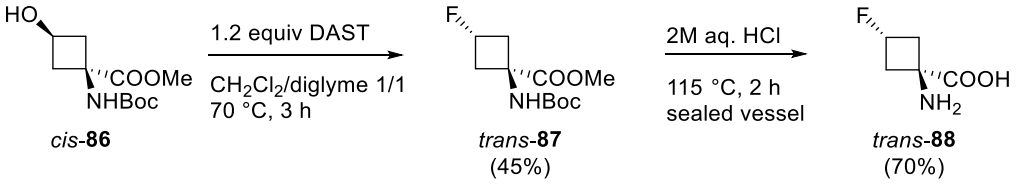
An important example of a ring fluorinated cyclobutane-containing amino acid is *trans*-1-amino-3-[^{18}F]cyclobutane-1-carboxylic acid (*trans*-[^{18}F]FACBC) *trans*-**85** or [^{18}F]fluciclovine. This unnatural ^{18}F-labelled amino acid is used as a tracer in Positron Emission Tomography (PET), an imaging technique.[28] PET-tracers are molecules that are labelled with a radioactive isotope, for example ^{18}F. When this

radioactive isotope emits a positron from its nucleus, this positron will come in contact with an electron and annihilation will occur, a process in which two gamma-rays are produced. These gamma-rays can be detected, and as such the place of annihilation can be determined. 2-^{18}F-Fluoro-2-deoxy-D-glucose ([^{18}F]FDG) is a commonly used PET tracer. When this compound is administered to a patient, it accumulates more in tumors than in normal cells, since tumors have a higher rate of glucose metabolism. As such, Positron Emission Tomography is a technique to detect tumors. In many tumors there is also an increased amino acid transport as compared to normal tissues and therefore, the use of amino acids for tumor imaging is also well established. Since the use of natural amino acids in which a radioisotope is incorporated can lead to the formation of numerous radiolabelled metabolites, research has been devoted to the synthesis of ^{18}F-labelled unnatural amino acids, such as (*trans*-[^{18}F]FACBC) *trans*-**85**. This PET tracer is currently undergoing human clinical trials phase 2 for its validation as an imaging agent for the diagnosis and management of cancer treatment.[29]

The first synthesis of 1-amino-3-fluorocyclobutane-1-carboxylic acid (FACBC) labelled with fluorine-18 was reported in 1999 and comprised ten steps.[30] In this synthetic procedure, epichlorohydrine was converted into hydantoin **81** in four steps. A drawback of this synthesis was the low diastereoselectivity of the hydantoin-synthesis and the difficult scale-up. Therefore, in 2003 an improved synthesis was reported (Scheme 16).[31] In this pathway, hydantoin *cis*-**81** was obtained as the major diastereomer after a modified Strecker synthesis (*cis*/*trans* ratio after reaction: 5/1). Hydrolysis of the hydantoin ring toward the corresponding α-amino acid was achieved by heating in 3M aq. NaOH. Double protection of the amino acid furnished methyl 3-benzyloxy-1-(*tert*-butoxycarbonylamino)cyclobutanecarboxylate *cis*-**82**. The 3-benzyloxy substituent was transformed into a good leaving group by hydrogenolysis followed by treatment with trifluoromethanesulfonic anhydride, yielding triflate *cis*-**83**, a suitable precursor for the introduction of fluorine-18. In an automated radiosynthesis, triflate *cis*-**83** was reacted with K^{18}F which led to the formation of fluorinated cyclobutane *trans*-**84**. In a last step, treatment with HCl furnished the deprotected [^{18}F]-1-amino-3-fluorocyclobutanecarboxylic acid *trans*-**85**. The corresponding 'cold' FACBC *trans*-**88** was synthesized by reacting alcohol *cis*-**86** with DAST, followed by hydrolysis using 2M aq. HCl (Scheme 17).[30]



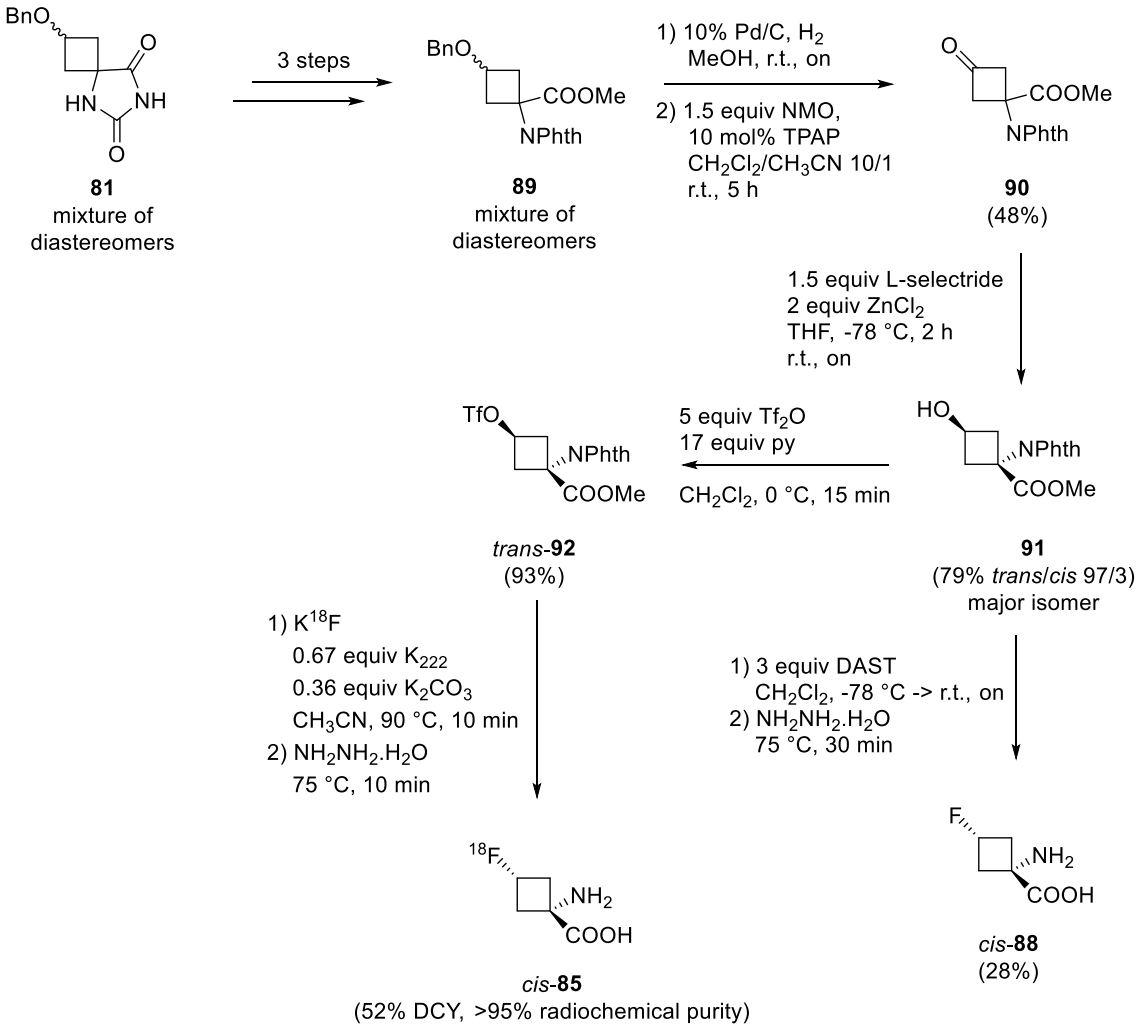
Scheme 16[31]



Scheme 17[31]

Next to *trans*-1-amino-3-fluorocyclobutanecarboxylic acid *trans*-**85**, the other isomer *cis*-**85** has also been synthesized and tested as a potential brain tumor imaging agent (Scheme 18).[32] In this synthetic pathway, the two isomers *cis*-**81** and *trans*-**81**, obtained after hydantion formation (Scheme 16) were not separated, but used as a diastereomeric mixture in the next steps. Thus, hydantoins **81** were converted into methyl cyclobutanecarboxylates **89** in three steps. After debenzylation using 10% Pd/C and oxidation of the resulting secondary alcohol toward cyclobutanone **90**, a diastereoselective reduction of the ketone was established, using L-selectride in combination with zinc chloride as a chelating Lewis acid. The introduction of fluorine was achieved using DAST in the case of the 'cold' amino acid *cis*-**88** and *via* triflation followed by treatment with $K^{18}F$ in case of the radiolabelled amino acid *cis*-**85**. In the last step, removal of the phthalimido protecting group was effectuated using hydrazine monohydrate. The biological evaluation of

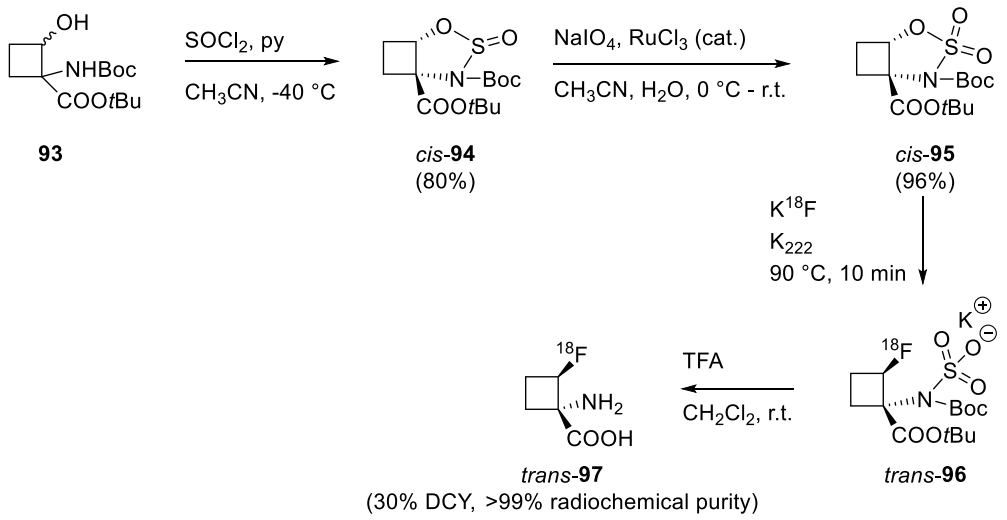
cis-[^{18}F]FACBC *cis*-**85** in rodent 9L gliosarcoma brain tumor model showed comparable results as its isomer *trans*-[^{18}F]FACBC *trans*-**85**, rendering it also a promising PET brain tumor imaging agent.



Scheme 18[32]

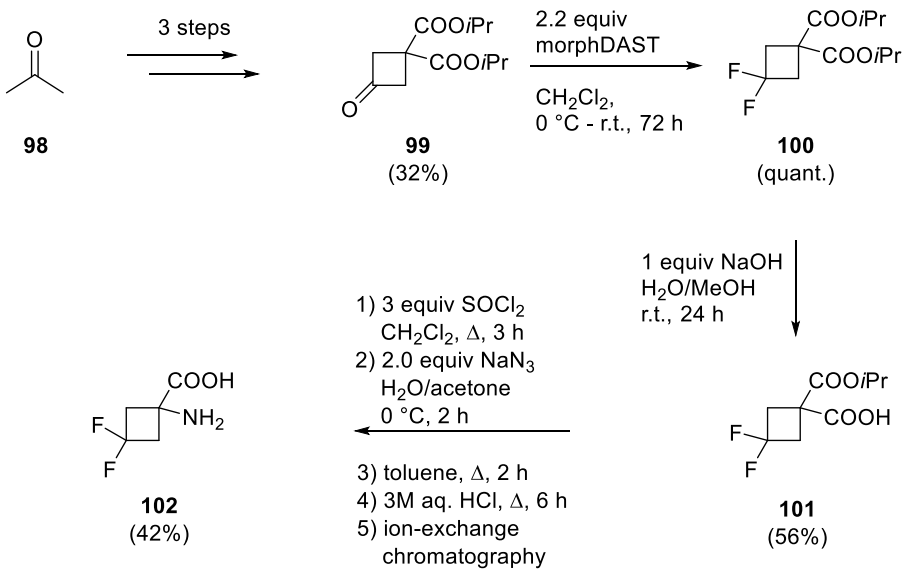
Furthermore, to test the potency of structural isomer *trans*-1-amino-2-[^{18}F]cyclobutane-1-carboxylic acid *trans*-**97** as a PET brain tumor imaging agent, a synthetic route toward this compound was also developed (Scheme 19).[33] Starting from 1,2-di(trimethylsilyloxy)cyclobutene, the intermediate *tert*-butyl 1-amino-2-hydroxycyclobutanecarboxylate **93** was prepared in six steps. The key step in the reaction sequence toward amino acid *trans*-**97** was the formation of the cyclic sulfamidite *cis*-**94** by reaction of amino alcohol **93** with thionyl chloride, exclusively yielding the *cis* derivative *cis*-**94**. This sulfamidite *cis*-**94** was oxidized toward sulfamidate *cis*-**95**, which was subsequently converted into ^{18}F-labelled *tert*-butyl cyclobutanecarboxylate *trans*-**96** by treatment with K^{18}F. Hydrolysis by treatment with trifluoroacetic acid

in CH_2Cl_2 afforded the desired *trans*-1-amino-2-[^{18}F]cyclobutane-1-carboxylic acid *trans*-**97**. Biological evaluation of this compound supported its candidacy as a promising PET brain tumor imaging agent.



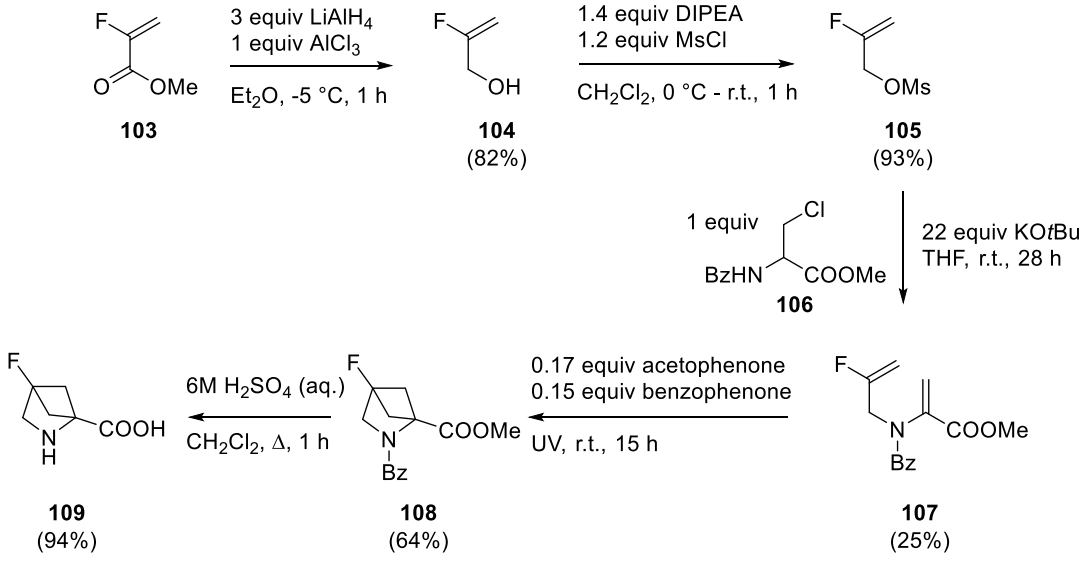
Scheme 19[33]

The synthesis of a difluorinated cyclobutane-containing α-amino acid, more specifically 1-amino-3,3-difluorocyclobutanecarboxylic acid **102** is depicted in Scheme 20.[34] Precursor **99** was synthesized from acetone **98** in three steps in 32% yield. Fluorination of cyclobutanone **99** was effectuated using morphDAST, leading to diisopropyl 3,3-difluorocyclopropane-1,1-dicarboxylate **100** in quantitative yield. The first step in the conversion of dicarboxylate **100** toward the corresponding amino acid comprised a monosaponification toward carboxylic acid **101**. Subsequently, transformation of the carboxyl group into an amino group was achieved by means of a Curtius reaction. In a last step, hydrolysis of the remaining isopropyl ester was established using 3M aq. HCl under reflux conditions, furnishing amino acid **102** in 42% yield after ion-exchange chromatography.



Scheme 20[34]

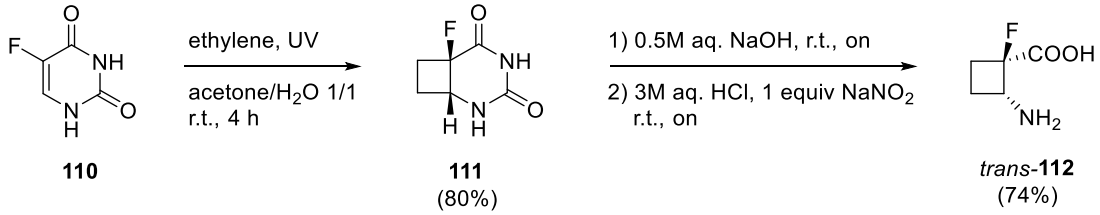
As a last example of a fluorinated α-amino acid containing a cyclobutane core, the synthesis of 4-fluoro-2,4-methanoproline **109** is described (Scheme 21).[35] Methyl 2-fluoroacrylate **103** was reduced toward allyl alcohol **104** using AlH_3, generated *in situ* from $LiAlH_4$ and $AlCl_3$, which was subsequently transformed into mesylate **105**. Coupling of this mesylate **105** with amino ester **106** afforded diene **107**, the key intermediate of this synthetic pathway. A photochemical intramolecular [2+2]-cycloaddition of diene **107** led to the formation of bicyclic compound **108** which was hydrolyzed toward 4-fluoro-2,4-methanoproline **109** in 94% yield.



Scheme 21[35]

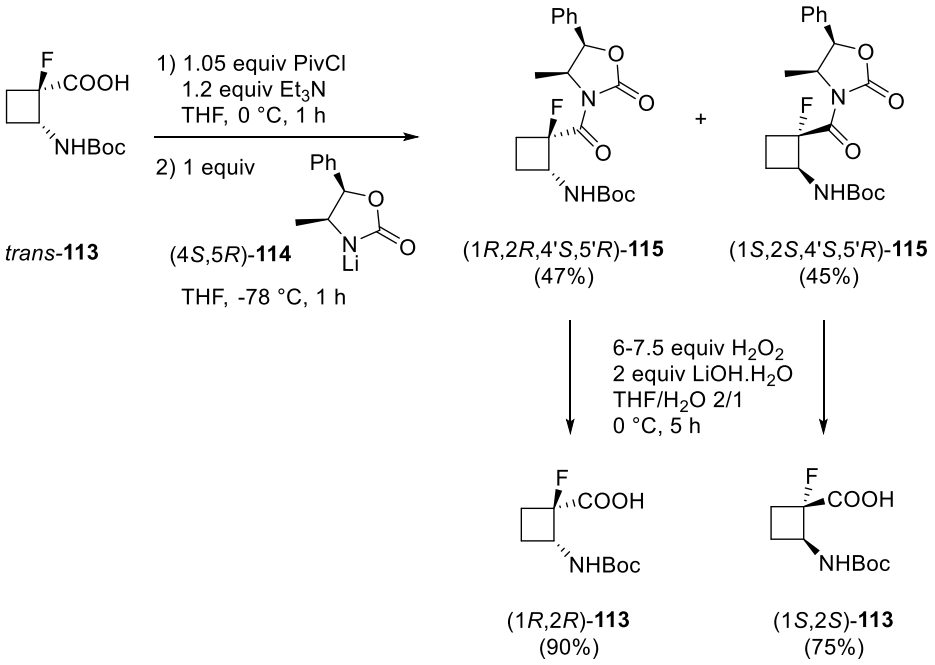
2.2.2 Ring fluorinated 2-aminocyclobutanecarboxylic acid derivatives

An important synthetic methodology for the synthesis of cyclobutanes is a [2+2]-cycloaddition reaction. Also for the synthesis of ring fluorinated 2-aminocyclobutanecarboxylic acid derivatives, the [2+2]-cycloaddition strategy has been applied. In that respect, the photocycloaddition between fluorinated nucleic bases and various olefins has been studied extensively, often leading to the formation of polycyclic compounds containing a fluorinated cyclobutane moiety.[36] Since this exceeds the scope of this literature overview, these examples will not be discussed in detail. In one case however, the [2+2]-cycloaddition between 5-fluorouracil **110** and ethylene was used for the synthesis of the bicyclic compound **111**, which was transformed into *trans*-2-amino-1-fluorocyclobutanecarboxylic acid *trans*-**112** (Scheme 22).[37]



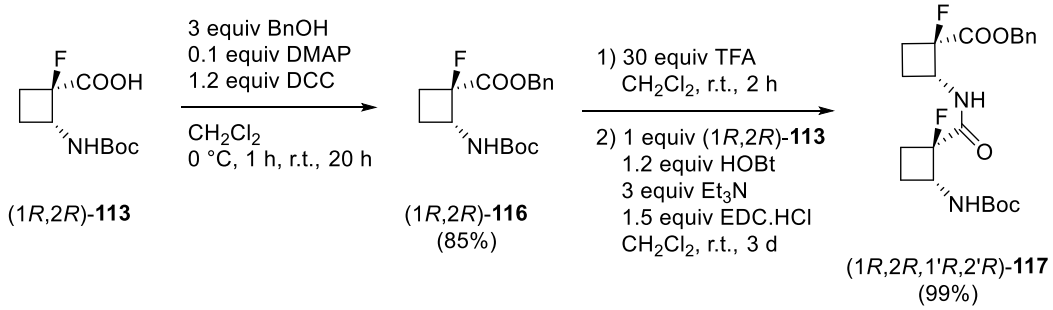
Scheme 22[37]

N-Boc-2-amino-1-fluorocyclobutanecarboxylic acid *trans*-**113** was prepared *via* the same methodology as described above (Scheme 22), starting from 1-Boc-5-fluorouracil (Scheme 23).[38] Chiral derivatisation of this compound *trans*-**113** by coupling with lithiated oxazolidinone (4*S*,5*R*)-**114** furnished diastereomers **115** which were isolated in 47% and 45% yield. Removal of the oxazolidinone moiety was established by treatment with LiOOH furnishing enantiopure 1-fluorocyclobutanecarboxylic acids (1*R*,2*R*)-**113** and (1*S*,2*S*)-**113** in 90% and 75% yield, respectively.



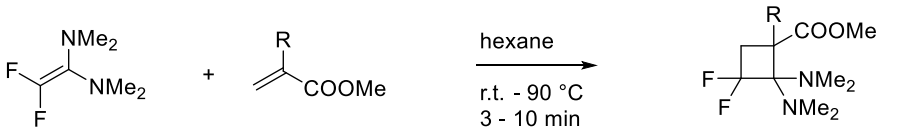
Scheme 23[38]

The incorporation of the enantiopure fluorinated β-aminocyclobutanecarboxylic acid (1*R*,2*R*)-**113** in homo-oligomers was achieved by using standard peptide coupling techniques.[38] The formation of dimer (1*R*,2*R*,1'*R*,2'*R*)-**117** is depicted in Scheme 24. The conversion of carboxylic acid (1*R*,2*R*)-**113** into the corresponding benzyl ester (1*R*,2*R*)-**116** was achieved by reaction with benzyl alcohol in the presence of DCC in dichloromethane. In the next step, the Boc-protecting group of cyclobutane (1*R*,2*R*)-**116** was removed and the corresponding amine was coupled with carboxylic acid (1*R*,2*R*)-**113** to give dipeptide (1*R*,2*R*,1'*R*,2'*R*)-**117** in excellent yield. The synthesis of four- and six-membered oligomers proceeded *via* the same methodology. After investigation of their conformational preference, it was concluded that these homo-oligomers adopt a strand-like secondary structure.



Scheme 24[38]

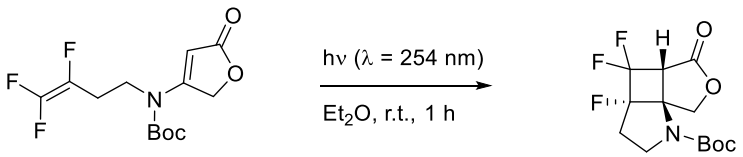
Another example of a [2+2]-cycloaddition reaction leading to fluorinated 2-aminocyclobutanecarboxylic acid derivatives is presented in Scheme 25.[39] The reaction between difluoroketene aminal **118** with acrylates **119** in hexane at room temperature or 90 °C, depending on the substrate, afforded methyl 3,3-difluorocyclobutanecarboxylates **120** as sole end products, which were isolated in very good yields.



118 **119a** (R = H) **119b** (R = Me) **120a** (R = H, 87%) **120b** (R = Me, 84%)

Scheme 25[39]

Furthermore, an intramolecular [2+2]-photocycloaddition of the trifluorovinyl-containing scaffold **121**, initiated by radiation at 254 nm, led to the formation of a tricyclic compound **122** as a single diastereomer (Scheme 26).[40]

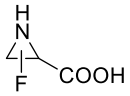


121 **122** (73%)

Scheme 26[40]

2.3 Synthesis of ring fluorinated aziridine-2-carboxylates

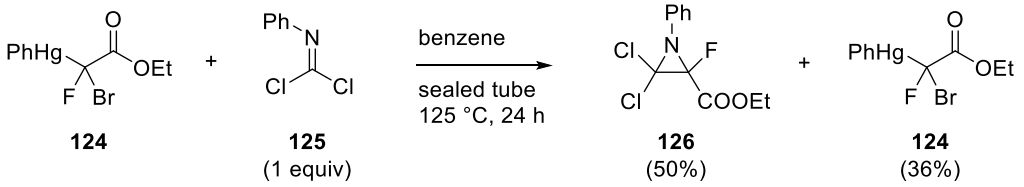
Aziridine-2-carboxylates are attractive substrates in synthetic chemistry since they comprise two electrophilic centres, the strained aziridine ring and the carboxylate functionality.[41] Because they are also a member of the class of small-membered ring-containing amino acid derivatives, the synthesis of ring fluorinated aziridine-2-carboxylates **123** will be discussed in this section (Figure 7).



123

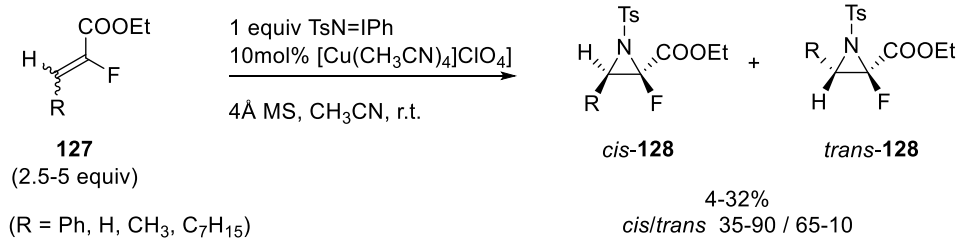
Figure 7

The first synthesis of a 2-fluoroaziridine-2-carboxylate was reported in 1973 and involves the addition of a carbenoid compound onto a C=N double bond (Scheme 27).[42] Organomercury compound **124**, prepared from ethyl bromofluoroacetate and phenylmercuric chloride in the presence of KO*t*Bu, was used as a CFCOOEt transfer reagent which added to the C=N bond of *N*-phenyliminophosgene **125**. This reaction led to the formation of ethyl *N*-phenyl-3,3-dichloro-2-fluoroaziridine-2-carboxylate **126** in 50% yield next to 36% recovery of the starting organomercury compound **124**. This reaction could either proceed *via* the intermediate α-fluoro-α-ethoxycarbonylcarbene or *via* a direct transfer process, but the mechanism was not elucidated.



Scheme 27[42]

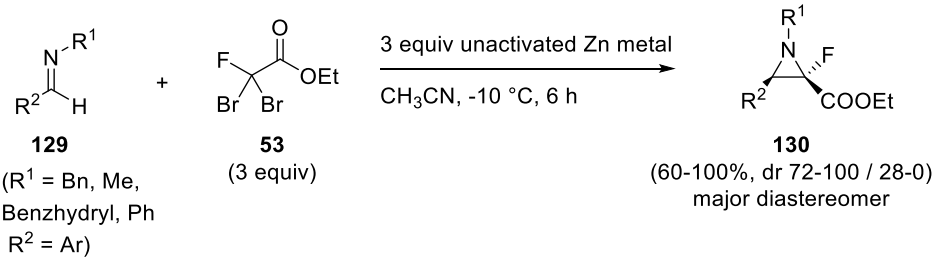
In the second example, depicted in Scheme 28, the fluorinated aziridine was formed by the addition of a nitrene across an α-fluoro-α,β-unsaturated ester **127**, using the Evans aziridination procedure with TsN=IPh as the nitrene source.[43] This reaction proceeded sluggishly, affording the aziridines *cis*-**128** and *trans*-**128** as a diastereomeric mixture in a varying ratio and with low isolated yields (4-32%).



Scheme 28[43]

Additionally, two other nitrene sources were used in the reaction with ethyl 2-fluoro-3-phenylacrylate **127** (R = Ph), more specifically ethyl *N*-[(*p*-nitrobenzenesulfonyl)oxy]carbamate and 3-amino-2-trifluoromethylquinazolin-4(3*H*)-one, leading to the corresponding aziridines in similar low yields (27-32%). Furthermore, ethyl *N*-[(*p*-nitrobenzenesulfonyl)oxy]carbamate was also used as a nitrene source in the reaction with methyl 3,3-difluoro-2-trifluoromethylacrylate leading to the formation of the corresponding fluorinated aziridine-2-carboxylate in 88% yield.[44]

As a last example, the Reformatsky-type aza-Darzens reaction between ethyl dibromofluoroacetate **53** and various aromatic imines **129** was optimized and directed toward the synthesis of fluorinated ethyl aziridine-2-carboxylates **130** (Scheme 29).[45] In a previous report, 2-fluoroaziridine-2-carboxylates were described as side products in a Reformatsky-type synthesis of α-bromo-α-fluoro-β-lactams, starting from ethyl dibromofluoroacetate **53** and various imines.[46] By changing the solvent from Et_2O to CH_3CN and using unactivated Zn metal in the Reformatsky reaction, the selective formation of aziridines **130** was achieved, which were isolated in 60-100% yield with a varying diastereomeric ratio, depending on the substituents R^1 and R^2.



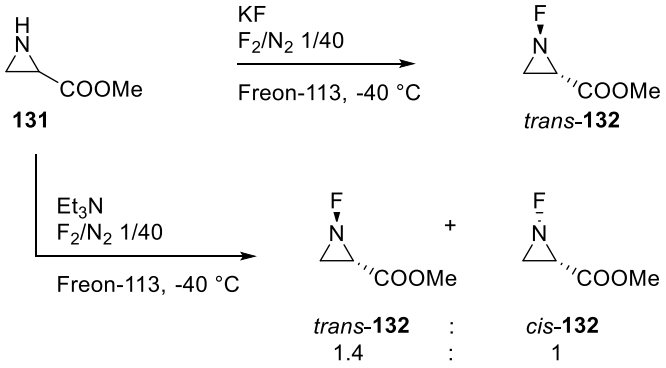
129
(R^1 = Bn, Me, Benzhydryl, Ph
R^2 = Ar)

53
(3 equiv)

130
(60-100%, dr 72-100 / 28-0)
major diastereomer

Scheme 29[45]

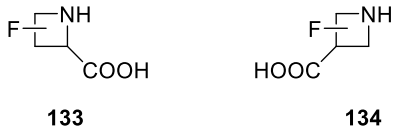
Methyl 1-fluoroaziridine-2-carboxylates **132** have also been synthesized, *via* fluorination of methyl aziridine-2-carboxylate **131** (Scheme 30).[47] This fluorination reaction was performed in a diastereoselective way, since the selective formation of *trans*-**132** was achieved when the reaction was performed in the presence of KF, while a mixture of *trans*-**132** and *cis*-**132** was formed upon reaction in the presence of triethylamine. This can be explained by the presence of an intramolecular hydrogen bond in aziridine **131**, which is broken by triethylamine and subsequent attack of F_2 at the nitrogen atom occurs *cis* or *trans* relative to the ester function. However, in the presence of KF there is retention of the hydrogen bond, leading to exclusive *trans*-attack of F_2. No yields were reported for these reactions. Other derivatives of 1-fluoroaziridine-2-carboxylates have also been synthesized using the same methodology.[48] The compounds are of interest since it was shown that aziridines **132** have an extraordinary high barrier to nitrogen inversion. Furthermore, alkyl 1-fluoroaziridine-2,2-dicarboxylates react in a stereoselective way with nucleophiles since only the acyl group in *trans* configuration to the fluorine substituent reacts with the nucleophile.



Scheme 30[47]

2.4 Synthesis of ring fluorinated azetidine-2-carboxylates and azetidine-3-carboxylates

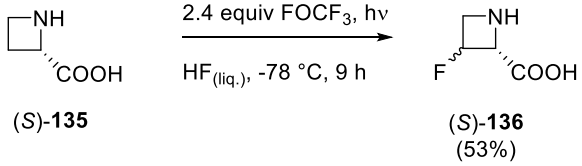
In this section, the synthesis of fluorinated azetidine-2-carboxylates **133** and azetidine-3-carboxylates **134** will be described (Figure 8). Since azetidin-2-ones (or β-lactams) can be seen as a separate class of compounds, the synthesis of their ring fluorinated analogues will not be discussed in this literature overview.



133 **134**

Figure 8

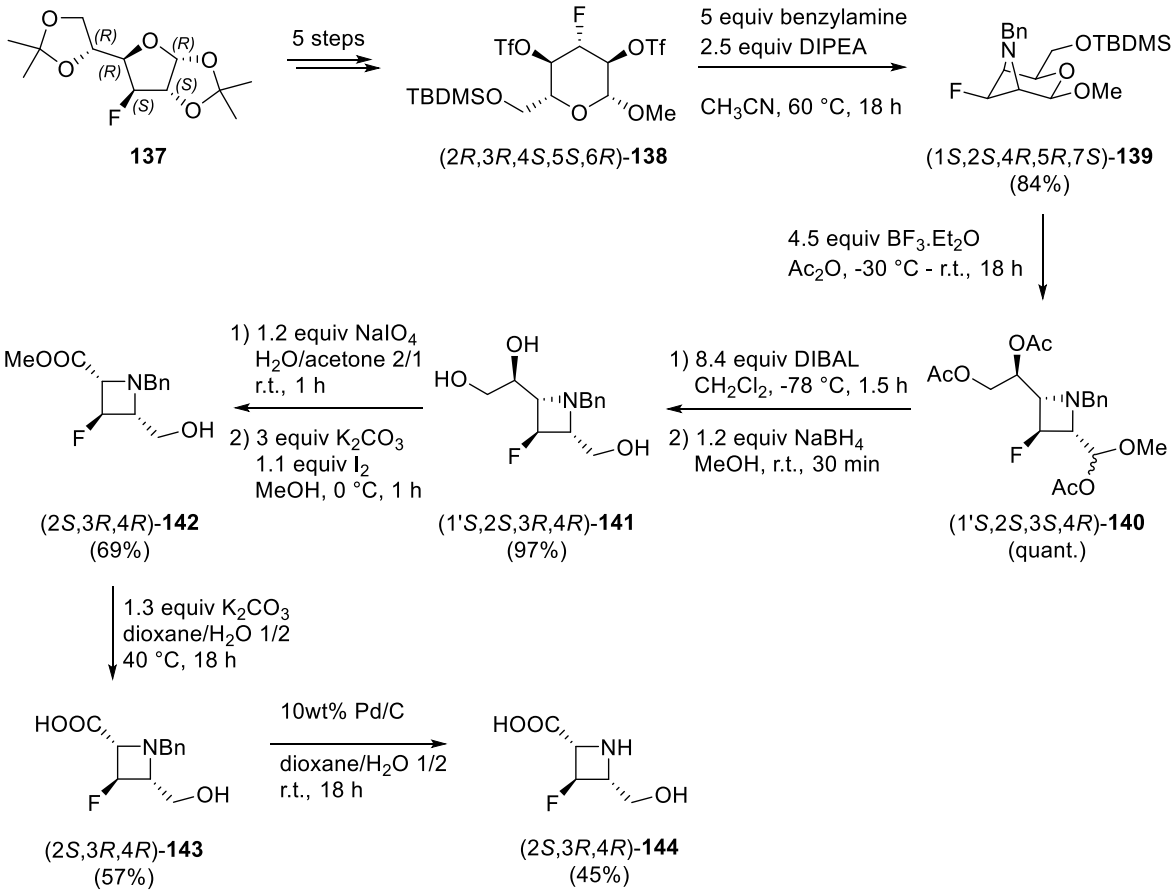
In a first example, 3-fluoroazetidine-2-carboxylic acid (*S*)-**136** was prepared *via* a substitutive fluorination of L-azetidine-2-carboxylic acid (*S*)-**135** using fluorooxytrifluoromethane gas in liquid HF (Scheme 31).[49]



Scheme 31[49]

Very recently, the synthesis of functionalized optically pure derivatives of 3-fluoroazetidine-2-carboxylic acid was reported, as novel peptide building blocks.[50] In Scheme 32, only the synthesis of (2*S*,3*R*,4*R*)-3-fluoro-4-hydroxymethylazetidine-2-carboxylic acid (2*S*,3*R*,4*R*)-**144** is presented, the synthesis of the other

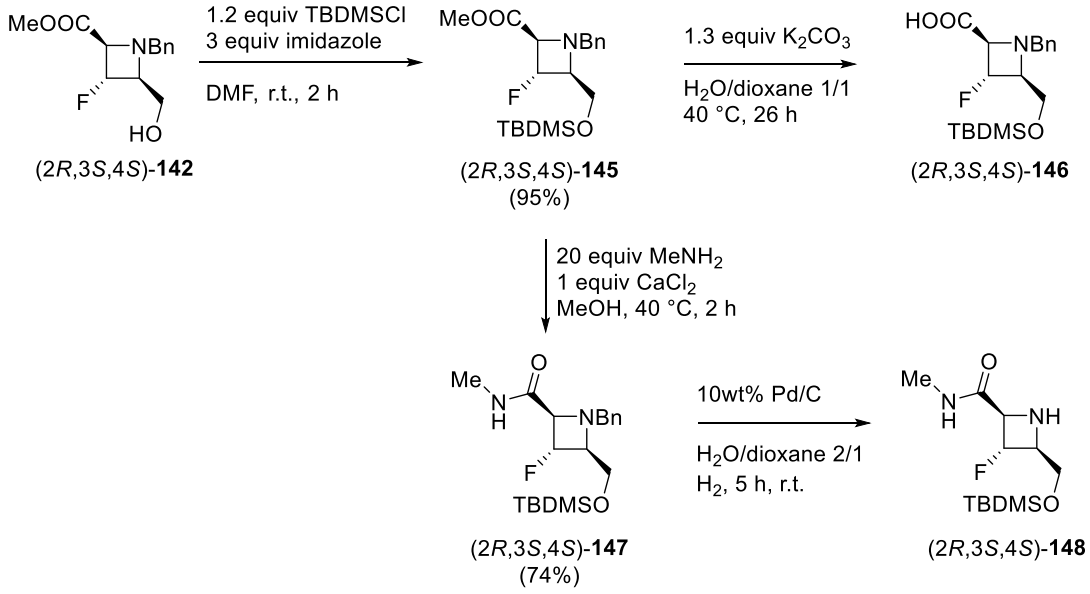
enantiomer proceeding analogously. First, the diacetonide of 3-fluoroglucose **137** was transformed into pyranose ditriflate (2*R*,3*R*,4*S*,5*S*,6*R*)-**138** in five steps. Subsequently, azetidine-formation was achieved by treatment of ditriflate (2*R*,3*R*,4*S*,5*S*,6*R*)-**138** with an excess of benzylamine. Treatment of bicyclic azetidine (1*S*,2*S*,4*R*,5*R*,7*S*)-**139** with boron(III) fluoride etherate in acetic anhydride gave azetidine (1'*S*,2*S*,3*S*,4*R*)-**140** in quantitative yield, which was reduced in two steps toward triol (1'*S*,2*S*,3*R*,4*R*)-**141**. Next, oxidative cleavage of the diol moiety in compound (1'*S*,2*S*,3*R*,4*R*)-**141** followed by treatment with iodine in MeOH gave rise to the formation of methyl ester (2*S*,3*R*,4*R*)-**142**. Hydrolysis of the ester toward carboxylic acid (2*S*,3*R*,4*R*)-**143** was achieved by treatment with K_2CO_3, and subsequent removal of the benzyl group *via* hydrogenolysis led to the formation of the unprotected (2*S*,3*S*,4*R*)-3-fluoro-4-hydroxymethylazetidine-2-carboxylic acid (2*S*,3*R*,4*R*)-**144**. Both enantiomers were tested as potential inhibitors of glycosidases, but no activity was observed.



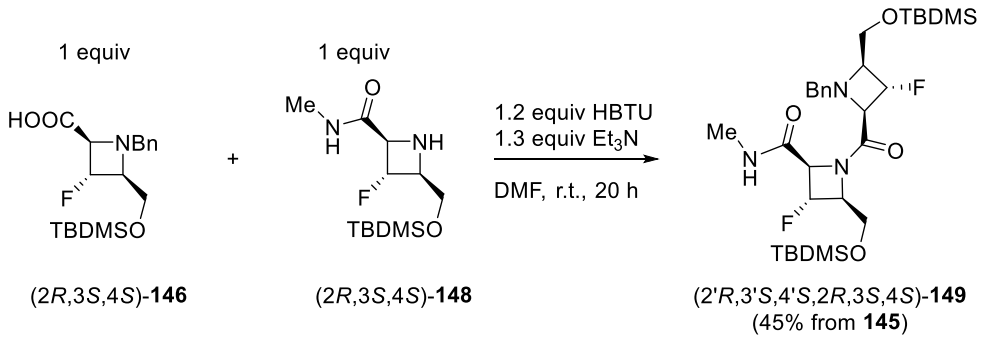
Scheme 32[50]

Furthermore, the formation of the stable dipeptide, consisting of two units of (2*R*,3*S*,4*S*)-3-fluoro-4-hydroxymethylazetidine-2-carboxylic acid (2*R*,3*S*,4*S*)-**144** was described. First, protection of the

hydroxymethyl moiety was achieved by treatment of azetidine (2*R*,3*S*,4*S*)-**142** with TBDMSCl in DMF, leading to *tert*-butyldimethylsilylether (2*R*,3*S*,4*S*)-**145** (Scheme 33). Subsequently, hydrolysis of the methyl ester of azetidine (2*R*,3*S*,4*S*)-**145** using K_2CO_3 in aqueous dioxane furnished azetidine-2-carboxylic acid (2*R*,3*S*,4*S*)-**146**. Upon treatment of methyl ester (2*R*,3*S*,4*S*)-**145** with methylamine, amide (2*R*,3*S*,4*S*)-**147** was formed, which was subsequently debenzylated to give free amine (2*R*,3*S*,4*S*)-**148**. Finally, dipeptide (2'*R*,3'*S*,4'*S*,2*R*,3*S*,4*S*)-**149** was formed by stirring a mixture of azetidine-2-carboxylic acid (2*R*,3*S*,4*S*)-**146** and azetidine (2*R*,3*S*,4*S*)-**148** in the presence of HBTU and Et_3N in DMF (Scheme 34).



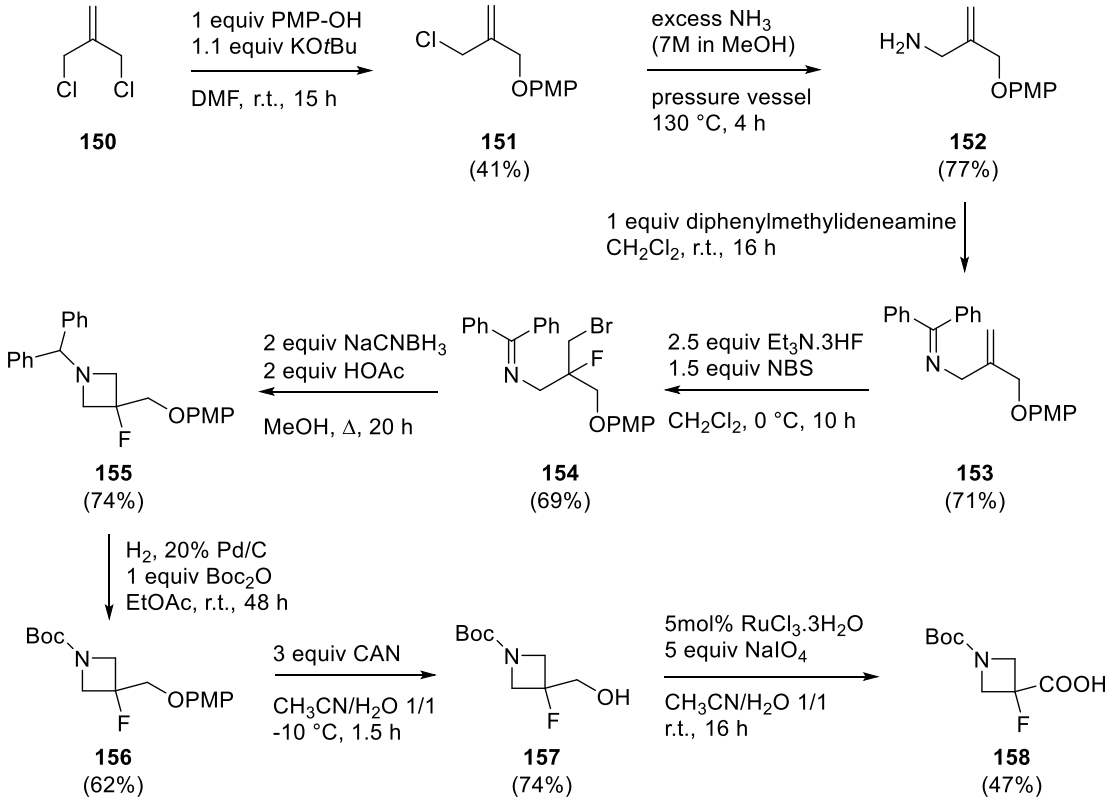
Scheme 33



Scheme 34[50]

A third example of a ring fluorinated amino acid with an azetidine core comprises the synthesis of *N*-Boc protected β-amino acid **158** (Scheme 35).[51] Allylamine **152** was prepared from dichlorinated isobutene **150**

in two steps *via* a sequential nucleophilic substitution of the two chlorine atoms. In the next step, transimination with diphenylmethylideneamine afforded imine **153**, which was used as the substrate for a bromofluorination reaction toward imine **154** using $Et_3N.HF$ in the presence of NBS. Reduction of imine **154** and subsequent ring closure was achieved by treatment with $NaCNBH_3$ in MeOH at reflux temperature after which hydrogenolysis in the presence of Boc anhydride yielded *N*-Boc azetidine **156**. Subsequently, oxidative cleavage of the *p*-methoxyphenyl ether was achieved by treatment of azetidine **156** with CAN, yielding 3-hydroxymethylazetidine **157**, which was converted into carboxylic acid **158** in the last step, by treatment with $NaIO_4$ in the presence of $RuCl_3.3H_2O$.



Scheme 35[51]

2.5 Conclusion

Although fluorinated amino acids can be seen as interesting scaffolds in synthetic and medicinal chemistry, the number of synthetic routes toward the small-membered ring analogues remains rather limited.

In this regard, the class of ring fluorinated cyclopropyl-containing amino acids has been explored the most. As can be seen in this literature overview, various examples of mono- and difluorinated α-ACC derivatives

have been described in the literature, including diastereoselective and enantioselective synthetic pathways. In contrast, only one example of a fluorinated β-ACC derivative has been reported. This is probably due to the inherent instability of β-ACC due to its donor-acceptor substituted cyclopropane structure. Therefore, the synthesis of fluorinated β-ACC derivatives remains a challenge which should be encountered to gain insight in the reactivity of these strained compounds.

The chemistry of cyclobutyl-containing amino acids has also been explored relatively well. As a member of this class of constrained amino acids, the PET tracer *trans*-1-amino-3-[^{18}F]cyclobutane-1-carboxylic acid is a nice example of the application of a non-proteinogenic fluorinated amino acid. Furthermore, the stereoselective synthesis of a fluorinated β-ACBC derivative was reported, as well as its incorporation in homo-oligomers.

In contrast, as can be seen in this literature overview, fluorinated amino acids containing an aziridine or an azetidine ring have been studied to a very limited extent. However, given the broad applicability of aziridines[52] and azetidines[53] as versatile building blocks, the development of novel synthetic routes toward ring fluorinated aziridine- and azetidine-containing amino acids remains a challenge which is of great interest.

3 Results and discussion

3.1 Stereoselective synthesis of both enantiomers of *trans*-2-(diphenylmethylideneamino)cyclopropanecarboxylic acid using a chiral pool approach and their incorporation in dipeptides[54]

3.1.1 Introduction

As described in the introduction, the interest in cyclic β-amino acids has increased significantly in the past decades,[9e,55] which is due to the ability of β-amino acids to improve the metabolic stability of β-peptides in which they are incorporated. Moreover, β-peptides represent an important class of foldamers,[7,56] as they can adopt various secondary structures including helices, sheets and turns.[56,9a,9d,57] The smallest carbocyclic β-amino acid is β-aminocyclopropanecarboxylic acid (β-ACC) **159**, a carbocyclic analogue of β-alanine. β-ACC **159** itself has never been synthesized due to the inherent instability of this small-membered ring caused by its 1,2-donor-acceptor substituted cyclopropane structure.[58] Therefore, a suitable stabilizing group at nitrogen is essential to avoid spontaneous ring opening of the cyclopropane core, which complicates the synthesis of β-ACC derivatives and their incorporation in peptides.[12,59] Moreover, due to the presence of two stereogenic centres in the cyclopropane ring, β-aminocyclopropanecarboxylic acid **159** exists as four stereoisomers (Figure 9). This entails an extra challenge in the development of a strategy for the synthesis of enantiopure β-ACC derivatives.

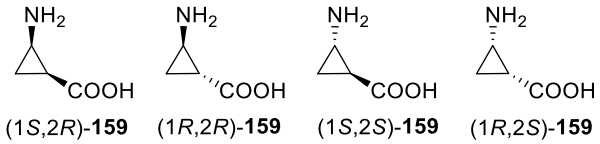


Figure 9

Although different asymmetric synthetic approaches toward 2-aminocyclopropanecarboxylates have been reported,[60] the elaboration of synthetic pathways toward β-ACC derivatives with no extra functionalization of the cyclopropane core remains rather scarce. An enantiomerically enriched *cis*-2-aminocyclopropanecarboxylic acid derivative (63% *ee*) was synthesized using a chemoselective hydrolysis of a cyclopropane *meso*-diester with Pig Liver Esterase (PLE) followed by appropriate functional

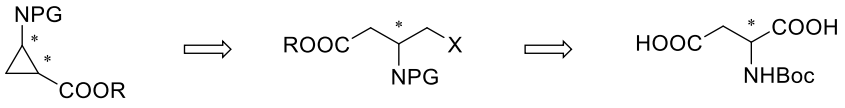
group transformation.[61] Enamides have proved to serve as valuable precursors in the synthesis of unsubstituted *N*-stabilized β-ACC derivatives *via* a cyclopropanation reaction using ethyl diazoacetate as a carbene source in the presence of a catalyst.[62] An asymmetric cyclopropanation reaction of styrene with ethyl diazoacetate afforded an unsubstituted *trans*-β-ACC derivative (90% *ee*) in five steps using a chiral (salen)Ru(II) cyclopropanation catalyst.[63] Noteworthy, only one synthetic route toward an unsubstituted chiral β-aminocyclopropanecarboxylic acid using a chiral pool approach has been described in the literature, more specifically starting from the expensive chiral building block benzyl (*S*)-(+)-glycidyl ether.[64] The only other synthesis starting from a chiral building block, D-glyceraldehyde, leads to an enantiomerically pure substituted *trans*-1-methyl-β-ACC derivative in 9 steps.[61]

Next to their synthesis, also the incorporation of *cis*-,[60a,9b,65] and to a lesser extent *trans*-β-aminocyclopropanecarboxylates[60a] in peptides, allowing to influence their structural conformation, has received a lot of attention in recent years. The synthesis of a *cis*-β-ACC-containing pseudopeptide, starting from a *meso*-anhydride and (*S*)-prolinate is the only example that can be mentioned regarding the incorporation of an unsubstituted β-ACC building block in peptides.[66]

In view of these important gaps in the chemistry of chiral β-ACCs, in a first part of this PhD thesis, the synthesis of a new enantiopure unsubstituted (-)-*trans*-β-aminocyclopropanecarboxylic acid *via* a stereoselective base-induced ring closure is described, starting from an (*S*)-aspartic acid derivative as chiral building block. The (+)-*trans*-β-ACC enantiomer was synthesized *via* the same pathway starting from the (*R*)-aspartic acid derivative. Surprisingly, (*S*)-aspartic acid, one of the twenty proteinogenic amino acids and a naturally occurring β-amino acid, has never been used as a chiral building block in the synthesis of enantiopure β-aminocyclopropanecarboxylic acids. Moreover, the incorporation of these new *trans*-β-aminocyclopropanecarboxylic acids in dipeptides was studied as well.

3.1.2 Synthesis of *trans*-2-(diphenylmethylideneamino)cyclopropanecarboxylic acids

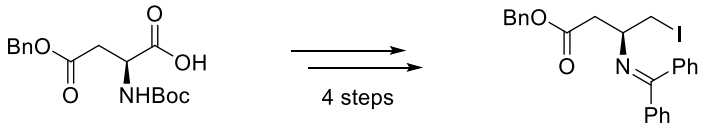
By using acyclic aspartic acid derivatives **162** as chiral building blocks for the synthesis of β-ACCs **160**, the introduction of the cyclopropane core was envisaged to proceed *via* a 1,3-cyclization reaction (Scheme 36). Therefore, the synthesis of an eligible precursor **161**, bearing a leaving group in γ-position and a suitably stabilized amino group in β-position, starting from these aspartic acid derivatives **162** had to be developed.



160 **161** **162**

Scheme 36

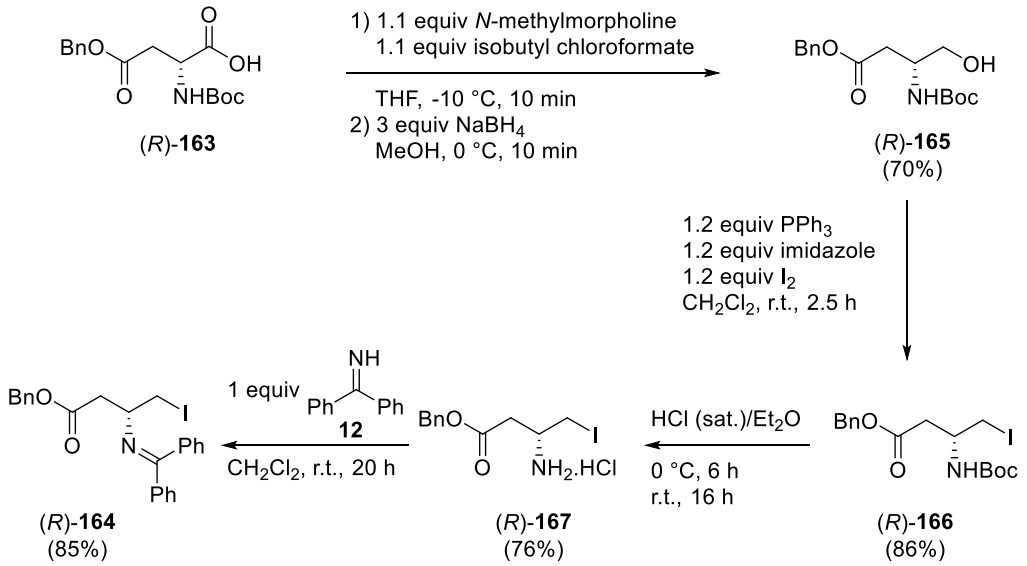
In a previous Master thesis,[13] (*S*)-benzyl 3-diphenylmethylideneamino-4-iodobutanoate (*S*)-**164** was synthesized in four steps starting from (*S*)-β-benzyl *N*-(*tert*-butoxycarbonyl)aspartate (*S*)-**163**, in 29% total yield (Scheme 37).



(*S*)-**163** (*S*)-**164** (29%)

Scheme 37[13]

In this PhD thesis, the same synthetic pathway, presented in detail in Scheme 38, was applied for the synthesis of the other enantiomer (*R*)-benzyl 3-diphenylmethylideneamino-4-iodobutanoate (*R*)-**164**. The carboxylic acid moiety of aspartate (*R*)-**163** was converted into the corresponding alcohol (*R*)-**165** in 70% yield by reduction using $NaBH_4$ after activation with isobutyl chloroformate.[67] In a next step, a modified Appel reaction using a PPh_3/I_2 complex was applied for the conversion of β-amino alcohol (*R*)-**165** into iodide (*R*)-**166**, which was isolated in 86% yield.[68] In theory, this *N*-Boc protected iodide (*R*)-**166** could serve as a direct precursor in the synthesis of β-ACCs, although competition with formation of the corresponding aziridines could be expected.[69] However, it has been demonstrated that the presence of only one electron-withdrawing group at nitrogen in such type of precursors is not sufficient to allow cyclization to 1,2-donor-acceptor substituted cyclopropanes.[70] Therefore, another group at nitrogen was introduced, more specifically a diphenylmethylidene group, which has already been used previously as a stabilizing group in the synthesis of donor-acceptor substituted cyclopropanes.[12a,70a] Therefore, Boc-deprotection of the amino group of β-amino ester (*R*)-**166** was achieved under acidic conditions affording β-iodoammonium salt (*R*)-**167** in 76% yield. Subsequent transimination of (*R*)-**167** with diphenylmethylideneamine **12** yielded enantiopure (*R*)-benzyl 3-diphenylmethylideneamino-4-iodobutanoate (*R*)-**164**, as a direct precursor for the synthesis of novel chiral unsubstituted β-aminocyclopropanecarboxylates.

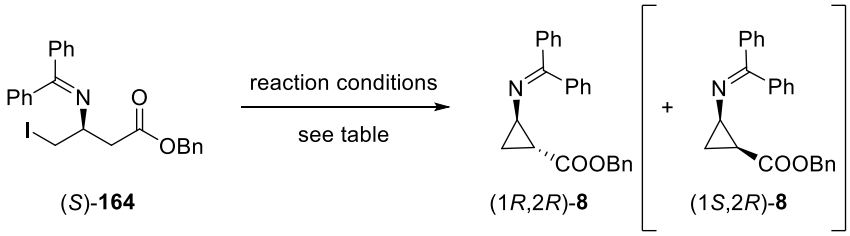


Scheme 38

With γ-iodo β-amino esters (*S*)-**164** and (*R*)-**164** in hand, the base-induced ring closure of these precursors toward the envisaged chiral benzyl cyclopropanecarboxylates was investigated and optimized (Table 1). In previous research, KO*t*Bu was already evaluated as a base to initiate the ring closure of γ-iodo β-amino ester (*S*)-**164**. Although treatment of ester (*S*)-**164** with KO*t*Bu gave rise to the formation of the envisaged β-aminocyclopropanecarboxylates **8**, this reaction proceeded with a low diastereoselectivity (dr *trans* : *cis* 79-61 : 21-39) and also led to the formation of a side product, probably due to a transesterification reaction. Following these moderate results, the use of another base, more specifically the stronger nitrogen base potassium hexamethyldisilazide (KHMDS), was evaluated in the ring closure reaction. When (*S*)-benzyl 4-iodobutanoate (*S*)-**164** reacted with 1.1 equiv KHMDS in THF for five minutes at -78 °C, 92% of the starting product was converted toward cyclopropanes **8**, with no formation of side products. Moreover, an improvement of the diastereomeric ratio of cyclopropanes **8** was observed (dr *trans* : *cis* 88 : 12) (Table 1, entry 1). Prolongation of the reaction time to ten minutes led to a full conversion of the starting material toward cyclopropanes **8** in a good diastereomeric ratio (dr *trans* : *cis* 91 : 9) (Table 1, entry 2). In an attempt to improve the diastereomeric ratio, the reaction time was prolonged toward one and two hours, with some improvement of the diastereomeric ratio (up to 99 : 1), but no improvement of the yield of cyclopropanecarboxylate (1*R*,2*R*)-**8** (Table 1, entries 3-4). From these attempts, (1*R*,2*R*)-*trans*-benzyl cyclopropanecarboxylate (1*R*,2*R*)-**8** was isolated in a good yield of 81% (resp. 80%) (dr > 99 : 1). When (*S*)-benzyl 4-iodobutanoate (*S*)-**164** reacted with KHMDS at a higher temperature, a similar variable diastereomeric ratio was observed (dr *trans* : *cis* up to 99 : 1) and (1*R*,2*R*)-*trans*-benzyl 2-(diphenylmethylideneamino)cyclopropanecarboxylate (1*R*,2*R*)-**8** was isolated in 74% yield (dr > 99 : 1)

after recrystallization (Table 1, entry 5). The use of more equivalents of base was also evaluated but did not lead to an improvement of the diastereomeric ratio or the yield (Table 1, entry 6). Noteworthy, treatment of pure *trans*-(1*R*,2*R*)-benzyl 2-(diphenylmethylideneamino)cyclopropanecarboxylate (1*R*,2*R*)-**8** with KHMDS under similar reaction conditions (THF, -78 °C, 1 h), in an attempt to see whether *trans*/*cis* isomerisation took place, only led to degradation of this cyclopropane derivative.

Table 1: Synthesis of 2-(diphenylmethylidenamino)cyclopropanecarboxylate (1*R*,2*R*)-8



(*S*)-**164** (1*R*,2*R*)-**8** (1*S*,2*R*)-**8**

Entry	Reaction conditions	dr *trans* : *cis*[a]	Yield (1*R*,2*R*)-**8**[b]
1	1.1 equiv KHMDS, THF, -78 °C, 5 min	88 : 12[c]	70%
2	1.1 equiv KHMDS, THF, -78 °C, 10 min	91 : 9	79%
3	1.1 equiv KHMDS, THF, -78 °C, 1 h	95 : 5	81%
4	1.1 equiv KHMDS, THF, -78 °C, 2 h	99 : 1	80%
5	1.1 equiv KHMDS, THF, 0 °C, 5 min	99 : 1	74%
6	1.5 equiv KHMDS, THF, -78 °C, 1 h	93 : 7	65%

[a] Determined *via* ^{1}H NMR analysis of the crude reaction mixture. [b] dr *trans* : *cis* > 99 : 1. [c] 92% conversion.

The relative configuration of cyclopropane (1*R*,2*R*)-**8** was assigned based on comparison of the coupling constants in the ^{1}H NMR signal corresponding to H_A with literature values. The literature values of the vicinal coupling constants *trans*-$^3J_{H_A,H_B}$ (= 2.5 Hz), *trans*-$^3J_{H_A,H_C}$ (= 4.7 Hz) and *cis*-$^3J_{H_A,H_D}$ (= 7.4 Hz) are comparable to the values of the observed vicinal coupling constants *trans*-$^3J_{H_A,H_B}$ (= 3.0-3.2 Hz), *trans*-$^3J_{H_A,H}$ (= 4.7-4.9 Hz) and *cis*-$^3J_{H_A,H_D}$ (= 7.5-7.7 Hz) of the similar racemic *trans*-β-ACC derivatives **168**[12a] and **169**.[71]

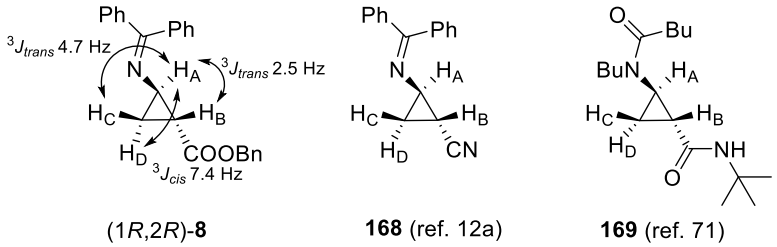
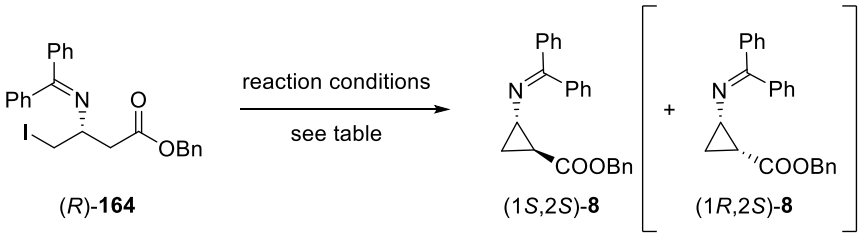


Figure 10

The reaction of the enantiomeric (*R*)-benzyl 3-(diphenylmethylideneamino)-4-iodobutanoate (*R*)-**164** with KHMDS, performed under similar reaction conditions (1.1 equiv KHMDS, -78 °C, 1 h), afforded cyclopropanes **8** in a good diastereomeric ratio (dr *trans* : *cis* 97 : 3) from which (1*S*,2*S*)-benzyl 2-(diphenylmethylideneamino)cyclopropanecarboxylate (1*S*,2*S*)-**8** was isolated in 75% yield after recrystallization (dr > 99 : 1) (Table 2, entry 1). Enantiomer (*R*)-**164** was also treated with KHMDS at room temperature for one hour, but this resulted in a lower diastereomeric ratio (dr *trans* : *cis* 87 : 13) and yield (Table 2, entry 2).

Table 2: Synthesis of 2-(diphenylmethylidenamino)cyclopropanecarboxylate (1*S*,2*S*)-8.



Entry	Reaction conditions	dr *trans* : *cis*[a]	Yield (1*S*,2*S*)-**8**[b]
1	1.1 equiv KHMDS, THF, -78 °C, 1 h	97 : 3	75%
2	1.1 equiv KHMDS, THF, r.t., 1 h	87 : 13	56%

[a] Determined *via* ^{1}H NMR analysis of the crude reaction mixture. [b] dr *trans* : *cis* > 99 : 1.

As can be seen in Table 1, the diastereomeric outcome of the ring closure of compound (*S*)-**164** is influenced by the reaction time. More specifically, the use of a longer reaction time leads preferably to the formation of *trans* derivative (1*R*,2*R*)-**8** which is clear from the increasing diastereomeric ratio (dr *trans* : *cis* up to 99 : 1). Interpretation of these results can lead to the conclusion that *trans* cyclopropane (1*R*,2*R*)-**8** is formed under thermodynamic control. Possibly, *cis* derivative (1*S*,2*R*)-**8** is converted into *trans*

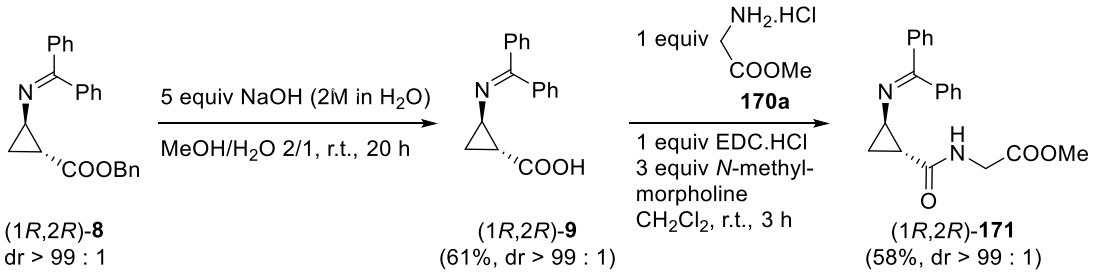
derivative (1*R*,2*R*)-**8** *via* deprotonation followed by a diastereoselective reprotonation step. However, the diastereoselective outcome of this reaction was not completely reproducible since varying diastereomeric ratios (dr *trans* : *cis* 95 : 5 - 99 : 1) were obtained when the reaction was repeated at -78 °C for two hours. Furthermore, the ring closure of the other enantiomer (*R*)-**164** gave a lower diastereomeric ratio (dr *trans* : *cis* 87 : 13) when this reaction was performed at room temperature (Table 2, entry 2), while these reaction conditions should lead to thermodynamic control. In order to elucidate the mechanism of the ring closure reaction further, it would be usefull to isolate *cis* derivatives (1*S*,2*R*)-**8** and (1*R*,2*S*)-**8** and investigate whether these compounds can be converted into the corresponding *trans* derivatives *via* isomerisation.

In an attempt to isolate (1*S*,2*R*)-*cis*-benzyl 2-(diphenylmethylideneamino)cyclopropanecarboxylate (1*S*,2*R*)-**8**, other reaction conditions were evaluated in order to invert the diastereomeric ratio of cyclopropanes **8**. Addition of 1 equiv of KCl or 1.1 equiv of $ZnCl_2$ to the reaction of (*S*)-benzyl butanoate (*S*)-**164** with KHMDS in THF at -78 °C or 0 °C did not increase the amount of *cis*-isomer (1*S*,2*R*)-**8** and resulted in a sluggish reaction with the formation of unidentified side products. Also the addition of 18-crown-6 to the cyclization reaction did not lead to an inversion of the diastereomeric ratio and only lowered the conversion of the reaction. By adding these additives to the reaction, it was attempted to create a more 'naked' anion in the intermediate, so that internal solvation by the diphenylmethylideneamine function might take place which could lead to preferential formation of the *cis*-cyclopropane.[72]

3.1.3 Saponification and peptide formation

In a last step toward the synthesis of the unprotected *C*-terminal β-aminocyclopropanecarboxylic acids, a saponification reaction of cyclopropanecarboxylic esters **8** was performed by treatment with aqueous NaOH (in methanol). This reaction proceeded smoothly and afforded cyclopropanecarboxylic acids **9** in 61-77% yield without observation of *trans*/*cis* isomerisation (based on detailed analysis of the well-resolved signals in the ^{1}H NMR spectrum) (Scheme 39 and Scheme 40). Subsequently, the stability of cyclopropanecarboxylic acids **9** toward a peptide coupling reaction with methyl glycinate hydrochloride **170a** was evaluated. In a first attempt, (1*R*,2*R*)-cyclopropanecarboxylic acid (1*R*,2*R*)-**9** was reacted with methyl glycinate **170a** in the presence of 1.05 equivalents dicyclohexylcarbodiimide (DCC) and Et_3N in EtOAc. After detailed analysis of the reaction mixture, it was concluded that carboxylic acid (1*R*,2*R*)-**9** had reacted with DCC but the subsequent coupling of the activated acid with methyl glycinate failed, and peptide (1*R*,2*R*)-**171** was not detected. The use of another coupling reagent, more specifically 1-ethyl-3-(3-*N*,*N*-dimethylaminopropyl)carbodiimide (HCl salt) (EDC.HCl), proved to be more successful.

Reaction of cyclopropanecarboxylic acid (1*R*,2*R*)-**9** with 1 equivalent of methyl glycinate (HCl salt) **170a** in CH_2Cl_2 for three hours at room temperature in the presence of EDC.HCl and *N*-methylmorpholine afforded dipeptide (1*R*,2*R*)-**171** which was isolated in 58% yield after column chromatography (Scheme 39). Peptide (1*S*,2*S*)-**171** was formed under similar reaction conditions and was isolated in 68% yield (Scheme 40).

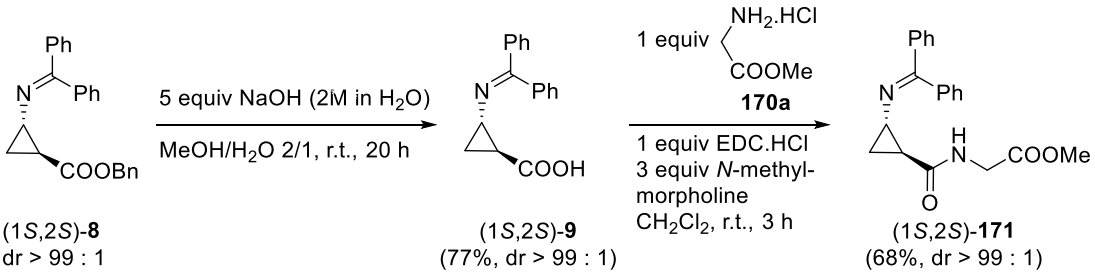


(1*R*,2*R*)-**8**
dr > 99 : 1

(1*R*,2*R*)-**9**
(61%, dr > 99 : 1)

(1*R*,2*R*)-**171**
(58%, dr > 99 : 1)

Scheme 39



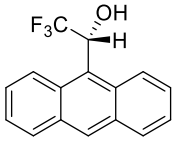
(1*S*,2*S*)-**8**
dr > 99 : 1

(1*S*,2*S*)-**9**
(77%, dr > 99 : 1)

(1*S*,2*S*)-**171**
(68%, dr > 99 : 1)

Scheme 40

The enantiomeric purity of peptides (1*R*,2*R*)-**171** and (1*S*,2*S*)-**171** was confirmed using ^{1}H NMR analysis using (*R*)-Pirkle's alcohol (*R*)-**172** (Figure 11). When two equivalents of (*R*)-1-(9-anthryl)-2,2,2-trifluoroethanol (*R*)-**172** were added to a prepared mixture (1:1) of peptides (1*R*,2*R*)-**171** and (1*S*,2*S*)-**171**, spectral nonequivalences of the signals from the NH-proton and NCH_2-protons appeared in the ^{1}H NMR spectrum (300 MHz, $CDCl_3$). When two equivalents of (*R*)-Pirkle's alcohol (*R*)-**172** were added to peptide (1*R*,2*R*)-**171** or peptide (1*S*,2*S*)-**171**, no chemical shift nonequivalences could be observed in the ^{1}H NMR spectrum, confirming the enantiomeric purity of peptides **171**.



(*R*)-Pirkle's alcohol
(*R*)-**172**

Figure 11

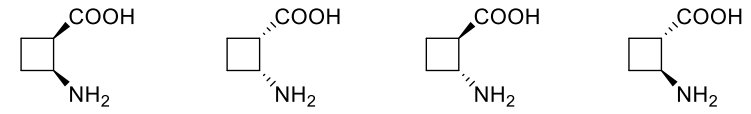
3.1.4 Conclusion

In conclusion, a stereoselective synthesis of novel *trans*-β-aminocyclopropanecarboxylic acids **9** was developed, using a chiral pool approach. The key step in the reaction sequence, more specifically the base-induced ring closure was optimized and afforded (1*R*,2*R*)- and (1*S*,2*S*)-*trans*-benzyl 2-(diphenylmethylideneamino)cyclopropanecarboxylates **8** in very good diastereoselectivity and high yield. These new unsubstituted *N*-stabilized β-ACC derivatives were converted into the *C*-terminal unprotected β-ACCs **9** and were incorporated in dipeptides **171** using standard peptide coupling reaction conditions. This procedure opens challenges for the synthesis of novel peptides incorporating unsubstituted β-ACCs, with possible interesting biological properties.

3.2 Synthesis of novel β-aminocyclobutanecarboxylic acid derivatives by a solvent-free aza-Michael addition and subsequent ring closure[73]

3.2.1 Introduction

2-Aminocyclobutanecarboxylates (β-ACBCs) comprise a second class of β-amino acids with a small-membered carbocyclic ring as their core structure. The most common way to synthesize β-ACBC derivatives uses a [2+2]-cycloaddition strategy, for example between an enamine and an acrylate,[74] or between ethylene and an uracil derivative followed by opening of the heterocyclic ring.[37,75] Using the latter method, the four enantiomers of β-aminocyclobutanecarboxylic acid **173** have been synthesized, each in enantiomerically pure form (Figure 12).[76] Another approach uses ethylene and maleic anhydride as starting compounds for the [2+2]-cycloaddition, followed by an enzymatic desymmetrization of the resulting *meso* diester and Curtius rearrangement.[61]



(1*R*,2*S*)-**173** (1*S*,2*R*)-**173** (1*R*,2*R*)-**173** (1*S*,2*S*)-**173**

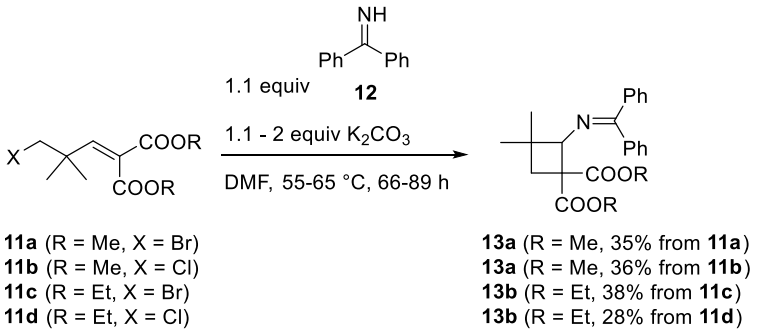
Figure 12

A poorly studied subclass of β-ACBC derivatives are β-aminocyclobutanedicarboxylic acids, which are 1,2-donor-acceptor (DA) substituted cyclobutanes which are prone to ring opening[77] and [4+2]-annulation reactions,[78] due to the presence of an extra electron-withdrawing ester function. In this part of this PhD thesis, the synthesis of new β-aminocyclobutanedicarboxylic acid derivatives *via* an aza-Michael Induced Ring Closure (MIRC) reaction was investigated, using 3-halopropylidenemalonate derivatives as substrates. This approach was based on previous research, where dialkyl 2-bromoethylidenemalonates and dialkyl 3-chloropropylidenemalonates proved to be suitable substrates for the MIRC reaction toward a range of functionalised cyclopropanes and some cyclobutanes.[12c,12d,79]

3.2.2 Synthesis of 3,3-dimethyl-2-aminocyclobutane-1,1-dicarboxylates

In a previous Master thesis, β-ACBC derivatives **13a** and **13b** were synthesized in one step *via* the MIRC reaction, by treatment of malonates **11a-d** with diphenylmethylideneamine in DMF at 55-65 °C in the

presence of K_2CO_3 as a mild base, albeit in rather low yields after recrystallization from MeOH (Scheme 41).[13]



11a (R = Me, X = Br)
11b (R = Me, X = Cl)
11c (R = Et, X = Br)
11d (R = Et, X = Cl)

13a (R = Me, 35% from **11a**)
13a (R = Me, 36% from **11b**)
13b (R = Et, 38% from **11c**)
13b (R = Et, 28% from **11d**)

Scheme 41[13]

In an attempt to improve the yield of this transformation, other reaction conditions were explored (Table 3). When *tert*-butanol was used as solvent in the presence of triethylamine as a base, the Michael addition of diphenylmethylideneamine across malonate **11b** was observed, but the intramolecular substitution of the leaving group in δ-position did not occur. Thus, acyclic β-amino ester **174b** was isolated in 57% yield after recrystallization from Et_2O (Table 3, entry 1). The use of the solvent mixture *t*-BuOH/Et_2O in a ratio of 4/1 increased the yield of the Michael addition of diphenylmethylideneamine across alkylidenemalonate **11b** to 67% and shortened the reaction time (Table 3, entry 2). The low solubility of adduct **174b** in Et_2O led to a better conversion of the starting product **11b**, disfavouring the reverse retro-Michael reaction. 3-Bromoalkylidenemalonate **11a** was treated with diphenylmethylideneamine under similar reaction conditions to obtain pure β-amino ester **174a** in 56% yield (Table 3, entry 3). Unfortunately, the Michael addition of diphenylmethylideneamine leading to dimethyl malonates **174a** and **174b** proved to be poorly reproducible under these conditions. Furthermore, the addition of diphenylmethylideneamine across diethyl alkylidenemalonates **11c-d** appeared to be even more problematic, which is probably due to the steric hindrance caused by the presence of the two geminal ethyl esters on the double bond. When diethyl 2-(3-chloro-2,2-dimethylpropylidene)malonate **11d** was treated with three equivalents of diphenylmethylideneamine, only 66% conversion of the starting product to the corresponding β-amino ester **174d** was observed after six days of reaction (Table 3, entry 4). In addition, the presence of an excess of diphenylmethylideneamine in the crude reaction mixture made isolation of the Michael adduct **174d** very difficult to virtually impossible.

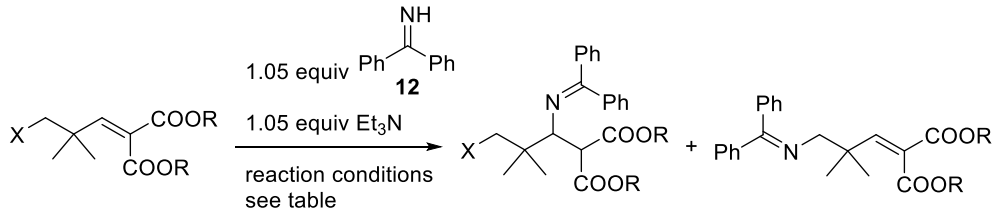
Therefore, other conditions for the Michael addition of diphenylmethylideneamine across 3-halo-alkylidenemalonates **11** had to be explored. Neither altering the solvent (*t*-BuOH/THF 4/1, Et_2O, THF,

CH_2Cl_2, CH_3CN) did lead to better results, nor did the use of other bases (NaH, KO*t*Bu) or addition of a Lewis acid ($MgBr_2$). The reaction was also conducted under microwave irradiation and in a pressure vial, but again no good conversion of substrates **11** to the corresponding acyclic β-amino esters **174** was observed.

After many attempts, it was found that the Michael-type addition of diphenylmethylideneamine **12** across alkylidenemalonates **11**, using triethylamine as a base, could be achieved in the absence of a solvent (neat conditions). Treatment of alkylidenemalonates **11a**,**b**,**d** with 1.05 equivalents diphenylmethylideneamine in the presence of triethylamine at 60 °C for 4-48 hours led to a full conversion to the corresponding Michael adducts **174a**,**b**,**d**, which were isolated in 67-79% yield after recrystallization from Et_2O (Table 3, entries 5-7). The reaction of diethyl 2-(3-bromo-2,2-dimethylpropylidene)malonate **11c** and diphenylmethylideneamine **12**, however, gave rise to the formation of an alternative product, more specifically diethyl 2-[2,2-dimethyl-3-(diphenylmethylideneamino)propylidene]malonate **175b** (Table 3, entry 8). The steric hindrance caused by the presence of the two geminal ethyl esters hampered the Michael-type addition of the nucleophile across the activated double bond, and in combination with the presence of a good leaving group (in this case bromide), a direct substitution of the leaving group by the nucleophile was more favorable. Detailed spectroscopic follow-up of the reactions showed that this substitution reaction did not occur when malonates **11a**, **11b** and **11d** were used as substrates. The reaction of malonate **11c** and diphenylmethylideneamine proceeded more selective toward the Michael adduct **174c** at room temperature but in this case, a longer reaction time was required (Table 3, entry 9).

In this manner, a very simple, practical and more sustainable method for the Michael-type addition of diphenylmethylideneamine across alkylidenemalonates **11a-d**, without the use of hazardous and volatile solvents, was developed. In the recent literature, other examples of solvent free aza-Michael additions across unsaturated substrates have been reported.[80]

Table 3: Michael-type addition of diphenylmethylideneamine 12 across 3-halopropylidenemalonates 11



11a (X = Br, R = Me)
11b (X = Cl, R = Me)
11c (X = Br, R = Et)
11d (X = Cl, R = Et)

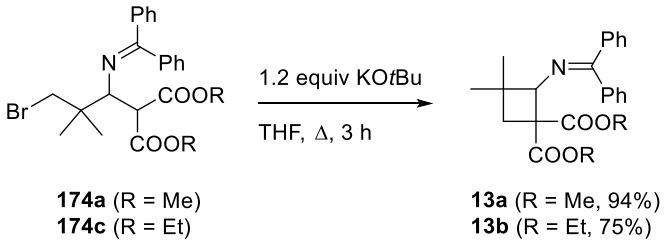
174a (X = Br, R = Me)
174b (X = Cl, R = Me)
174c (X = Br, R = Et)
174d (X = Cl, R = Et)

175a (R = Me)
175b (R = Et)

Entry	Substrate	Reaction conditions	Compound (Yield)[a]
1	**11b**	*t*-BuOH, Δ, 72 h	**174b** (57%)
2	**11b**	*t*-BuOH/Et_2O 4/1, Δ, 55 h	**174b** (67%)
3	**11a**	*t*-BuOH/Et_2O 4/1, Δ, 24 h	**174a** (56%)
4	**11d**	*t*-BuOH/Et_2O 4/1, Δ, 6 d[b]	**174d** (-)[c]
5	**11a**	neat, 60 °C, 4 h	**174a** (79%)
6	**11b**	neat, 60 °C, 24 h	**174b** (78%)
7	**11d**	neat, 60 °C, 48 h	**174d** (67%)
8	**11c**	neat, 60 °C, 20 h	**175b** (38%)
9	**11c**	neat, r.t., 119 h	**174c** (76%)

[a] Isolated yield after recrystallization from Et_2O. [b] Reaction was conducted with 3 equiv diphenylmethylideneamine and 3 equiv Et_3N. [c] 66% conversion after 6 days, compound **174d** was not isolated.

In order to convert β-amino esters **174a-d** into the targeted β-aminocyclobutanecarboxylic acid derivatives **13a** and **13b**, they were treated with a base to enable ring closure. Reaction of 2-[3-bromo-2,2-dimethyl-1-(diphenylmethylideneamino)propyl]malonates **174a** and **174c** with 1.2 equivalents of KO*t*Bu in THF for three hours at reflux temperature afforded β-aminocyclobutanecarboxylic acid derivatives **13a** and **13b** in good to excellent yields (Scheme 42).

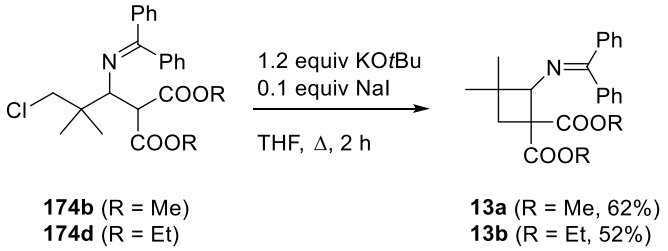


174a (R = Me)
174c (R = Et)

13a (R = Me, 94%)
13b (R = Et, 75%)

Scheme 42

The cyclization of dimethyl 2-[3-chloro-2,2-dimethyl-1-(diphenylmethylideneamino)propyl]malonate **174b** to the corresponding cyclobutane **13a** was less straightforward. When KO*t*Bu in *tert*-butanol under reflux or KHMDS or LiHMDS in THF at room temperature were used as basic conditions, the cyclization of malonate **174b** to cyclobutane **13a** was sluggish (0-66% conversion) and suffered from competitive retro-Michael addition giving rise to dimethyl alkylidenemalonate **11b** (up to 50%). The presence of chloride as leaving group and the sterically impeding geminal methyl groups prevented a smooth cyclobutanation of diester **174b**. Fortunately, the addition of a catalytic amount of NaI to achieve an *in situ* substitution of chloride by iodide, to the reaction of malonates **174b** and **174d** with KO*t*Bu in THF under reflux conditions, led to the desired clean cyclization to β-ACBC derivatives **13a** and **13b** which were isolated in 52-62% yield (Scheme 43).



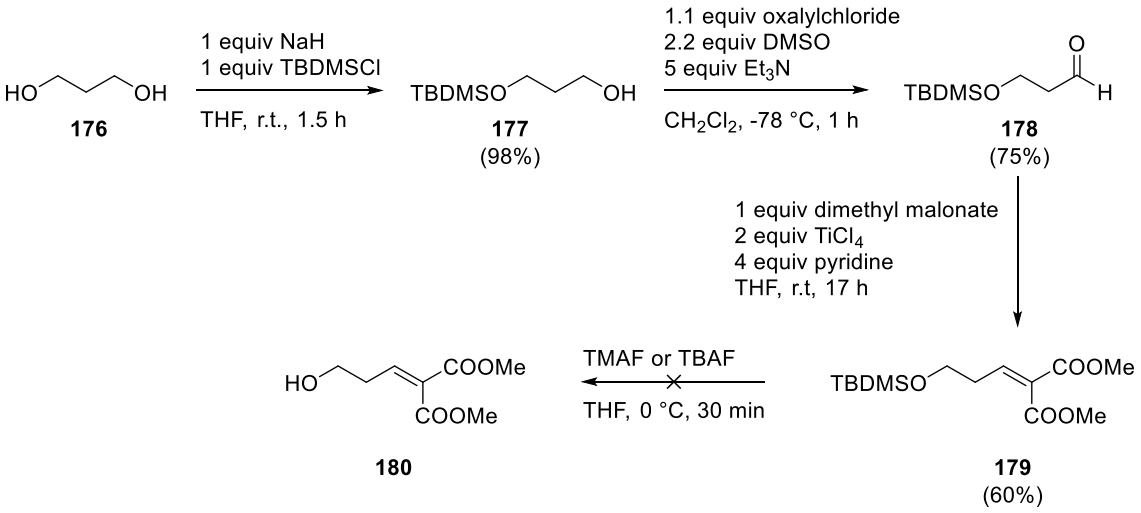
174b (R = Me)
174d (R = Et)

13a (R = Me, 62%)
13b (R = Et, 52%)

Scheme 43

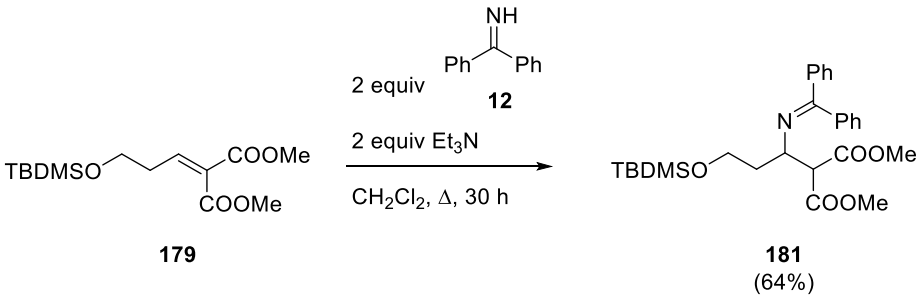
3.2.3 Attempted synthesis of 2-aminocyclobutane-1,1-dicarboxylates

In analogy with 3,3-*gem*-dimethyl-β-ACBC derivatives **13**, the synthesis of the corresponding 3,3-nor-dimethylderivatives was also attempted. To this end, precursor **179** was synthesized in three steps starting from 1,3-propanediol **176**. First, diol **176** was converted into *tert*-butyldimethylsilylether **177** by treatment with TBDMSCl in the presence of NaH[81] and subsequent oxidation toward aldehyde **178** was achieved using Swern oxidation conditions.[82] In the next step, the Knoevenagel condensation of aldehyde **178** with dimethyl malonate in the presence of titanium(IV) chloride and pyridine afforded propylidenemalonate **179** in 60% yield (Scheme 44).



Scheme 44

The next step in this synthetic route was the conversion of the *tert*-butyldimethylsilyloxy group into a good leaving group. Therefore, silyl ether **179** was treated with 1.05 equivalents of tetrabutylammonium fluoride (TBAF) in THF at 0 °C for 30 minutes, but unfortunately, this reaction led to the formation of a complex reaction mixture. Also upon use of tetramethylammonium fluoride (TMAF) as the fluoride source, a complex reaction mixture was obtained. It was concluded that the envisioned alcohol **180**, comprising both nucleophilic and electrophilic sites, is probably an unstable compound. Therefore, it was decided to use propylidenemalonate **179** as the Michael acceptor in the next step. While treatment of propylidenemalonate **179** with diphenylmethylideneamine **12** in *tert*-butanol in the presence of Et_3N only led to a partial conversion, the use of dichloromethane as a solvent gave better results and adduct **181** was isolated in 64% yield after recrystallization from Et_2O (Scheme 45).



Scheme 45

In the next step, the removal of the *tert*-butyldimethylsilyl protecting group in compound **181** was evaluated. Unfortunately, while treatment of adduct **181** with TBAF or TMAF at 0 °C in THF only led to recovery of the starting material, the formation of a complex reaction mixture was observed when the

reaction was performed at room temperature. Since the removal of the TBDMS protecting group of compounds **179** and **181** could not be achieved, this reaction pathway toward 2-aminocyclobutane-1,1-dicarboxylates was not further explored.

3.2.4 Conclusion

In conclusion, a novel method to synthesize highly substituted β-ACBC derivatives starting from 3-halopropylidenemalonates was developed, using diphenylmethylideneamine in a solvent-free aza-Michael addition followed by a base-induced ring closure. The synthesis of the corresponding 3,3-nor-dimethyl derivatives could not be effectuated due to the troublesome removal of the *tert*-butyldimethylsilyl protecting group of the precursors.

3.3 Synthesis of dialkyl 2-amino-3,3-difluorocyclopropane-1,1-dicarboxylates

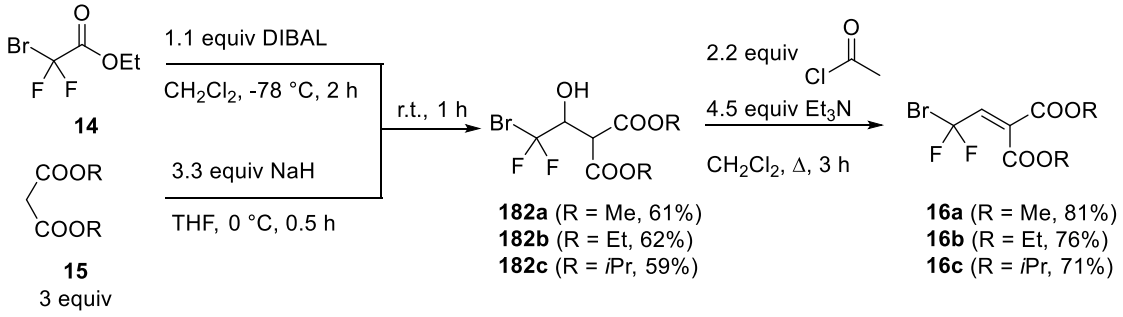
3.3.1 Introduction

As is shown in the literature overview, synthetic pathways toward ring fluorinated α-ACC derivatives have been relatively well studied.[17,21-26] In contrast, the chemistry of the corresponding ring fluorinated β-ACC derivatives comprises a very scarcely investigated field.[22] This can be attributed to the inherent instability of β-ACC caused by the 1,2-donor-acceptor substituted cyclopropane structure.[83] Furthermore, fluorinated cyclopropanes in general show an enhanced reactivity, resulting in a decreased stability.[84] Since the synthesis of 2-amino-3,3-difluorocyclopropanecarboxylates has never been described in the literature, in the third part of this PhD thesis, a synthetic route toward these elusive compounds was developed.

3.3.2 Synthesis of dialkyl 2-amino-3,3-difluorocyclopropane-1,1-dicarboxylates

Analogously to the synthesis of β-ACBC derivatives **13**, which was achieved *via* the addition of a nitrogen nucleophile to a Michael acceptor followed by a base-induced ring closure, the synthesis of fluorinated β-ACC derivatives was envisioned using dialkyl 2-(2-bromo-2,2-difluoroethylidene)malonates **16** as substrates. This work is also based on previous research in our group, in which the synthesis of dialkyl 3,3-dialkyl-2-aminocyclopropane-1,1-dicarboxylates was developed, *via* a Michael Induced Ring Closure (MIRC) reaction starting from dialkyl 2-(2-bromo-2,2-dialkylethylidene)malonates.[12c,12d]

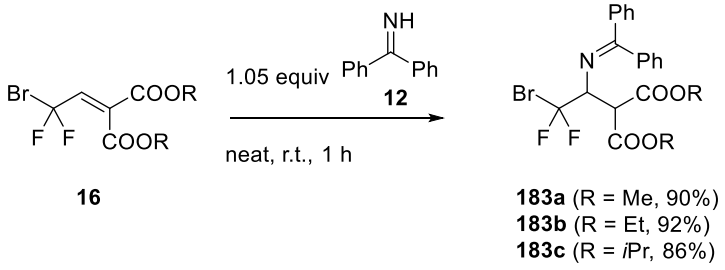
Dialkyl 2-(2-bromo-2,2-difluoroethylidene)malonates **16** were synthesized using ethyl bromodifluoroacetate **14** as a building block (Scheme 46). Treatment of ester **14** with DIBAL led to the formation of an intermediate aluminium hemiacetal, which was used without work-up in the reaction with the sodium enolates derived from malonates **15**,[85] affording alcohols **182**. In the next step, alcohols **182** were treated with acetyl chloride in the presence of Et_3N, resulting in acetylation of the alcohol and subsequent elimination to give dialkyl 2-(2-bromo-2,2-difluoroethylidene)malonates **16**.



Scheme 46

3.3.2.1 Aza-Michael addition of diphenylmethylideneamine

In a first part, the aza-Michael addition of diphenylmethylideneamine 12 across ethylidenemalonates **16** was evaluated. Based on the results in the previous section,[73] compound **16a** (R = Me) was treated with 1.05 equivalents of diphenylmethylideneamine **12** in the presence of 1.05 equivalents Et_3N, under neat reaction conditions at room temperature. This led to the formation of adduct **183a**, which was isolated in 75% yield after column chromatography and recrystallization from MeOH to remove residual benzophenone. The aza-Michael addition of diphenylmethylideneamine across ethylidenemalonates **16** also proceeded smoothly in absence of Et_3N and adducts **183** were isolated in excellent yields after recrystallization (Scheme 47). Dialkyl 2-(2-bromo-2,2-difluoroethylidene)malonates **16** are excellent Michael acceptors due to the activation by the two electron-withdrawing ester groups and the two fluorine atoms.



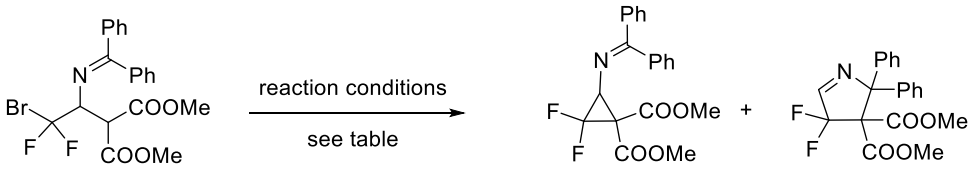
Scheme 47

Having adducts **183** in hand, their base-induced ring closure toward the corresponding cyclopropanes was evaluated (Table 4). In a first attempt, adduct **183a** was treated with NaOMe (2M in MeOH) at 0 °C, but after work-up only starting material was recovered (Table 4, entry 1). In contrast, when this reaction was conducted at room temperature, degradation of the starting compound was observed, affording a mixture in which only benzophenone and diphenylmethylideneamine were detected (Table 4, entry 2).

Subsequently, compound **183a** reacted with 1.2 equivalents KO*t*Bu in THF for one hour at room temperature, but no reaction was observed (Table 4, entry 3). By increasing the reaction temperature to reflux temperature, a full conversion of the starting compound was observed after two hours. LC-MS analysis of the reaction mixture revealed the presence of two products with the same molecular weight, corresponding to the molecular weight of the envisioned cyclopropanedicarboxylate **184a**. After detailed analysis of the ^{1}H NMR spectrum of the reaction mixture, the two compounds in the reaction mixture were identified as cyclopropane **184a** and pyrroline **185a**, in a ratio of 13 : 87 (Table 4, entry 4). The latter compound is formed as the result of a rearrangement of cyclopropane **184a**. In previous research, rearrangement of the related dimethyl 3,3-dimethyl-2-(diphenylmethylideneamino)cyclopropane-1,1-dicarboxylate, in which the cyclopropane ring is substituted by two methyl groups instead of two fluorine atoms, toward the corresponding pyrroline was also observed. In that case however, prolonged heating in DMF at reflux temperature[86] or treatment with NaCl in a DMSO/H_2O mixture at reflux temperature for 23 hours[12c] were necessary to initiate this rearrangement. Apparently, due to the presence of the two fluorine atoms, difluorinated cyclopropane **184a** is more prone to ring expansion than its dimethylated analogue. In an attempt to obtain cyclopropane **184a** in a higher amount, the reaction of adduct **183a** with KO*t*Bu at reflux temperature was repeated and after 45 minutes a sample was taken and analysed *via* ^{1}H NMR. At that moment, a reaction conversion of 62% was observed and cyclopropane **184a** and pyrroline **185a** were present in almost equal amounts (Table 4, entry 5). The reaction was stopped after an additional 15 minutes and ^{1}H NMR analysis of the reaction mixture revealed no further progress of the reaction, but a change in the ratio cyclopropane **184a** : pyrroline **185a**, with pyrroline **185a** being the major product (Table 4, entry 6). It was found that a small change in the reaction conditions had a large effect on the ring transformation of cyclopropane **184a** toward pyrroline **185a**. For example, when the reaction was conducted using 1.1 equivalents of KO*t*Bu instead of 1.2 equivalents, leaving the other reaction conditions unaltered, a different ratio of reaction products was obtained, with a higher reaction conversion and a higher amount of pyrroline in the case of 1.2 equivalents (Table 4, entries 6,7). In a next attempt, two equivalents of base were used at reflux temperature in an attempt to achieve a high conversion of the starting material in a shorter reaction time, possibly reducing the amount of pyrroline **185a**. Indeed, under these reaction conditions cyclopropane **184a** was found to be the major reaction product (Table 4, entry 8). However, a large amount of benzophenone was present, indicating degradation of the starting material or the reaction products under these reaction conditions. An extra increase of the number of equivalents of base gave no better results since treatment of adduct **183a** with three equivalents of KO*t*Bu in THF for 15 minutes at reflux temperature led to the formation of a complex reaction mixture (Table 4, entry 9).

Other reaction conditions, for example adding the base portionwise or using Et_2O as the solvent, also did not lead to better results. It was concluded that the reaction of adduct **183a** with 1.1 equivalents of KO*t*Bu in THF under reflux conditions for one hour were the best reaction conditions to obtain cyclopropane **184a**, albeit in a low yield of 20% (Table 4, entry 7). The selective formation of pyrroline **185a** was effectuated by reacting adduct **183a** with 1.1 equivalents of KO*t*Bu in THF under reflux conditions for four hours, and pyrroline **185a** was isolated in 73% yield (Table 4, entry 10). In all cases, a fourth reaction product was present after work-up, based on analysis of the ^{19}F NMR spectrum, in which a small singlet was present at -152.12 ppm. Unfortunately, this compound could not be isolated and thus not identified.

Table 4: Ring closure of dimethyl 2-[(2-bromo-2,2-difluoro-1-diphenylmethylideneamino)ethyl]malonate 183a



183a **184a** **185a**

Entry	Reaction conditions	Ratio[a] **183a** : **184a** : **185a**	Compound (Yield)[b]
1	1.05 equiv NaOMe,[c] MeOH, 0 °C, 1 h	100 : 0 : 0	-
2	1.05 equiv NaOMe,[c] MeOH, r.t., 2 h	-[d]	-
3	1.2 equiv KO*t*Bu,[e] THF, r.t., 1 h	100 : 0 : 0	-
4	1.2 equiv KO*t*Bu,[e] THF , Δ, 2 h	0 : 13 : 87	**185a** (45%)
5	1.2 equiv KO*t*Bu,[e] THF, Δ, 45 min	38 : 27 : 34	-
6	1.2 equiv KO*t*Bu,[e] THF, Δ, 1 h	37 : 10 : 53	-
7	1.1 equiv KO*t*Bu,[e] THF, Δ, 1 h	45 : 24 : 31	**184a** (20%)
8	2 equiv KO*t*Bu,[e] THF, Δ, 15 min	21 : 56 : 23[f]	-
9	3 equiv KO*t*Bu,[e] THF, Δ, 15 min	-[g]	-
10	1.1 equiv KO*t*Bu,[e] THF, Δ, 4 h	9 : 4 : 87	**185a** (73%)

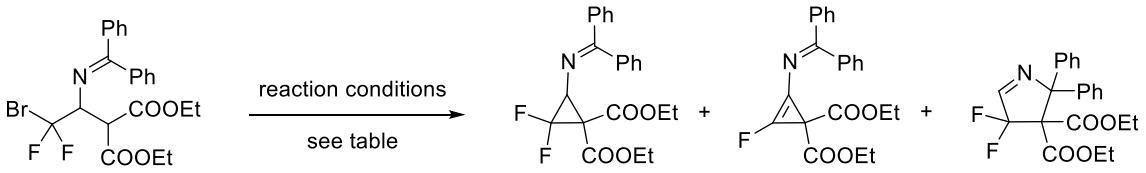
[a] Determined *via* ^1H NMR analysis of the crude reaction mixture. [b] Isolated yield. [c] 2M in MeOH. [d] Only benzophenone and diphenylmethylideneamine were distinguished in the reaction mixture.[e] 1M in THF. [f] A large amount of benzophenone was present in the reaction mixture. [g] Complex reaction mixture.

Subsequently, the base-induced ring closure of diethyl 2-[2-bromo-2,2-difluoro-1-(diphenylmethylidene-amino)]malonate **183b** was evaluated. Applying the reaction conditions which gave the best conversion toward cyclopropane **184a** (1.1 equiv KO*t*Bu, THF, Δ, 1 h) led to the formation of cyclopropane **184b** as the major reaction product, with a reaction conversion of 94% (Table 5, entry 1). However, next to cyclopropane **184b** and pyrroline **185b**, a third reaction product was present in the reaction mixture. After purification of the reaction mixture, this compound was identified as fluorinated diethyl cyclopropenedicarboxylate **186b**, which was isolated in 10% yield.

Fluorinated aminocyclopropenes and fluorinated alkyl cyclopropenecarboxylates have never been described in the literature before. The synthesis of fluorinated cyclopropenes has been reported and also a lot of attention has been devoted to calculation studies regarding the structure of these small-membered strained rings.[84,87] However, the majority of attention has been devoted to the synthesis of cyclopropenes which are substituted by fluorine at the C3 carbon, while less examples are known of cyclopropenes in which the fluorine atom is attached to the double bond.[88] While cyclopropane **184b** was not stable and rearranged readily toward pyrroline **185b** upon storage at room temperature, diethyl cyclopropenedicarboxylate **186b** was more stable and could be stored at room temperature for several days. Possibly, this higher stability is due to the reduced Pitzer strain in this more planar cyclopropene. In diethyl cyclopropanedicarboxylate **184b**, the two fluorine atoms are eclipsed with the two ester functions, leading to a substantial electronic repulsion, while this interaction is not present in diethyl cyclopropenedicarboxylate **186b**.

The ^{19}F NMR spectrum of cyclopropene **186b** showed a singlet at -151.97 ppm, and thus it was concluded that the unknown compound which was formed upon reaction of dimethyl ethylidenemalonate **183a** with KO*t*Bu (see discussion Table 4) was the corresponding dimethyl cyclopropenedicarboxylate. But as mentioned before, this compound was never isolated. Furthermore, from this first attempt (Table 5, entry 1), cyclopropane **184b** was isolated in 15% yield. Prolonging the reaction time to two hours led to a higher conversion of the starting material and also a higher amount of pyrroline **185b**, which was isolated in 26% yield (Table 5, entry 2). In this case, cyclopropene **186b** was again present in a trace amount and was isolated in 1% yield. To achieve the highest conversion of adduct **183b** toward pyrroline **185b**, the reaction time was prolonged to five hours and pyrroline **185b** was isolated in 39% yield (Table 5, entry 3). In a last attempt, adduct **183b** was treated with 1.5 equivalents of KO*t*Bu for 30 minutes, leading to a mixture with cyclopropane **184b** being the major compound which was isolated in 22% yield (Table 5, entry 4).

Table 5: Ring closure of diethyl 2-[(2-bromo-2,2-difluoro-1-diphenylmethylideneamino)ethyl]malonate 183b



183b **184b** **186b** **185b**

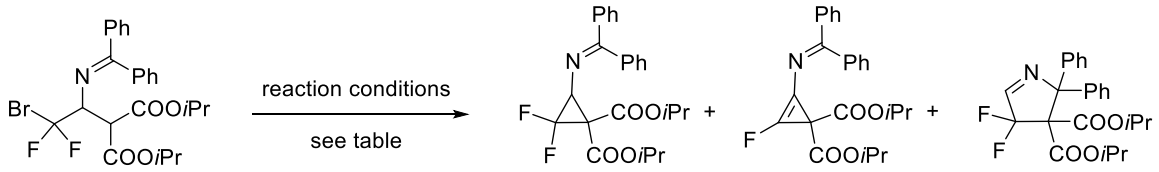
Entry	Reaction conditions	Ratio[a] **183b** : **184b** : **186b** : **185b**	Compound (Yield)[b]
1	1.1 equiv KO*t*Bu,[c] THF, Δ, 1 h	6 : 51 : 18 : 25	**184b** (15%) + **186b** (10%)
2	1.1 equiv KO*t*Bu,[c] THF, Δ, 2 h	0 : 41 : trace: 59	**186b** (1%) + **185b** (26%)
3	1.2 equiv KO*t*Bu,[c] THF, Δ, 5 h	0 : 0 : 17 : 83	**185b** (39%)
4	1.5 equiv KO*t*Bu,[c] THF, Δ, 30 min	0 : 66 : 3 : 31	**184b** (22%) + **185b** (11%)

[a] Determined *via* ^{1}H NMR analysis of the crude reaction mixture. [b] Isolated yield. [c] 1M in THF.

As a last substrate, the base-induced ring closure of diisopropyl malonate **183c** was investigated (Table 6). In a first attempt, adduct **183c** reacted with 1.5 equivalents of KO*t*Bu for 30 minutes at reflux temperature in THF (Table 6, entry 1), since under these reaction conditions the best conversion toward diethyl cyclopropanedicarboxylate **184b** was obtained (Table 5, entry 4). Satisfyingly, full conversion of the starting material was observed, with cyclopropane **184c** being the major reaction product which was isolated in a good yield of 56% (Table 6, entry 1). Next, the synthesis of pyrroline **185c** was envisioned. Therefore, the reaction time was prolonged to three hours. After work-up, cyclopropane **184c** was again the major reaction product, despite the long reaction time of three hours. Also, a larger amount of cyclopropene **186c** was present, which was isolated in 10% yield after purification of the reaction mixture (Table 6, entry 2). In a next attempt, adduct **183c** reacted with 1.2 equivalents of KO*t*Bu in THF at reflux temperature for three hours (Table 6, entry 3). In an attempt to convert cyclopropane **184c**, which was the major reaction product, into pyrroline **185c**, the reaction mixture was redissolved in THF and stirred at reflux temperature for four hours. After evaporation of the solvent, a change in the ratio **184c** : **185c** was observed and both products were present in almost equal amounts (Table 6, entry 4). To obtain a full conversion toward pyrroline **185c**, this reaction mixture was stirred in CH_3CN for two hours at reflux temperature, leading to an almost full conversion toward pyrroline **185c** (Table 6, entry 4). Unfortunately, pyrroline **185c** could not be isolated in pure form, since this compound could not be separated from

benzophenone. Although the rearrangement of cyclopropane **184c** toward pyrroline **185c** was effectuated by heating in THF or CH_3CN, this was also accompanied by degradation of the reaction products since the amount of benzophenone in the reaction mixture increased after each step.

Table 6: Ring closure of diisopropyl 2-[(2-bromo-2,2-difluoro-1-diphenylmethylideneamino)ethyl]malonate 183c



183c **184c** **186c** **185c**

Entry	Reaction conditions	Ratio[a] **183c** : **184c** : **186c** : **185c**	Compound (Yield)[b]
1	1.5 equiv KO*t*Bu,[c] THF, Δ, 30 min	0 : 80 : 6: 14	**184c** (56%)
2	1.5 equiv KO*t*Bu,[c] THF, Δ, 3 h	0 : 74 : 14 : 13	**186c** (10%)
3	1.2 equiv KO*t*Bu,[c] THF, Δ, 3 h	0 : 69 : 4 : 27	-
4	Reaction mixture entry 3, THF, Δ, 4 h	0 : 52 : 2 : 46	-
5	Reaction mixture entry 4, CH_3CN, Δ, 2 h	0 : 0 : 7 : 93	**185c** (45%)[d]

[a] Determined *via* ^{1}H NMR analysis of the crude reaction mixture. [b] Isolated yield. [c] 1M in THF. [d] 66% purity, mixture with benzophenone.

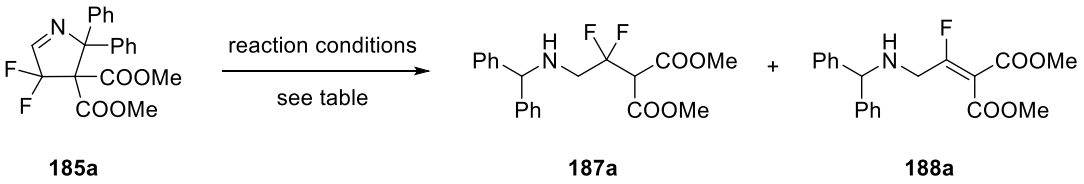
The low yields of cyclopropanes **184**, cyclopropenes **186** and pyrrolines **185** are due to their instability during their synthesis, work-up, purification and storage. Cyclopropane **184a** for example, already converts into pyrroline **185a** upon storage at -18 °C. Therefore, the temperature of the water bath during evaporation was always kept as low as possible and purification using flash chromatography was always performed by applying pressure to the column, keeping the contact time with SiO_2 as short as possible.

In the next step, the reduction of pyrrolines **185** toward the corresponding fluorinated pyrrolidines was attempted. Fluorinated pyrrolidines belong to a class of fluorinated azaheterocycles that has been studied previously in our research group.[89] This reduction would give an entry toward fluorinated β-proline derivatives, a class of fluorinated β-amino acids that has received only limited attention.[90]

In a first attempt, pyrroline **185a** was treated with 2.5 equivalents of $NaCNBH_3$ in the presence of acetic acid (1.2 equiv) in methanol at room temperature for 15 hours. However, after work-up, a complex

reaction mixture was obtained. Next, pyrroline **185a** was reacted with $NaCNBH_3$ in the presence of a catalytic amount of *p*-toluenesulfonic acid in THF for 22 hours, which led to a full conversion of the starting material.[91] After analysis of the crude reaction mixture, it was concluded that instead of the envisaged pyrrolidine, a mixture of acyclic amino esters **187a** and **188a** (ratio **187a** : **188a** = 3: 1) was formed (Table 7, entry 1). The formation of amino ester **187a** can be rationalized as follows (Scheme 48). Initial reduction of the imine function in pyrroline **185a** leads to the formation of pyrrolidine **189a**, which appears to be unstable under the reaction conditions and undergoes ring opening to give acyclic imine **190a**. Subsequently, under these reductive reaction conditions, imine **190a** is converted into amino ester **187a**. Upon basic work-up, amino ester **187a** is converted into amino ester **188a** *via* an E_1cb-type elimination reaction. Unfortunately, when the purification of the reaction mixture was attempted, compounds **187a** and **188a** were not recovered. Furthermore, the formation of amino esters **187a** and **188a** under these reaction conditions was not reproducible, since repeating this reaction (2 equiv $NaCNBH_3$, 0.1 equiv *p*-TsOH, THF, r.t., 22 h) only led to the formation of a complex reaction mixture. In a next attempt, pyrroline **185a** was treated with $NaCNBH_3$ in the presence of acetic acid in acetonitrile for 30 minutes at 0 °C.[92] After work-up, a mixture of amino esters **187a** and **188a** was obtained, in a ratio **187a** : **188a** = 68 : 32 but again, the purification of this mixture failed (Table 7, entry 2). In an attempt to trap pyrrolidine **189a**, pyrroline **185a** was first stirred in acetonitrile in the presence of acetyl chloride to effectuate *N*-acetylation, before three equivalents of $NaCNBH_3$ were added. Then, the reaction mixture was stirred for three hours at room temperature but this resulted in the formation of a complex reaction mixture in which the *N*-acetyl derivatives of amino esters **187a** and **188a** were not present (Table 7, entry 3). Next, the effect of the addition of both acetic acid and acetyl chloride to the reaction mixture was investigated in the reaction of pyrroline **185a** with $NaCNBH_3$ (Table 7, entry 4). Again a mixture of amino esters **187a** and **188a** was obtained. Purification of this mixture *via* flash column chromatography afforded amino ester **188a** in pure form (29% yield) but this compound appeared to be unstable and no full characterization could be performed. The instability of compounds **187a** and **188a** explains why a complex reaction mixture was obtained when pyrroline **185a** was reacted with $NaCNBH_3$ under the standard reaction conditions using acetic acid in methanol and why the reaction using $NaCNBH_3$ in the presence of *p*-toluenesulfonic acid was not reproducible. Compounds **187a** and **188a** already degrade upon storage at room temperature for one hour or when a temperature of 37 °C was applied for the evaporation of the solvent after work-up. Thus, the formation of the complex reaction mixture under these reaction conditions was due to the instability of compounds **187a** and **188a**.

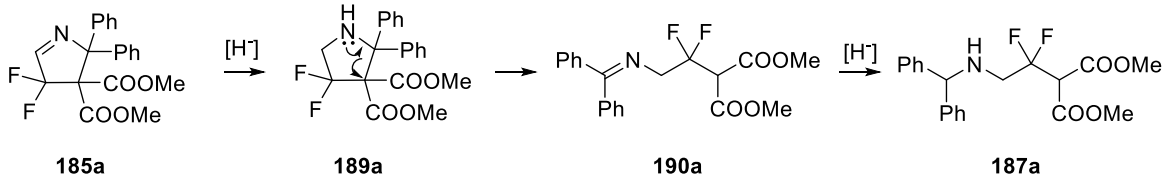
Table 7: Reduction of pyrroline 185a



185a **187a** **188a**

Entry	Reaction conditions	Result
1	2 equiv $NaCNBH_3$, 0.1 equiv *p*-TsOH, THF, r.t., 22 h	**187a** : **188a** = 75 : 25[a]
2	2 equiv $NaCNBH_3$, 2 equiv AcOH, CH_3CN, 0 °C, 30 min	**187a** : **188a** = 68 : 32[a]
3	1) 5 equiv AcCl, CH_3CN, r.t., 1 h 30 min 2) 3 equiv $NaCNBH_3$, MeOH, r.t., 3 h	Complex reaction mixture
4	2 equiv $NaCNBH_3$, 2 equiv AcOH, 2 equiv AcCl, CH_3CN, 0 °C, 20 min	**187a** : **188a** = 65 : 35[a] (29% **188a**)[b]

[a] Determined *via* ^1H NMR analysis of the crude reaction mixture. [b] Isolated yield.

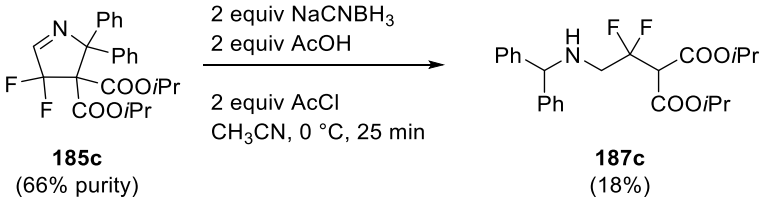


185a **189a** **190a** **187a**

Scheme 48

The transformation of pyrroline **185a** was also attempted *via* a nucleophilic addition across the C=N double bond by NaOMe or 4-methoxyphenol, but this only led to the formation of a complex reaction mixture.

Reduction of pyrroline **185c** using $NaCNBH_3$ in the presence of acetic acid and acetyl chloride afforded difluorinated amino ester **187c**, while only a trace amount of the corresponding monofluorinated diester was present in the reaction mixture. Apparently, due to the steric hindrance caused by the two isopropyl esters, the elimination of fluoride is more difficult. Amino ester **187c** was isolated in 18% yield but again, this compound proved to be unstable and could not be fully characterized.

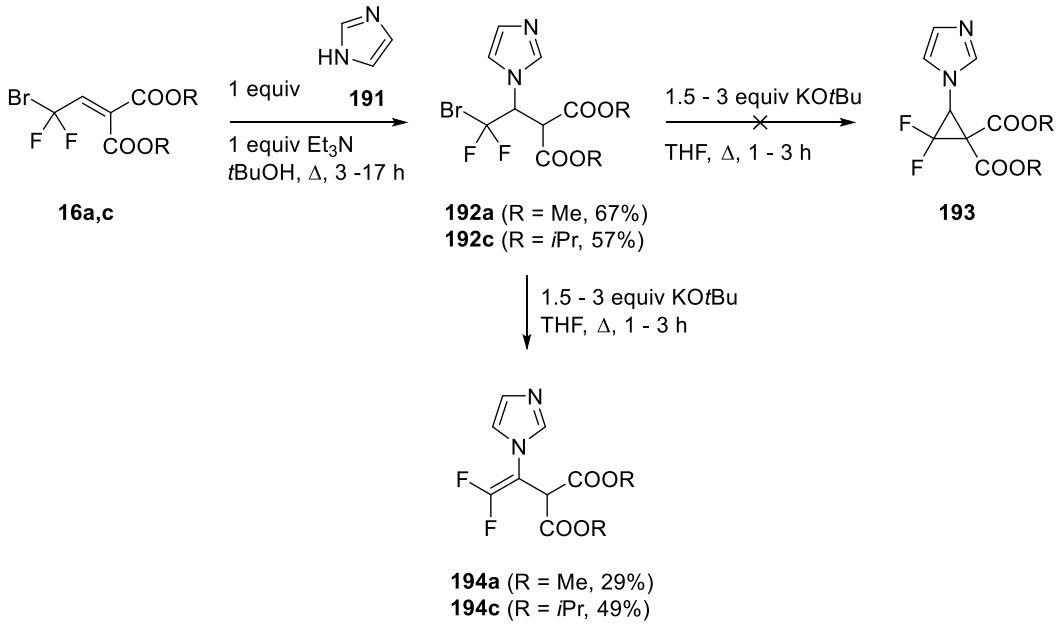


Scheme 49

Next to the reduction using $NaCNBH_3$, other reducing agents were also evaluated. However, while the use of $NaBH_4$, $NaBH(OAc)_3$ or $LiAlH(OtBu)_3$ gave no reaction, reaction with $LiAlH_4$ or H_2 in the presence of Pt/C led to the formation of a complex reaction mixture.

3.3.2.2 Aza-Michael addition of imidazole

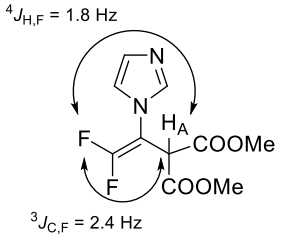
In the next part, imidazole **191** was evaluated as another nitrogen nucleophile, and was reacted with ethylidenemalonates **16a**,**c** in the presence of Et_3N in *tert*-butanol (Scheme 50). Although this reaction was carried out at reflux temperature for several hours, only adducts **192** was isolated from the reaction mixture and no subsequent ring closure was observed.



Scheme 50

In order to convert adduct **192a** into the envisioned cyclopropane **193a**, this compound was treated with 1.5 equivalents of KO*t*Bu in THF at reflux temperature for one hour, after which extra KO*t*Bu was added (1.5 equiv) and the stirring was continued for another two hours. According to LC-MS analysis of the

reaction mixture, one major product was formed, with a molecular weight corresponding to that of cyclopropane **193a**. However, after purification of this compound *via* preparative TLC and detailed analysis of the ^{1}H NMR, ^{13}C NMR and HSQC spectra, it was concluded that the product of this reaction was not cyclopropane **193a** but enamine **194a**. In the ^{1}H NMR spectrum a doublet ($^{4}J_{H,F}$ = 1.8 Hz) was present at 4.54 ppm, corresponding to H_A (Figure 13). Indeed, the size of this coupling constant indicates an allylic coupling between proton and fluorine, which is in accordance with some examples found in literature.[93] Furthermore, *via* analysis of the HSQC spectrum it can be seen that the carbon atom attached to H_A also shows a very small allylic coupling with fluorine ($^{3}J_{C,F}$ = 2.4 Hz). In both cases, the coupling with the other fluorine atom was not resolved in the spectrum.



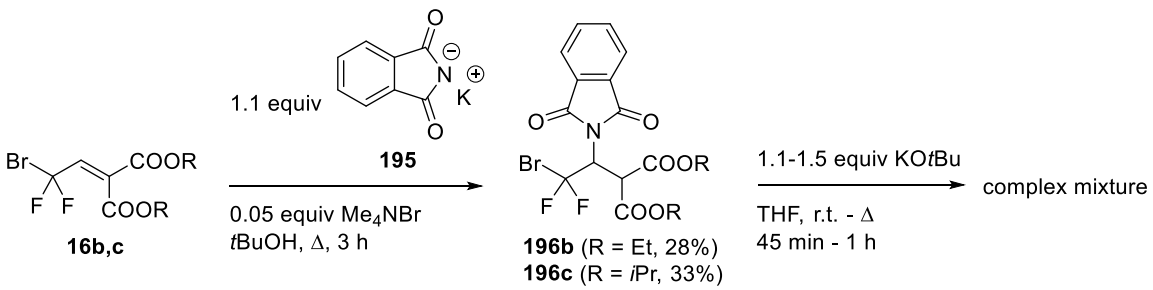
194a

Figure 13

Furthermore, diisopropyl diester **192c** was also converted into enamine **194c**, which was isolated in 49% yield (Scheme 50).The low yields are due to loss of the product during purification *via* preparative TLC.

3.3.2.3 Aza-Michael addition of potassium phthalimide

In a next part, ethylidenemalonates **16b**,**c** reacted with potassium phthalimide **195** in the presence of tetramethylammonium bromide in *tert*-butanol at reflux temperature, affording adducts **196b**,**c** in low yields (28-33%) (Scheme 51). When these adducts were treated with base in THF in the next step, at room temperature for **196c** or at reflux temperature for **196b**, this only led to the formation of a complex reaction mixture.



Scheme 51

3.3.3 Conclusion

In conclusion, three different nucleophiles were evaluated for the synthesis of fluorinated β-ACC derivatives *via* a MIRC reaction starting from ethylidenemalonates **16**. The use of diphenylmethylideneamine gave the best results and led to the formation of unprecedented fluorinated β-ACC derivatives **184**. However, these compounds were unstable and rearranged toward fluorinated pyrrolines **185**. Pyrrolines **185** were in turn converted into unstable acyclic γ-amino esters **187** *via* reduction. When imidazole was reacted with ethylidenemalonates **16**, Michael adducts **192** were formed, but these could not be converted into the corresponding cyclopropanes **193**. Instead, formation of enamines **194** was observed. Finally, the use of potassium phthalimide **195** only led to complex reaction mixtures when cyclization was attempted.

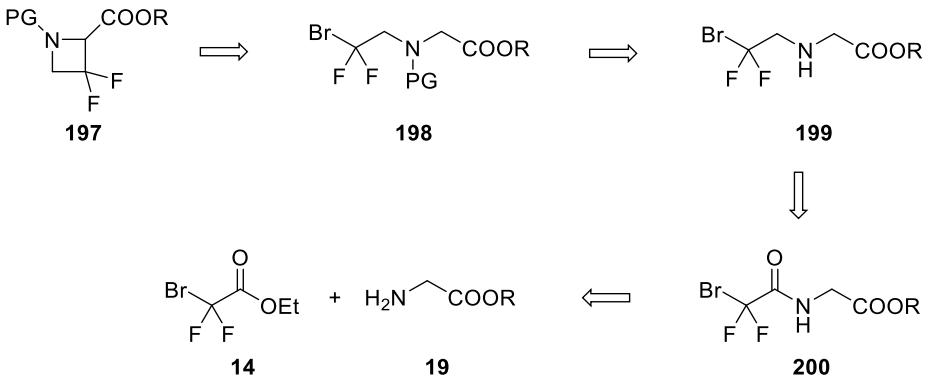
3.4 Attempted synthesis of 3-fluoro- and 3,3-difluoroazetidine-2-carboxylates

3.4.1 Introduction

As mentioned in the literature overview, only two examples on the synthesis of 3-fluoroazetidine-2-carboxylic acid derivatives have been reported before. The first method comprises the fluorination of azetidine-2-carboxylic acid using the highly toxic trifluoromethyl hypofluorite gas in liquid HF.[49] The second method was reported only very recently and describes the formation of 4-hydroxymethylated derivatives of 3-fluoroazetidine-2-carboxylic acid.[50] In this part of this PhD thesis, it was attempted to develop a general synthetic route toward these strained fluorinated amino acid derivatives, without the presence of an extra substituent at the 4-position.

3.4.2 Synthesis of amino esters

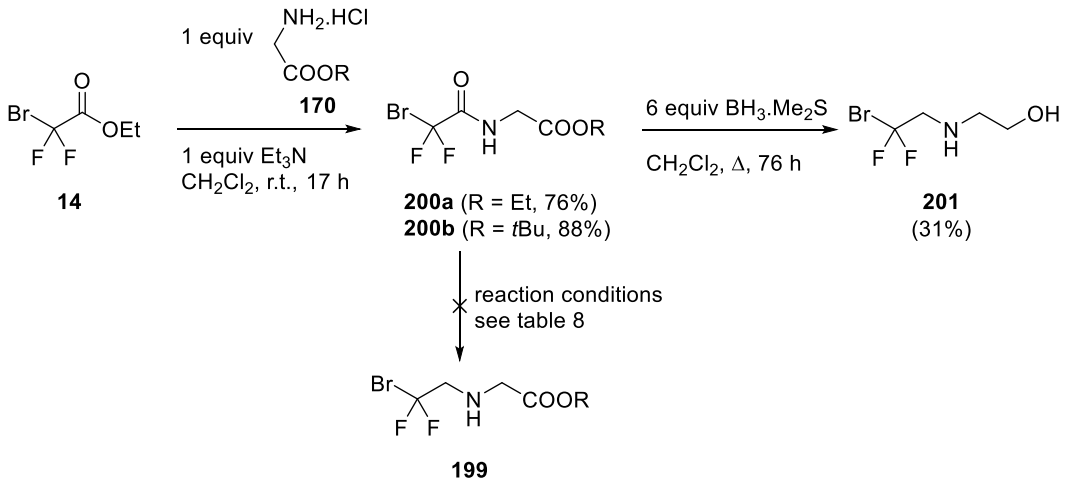
Inspired by the work of Couty,[14a,14b] the synthesis of difluorinated azetidine-2-carboxylates **197** was envisioned *via* cyclisation of bromodifluorinated precursors **198** (Scheme 52). It was believed that these precursors could be synthesized starting from ethyl bromodifluoroacetate **14**, *via* sequential amidation by reaction with glycine esters **19**, selective reduction of the resulting amide moiety of compounds **200** and protection of the amine to give precursors **198**.



Scheme 52

In a first step, ethyl bromodifluoroacetate **14** was brought into reaction with the hydrochloric salt of ethyl glycinate **170b** in dichloromethane in the presence of Et_3N, leading to the formation of amide **200a** in good yield. The next step in this reaction sequence was the selective reduction of the amide moiety toward amino ester **199a**. Unfortunately, this reduction proved to be not straightforward. First, the use of borane

dimethylsulfide complex ($BH_3.Me_2S$) in CH_2Cl_2 was evaluated in the reaction with amide **200a**. Independent of the number of equivalents (3 - 12 equiv), the reaction temperature (r.t. - Δ) or the reaction time (1.5 - 20 h), no conversion toward the envisioned amino ester **199a** was observed and only the starting compound **200a** was recovered (Table 8, entries 1-5). Only when the reaction of amide **200a** with six equivalents of $BH_3.Me_2S$ was carried out for a prolonged reaction time of 76 h, a reduction was observed, but the compound that was obtained was amino alcohol **201**, formed by a reduction of all carbonyls in compound **200a** (Table 8, entry 6). When borane was used as the THF-complex at room temperature, again no reaction occurred (Table 8, entry 7) or a complex mixture was obtained when the reaction was conducted at reflux temperature using 10 equivalents of BH_3.THF (Table 8, entry 8). In a next attempt, the use of monochloroalane, prepared *in situ* from $AlCl_3$ and $LiAlH_4$, was evaluated, but under these reaction conditions, amino alcohol **201** was again formed as the end product (Table 8, entry 9). In an attempt to avoid the reduction of the ester moiety, the bulkier *tert*-butyl ester **200b** was also prepared and subjected to reductive reaction conditions. In this case, treatment of amide **200b** with three equivalents of $BH_3.Me_2S$ in dichloromethane under reflux conditions also led to the undesired formation of amino alcohol **201** (Table 8, entry 10).



Scheme 53

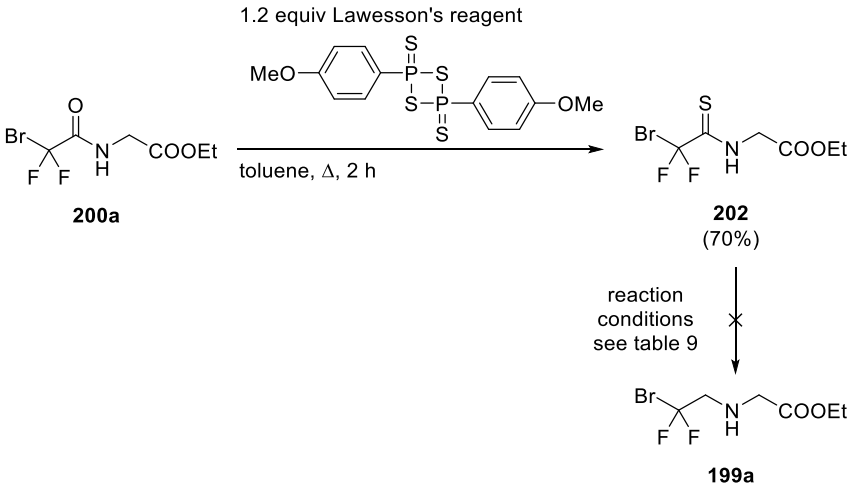
Table 8: Attempted selective reduction of amido esters 200

Entry	Substrate	Reaction conditions	Result
1	**200a**	3 equiv $BH_3.Me_2S$, CH_2Cl_2, r.t., 17 h	No reaction
2	**200a**	10 equiv $BH_3.Me_2S$, CH_2Cl_2, r.t., 2 h	No reaction
3	**200a**	3 equiv $BH_3.Me_2S$, CH_2Cl_2, Δ, 20 h	No reaction
4	**200a**	10 equiv $BH_3.Me_2S$, CH_2Cl_2, Δ, 3 h	No reaction
5	**200a**	12 equiv $BH_3.Me_2S$,[a] CH_2Cl_2, Δ, 1.5 h	No reaction
6	**200a**	6 equiv $BH_3.Me_2S$, CH_2Cl_2, Δ, 76 h	**201** (31%)[b]
7	**200a**	1 equiv BH_3.THF, THF, r.t., 3 h	No reaction
8	**200a**	10 equiv BH_3.THF, THF, r.t., 3 h	Complex reaction mixture
9	**200a**	1 equiv $AlCl_3$, 3 equiv $LiAlH_4$, Et_2O, 0 °C, 2 h	**201** (50% crude)
10	**200b**	3 equiv $BH_3.Me_2S$, CH_2Cl_2, Δ, 24 h	**201** (60% crude)

[a] Added in portions of 2 equiv every 10 minutes. [b] Isolated yield.

Since the selective reduction of the amide moiety of compounds **200** proved to be difficult, another strategy was employed. Since the reduction of thioamides in the presence of ester functions has been reported, amide **200a** was converted into thioamide **202**. While treatment of amide **200a** with Lawesson's reagent in benzene at reflux temperature for 3.5 hours resulted only in partial conversion toward thioamide **202**, the use of toluene as the solvent led to full conversion and thioamide **202** was isolated in 70% yield (Scheme 54). Subsequently, the selective reduction of the thioamide moiety of compound **202** was investigated. In a first attempt, thioamide **202** was treated with $NiCl_2.6H_2O$ in the presence of $NaBH_4$, in order to form nickel boride *in situ*,[94] but these reaction conditions only led to the formation of a complex reaction mixture (Table 9, entry 1). In contrast, treatment of amide **202** with Raney Nickel in a solvent mixture containing EtOH, THF and water at room temperature for one hour only led to recovery of the starting material (Table 9, entry 2).[95] Another attempt for desulfurization comprised the alkylation of the thioamide with methyl iodide, followed by reduction. Unfortunately, upon treatment of thioamide **202** with MeI in the absence or in the presence of a base, no reaction was observed (Table 9, entries 3-4).[96] A last attempt comprised the addition of $BH_3.Me_2S$, but in this case, either no reaction was observed at room

temperature, or a complex reaction mixture was obtained when reflux temperature was applied (Table 9, entries 5-6).

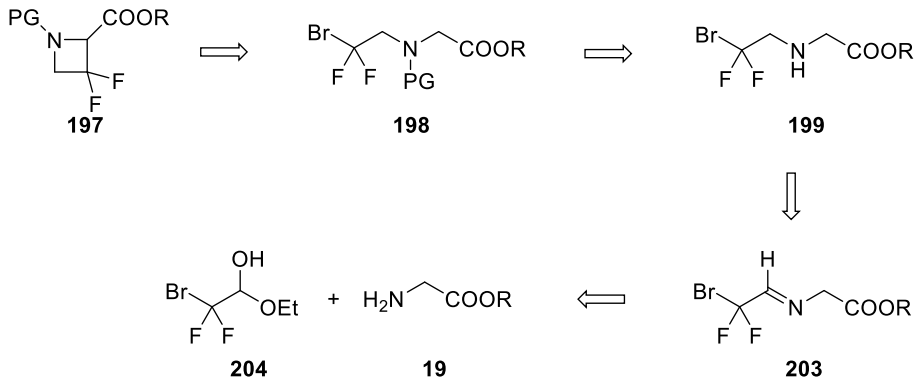


Scheme 54

Table 9: Attempted reduction of thioamide 202

Entry	Reaction conditions	Result
1	8 equiv $NiCl_2.6H_2O$, 2.4 equiv $NaBH_4$, THF/MeOH 1/1, r.t., 3 h	Complex reaction mixture
2	RaNi (in H_2O), THF/EtOH 1/1, r.t., 1 h	No reaction
3	5 equiv MeI, THF, r.t., 17 h	No reaction
4	1.2 equiv NaH, 5 equiv MeI, THF, r.t., 20 h	No reaction
5	3 equiv $BH_3.Me_2S$, CH_2Cl_2, r.t., 1 h	No reaction
6	3 equiv $BH_3.Me_2S$, CH_2Cl_2, Δ, 2 h	Complex reaction mixture

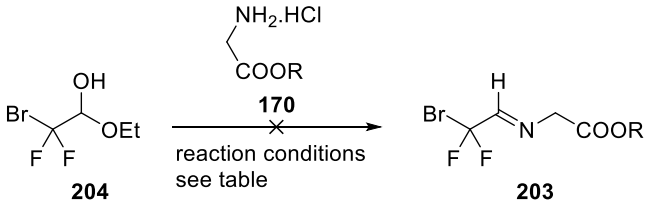
Since all attempts to achieve a selective reduction of the amide moiety in the presence of the ester functionality failed, this pathway was abandoned and an alternative approach was sought, which comprised the synthesis of aldimines **203** starting from hemiacetal **204** and glycine esters **19** (Scheme 55). The reduction of aldimines **203** in the presence of an ester function was believed to be more straightforward.



Scheme 55

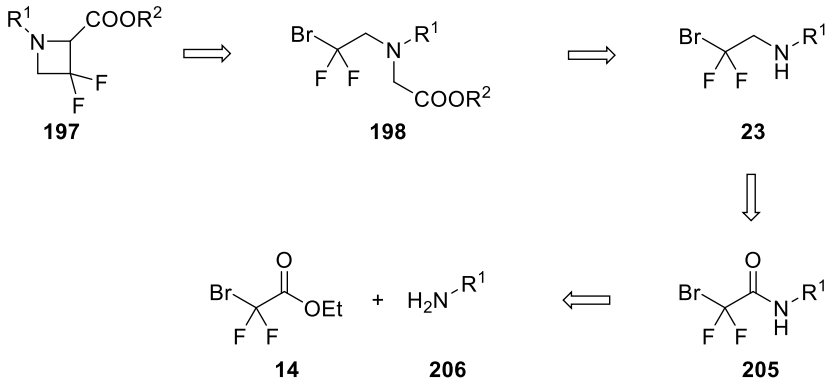
Unfortunately, the synthesis of aldimines **203** could not be effectuated. Treatment of hemiacetal **204**, prepared *via* reduction of ethyl bromodifluoroacetate **14**,[97] with glycine esters **170b** and **170a** under Dean-Stark conditions in the presence of triethylamine in toluene led to the formation of a complex reaction mixture. Also the use of milder reaction conditions, by using triethylamine and $MgSO_4$ in dichloromethane, afforded a complex reaction mixture (Table 10).

Table 10: Attempted synthesis of aldimines 203



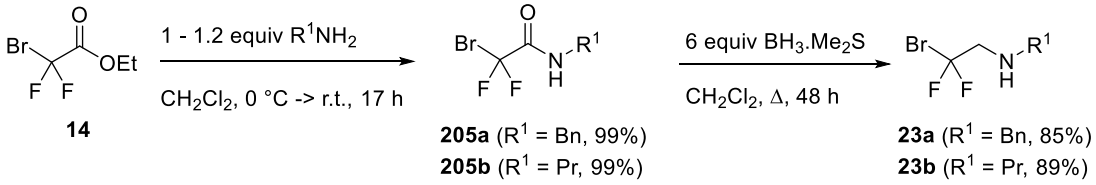
Entry	Substrate **170**	Reaction conditions	Result
1	**170b** (R = Et)	1 equiv **170b**, 1 equiv Et_3N, toluene, Dean-Stark, 3 h	Complex reaction mixture
2	**170a** (R = Me)	1 equiv **170a**, 1 equiv Et_3N, toluene, Dean-Stark, 3 h	Complex reaction mixture
3	**170a** (R = Me)	1 equiv **170a**, 1 equiv Et_3N, 2 equiv $MgSO_4$, CH_2Cl_2, r.t., 1 h	Complex reaction mixture

Because both of the above-mentioned routes toward precursors **198** failed, an alternative pathway was evaluated (Scheme 56). It was decided to introduce the ester function of amino esters **198** after reduction of amides **205** toward amines **23**, thus avoiding the need for a selective reduction.



Scheme 56

To this end, secondary fluorinated amines **23** were synthesized by reacting ethyl bromodifluoroacetate **14** with different amines leading to amides **205**, which in turn were reduced using borane dimethylsulfide complex in dichloromethane under reflux (Scheme 57).[15]

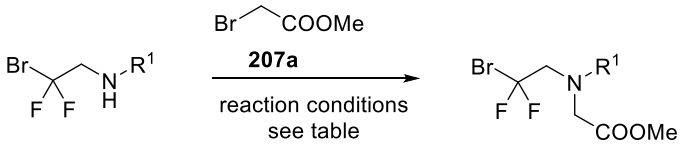


Scheme 57

To achieve the coupling between amines **23** with methyl bromoacetate **207a**, various reaction conditions were applied (Table 11). In a first attempt, amine **23a** was treated with 1.2 equivalents of methyl bromoacetate **207a** in the presence of triethylamine, but this reaction gave no conversion, neither at room temperature nor at 70 °C (Table 11, entries 1-2). Subsequently, amine **23a** was treated with sodium hydroxide in dichloromethane using tetrabutylammonium iodide (TBAI) as phase transfer catalyst (Table 11, entry 3). Unfortunately, also in this case no reaction was observed. The use of NaH as a base either gave no conversion when the reaction was performed at 0 °C for one hour (Table 11, entry 4) or led to the formation of a complex reaction mixture upon reaction at room temperature for 20 h (Table 11, entry 5). Using *N*-propyl-2-bromo-2,2-difluoroethylamine **23b** as substrate, the use of triethylamine in the presence of a catalytic amount of DMAP in dichloromethane was evaluated, with or without the addition of sodium iodide, but again no conversion toward the corresponding amino ester **198b** was observed (Table 11, entries 6-7). The use of neat reaction conditions by stirring amine **23b** and bromoacetate **207a** in the presence of triethylamine was also ineffective (Table 11, entry 8). Although the alkylation of secondary amines with bromoacetates **207** normally proceeds under mild reaction conditions,[98] the reaction with

amines **23** proved to be less straightforward. The lower reactivity of amines **23** is due to the decreased nucleophilicity of the amine nitrogen, caused by the electron-withdrawing effect of the two fluorine atoms.

Table 11: Attempted synthesis of amino esters 198 starting from amines 23



23a (R^1 = Bn)
23b (R^1 = Pr)

198a (R^1 = Bn)
198b (R^1 = Pr)

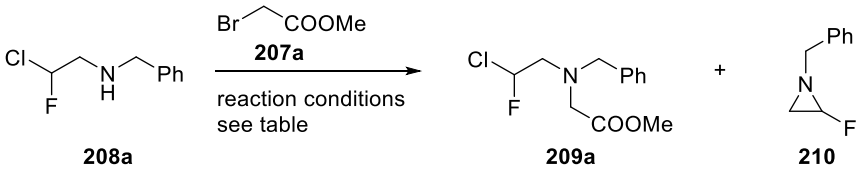
Entry	Substrate	Reaction conditions	Result
1	**23a**	1.2 equiv **207a**, 2 equiv Et_3N, DMSO, r.t., 4 h	No reaction
2	**23a**	1.2 equiv **207a**, 2 equiv Et_3N, DMSO, 70 °C, 24 h	No reaction
3	**23a**	1.2 equiv **207a**, 3.5 equiv NaOH[a], 0.2 equiv TBAI, CH_2Cl_2, r.t., 17 h	No reaction
4	**23a**	1.2 equiv **207a**, 1 equiv NaH, DMF, 0 °C, 1 h	No reaction
5	**23a**	1.2 equiv **207a**, 1 equiv NaH, DMF, r.t., 20 h	Complex reaction mixture
6	**23b**	1 equiv **207a**, 1 equiv Et_3N, 0.1 equiv DMAP, CH_2Cl_2, Δ, 17 h	No reaction
7	**23b**	1.2 equiv **207a**, 1.2 equiv Et_3N, 0.1 equiv DMAP, 1 equiv NaI, CH_2Cl_2, Δ, 24 h	No reaction
8	**23b**	1.2 equiv **207a**, 1.2 equiv Et_3N, r.t., 18 h	No reaction

[a] 2M in H_2O.

Bearing in mind the disadvantageous effect of fluorine atoms on the nucleophilicity of the amine nitrogen atom, amine **208a** was prepared, containing only one fluorine substituent at the β-position.[15] At the same time, more stringent reaction conditions were applied, by the use of LiHMDS as the base (Table 12). In a first attempt, amine **208a** was treated with 1.1 equivalents LiHMDS and 1.1 equivalents of methyl bromoacetate **207a** in THF at -78 °C (Table 12, entry 1). Upon analysis of the reaction mixture, the presence of aziridine **210** was observed, next to a trace amount of the desired amino ester **209a**. The formation of aziridine **210** under these reaction conditions is not surprising, since treatment of amine **208a** with 1.5

equivalents of LiHMDS in THF at -10 °C for three hours has been used as a preparation method for 2-fluoroaziridine **210**.[15] The presence of a trace amount of amino ester **209a** in the reaction mixture was encouraging and the reaction conditions were adapted in an attempt to direct the reaction toward the selective formation of amino ester **209a**. Increasing the number of equivalents of methyl bromoacetate **207a** led to a higher conversion toward amino ester **209a**, but still a significant amount of aziridine **210** was present in the reaction mixture (Table 12, entries 2-3). Finally, the use of seven equivalents of methyl bromoacetate **207a** and no addition of extra solvent led to a selective conversion of amine **208a** toward amino ester **209a**, which was isolated in 79% yield (Table 12, entry 4).

Table 12: Synthesis of amino ester 209a from amine 208a



Entry	Reaction conditions	Ratio[a] **208** : **209a** : **210**	Yield **209a**
1	1.1 equiv **207a**, 1.1 equiv LiHMDS,[b] THF, -78 °C, 1 h	55 : trace : 45	-
2	3 equiv **207a**, 1.1 equiv LiHMDS,[b] THF, -78 °C – r.t., 19 h	29 : 20 : 51	-
3	5 equiv **207a**, 1.1 equiv LiHMDS,[b] THF, -78 °C - r.t., 20 h	14 : 31 : 55	25%
4	7 equiv **207a**, 1.1 equiv LiHMDS,[b] 0 °C – r.t., 23 h	0 : 100 : 0	79%

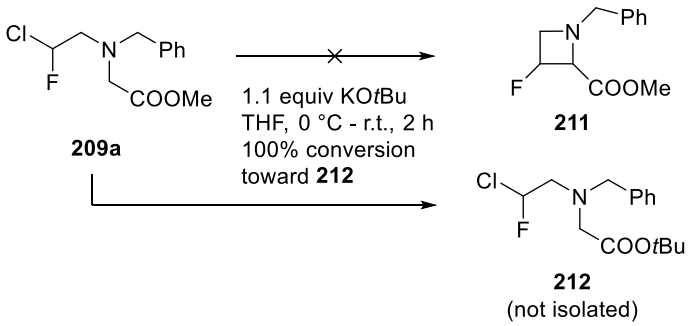
[a] Determined *via* ^{1}H NMR analysis of the crude reaction mixture. [b] 1M in THF.

Subsequently, these optimized reaction conditions were applied to bromodifluorinated amines **23**. Due to the lower nucleophilicity of these amines, a higher reaction temperature of 70 °C had to be applied, achieving a selective conversion of amines **23** toward amino esters **198a**,**c**,**d** which were isolated in moderate to good yields (Scheme 58).

Scheme 58

3.4.3 Attempted ring closure toward 3-fluoro- and 3,3-difluoroazetidine-2-carboxylates

Having precursors **198** and **209** in hand, their ring closure toward the envisioned fluorinated azetidines was evaluated. In a first attempt, monofluorinated amino ester **209a** was treated with 1.1 equivalents of KO*t*Bu for two hours at room temperature. After analysis of the reaction mixture, it was concluded that KO*t*Bu had reacted as a nucleophile leading to transesterification toward the corresponding *tert*-butyl ester **212** (Scheme 59). This compound **212** was tentatively identified from the crude reaction mixture *via* ^{1}H NMR and LC-MS analysis, but was not isolated.



Scheme 59

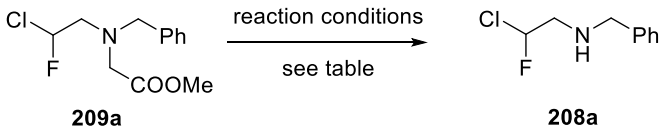
To avoid this transesterification reaction, the use of NaOMe was evaluated next. While reaction of amino ester **209a** with NaOMe in THF at 0 °C or at room temperature for three hours only led to recovery of the starting material, increasing the temperature to reflux temperature led to the formation of a complex reaction mixture after three hours of reaction.

Next, the use of the stronger base LiHMDS was assessed, which was a suitable base for the synthesis of azetidine-2-carboxylates starting from very similar non-fluorinated amino esters.[14b] First, precursor **209a** was treated with 1.2 equivalents of LiHMDS in THF at -78 °C for two hours (Table 13, entry 1). However,

no reaction was observed. Surprisingly, after stirring amino ester **209a** in the presence of 1.1 equivalents of LiHMDS at 0 °C for one hour, 64% conversion toward amine **208a** was observed (Table 13, entry 2). Apparently, these reaction conditions lead to removal of the methoxycarbonylmethyl group of amino ester **209a**. This conversion is very peculiar and has not been observed in the literature upon treatment of alkoxycarbonylmethylamines with LiHMDS. However, the reductive removal of an alkoxycarbonylmethyl group has been reported by photoactivated electron transfer from a neutral organic donor or in the presence of lithium.[99] The addition of 0.2 equivalents KI to the reaction mixture also did not lead to ring closure toward the envisioned azetidine **211** and again 60% conversion toward secondary amine **208a** was observed (Table 13, entry 3). When the reaction of precursor **209a** with LiHDMS was performed in a THF/HMPA 10/1 mixture,[14a] no reaction was observed after two hours at 0 °C (Table 13, entry 4). Increasing the reaction temperature to room temperature gave no conversion after one hour of reaction, but led to the formation of a complex reaction mixture, in which amine **208a** was not detected, when the reaction time was prolonged to 17 hours (Table 13, entry 5). Apparently, the lithium ion plays a role in the removal of the methoxycarbonylmethyl group leading to the formation of amine **208a**. To test the influence of the cation in this reaction, precursor **209a** was reacted with 1.1 equivalents of KHMDS in THF at 0 °C for one hour (Table 13, entry 6). After this time, no reaction conversion was observed, neither toward the envisioned azetidine **211**, nor toward secondary amine **208a**. It can be concluded that the lithium cation of LiHMDS is essential for the removal of the methoxycarbonylmethyl group from nitrogen, but its specific role remains unclear. Since the reaction of precursor **209a** with KHMDS at 0 °C gave no conversion at all, this reaction was repeated at room temperature for two hours. Follow-up of this reaction also indicated no conversion, so to test if deprotonation at the α-position of the ester took place, the mixture was quenched with D_2O and stirred for 30 minutes at room temperature. After analysis of the reaction mixture, it was concluded that no deuterium atom was present in the end product and thus amino ester was not deprotonated by KHMDS. This is in contrast to an example in the literature, were very similar glycinates, containing a $-CH_2CF_3$ substituent at nitrogen, were alkylated at the α-position of the ester function by treatment with KHMDS and a suitable alkyl halide. Thus, in that case, deprotonation did occur, although the alkylation only proceeded with activated alkyl halides like allyl bromide, while no alkylation occurred using allyl chloride or butyl bromide as the electrophile.[100] Also when NaHMDS was used, no reaction was observed after one hour at 0 °C (Table 13, entry 8), and no deprotonation occurred after stirring the reaction mixture at room temperature for 2.5 hours (Table 13, entry 9). As another example of a nitrogen base with a litium cation, precursor **209a** was treated with LiTMP, freshly prepared from tetramethylpiperidine and BuLi, at -78 °C (Table 13, entry 10). This mixture was stirred at the same

temperature for one hour and was then allowed to warm to room temperature and stirred for another 17 hours. However, after work-up, starting compound **209a** was present in the reaction mixture, next to some unidentified side products.

Table 13: Attempted ring closure of amino ester 209a



209a **208a**

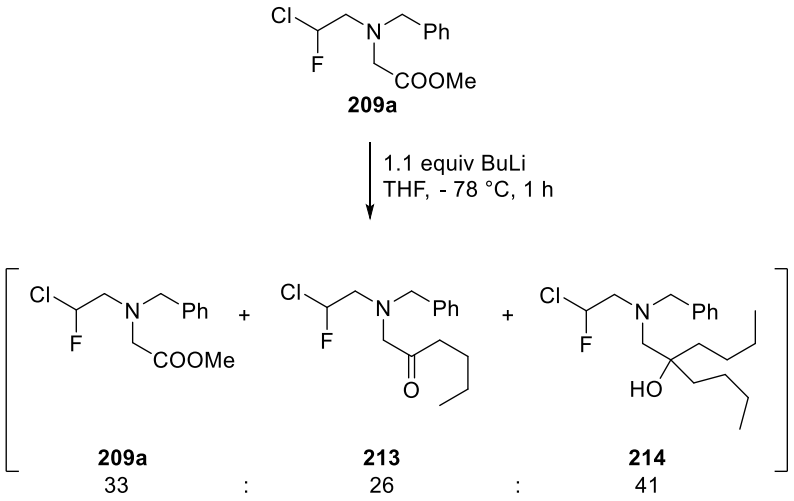
Entry	Reaction conditions	Result
1	1.2 equiv LiHMDS, THF, -78 °C, 2 h	No reaction
2	1.1 equiv LiHMDS, THF, 0 °C, 1 h	64% conversion[a]
3	1.1 equiv LiHMDS, 0.2 equiv KI, THF, 0 °C, 1 h	60% conversion[a]
4	1.2 equiv LiHMDS, THF/HMPA 10/1, 0 °C, 2 h	No reaction
5	1.2 equiv LiHMDS, THF/HMPA 10/1, r.t., 17 h	Complex reaction mixture
6	1.1 equiv KHMDS, THF, 0 °C, 1 h	No reaction
7	1) 1.1 equiv KHMDS, THF, r.t., 2 h 2) D_2O, r.t., 30 min	No reaction
8	1.1 equiv NaHMDS, THF, 0 °C, 1 h	No reaction
9	1) 1.1 equiv NaHMDS, THF, r.t., 2.5 h 2) D_2O, r.t., 30 min	No reaction
10	1.1 equiv LiTMP, THF, -78 °C, 1 h, then r.t., 17 h	**209a** + side products
11	1.1 equiv LDA, 2 equiv TMSCl, THF, -78 °C, 20 min, then r.t., 1 h	No reaction

[a] Determined *via* ^{1}H NMR analysis of the crude reaction mixture.

A possible reaction mechanism for the removal of the methoxycarbonylmethyl group could include silylation of compound **209a**, followed by degradation towards amine **208a**. To test this hypothesis, it was attempted to silylate amino ester **209a** by treatment with LDA, followed by the addition of TMSCl.[101] However, after stirring this reaction mixture at -78 °C for 20 minutes, followed by one hour at room temperature, no reaction could be observed (Table 13, entry 11).

Alternatively, the formation of amine **208a** could be the result of the nucleophilic attack of the base LiHMDS at the α-carbon of the amino ester, followed by expulsion of amine **208a** as leaving group. In that case, methyl bis(trimethylsilyl)glycinate should be formed as a byproduct. The reaction of amino ester **209a** with LiHMDS was repeated using the reaction conditions mentioned in Table 13, entry 2 (1.1 equiv LiHMDS, THF, 0 °C, 1 h). The reaction mixture was analysed using GC-MS without work-up, but methyl bis(trimethylsilyl)glycinate could not be detected, while amine **208a** was again present in the reaction mixture.

Upon treatment of precursor **209a** with butyllithium the envisaged azetidine was also not formed. Instead, addition of butyllithium across the carbonyl led to formation of ketone **213** and tertiary alcohol **214** in a mixture with starting compound **209a** (Scheme 60). The purification of this mixture was attempted *via* column chromatography, but this failed since reaction products **209a**, **213** and **214** could not be separated.



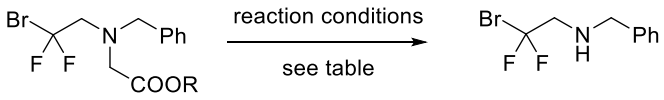
Scheme 60

Next, precursor **209a** was reacted with 1.2 equivalents of NaH in THF. However, no reaction was observed after two hours at 0 °C or at room temperature. To test if deprotonation had occurred, the reaction of precursor **209a** with NaH at room temperature was repeated and quenched with D_2O after two hours. Again no incorporation of deuterium was observed, and it was concluded that NaH did not deprotonate precursor **209a**.

Next, the reactivity of the difluorinated analogues **198** toward bases was evaluated, to see if similar results could be observed (Table 14). Thus, benzyl ester **198c** reacted with 1.1 equivalents of LiHMDS in THF at 0 °C and after one hour, 25% conversion toward secondary amine **23a** was observed, without any conversion toward the envisaged azetidine. Again, removal of the alkoxycarbonylmethyl group at nitrogen

occurred and it was concluded that this reaction was independent of the alcohol part of the ester. Also the reaction of methyl ester **198a** with 1.1 equivalents of LiHMDS led to the formation of amine **23a** (40% conversion after one hour).

Table 14: Attempted ring closure of amino esters 198



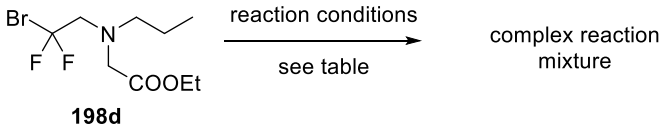
198 **23a**

Entry	Substrate	Reaction conditions	Result[a]
1	**198c** (R = Bn)	1.1 equiv LiHMDS, THF, 0 °C, 1 h	25% conversion
2	**198a** (R = Me)	1.1 equiv LiHMDS, THF, 0 °C, 1 h	40% conversion

[a] Determined *via* ^{1}H NMR analysis of the crude reaction mixture.

To test the influence of the substituent at nitrogen, the ring closure of *N*-propyl amino ester **198d** was also evaluated. Thus, amino ester **198d** was treated with 1.1 equivalents of LiHMDS at 0 °C for two hours (Table 15, entry 1). However, in this case, no formation of the corresponding secondary amine **23b** was observed. Instead, after work-up a complex mixture was obtained, in which only amino ester **198d** was detected. It was concluded that the substituent at nitrogen has an influence on the removal of the alkoxycarbonylmethyl group leading to the corresponding secondary amines, but the nature of this influence remains unclear. Amino ester **198d** was also treated with LiHMDS under other reaction conditions (1 equiv Ag_2CO_3, toluene, r.t., 2 h), but again a complex mixture was obtained in which only starting compound **198d** was detected (Table 15, entry 2).

Table 15: Attempted ring closure of amino ester 198d



198d

Entry	Reaction conditions	Result
1	1.1 equiv LiHMDS, THF, 0 °C, 2 h	**198d** in a complex mixture
2	1.05 equiv LiHMDS, 1 equiv Ag_2CO_3, toluene, r.t., 2 h	**198d** in a complex mixture

The removal of the alkoxycarbonylmethyl substituent on nitrogen upon treatment of amino esters **209** and **198a**,**c** with LiHMDS is interesting and should be investigated more thoroughly. However, in the timeframe of this PhD thesis, this was not possible.

3.4.4 Conclusion

In this part of this PhD thesis, the synthesis of fluorinated azetidine-2-carboxylates was attempted. The synthesis of amino esters **209** and **198** was not straightforward, but after many attempts, a pathway toward these precursors **209** and **198** was developed and optimized. However, the ring closure toward the envisioned azetidines could not be effectuated. While the use of LiHMDS led to conversion of precursors **209** and **198a**,**c** to the corresponding secondary amines by removal of the alkoxycarbonylmethyl group, no deprotonation of the amino esters was observed upon use of KHMDS, NaHMDS or NaH. Finally, the use of KO*t*Bu and BuLi led to a nucleophilic addition across the carbonyl moiety of the ester function. It is clear that the presence of the fluorine atoms has an influence on the behavior of these amino esters, since the corresponding non-fluorinated analogues are suitable substrates for the synthesis of azetidine-2-carboxylates.

3.5 Synthesis of fluorinated heterocycles by exploring the nucleophilic vinylic substitution (S_NV) reaction of *gem*-difluoroenamides

3.5.1 Introduction

The class of enamides represents an interesting group of compounds, since they demonstrate an enhanced stability as compared to enamines, but still exhibit a rather nucleophilic reactivity.[102] A significant amount of research has already been devoted to the class of β,β-dihaloenamines and β,β-dihalogenated enamides.[103] In contrast, while some β,β-difluorinated enamines have been used as building blocks, for example, in the synthesis of difluorocysteine and -serine derivatives,[104] dipeptides,[105] difluoroimines[106] and various α,α-difluoro-β-hydroxycarbonyl compounds,[107] the chemistry of difluoroenamides has received only very limited attention. To our knowledge, this reactivity was exploited only twice toward the synthesis of fluorinated heterocycles, more specifically toward isoxazolidines and dihydropyrans[108] or oxazoles.[109] Furthermore, one example was found in which the intermediacy of a difluoroenamide was postulated in the synthesis of morpholino-fused diketopiperazines.[110] Also, while *gem*-difluoroalkenes have been used in a nucleophilic vinylic substitution reaction (S_NV) for the synthesis of a variety of fluorinated heterocycles,[111] their nitrogen-substituted analogues have received less attention. This is remarkable since the presence of two fluorine atoms at the β-carbon atom of enamide **25** in combination with an electron-withdrawing acyl or sulfonyl group (R^2) at nitrogen, will lead to a highly polarized double bond and an electron-deficient difluorinated carbon atom (Figure 14). If this effect could predominate the electron-donating effect of the enamide nitrogen atom, enamide **25** would be an example of an electrophilic enamide readily reacting with nucleophiles. In this way, the introduction of two fluorine atoms at the β-position could be seen as an efficient way to induce umpolung of the enamide functionality.[112] The potential to use this chemistry in a way that fundamentally deviates from the reactivity of Stork enamines and enamides **215**[113] is the basis of this part of this PhD thesis (Figure 14).

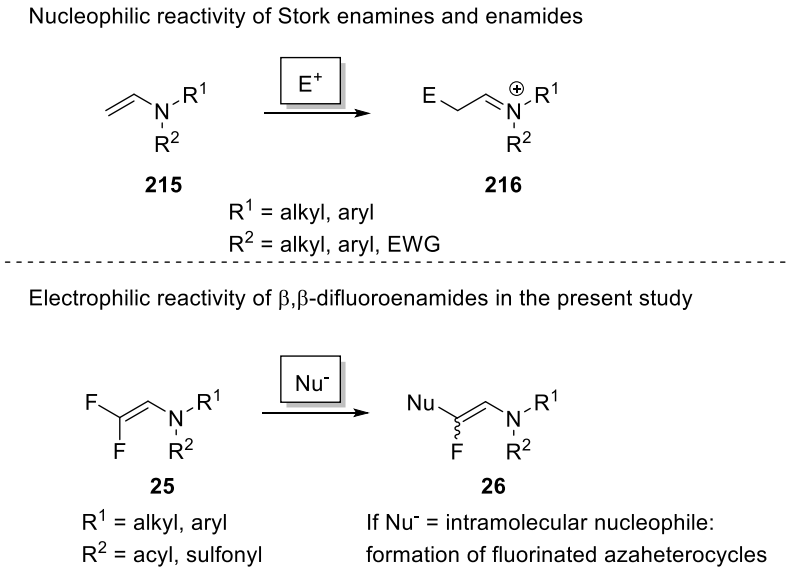
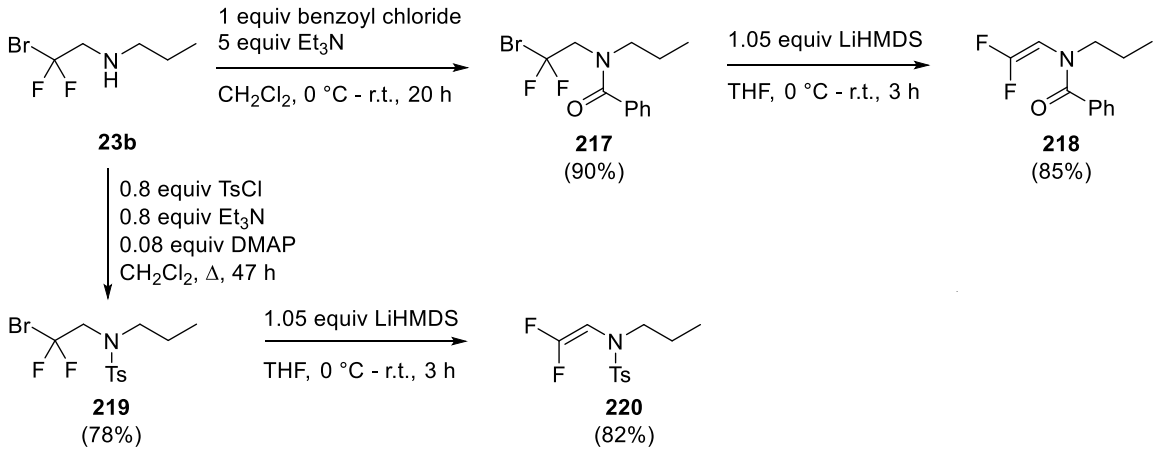


Figure 14

3.5.2 Synthesis of β,β-difluorinated enamides

In the first part of this work, the synthesis of novel β,β-difluoroenamides **218** and **220** was developed (Scheme 61). *N*-Propyl-2-bromo-2,2-difluoroethylamine **23b** was used as the starting compound for this synthesis while protection of the secondary amine was necessary in order to avoid aziridine formation upon treatment of amine **23b** with base.[15] Therefore, amine **23b** was protected as benzamide **217** or tosylamide **219** in good yield by treatment with benzoyl chloride or *p*-toluenesulfonyl chloride, respectively, in dichloromethane in the presence of base. In a final step, benzamide **217** and tosylamide **219** were treated with LiHMDS in THF at 0 °C to room temperature for three hours in order to achieve dehydrobromination, smoothly leading to the formation of new difluorinated enamides **218** and **220** (82-85% yield).



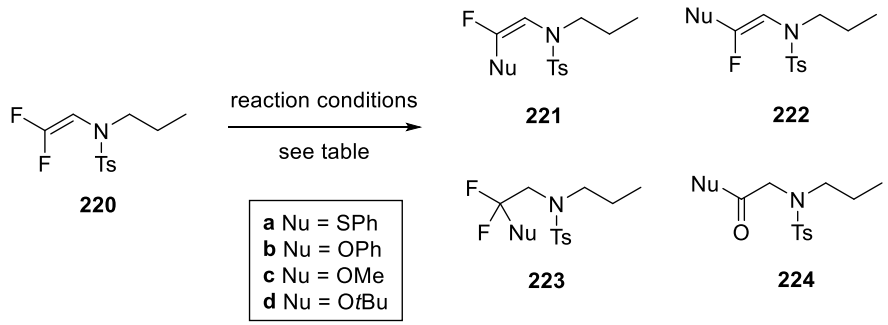
Scheme 61

3.5.3 Reactivity of β,β-difluorinated enamides 218 and 220 toward nucleophiles

To test the potential electrophilic reactivity of enamides **218** and **220**, a reactivity study with different nucleophiles was performed. First, tosylated enamide **220** was treated with benzylamine under various reaction conditions (in the presence of K_2CO_3 or LiHMDS, in CH_2Cl_2, CH_3CN or THF, at 0 °C or reflux conditions), but no conversion of products was observed. Next, enamide **220** was reacted with thiophenol in the presence of Et_3N in acetonitrile at reflux temperature, but again only the starting compound **220** was recovered (Table 16, entry 1). However, when the reaction with thiophenol was conducted using KOH as a base, a mixture of the isomeric fluorinated enamides **221a** and **222a** (ratio **221a** : **222a** = 8 : 2) was obtained, from which enamide **221a** was isolated in 69% yield (Table 16, entry 2). β-Fluoroenamides **221a** and **222a** are the products of a nucleophilic substitution at the vinylic CF_2 carbon atom of enamide **220**, most probably *via* a non-concerted two-step process (S_NV reaction),[111a,114] i.e. addition of the nucleophile across the double bond is followed by elimination of fluoride (Scheme 62, path a). When enamide **220** was treated with 1.2 equivalents of phenol in the presence of KOH, four different products were detected in the reaction mixture after work-up, i.e. the isomeric enamides **221b** and **222b**, addition product **223b** (formed by protonation of intermediate **225** (Scheme 62, path b)) and amino ester **224b**, in a ratio of **221b** : **222b** : **223b** : **224b** = 4 : 2 : 1 : 3. After purification of this mixture (column chromatography, SiO_2), only two compounds were isolated, more specifically adduct **223b** (10%) and amino ester **224b** (85%) (Table 16, entry 3). Apparently, enamides **221b** and **222b** were not stable upon prolonged exposure to SiO_2 and hydrolyzed toward amino ester **224b**. When the reaction of enamide **220** with phenol was repeated and the reaction mixture was purified *via* flash column chromatography (SiO_2), a mixture of isomers **221b** and **222b** was isolated in 32% total yield (ratio **221b** : **222b** = 8 : 2) (Table 16, entry 4). Finally, two additional

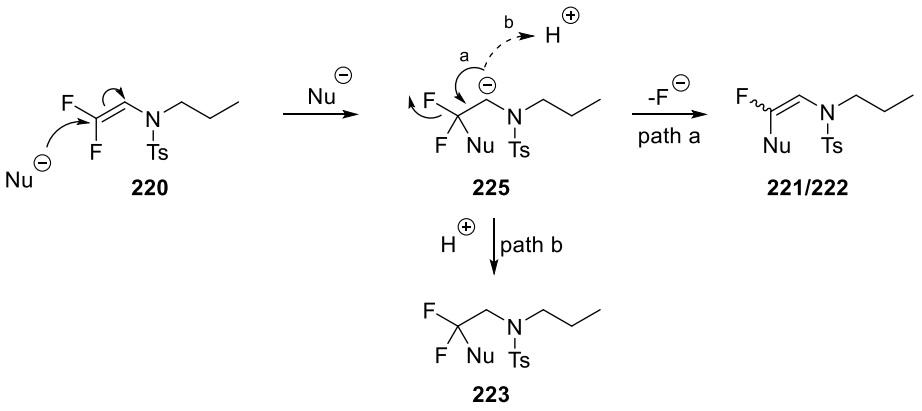
nucleophiles were evaluated in this addition-elimination reaction (Table 16, entries 5-6). The reaction of enamide **220** with both sodium methoxide (in MeOH/THF) and potassium *tert*-butoxide (in THF) gave a smooth conversion toward a mixture of isomers **221** and **222**. In the case of NaOMe, compounds **221c** and **222c** were separated by column chromatography, whereas only addition product **221d** of KO*t*Bu was isolated in 46% yield.

Table 16: Reactivity of enamide 220 toward nucleophiles



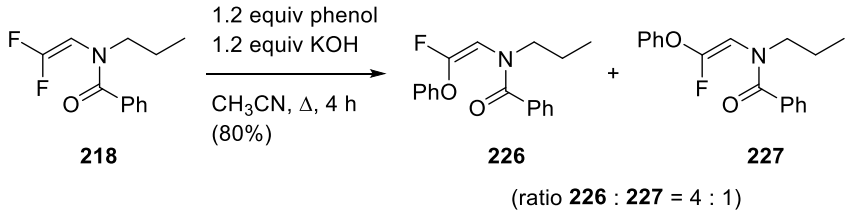
Entry	Nucleophile (equiv)	Reaction conditions	Ratio[a] **221**:**222**:**223**:**224**	Compound (%)[b]
1	thiophenol (1)	1 equiv Et_3N, CH_3CN, 0 °C - Δ, 24 h	1 : 0 : 0 : 0	-
2	thiophenol (1.2)	1.2 equiv KOH, CH_3CN, Δ, 20 h	8 : 2 : 0 : 0	**221a** (69)
3	phenol (1.2)	1.2 equiv KOH, CH_3CN, Δ, 20 h	4 : 2 : 1 : 3	**223b** (10) + **224b** (85)[c]
4	phenol (1.2)	1.2 equiv KOH, CH_3CN, Δ, 20 h	4 : 2 : 1 : 3	**221b**/**222b** (32)[d]
5	NaOMe (1.1)[e]	THF, r.t., 3 h	8 : 2 : 0 : 0	**221c** (57) + **222c** (15)
6	KO*t*Bu (1.1)	THF, 0 °C - r.t., 2 h	8 : 2 : 0 : 0	**221d** (46)

[a] Determined *via* ^{1}H NMR analysis of the crude reaction mixture. [b] Isolated yield. [c] Formed due to hydrolysis of **221b**/**222b** upon prolonged exposure to silica. [d] Ratio **221b** : **222b** = 8 : 2; the isomers could not be separated. [e] 1M in MeOH.



Scheme 62

The reaction of β,β-difluorinated enamide **218** with phenol under similar reaction conditions (1.2 equiv phenol, 1.2 equiv KOH, CH_3CN, reflux), also led to the formation of a mixture of (*E*)-β-fluoro-β-phenoxyenamide **226** and (*Z*)-β-fluoro-β-phenoxyenamide **227**, which could not be separated *via* column chromatography, in 80% yield (Scheme 63).



Scheme 63

The differentiation between the isomeric β-fluoroenamides **221** and **222** was made based on comparison of the value of the vicinal coupling constant $^3J_{H,F}$ of the signal of the hydrogen atom at the α-position of the vinylic double bond. More specifically, in case of the oxygen-substituted monofluorinated enamides **221b-d** and **222b-d**, *Z*-$^3J_{H,F}$ (H and F in a *Z* configuration) has a value of 0.7-1.7 Hz, while *E*-$^3J_{H,F}$ (H and F in an *E* configuration) results in a much larger value of 19-22 Hz. For the sulfur analogues **221a** and **222a** larger coupling constants were observed, with a value of 5.5 Hz for *Z*-$^3J_{H,F}$ and a larger value of 25.0 Hz for *E*-$^3J_{H,F}$. In case of fluoroenamides **226** and **227**, a less resolved ^{1}H NMR was obtained due to hindered rotation of the amide bond. However, the differentiation between the isomers could still be made since the signal of the hydrogen at the α-position of the vinylic double bond appeared as a broad singlet in case of isomer **226** and as a doublet with a coupling constant *E*-$^3J_{H,F}$ of 19.7 Hz in case of isomer **227**.

A possible explanation for the moderate stereoselectivity of this addition-elimination reaction toward enamides **221** and **226** (H and F in a *Z* configuration) can be found by evaluating the conformation of the

intermediate carbanions after addition of the nucleophile (Figure 15). To allow fluoride elimination, the lone pair of the intermediate carbanion and the fluorine atom must adopt antiperiplanar positions, which is the case in two possible transition state models **TS-A** and **TS-B**. In **TS-B**, the substituted nitrogen atom is situated in a gauche conformation between the two fluorine atoms, generating an important electronic repulsion. In **TS-A**, only one repulsive interaction between the nitrogen atom and fluorine is possible, rendering this conformer energetically more favoured. On the other hand, in **TS-A** a mild steric hindrance is present between the nitrogen atom and the nucleophile. The combination of these two factors, more specifically electronic repulsion (which is the main factor) and steric hindrance, leads to the moderate stereoselectivity.[115]

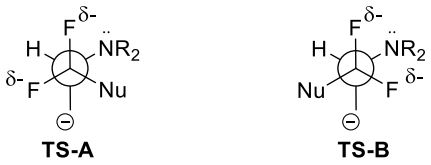
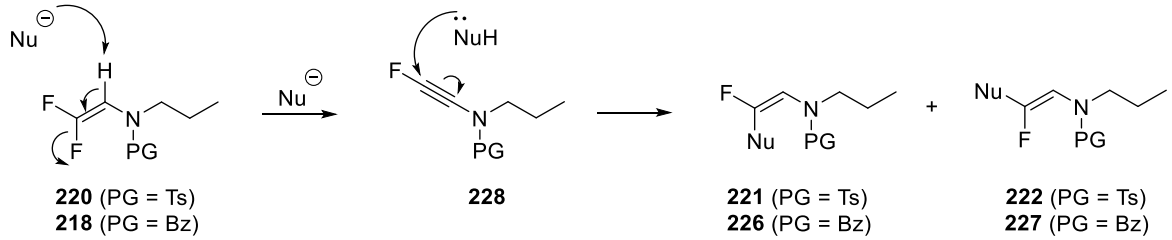


Figure 15

An alternative pathway for the formation of the substituted enamides **221**, **222**, **226** and **227** comprises initial formation of the corresponding ynamide **228** due to a base-promoted elimination of HF from enamides **218** and **220**, followed by the addition of the nucleophile (Scheme 64). In this case however, formation of the ynamide moiety of compound **228** by dehydrofluorination would result in protonation of the nucleophile and formation of the conjugated acid. For example, if treatment of enamide **220** with NaOMe (Table 16, entry 5), would lead to the corresponding ynamide, MeOH should be a good nucleophile to add across the triple bond. However, upon stirring ynamide **266a** (*vide infra*) in MeOH for a prolonged time, no addition of MeOH was observed. Therefore, it is believed that these transformations operate through an initial addition of the nucleophile, followed by elimination of fluoride.

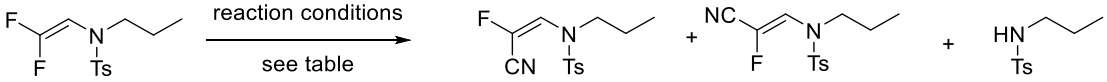


Scheme 64

In a next part, the addition-elimination reaction of carbon nucleophiles across enamide **220** was also evaluated. As a first nucleophile, KCN was reacted with difluoroenamide **220** in the presence of $NaHCO_3$ in

DMSO at room temperature for 45 hours. After work-up, a mixture of three compounds was obtained, more specifically the isomeric substituted fluoroenamides **229** and **230** and *N*-propyl-*p*-toluenesulfonamide **231** (Table 17, entry 1).[116] Also in this case, a nucleophilic vinylic substitution reaction was observed, leading to the formation of two isomers **229** and **230**, with a moderate stereoselectivity toward monofluoroenamide **229** (ratio **229** : **230** = 2 : 1). Additionally, a significant amount of *N*-propyl-*p*-toluenesulfonamide **231** was present in the reaction mixture, a compound which was never formed upon reaction of difluoroenamide **220** with sulfur and oxygen nucleophiles (Table 16). A possible mechanism for the formation of compound **231** is presented in Scheme 65. Compounds **229** and **230** could display the reactivity of Michael acceptors due to the presence of the electron withdrawing nitrile substituent. Thus, Michael-type addition of cyanide across the double bond of **229** or **230** leads to the formation of compound **232** after elimination of amide **233**. Upon extractive work-up, unsaturated dinitrile **232** is probably discarded with the water phase, since this compound was never detected, and potassium salt **233** is protonated to give *N*-propyl-*p*-toluenesulfonamide **231**. The use of ten equivalents of $NaHCO_3$ led to a similar reaction outcome (Table 17, entry 2). Changing the base to triethylamine and using dry DMF as the solvent also did not lead to better results and again a significant amount of tosylated amine **231** was present in the reaction mixture, albeit in a slightly lower amount (Table 17, entry 3). However, a higher selectivity toward enamide **229** was observed (ratio **229** : **230** = 3 : 1). Upon use of NaCN as the cyanide source again a higher amount of amine **231** was present in the reaction mixture, with a ratio of **229** : **230** = 2.5 : 1. After purification, a mixture of isomeric fluoroenamides **229** and **230** was obtained, in a ratio **229** : **230** = 3 : 1. Performing the reaction at a higher temperature of 40 °C led to the formation of a higher amount of sulfonamide **231** while still a long reaction time was needed to achieve a full conversion of the starting material. However, a mixture of enamides **229** and **230** was isolated in 30% yield (ratio **229** : **230** = 3 : 2) (Table 17, entry 5). Changing the solvent to acetone did not lead to better results since no conversion was observed after 17 hours of reaction at reflux temperature (Table 17, entry 6).

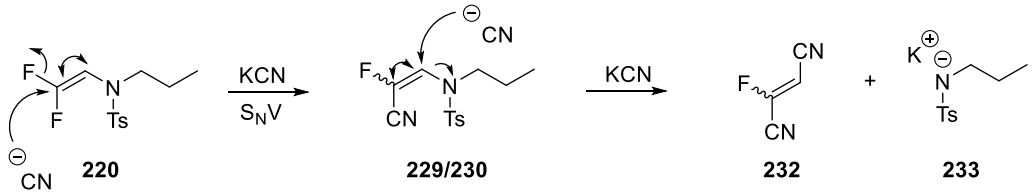
Table 17: Reactivity of enamide 220 toward cyanide nucleophiles



220 **229** **230** **231**

Entry	Reaction conditions	Ratio[a] **220** : **229** : **230** : **231**	Yield **229**+**230**
1	2 equiv KCN, 2 equiv $NaHCO_3$, DMSO, r.t., 45 h	0 : 39 : 19 : 42	-
2	2 equiv KCN, 10 equiv $NaHCO_3$, DMSO, r.t., 24 h	4 : 36 : 17 : 43	-
3	2 equiv KCN, 2 equiv Et_3N, DMF (dry), r.t., 24 h	8 : 43 : 16 : 34	-
4	2 equiv NaCN, 2 equiv Et_3N, DMF (dry), r.t., 7 h	5 : 37 : 14 : 44	40%[b]
5	2 equiv KCN, 2 equiv Et_3N, DMF, 40 °C, 23 h	0 : 24 : 14 : 64	30%[c]
6	1.05 equiv KCN, 2 equiv Et_3N, acetone, Δ, 17 h	100 : 0 : 0 : 0	-

[a] Determined *via* ^{1}H NMR analysis of the crude reaction mixture. [b] Ratio **229** : **230** = 3 : 1. [c] Ratio **229** : **230** = 3 : 2.

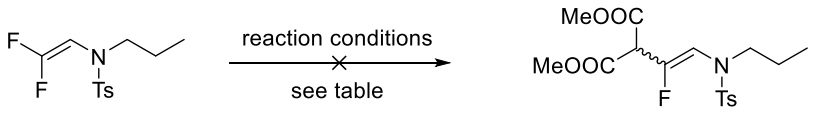


220 **229/230** **232** **233**

Scheme 65

The reactivity of β,β-difluoroenamide **220** toward dimethyl malonate was also investigated, but no reaction was observed under various reaction conditions (Table 18). Also the reaction of enamide **220** with the Grignard reagent ethylmagnesium bromide only led to recovery of the starting material.

Table 18: Reactivity of enamide 220 toward dimethyl malonate

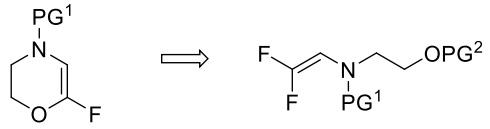


220 **234**

Entry	Reaction conditions	Result
1	1 equiv dimethyl malonate, 1 equiv pyridine, THF, 0 °C - r.t., 21 h	No reaction
2	1 equiv dimethyl malonate, 1.2 equiv K_2CO_3, acetone, Δ, 18 h	No reaction
3	1.05 equiv dimethyl malonate, 1.05 equiv NaH, THF, Δ, 20 h	No reaction

3.5.4 Synthesis of 6-fluoro-3,4-dihydro-2*H*-1,4-oxazines

In the next part, the reactivity of β,β-difluorinated enamides **218** and **220** toward oxygen nucleophiles (Table 16, Scheme 63) was expanded to the synthesis of novel heterocyclic monofluorinated compounds by incorporating the oxygen nucleophile and the electrophilic β,β-difluoroenamide unit in the same precursor, thus enabling an intramolecular vinylic nucleophilic substitution. As such, the synthesis of precursors **236** was envisioned, with a two-atom containing linker between the nitrogen atom and the oxygen nucleophile, which should lead to the formation of fluorinated 2*H*-3,4-dihydro-1,4-oxazines **235** after ring closure (Scheme 66). *N*-Functionalized oxazines have been reported in the literature,[117] and these compounds exhibit interesting biological activities, for examples as transthyretin amyloid fibril inhibitors,[118] and they have been described as intermediates for the synthesis of bridged morpholines.[119] However, 6-fluoro-2*H*-3,4-dihydro-1,4-oxazines **235** have not been reported in the literature up to date.

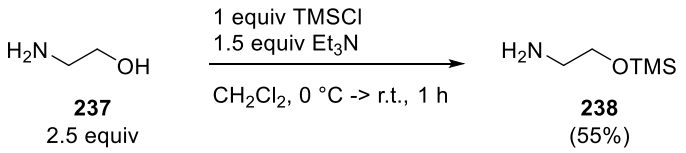


235 **236**

Scheme 66

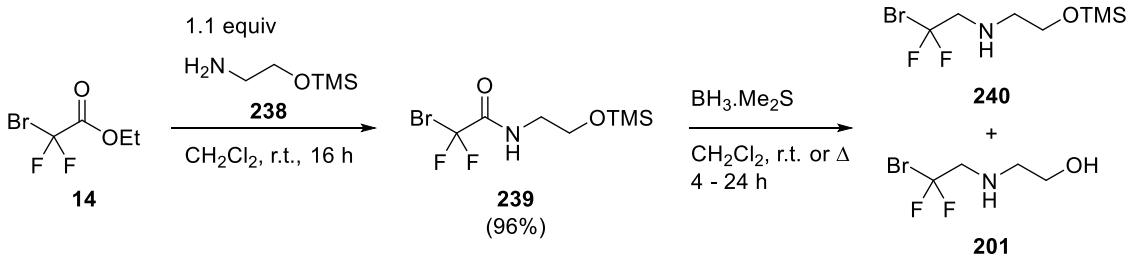
The first step in the synthetic sequence toward fluorinated enamides **236**, should be the coupling of ethyl bromodifluoroacetate with an amine containing a protected alcohol function, which could then in the last step be used as the oxygen nucleophile to achieve ring closure. As such, 2-aminoethanol **237** was protected

as trimethylsilylether **238**, by reaction with TMSCl in the presence of triethylamine, in 55% yield (Scheme 67).[120]



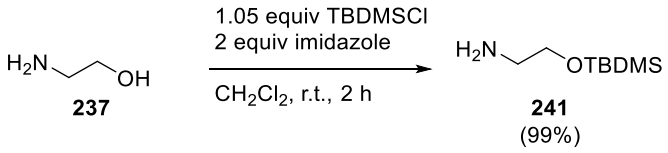
Scheme 67

Next, amine **238** reacted with ethyl bromodifluoroacetate **14** resulting in the formation of amide **239**, which was isolated in an excellent yield of 96% (Scheme 68). In the next step, the reduction of amide **239** toward amine **240** was investigated using borane dimethylsulfide complex as the reducing agent. However, despite the use of different reaction times and temperatures (4 - 24 h, r.t. or Δ), removal of the trimethylsilyl protecting group toward alcohol **201** was always observed, leading to mixtures of reaction products **201** and **240** and starting compound **239**, in varying ratios (Scheme 68). Therefore, the use of another protecting group had to be evaluated.



Scheme 68

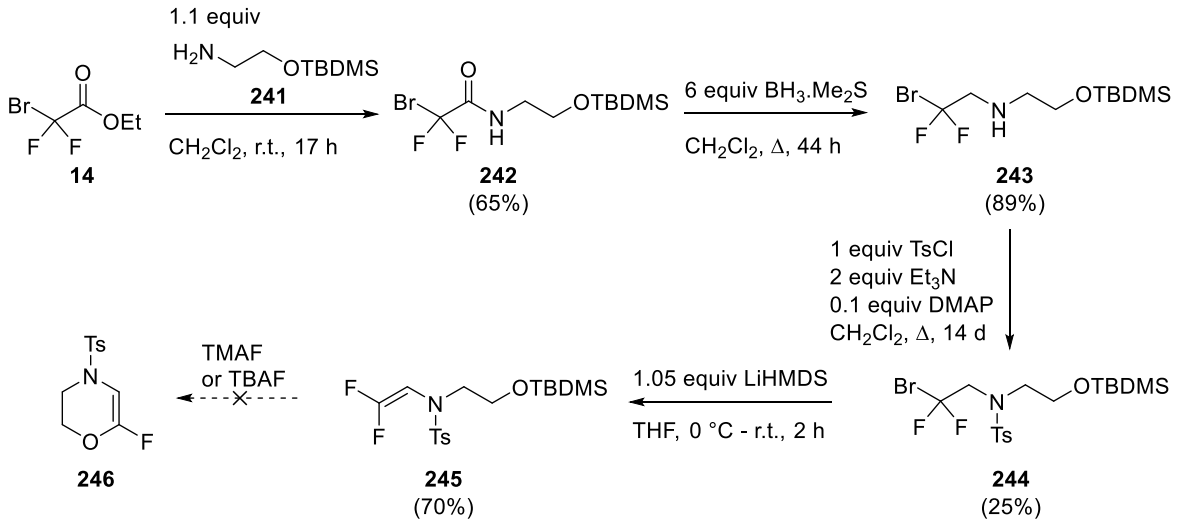
Thus, 2-aminoethanol **237** was treated with TBDMSCl in the presence of imidazole in dichloromethane for two hours at room temperature, giving a smooth conversion toward *tert*-butyldimethylsilylether **241** (Scheme 69).[121]



Scheme 69

Subsequently, compound **241** reacted with ethyl bromodifluoroacetate **14** to obtain amide **242** in 65% yield. The reduction of amide **242** was effectuated by reaction with $BH_3.Me_2S$, without concomitant

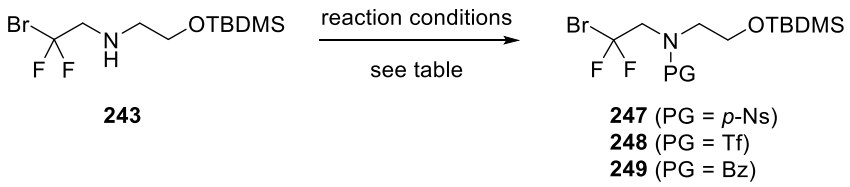
removal of the TBDMS protecting group, affording amine **243** in 89% yield. Next, a tosyl group was introduced at the amine nitrogen atom, by reaction with tosyl chloride in dichloromethane in the presence of triethylamine and DMAP. However, this reaction proceeded very slowly and after a prolonged reaction time of 14 days tosylamide **244** was isolated in a low yield of 25%. This tosylation reaction was also attempted in the presence of Ag_2O and KI,[122] but no better results were obtained. The dehydrobromination of tosylamide **244** proceeded smoothly and resulted in the formation of β,β-difluoroenamide **245** in 70% yield (Scheme 70). Next, the deprotection of the *tert*-butyldimethylsilyl ether of compound **245** was attempted. However, upon reaction of TBDMS ether **245** with TMAF or TBAF, either no reaction was observed at 0 °C, or a complex mixture was obtained when the reaction was performed at higher temperature, in which the envisioned oxazine **246** was present based on LC-MS analysis of the reaction mixture, but this compound could not be isolated.



Scheme 70

Based on these moderate results, the introduction of other protecting groups at nitrogen was evaluated. In a first attempt, the reaction of amine **243** with *para*-nitrobenzenesulfonylchloride (*p*-NsCl) gave no conversion toward the corresponding sulfonamide **247** (Table 19, entry 1). The reaction of amine **243** with triflic anhydride gave better results and trifluoromethanesulfonamide **248** was isolated in 75% yield after reaction in dichloromethane for 17 hours at room temperature (Table 19, entry 2). Also the reaction with benzoyl chloride proceeded smoothly toward benzamide **249**, which was isolated in a good yield of 71% (Table 19, entry 3).

Table 19: Protection of amine 243



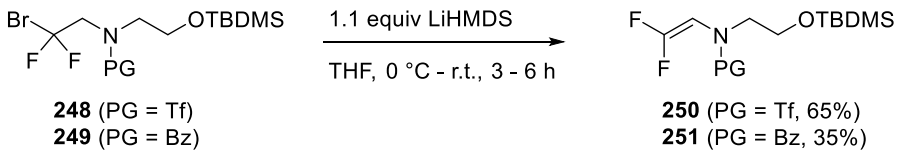
243

247 (PG = *p*-Ns)
248 (PG = Tf)
249 (PG = Bz)

Entry	PG	Reaction conditions	Result
1	*p*-Ns	1 equiv *p*-NsCl, 3 equiv Et_3N, CH_2Cl_2, r.t. – Δ, 48 h	No reaction
2	Tf	1.1 equiv Tf_2O, 1.2 equiv Et_3N, CH_2Cl_2, r.t., 17 h	75% **248**[a]
3	Bz	1 equiv benzoyl chloride, 1.1 equiv Et_3N, CH_2Cl_2, Δ, 4 h	71% **249**[a]

[a] Isolated yield.

In the next step, dehydrobromination of amines **248** and **249** by treatment with LiHMDS in THF led to the formation of β,β-difluoroenamides **250** and **251** in low to good yields (Scheme 71).



248 (PG = Tf)
249 (PG = Bz)

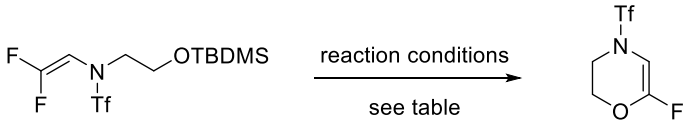
250 (PG = Tf, 65%)
251 (PG = Bz, 35%)

Scheme 71

Since the formation of enamide **250** was achieved in the highest overall yield, the TBDMS deprotection of this compound was studied in more detail (Table 20). In a first attempt, trifluoromethanesulfonamide **250** was treated with 1.05 equivalents of TMAF (tetramethylammonium fluoride) in THF at room temperature. After stirring this mixture at the same temperature for 20 hours, a reaction conversion of 30% was observed (Table 20, entry 1). Encouraged by this result, the reaction time was prolonged to 40 hours, but after work-up a complex reaction mixture was obtained and although oxazine **252** was present in this mixture, this compound could not be isolated (Table 20, entry 2). Also the reaction of **250** with TMAF at reflux conditions led to the formation of a complex reaction mixture (Table 20, entry 3). The reaction of enamide **250** with TBAF (tetrabutylammonium fluoride) gave better results since 100% conversion toward oxazine **252** was obtained after 30 minutes of reaction at 0 °C and compound **252** was isolated, albeit in a very low yield of 4% (Table 20, entry 4). The deprotection of compound **250** was also effectuated using a

catalytic amount of TBAF since upon ring closure toward oxazine **252**, fluoride is expelled as the leaving group. In this case, oxazine **252** was isolated in a slightly higher yield of 10% (Table 20, entry 5).

Table 20: Synthesis of 6-fluoro-4-(trifluoromethanesulfonyl)-3,4-dihydro-2*H*-1,4-oxazine 252



250 **252**

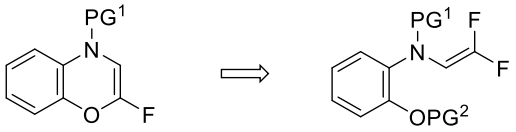
Entry	Reaction conditions	Result
1	1.05 equiv TMAF, THF, r.t., 20 h	30% conversion[a]
2	1.05 equiv TMAF, THF, r.t., 40 h	**252** in complex reaction mixture[b]
3	1.1 equiv TMAF, THF, Δ, 17 h	Complex reaction mixture
4	1.1 equiv TBAF, THF, 0 °C, 30 min	4% **252**[c]
5	0.2 equiv TBAF, THF, r.t., 17 h	10% **252**[c]

[a] Determined *via* ^{1}H NMR analysis of the crude reaction mixture. [b] Compound **252** could not be isolated. [c] Isolated yield.

The removal of the TBDMS protecting group of benzamide **251** was also attempted using TBAF at room temperature, but led to a mixture of compounds. However, LC-MS indicated the presence of the envisioned 1,4-oxazine and further optimization of this reaction is necessary.

3.5.5 Synthesis of 2-fluoro-1,4-benzoxazines[123]

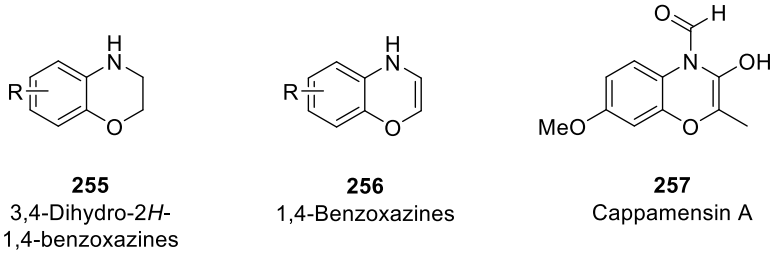
Since the synthesis of oxazine **252** proceeded sluggishly, it was decided to change the two atom linker in an attempt to improve the stability of the reaction compounds. Thus, the synthesis of benzofused oxazines **253** was envisaged, with enamides **254** as suitable precursors (Scheme 72).



253 **254**

Scheme 72

The class of dihydro-1,4-benzoxazines **255** has been studied extensively during the last decades, because compounds containing this scaffold are known to possess a broad range of interesting biological activities such as antidiabetic, antibacterial, anti-inflammatory and neuroprotective activity.[124] Recently, derivatives of 3,4-dihydro-2*H*-1,4-benzoxazine **255** were also identified as multi-isoform PI3K,[125] diacylglycerol acyltransferase[126] and angiogenesis inhibitors[127] and as potential dual antithrombotic compounds.[128] On the other hand, less research has been devoted to the synthesis of their unsaturated analogues, 1,4-benzoxazines **256**.[124a,129] Nevertheless, some of these compounds have also been shown to possess interesting biological activities. An example of a natural product containing the 1,4-benzoxazine core is cappamensin A **257**, isolated from the roots of *Capparis sikkimensis* (Figure 16). This substituted benzoxazine derivative shows a promising antitumor activity.[130] The development of analogues of cappamensin A, as potential antitumor agents, is therefore of great interest. Although benzoxazines containing a CF_3-group have already been synthesized,[131] examples of compounds carrying the fluorine substituent directly attached to the heterocyclic ring are barely known[132] and only one example of a 2-fluoro-1,4-benzoxazine derivative was found in literature.[133]



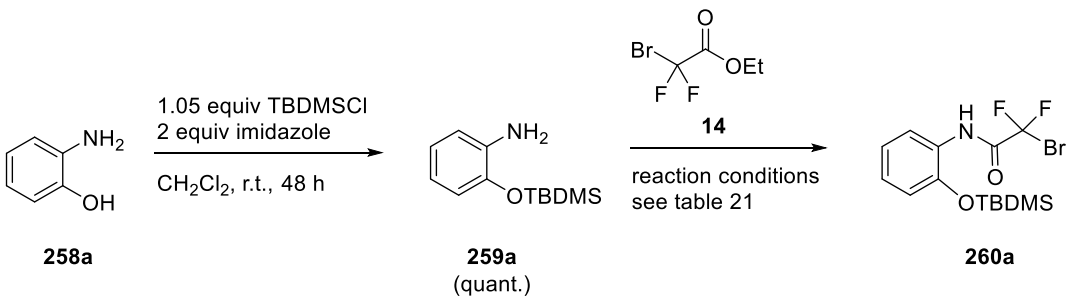
255
3,4-Dihydro-2*H*-
1,4-benzoxazines

256
1,4-Benzoxazines

257
Cappamensin A

Figure 16

For the synthesis of the precursor enamides **254**, 2-aminophenol **258a** was chosen as the building block (Scheme 73). First, alcohol **258a** was protected as its TBDMS ether, by reaction with TBDMSCl in the presence of imidazole in dichloromethane, affording compound **259a** in quantitative yield.[134] Next, the condensation of *tert*-butyldimethylsilyl ether **259a** with ethyl bromodifluoroacetate **14** was attempted. First, aniline **259a** was stirred in dichloromethane in the presence of ethyl bromodifluoroacetate **14** for 16 hours at room temperature, but no reaction was observed (Table 21, entry 1). Next, aniline **259a** was reacted with ester **14** in ethyl acetate at reflux temperature for 17 hours, but again only the starting compounds were recovered (Table 21, entry 2).[135] When aniline **259a** was treated with ester **14** under solvent-free reaction conditions at 80 °C, 65% conversion of the starting compounds was observed after 24 hours (Table 21, entry 3). However, upon purification of amide **260a** (SiO_2), removal of the TBDMS protecting group was observed and compound **260a** could not be recovered.



258a **259a** (quant.) **260a**

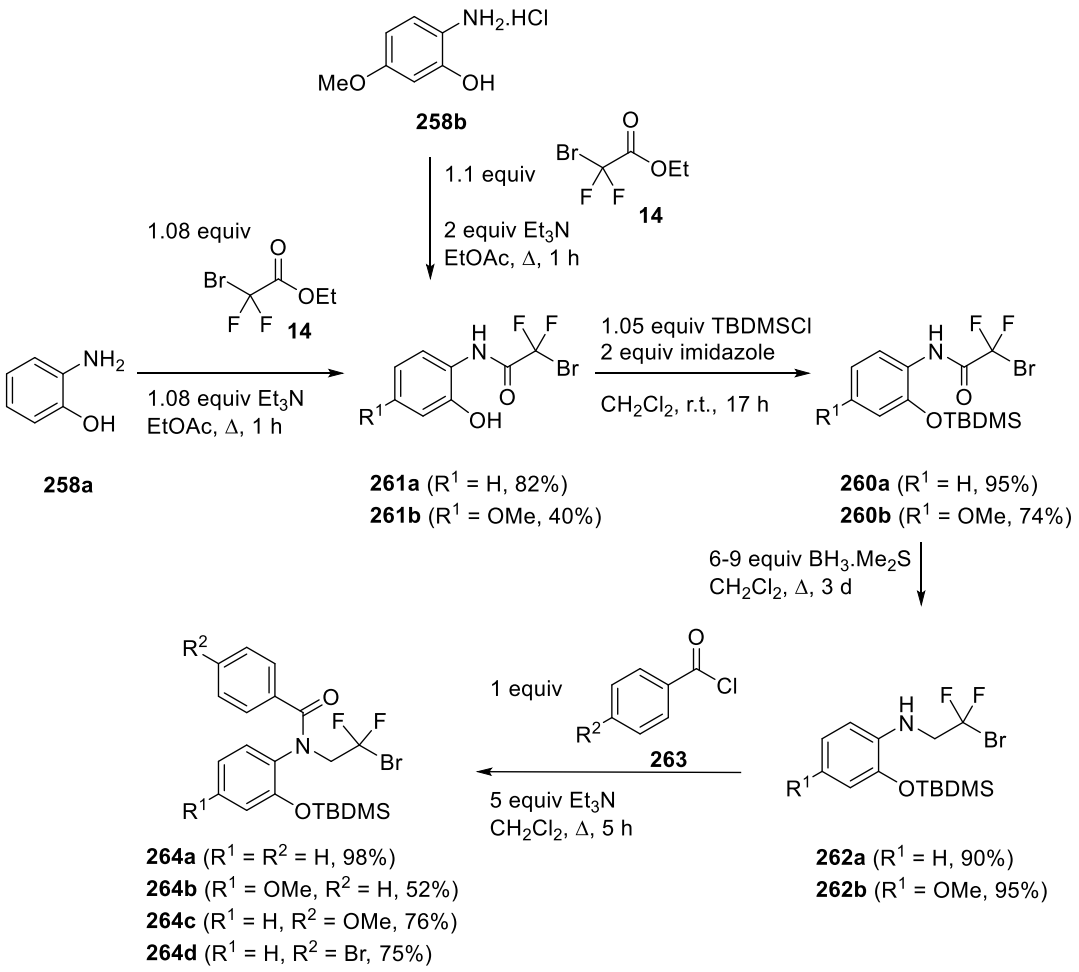
Scheme 73

Table 21: Synthesis of amide 260a from aniline 259a and ethyl bromodifluoroacetate 14

Entry	Reaction conditions	Result
1	1 equiv **259a**, 1 equiv **14**, CH_2Cl_2, r.t., 16 h	No reaction
2	1 equiv **259a**, 1 equiv **14**, 1 equiv Et_3N, EtOAc, Δ, 17 h	No reaction
3	1 equiv **259a**, 1 equiv **14**, neat, 80 °C, 24 h	65% conversion[a,b]

[a] Determined *via* ^{1}H NMR analysis of the crude reaction mixture. [b] Purification failed.

Because the amide formation by reaction of aniline **259a** with ethyl bromodifluoroacetate **14** was not straightforward, probably due to steric hindrance caused by the TBDMS protecting group, it was decided to change the reaction order. Thus, 2-aminophenol **258a** was reacted in the first step with ethyl bromodifluoroacetate **14**, leading to the selective formation of amide **261a** (Scheme 74). In the second step, protection of the phenolic oxygen atom was effectuated by treatment of benzamide **261a** with TBDMSCl in the presence of imidazole, which gave a clean conversion toward compound **260a** without the need of purification. The same reaction sequence was applied to substituted 2-aminophenol **258b**, leading to benzamide **260b**. Amides **260** were in turn reduced toward the secondary amines **262** using an excess of borane dimethylsulfide complex in CH_2Cl_2. The next step involved the protection of the nitrogen atom of amines **262**. Because the introduction of a tosyl group proceeded very slowly while the attempt to introduce a mesyl group gave no conversion at all, the use of a benzoyl protecting group was evaluated instead. Treatment of β-bromo-β,β-difluoroamines **262** with different benzoyl chlorides **263** in the presence of Et_3N led to the formation of *N*-(2-bromo-2,2-difluoroethyl)benzamides **264** as suitable precursors for the synthesis of fluorinated 1,4-benzoxazines (Scheme 74).

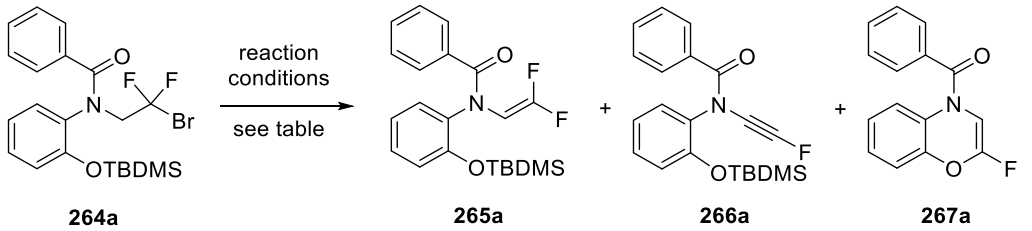


Scheme 74

The key step in the reaction sequence concerned the conversion of precursors **264** toward the envisioned 1,4-benzoxazines (Table 22). Therefore, benzamide **264a** was treated with LiHMDS, which led to the formation of a mixture of difluoroenamide **265a** and fluorinated ynamide **266a**, resulting from the LiHMDS-induced elimination of HF from enamide **265a** (Table 22, entry 1). Increasing the number of equivalents of LiHMDS led to a full conversion of amide **264a** toward ynamide **266a**, which was isolated in an excellent yield of 97% (Table 22, entry 2). The formation of ynamide **266a** can be explained by C-F bond activation by coordination of fluorine to the silicon atom in the *tert*-butyldimethylsilyl protecting group, enhancing the leaving group capacity of fluoride (Scheme 75).[136] This could also explain why amides **218** and **220** were not converted into the corresponding ynamides upon treatment with LiHMDS. Next, benzamide **264a** was treated with one equivalent of KO*t*Bu, leading to a selective conversion toward the envisioned benzoxazine **267a**, which was isolated in 80% yield (Table 22, entry 3). Since the use of LiHMDS or KO*t*Bu led to a different reaction outcome, other bases were evaluated in order to investigate the

possible reaction pathway. It was remarkable that the cleavage of the silyl ether did not occur upon treatment of benzamide **264a** with 2.2 equivalents of LiHMDS, even though under these conditions fluoride is expelled from the substrate (Table 22, entry 2). To test the influence of the cation, the reaction was repeated with NaHMDS and KHMDS (Table 22, entries 4-5). Thus, benzamide **264a** was treated with one equivalent of NaHMDS. LC-MS analysis of the reaction mixture after 15 minutes indicated the presence of four compounds, i.e. benzamide **264a**, enamide **265a**, ynamide **266a** and benzoxazine **267a**. Follow-up *via* LC-MS indicated no further progress of the reaction, so an extra equivalent of NaHMDS was added after three hours. After stirring for an additional three hours, the reaction was stopped and a mixture of enamide **265a** and benzoxazine **267a** was obtained in a ratio of 4 : 6, which could not be separated *via* column chromatography (Table 22, entry 4). Subsequently, benzamide **264a** was treated with one equivalent of KHMDS, which also led to the formation of a mixture of compounds **264a**, **265a**, **266a** and **267a** after 15 minutes of reaction at room temperature. Also in this case, an extra equivalent of base was added after three hours, and the reaction was stopped after an additional three hours. After work-up, only benzoxazine **267a** was detected, so it was assumed that both enamide **265a** and ynamide **266a** were intermediates in the formation of benzoxazine **267a**. It was concluded that the cation of the base plays an important role in the reaction outcome due to the different properties of the corresponding fluoride salts. Upon use of LiHMDS as the base, the reaction terminates at the stage of ynamide **266a** in which the silyl ether is not deprotected, so apparently the fluoride anion in LiF is not available for this reaction. When KHMDS is used, KF is formed, in which the fluoride anion is available for the deprotection reaction, since this reaction leads to the formation of benzoxazine **267a** after ring closure. This reactivity of alkali-metal fluorides may be explained by the higher lattice energy of LiF in comparison with NaF and KF.[137] Following these results, the use of LiO*t*Bu should also lead to the formation of a TBDMS-protected end product. Indeed, the reaction of benzamide **264a** with one equivalent of LiO*t*Bu afforded enamide **265a** as the sole end product, which was isolated in 73% yield (Table 22, entry 6).

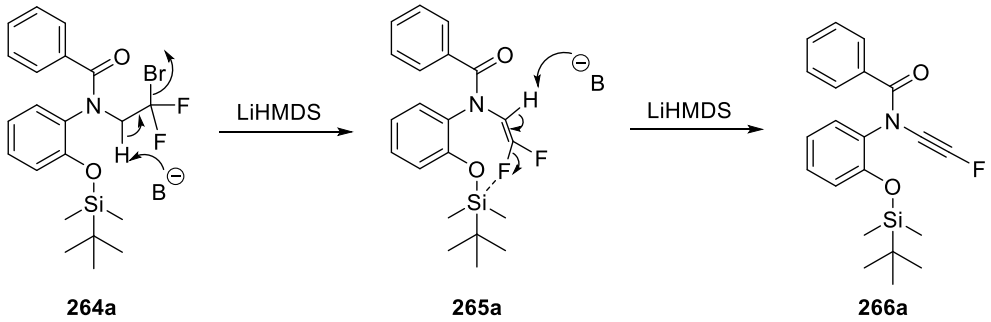
Table 22: Reactivity of benzamide 264a toward different bases



264a **265a** **266a** **267a**

Entry	Reaction conditions	Ratio[a] **264a** : **265a** : **266a** : **267a**	Compound (yield)[b]
1	1.1 equiv LiHMDS, THF, 0 °C, 3 h	3 : 3 : 4 : 0	-
2	2.2 equiv LiHMDS, THF, r.t., 2.5 h	0 : 0 : 1 : 0	**266a** (97%)
3	1 equiv KO*t*Bu, THF, r.t., 2 h	0 : 0 : 0 : 1	**267a** (80%)
4	2 equiv NaHMDS[c], THF, r.t., 6 h	0 : 4 : 0 : 6	-
5	2 equiv KHMDS[c], THF, r.t., 6 h	0 : 0 : 0 : 1	**267a** (54%)
6	1 equiv LiO*t*Bu, THF, Δ, 1.5 h	0 : 1 : 0 : 0	**265a** (73%)

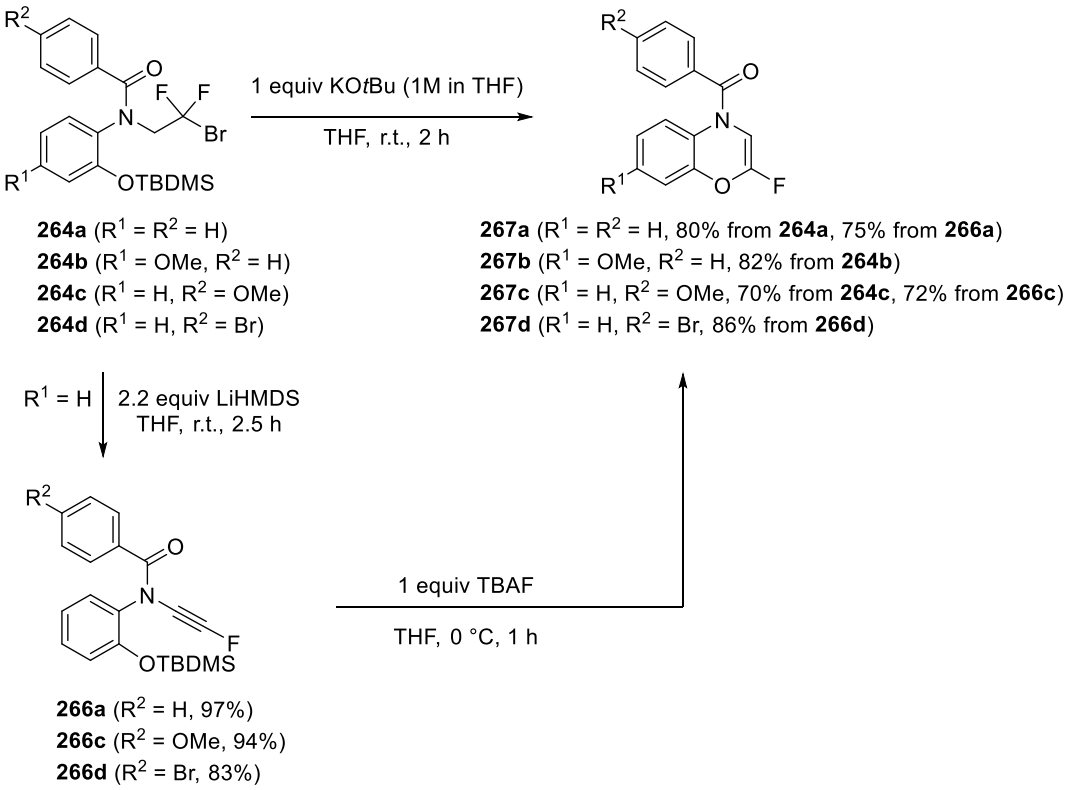
[a] Determined *via* ^{1}H NMR analysis of the crude reaction mixture. [b] Isolated yield. [c] 2nd equivalent was added after 3 h.



264a **265a** **266a**

Scheme 75

Subsequently, the optimized reaction conditions were used to convert benzamides **264a-d** toward benzoxazines **267** and fluorinated ynamides **266** in good to excellent yields (Scheme 76). In an attempt to prove the intermediacy of ynamides **266** in the formation of benzoxazines **267**, compounds **266** were treated with TBAF in THF in order to remove the TBDMS-protecting group, which led directly to the formation of benzoxazines **267**. The triple bond in ynamides **266** has an electrophilic reactivity which is prone to nucleophilic attack by the phenolic oxygen atom, leading to a smooth conversion toward benzoxazines **267** (Scheme 76).

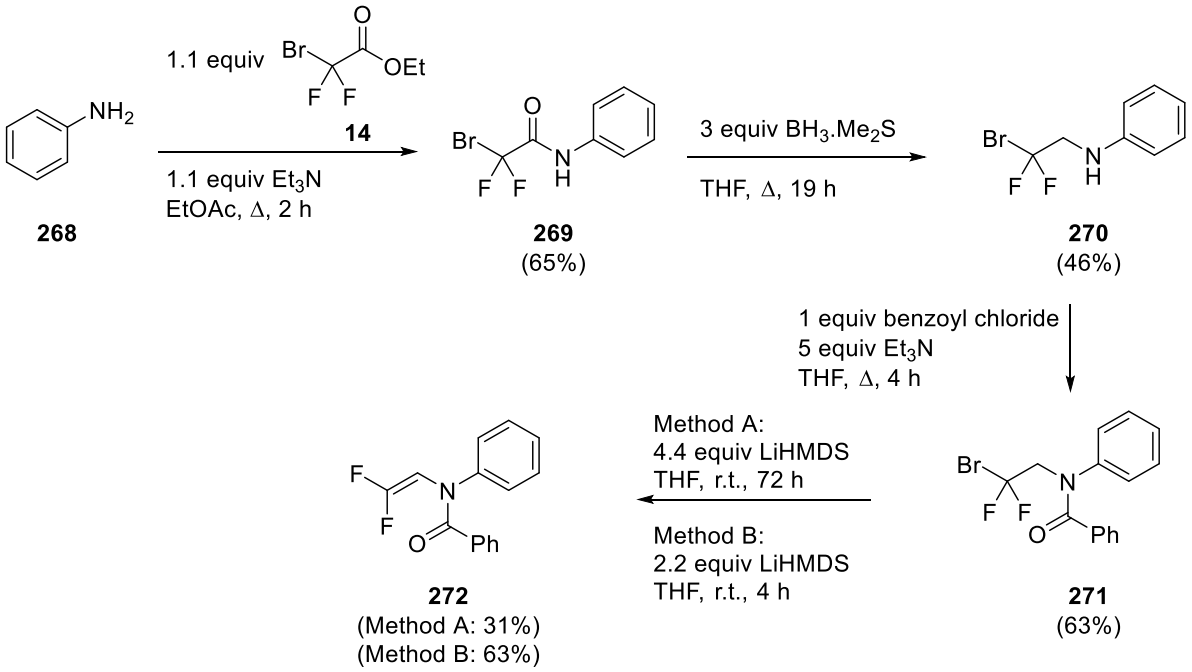


Scheme 76

The chemistry of halogenated ynamides has only been explored to a limited extent. While 2-iodoynamides have been used in for example cycloaddition[138] and benzannulation[139] reactions, the synthesis and reactivity of fluorinated ynamides is a totally unexplored field in organic chemistry. Only one report has been published in which the formation of a fluorinated ynamine was described, albeit in a very low yield of 5%.[140] Over the last years, the chemistry of ynamides has received much attention.[141] Due to the polarization of the triple bond, α-addition of nucleophiles across the triple bond is more common than β-addition, although a few examples of β-addition have been described.[142] Umpolung of the ynamide functionality, leading to addition of nucleophiles at the β-position, is usually achieved via a metal-catalyzed reaction. In this work, umpolung is achieved by the presence of a fluorine substituent at the β-position of the ynamide in combination with the electron-withdrawing group at nitrogen, leading to selective addition of the oxygen nucleophile at the β-position without the need of a metal catalyst.

To further verify the influence of the *tert*-butyldimethylsilyl ether on the formation of ynamides **266**, it was attempted to synthesize an ynamide without this silicon-containing substituent on the phenyl ring (Scheme 77). To this end, aniline **268** was reacted with ethyl bromodifluoroacetate **14**, giving amide **269** in 65% yield, which was subsequently converted into amine **270** by reduction using borane dimethylsulfide

complex in THF. Introduction of the benzoyl protecting group was effectuated by reacting amine **270** with benzoyl chloride in the presence of triethylamine, yielding benzamide **271**. In the next step, benzamide **271** was treated with LiHMDS in THF at 0 °C and the reaction was stirred at room temperature. After three hours, LC-MS analysis of the reaction mixture revealed the presence of enamide **272** and a trace of the starting compound **271**, while the corresponding ynamide was not detected. After an additional hour, an extra 2.2 equivalents LiHMDS were added to the reaction mixture and the stirring was continued for another 68 hours, while it was followed-up using LC-MS analysis. However, the ynamide was never observed in the reaction mixture and after work-up, enamide **272** was isolated in a low yield of 31%, probably due to the prolonged reaction time. This result is an extra indication of the influence of the *tert*-butyldimethylsilyloxy group on the formation of ynamides **266**, which most probably proceeds *via* a silicon-induced C-F activation. Enamide **272** was synthesized in a higher yield of 63% upon reaction of benzamide **271** with 2.2 equiv LiHMDS for three hours at room temperature.

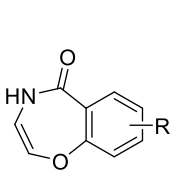


Scheme 77

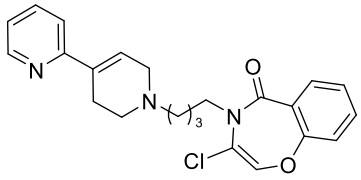
3.5.6 Synthesis of 2-fluoro-1,4-benzoxazepin-5-ones[123]

Another interesting class of benzo-fused heterocyclic compounds comprises 1,4-benzoxazepin-5-ones **273**. An important example of this type of compounds is the chlorinated analogue piclozotan **274**, a selective 5-HT_{1A} receptor partial agonist, which has shown *in vivo* neuroprotective effects.[143] Recently, it

has been reported that piclozotan **274** also has the potency to improve motor complications (for example spasms or involuntary movements of muscles) which are associated with levodopa therapy, administered to patients suffering from Parkinson's disease.[144] While trifluoromethylated derivatives have been described,[145] no reports were found in the literature concerning the synthesis of 2-fluoro- or 3-fluoro-1,4-benzoxazepin-5-ones.



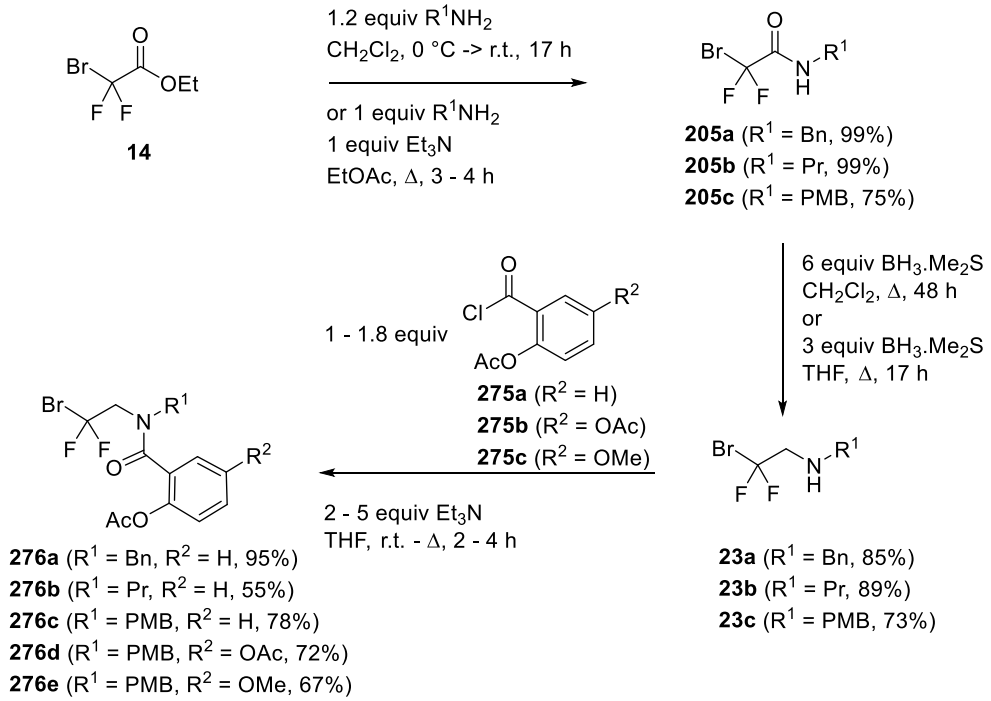
273
1,4-Benzoxazepin-5-ones



274
Piclozotan
(SUN-N4057)

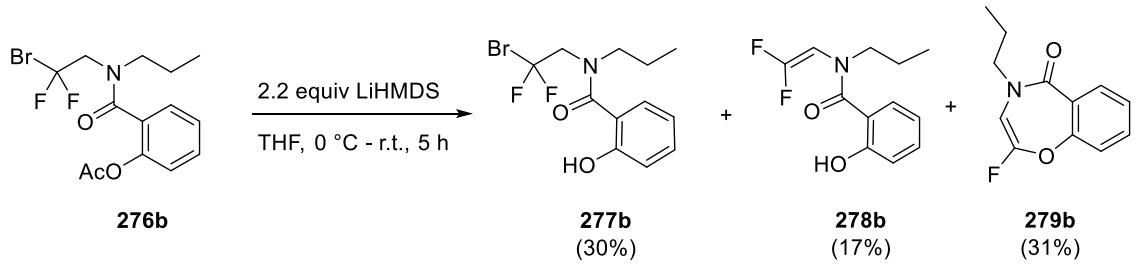
Figure 17

Therefore, in the next part of this work the synthesis of novel fluorinated benzo-fused seven-membered rings was developed. In the precursor, a three-carbon atom-containing linker had to be positioned between the enamide nitrogen atom and the oxygen nucleophile, in order to be able to form a seven-membered ring via the vinylic nucleophilic substitution reaction. In the synthetic route toward benzoxazines **267**, the oxygen nucleophile was already incorporated in the fluorinated secondary amines **262**, after which a benzoyl protecting group was introduced at nitrogen (Scheme 74). In the synthetic route toward the seven-membered ring analogues, it was chosen to incorporate the oxygen nucleophile in the aroyl group attached to nitrogen (Scheme 78). Therefore, a variety of secondary fluorinated amines was synthesized by reacting ethyl bromodifluoroacetate **14** with different amines leading to amides **205**, which in turn were reduced using borane dimethylsulfide complex in dichloromethane or THF under reflux. Subsequently, a functionalized benzoyl group was introduced at the nitrogen atom by treatment with *O*-acetylsalicyloyl chloride **275a**, leading to the formation of benzamides **276a-c**. Benzamides **276** are suitable precursors for the synthesis of fluorinated seven-membered rings, since there is a three carbon linker in between the nitrogen and oxygen atom. An advantage of this synthetic route is the possibility of a late stage functionalization, since various derivatives of 2-acetylsalicylic acid can be used for the introduction of the group at nitrogen. For example, acetylsalicyloyl chlorides **275b-c**, which were prepared from the corresponding carboxylic acids by reaction with thionyl chloride, were reacted with amine **23c**, leading to the formation of benzamides **276d-e** (Scheme 78).



Scheme 78

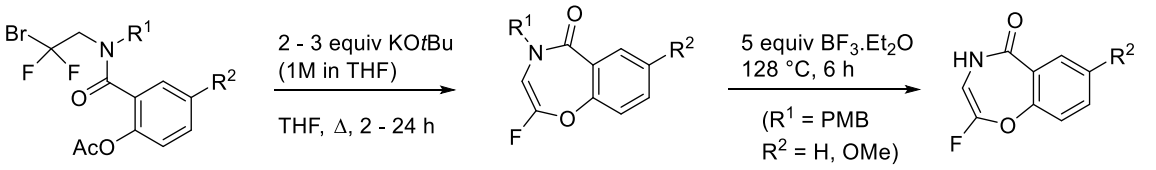
The final step in the synthesis of the fluorinated seven-membered heterocycles **279** comprised the ring closure of precursors **276a-e**, which should proceed *via* the conversion of benzamides **276a-e** in the corresponding difluorinated enamides, followed by ring closure. In a first attempt, benzamide **276b** (R^1 = Pr, R^2 = H) was treated with two equivalents of LiHMDS, which led to the formation of a mixture of three reaction products, i.e. deacetylated benzamide **277b**, β,β-difluoroenamide **278b** and benzoxazepinone **279b** (Scheme 79). The composition of this crude reaction mixture supports the intermediacy of β,β-difluoroenamide **278b** in the formation of benzoxazepinone **279b**. Moreover, it seems that the deacetylation of the phenolic oxygen occurs before the formation of the difluoroenamide moiety, since the brominated amide **277b** was also formed as an intermediate. This deacetylation reaction proceeds easily due to the good leaving group properties of the phenolic oxygen atom. This cleavage was also observed upon storage of benzamide **276b** at room temperature.



276b **277b** (30%) **278b** (17%) **279b** (31%)

Scheme 79

The presence of the envisioned 2-fluoro-1,4-benzoxazepin-5-one **279b** in the crude reaction mixture was a promising result. Subsequently, the use of potassium *tert*-butoxide was evaluated for the conversion of benzamides **276** into benzoxazepinones **279**. In that regard, benzamides **276a-e** were stirred in THF under reflux in the presence of 2-3 equivalents of KO*t*Bu, which gave a clean conversion toward the envisioned 2-fluoro-1,4-benzoxazepin-5-ones **279a-e**, which were isolated in good yields (Scheme 80). In case of 2,5-diacetoxybenzamide **276d**, three equivalents of KO*t*Bu had to be added to achieve a full conversion toward the double deacetylated compound **279d**. In a last step, the deprotection of the 4-methoxybenzyl-substituted benzoxazines **279c**,**e** was attempted. Initially, benzoxazepinone **279c** was treated with cerium ammonium nitrate in aqueous acetonitrile, but under these reaction conditions either no conversion was observed or a complex reaction mixture was formed, depending on the reaction temperature. Finally, the removal of the PMB protecting group was achieved by heating benzoxazepine **279c** in the presence of five equivalents of boron(III) fluoride etherate resulting in 4*H*-2-fluoro-1,4-benzoxazin-5-one **280a** in 51% yield. The same procedure was applied to benzoxazepinone **279e**, leading to the formation of 4*H*-benzoxazepinone **280b.** The deprotection of these fluorinated benzoxazepinones enables further functionalization of this scaffold.



276a-e

279a (R^1 = Bn, R^2 = H, 62%)
279b (R^1 = Pr, R^2 = H, 67%)
279c (R^1 = PMB, R^2 = H, 77%)
279d (R^1 = PMB, R^2 = OH, 86%)
279e (R^1 = PMB, R^2 = OMe, 88%)

280a (R^2 = H, 51%)
280b (R^2 = OMe, 54%)

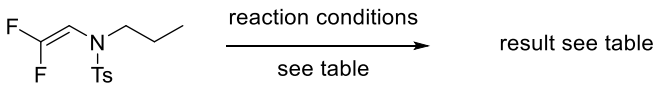
Scheme 80

3.5.7 Reactivity of *N*-tosyl-β,β-difluoroenamide 220 toward electrophiles

To test whether *N*-tosyl-β,β-difluoroenamide **220** displays any nucleophilic reactivity, despite the presence of the electron-withdrawing group at nitrogen and the two fluorine atoms at the β-position of the enamide, the reaction of this compound with a variety of electrophiles was investigated.

In a first attempt, the reaction of enamide **220** with isobutyraldehyde in dichloromethane under reflux only resulted in recovery of the starting compound **220** (Table 23, entry 1). The reaction of enamide **220** with allyl bromide under similar reaction conditions gave the same result (Table 23, entry 2). When the reaction with allyl bromide was repeated in the presence of aluminium(III) chloride, no reaction took place when the reaction was conducted at room temperature, while the formation of degradation compounds was observed when this reaction was performed at reflux temperature (Table 23, entries 3-4). In a next attempt, difluorinated enamide **220** was first treated with one equivalent *n*-butyllithium at -78 °C for 30 minutes, after which allyl bromide was added and the reaction was stirred for another three hours at 0 °C. However, this led to the formation of a complex reaction mixture (Table 23, entry 5). To test the stability of enamide **220** with respect to *n*-butyllithium, enamide **220** was stirred in the presence of one equivalent of *n*-BuLi for five hours at 0 °C (Table 23, entry 6). However, this also resulted in the formation of a complex reaction mixture. In a next attempt, enamide **220** reacted with LDA in THF at -78 °C for 30 minutes, after which allyl bromide was added and the reaction was continued for 30 minutes at 0 °C (Table 23, entry 7). Again, a complex reaction mixture was formed. Also upon reaction of enamide **220** with LDA, followed by the addition of one equivalent of methyl iodide, a complex reaction mixture was formed (Table 23, entry 8). Also the gold-catalyzed reaction of enamide **220** with phenylacetylene failed (Table 23, entry 9) since no reaction was observed.

Table 23: Reactivity of *N*-tosyl-β,β-difluoroenamide 220 toward electrophiles

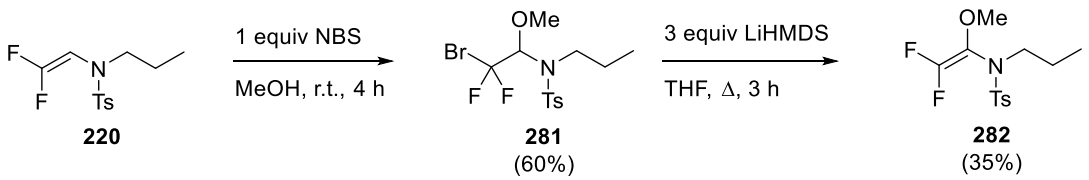


220

Entry	Reaction conditions	Result
1	1 equiv isobutyraldehyde, CH_2Cl_2, Δ, 4 h	No reaction
2	1 equiv allyl bromide, CH_2Cl_2, Δ, 4 h	No reaction
3	1 equiv allyl bromide, 1 equiv $AlCl_3$, THF, r.t., 15 h	No reaction
4	1 equiv allyl bromide, 1 equiv $AlCl_3$, THF, Δ, 15 h	**220** + degradation
5	1) 1 equiv *n*-BuLi, THF, -78 °C, 30 min 2) 1 equiv allyl bromide, THF, 0 °C, 3 h	Complex reaction mixture
6	1 equiv BuLi, THF, 0 °C, 5 h	Complex mixture
7	1) 1.2 equiv LDA, THF, -78 °C, 30 min 2) 1 equiv allyl bromide, THF, 0 °C, 30 min	Complex reaction mixture
8	1) 1.2 equiv LDA, THF, -78 °C, 30 min 2) 1 equiv MeI, THF, 0 °C, 2 h	Complex reaction mixture
9	1 equiv PhC≡CH, 5 mol% $AuCl_3$, CH_3CN, r.t., 6 h	No reaction

Upon treatment of difluoroenamide **220** with one equivalent of *N*-bromosuccinimide (NBS) in methanol at room temperature, the formation of compound **281** was observed, which was isolated in a good yield of 60% (Scheme 81). Compound **281** was in turn converted into β,β-difluorinated enamide **282** by treatment with LiHMDS in THF at reflux temperature, and enamide **282** was isolated in a low yield of 35%.

Thus, enamide **220** also shows nucleophilic character since an electrophilic addition reaction across the double bond was achieved. However, since all other attempts to react difluoroenamide **220** with electrophiles failed (Table 23), it was concluded that the nucleophilic character of difluoroenamide **220** is very limited.



Scheme 81

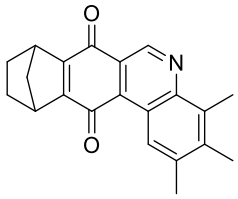
3.5.8 Conclusion

In conclusion, β,β-difluoroenamides **218** and **220** were synthesized as enamides with an electrophilic character. These compounds reacted readily with oxygen and sulfur nucleophiles in an S_NV reaction giving rise to the formation of substituted monofluorinated enamides. This reactivity was exploited toward the synthesis of novel six- and seven-membered heterocycles. While the formation of 6-fluoro-2*H*-3,4-dihydro-1,4-oxazines proceeded sluggishly, a straightforward synthesis toward novel 2-fluoro-1,4-benzoxazines and 2-fluoro-1,4-benzoxazepin-5-ones was developed. In the synthetic pathway toward the fluorinated benzoxazines, the formation of fluorinated ynamides was observed, as the first example of an efficient route toward this unexplored class of fluorinated compounds. Upon reaction of difluoroenamide **220** with electrophiles, it was concluded that this enamide shows very limited nucleophilic character since it only reacted with NBS in MeOH.

3.6 Synthesis of fluorinated 8,9,10,11-tetrahydro-8,11-methanobenzo[*j*]-phenanthridine-7,12-diones

3.6.1 Introduction

Mycobacterium tuberculosis is a pathogenic bacillus which causes the disease tuberculosis (TB), still one of the most deadly diseases worldwide, with an estimated number of 9.0 million new cases and 1.5 million deaths in 2013.[146] Due to the prevalence of multidrug resistant and extensively drug resistant TB, there is still a need for the development of new drugs.[147] In view of the ongoing interest of our research group in the synthesis of annulated phenanthridine-7,12-diones as antimycobacterial compounds,[148] and the often beneficial effects of the introduction of fluorine in biologically active compounds,[3c,149] it was decided to synthesize fluorinated derivatives of benzo[*j*]phenanthridine-7,12-diones. The synthesis of fluorinated phenanthridine-7,12-diones, benzo[*j*]phenanthridine-7,12-diones or 8,9,10,11-tetrahydro-8,11-methanobenzo[*j*]phenanthridine-7,12-diones has not been reported in the literature so far. In previous research at our department, it was found that 2,3,4-trimethyl-8,9,10,11-tetrahydro-8,11-methanobenzo[*j*]phenanthridine-7,12-dione **283a** possesses a good antimycobacterial activity with a MIC_{50} lower than 0.1 µg/mL (Figure 18).[148a,150] However, this compound showed a low specificity since it also showed activity toward other gram-positive and gram-negative bacteria as well as activity toward C-3A, J-774 and MRC-5 human cell lines.[151] In an attempt to improve the specificity, it was decided to synthesize fluorinated derivatives of annulated phenanthridine-7,12-dione **283a**.

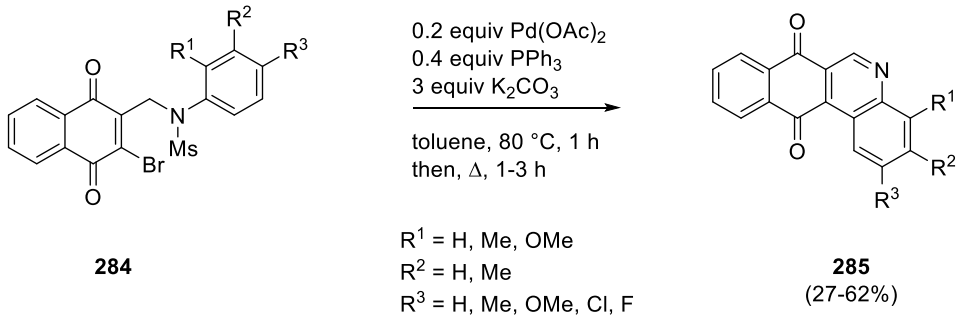


283a

Figure 18

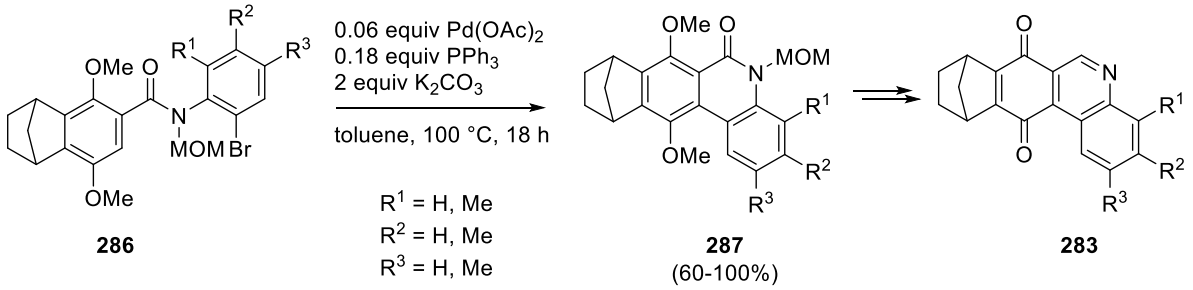
3.6.2 Synthesis of fluorinated 8,9,10,11-tetrahydro-8,11-methanobenzo[*j*]-phenanthridine-7,12-diones

In previous research at our department, the synthesis of substituted benzo[*j*]phenanthridine-7,12-diones **285** was developed, with the palladium-catalyzed intramolecular cyclization of methanesulfonamides **284** as the key step in the reaction sequence (Scheme 82).[148b] *N*-Methanesulfonyl-3-bromo-2-(arylamino)methyl-1,4-naphthoquinones **284** were synthesized starting from 2-bromomethyl-3-bromo-1,4-naphtoquinone *via* a nucleophilic substitution with various anilines followed by mesylation.



Scheme 82[148b]

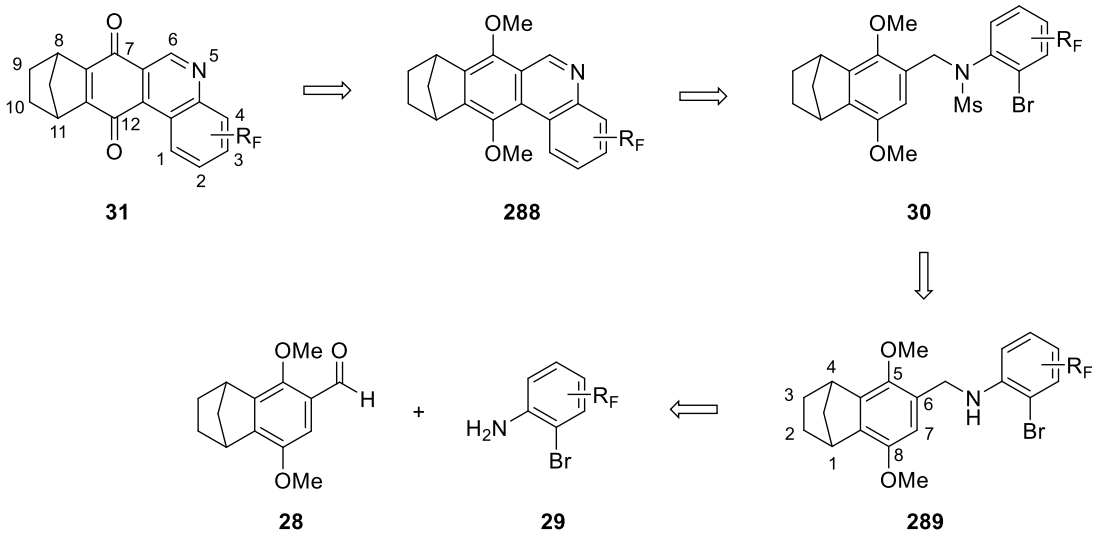
Furthermore, the synthesis of 8,9,10,11-tetrahydro-8,11-methanobenzo[*j*]phenanthridine-7,12-diones **283**, as 'out of plane derivatives' was also developed, *via* the palladium-catalyzed intramolecular cyclization of amides **286** toward cyclic amides **287** as the key step (Scheme 83).[150]



Scheme 83[150]

In this PhD thesis, the synthesis of fluorinated 8,9,10,11-tetrahydro-8,11-methanobenzo[*j*]-phenanthridine-7,12-diones **31** was envisioned, using a combination of the above-mentioned synthetic procedures. More specifically, in analogy with the synthetic pathway toward phenanthridines **285**, methanesulfonamides **30** were believed to be suitable substrates for the palladium-catalyzed ring closure toward phenanthridines **288**. For the synthesis of precursors **30**, aldehyde **28**, which was also the starting

compound for the synthesis of MOM-protected amides **286**, will be transformed into amines **289** *via* a reductive amination with various fluorinated 2-bromoanilines **29**. Mesylation of the amines **289** should lead to the formation of methanesulfonamides **30** (Scheme 84).

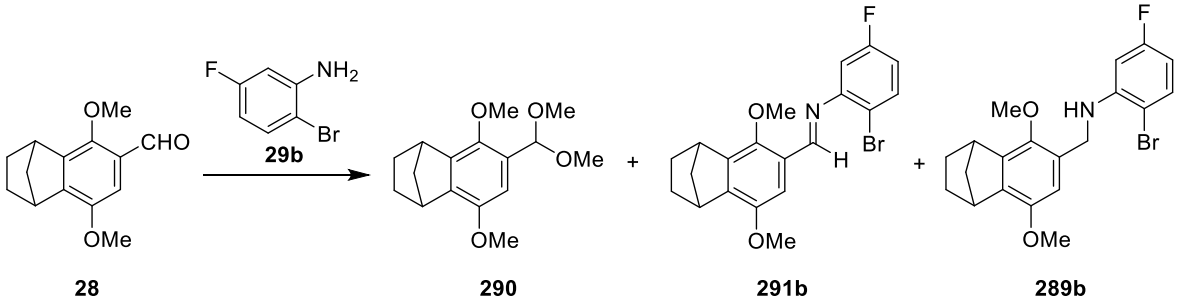


Scheme 84

3.6.2.1 Synthesis of anilines **289** *via* reductive amination

The reductive amination toward amines **289** was believed to be straightforward (Table 24). In a first attempt, aldehyde **28** reacted with 2-bromo-5-fluoroaniline **29b** in MeOH for one hour at room temperature, followed by the addition of one equivalent of $NaBH_4$ at 0 °C and stirring for another 30 minutes at room temperature.[152] However, after work-up, four compounds were present in the reaction mixture, more specifically aniline **29b**, acetal **290**, aldimine **291b** and the envisioned amine **289b**, which was only present in a very small amount (Table 24, entry 1). Since significant amounts of acetal **290** and unreduced aldimine **291b** were present in the reaction mixture, other reaction conditions were explored. In the second attempt, one equivalent of acetic acid was added to the reaction mixture and $NaCNBH_3$ was used as the reducing agent (Table 24, entry 2). Although amine **289b** was present in a larger amount while imine **291b** could not be observed, acetal **290** was again formed as a side product in a significant amount.

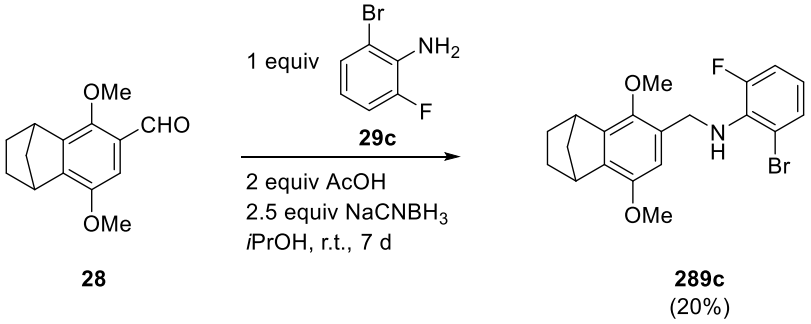
Table 24: Synthesis of aniline 289b starting from aldehyde 28 and aniline 29b



Entry	Reaction conditions	Ratio[a] **28** : **290** : **291b : 289b**
1	1) 1 equiv **29b**, MeOH, r.t., 1 h 2) 1 equiv $NaBH_4$, 0 °C - r.t., 30 min	0 : 47 :47 : 6
2	1) 1 equiv **29b**, 1 equiv AcOH, MeOH, r.t., 7 h 2) 1 equiv $NaCNBH_3$, MeOH, r.t., 18 h	0 : 54 : 0 : 46

[a] Determined *via* ^{1}H NMR analysis of the crude reaction mixture.

Since performing the imination reaction in MeOH led to the formation of acetal **290** as a side product, the use of isopropanol as a less-nucleophilic solvent was evaluated. Thus, aldehyde **28** was dissolved in *i*PrOH and reacted in a one-pot fashion with aniline **29c** in the presence of acetic acid and $NaCNBH_3$. After work-up, a mixture of aniline **29c**, amine **289c** and a compound which was tentatively identified as the alcohol resulting from aldehyde reduction, was obtained from which amine **289c** was isolated in a low yield of 20% (Scheme 85).



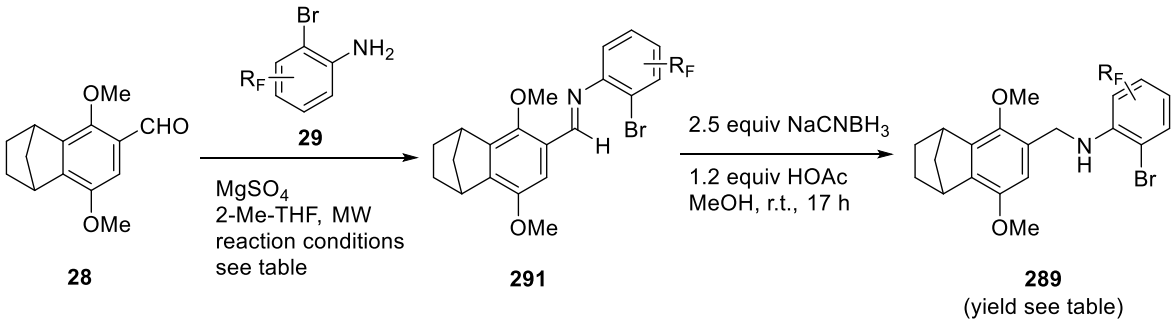
Scheme 85

Since this one-pot reductive amination in *i*PrOH gave no satisfying results, it was decided to optimize the imination step using other non-nucleophilic solvents. Upon treatment of aldehyde **28** with one equivalent

of aniline **29c** in the presence of two equivalents of $MgSO_4$ in THF at reflux temperature for 17 hours, only 50% conversion to the imine was achieved. Also the use of $Ti(OEt)_4$ in THF did not lead to better results, since an aqueous work-up was needed to remove the titanium salts, resulting in hydrolysis of the imine and irreproducible results.

Subsequently, the imination of aldehyde **28** in 2-methyltetrahydrofuran (2-Me-THF) under microwave irradiation was evaluated and the results are presented in Table 25. The conversion of aldehyde **28** toward imines **291** was determined based on ^1H NMR analysis of the crude reaction mixture. When an acceptable conversion was obtained, the reaction mixture was subjected to reductive reaction conditions by treatment with $NaCNBH_3$ in the presence of acetic acid in MeOH. In a first attempt, aldehyde **28** reacted with one equivalent of 2-bromo-4-fluoroaniline **29a** in 2-Me-THF in the presence of two equivalents $MgSO_4$ for two hours at 60 °C, leading to 50% conversion toward imine **291a** (Table 25, entry 1). Increasing the number of equivalents of aniline **29a** to two or three equivalents led to a higher conversion of 75% and 97%, respectively (Table 25, entries 2-3). The crude reaction mixture of this last attempt was subjected to reductive reaction conditions and amine **289a** was isolated in 67% yield starting from aldehyde **28** (Table 25, entry 3). Unfortunately, when these optimized reaction conditions were applied to the reaction of aldehyde **28** with anilines **29b**,**c**,**d**,**e**, the conversion toward the corresponding imines was only moderate. When aldehyde **28** reacted with 2-bromo-6-fluoroaniline **29c** for one hour at 60 °C, a conversion of 60% toward the corresponding imine was observed (Table 25, entry 4), while a longer reaction time of three hours led to an even lower conversion of 27% (Table 25, entry 5). The reaction of aniline **29b** with aldehyde **28** gave a higher conversion of 86% after one hour at 60 °C, but amine **289b** could only be isolated in moderate variable yields (23-53%) (Table 25, entry 6). Also the reaction of aldehyde **28** with trifluoromethylated anilines **29d** and **29e** gave a moderate conversion toward the corresponding imines **291d**,**e** (Table 25, entries 7-10).

Table 25: Synthesis of fluorinated anilines 289 *via* sequential imination and reduction

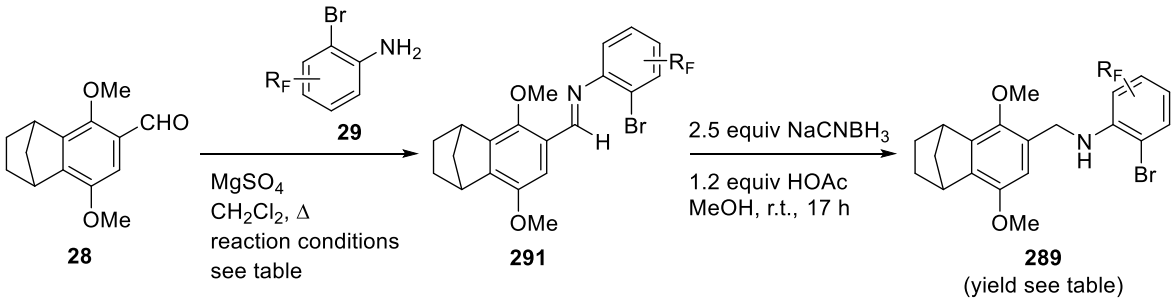


Entry	Reaction conditions microwave	Conversion of **28** toward imine **291**[a]	Yield[b] amine **289** (from aldehyde **28**)
1	1 equiv **29a** (4-F), 2 equiv $MgSO_4$, 60 °C, 2 h	50%	-
2	2 equiv **29a** (4-F), 2 equiv $MgSO_4$, 60 °C, 2 h	75%	-
3	3 equiv **29a** (4-F), 3 equiv $MgSO_4$, 60 °C, 45 min	97%	**289a** (67%)
4	3 equiv **29c** (6-F), 3 equiv $MgSO_4$, 60 °C, 1 h	60%	-
5	3 equiv **29c** (6-F), 3 equiv $MgSO_4$, 60 °C, 3 h	27%	-
6	3 equiv **29b** (5-F), 3 equiv $MgSO_4$, 60 °C, 1 h	86%	**289b** (23-53%)[c]
7	3 equiv **29e** (5-CF_3), 3 equiv $MgSO_4$, 60 °C, 1 h	70%	**289e** (13-32%)[c]
8	3 equiv **29e** (5-CF_3), 3 equiv $MgSO_4$, 100 °C, 40 min	56%	-
9	3 equiv **29d** (4-CF_3), 3 equiv $MgSO_4$, 60 °C, 75 min	79%	-
10	3 equiv **29d** (4-CF_3), 3 equiv $MgSO_4$, 100 °C, 40 min	38%	-

[a] Determined *via* ^1H NMR analysis fo the crude reaction mixture. [b] Isolated yield. [c] Variable yields were obtained from different attempts.

Following these moderate results, dichloromethane was evaluated next as the solvent for the imination reaction. Aldehyde **28** was treated with trifluoromethylated anilines **29d-e** in the presence of $MgSO_4$ under reflux conditions in CH_2Cl_2. Although a relatively long reaction time was needed (19-48 h), the conversion of aldehyde **28** into the corresponding imines **291d**,**e** was very good (96-97%). Eventually, amines **289d**,**e** were obtained in good yields (66-71% in two steps) after reduction using $NaCNBH_3$.

Table 26: Synthesis of trifluoromethylated anilines 289 *via* sequential imination and reduction



Entry	Reaction conditions	Conversion of **28** toward imine **291**[a]	Yield[b] amine **289** (from aldehyde **28**)
1	3 equiv **29e** (5-CF_3), 3 equiv $MgSO_4$, Δ, 48 h	96%	**289e** (71%)
2	3 equiv **29d** (4-CF_3), 3 equiv $MgSO_4$, Δ, 19 h	97%	**289d** (66%)

[a] Determined *via* ^{1}H NMR analysis fo the crude reaction mixture. [b] Isolated yield.

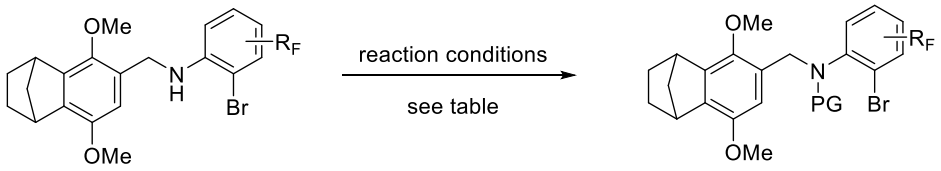
Additionally, it should be mentioned that the purification of amines **289a-e** was not straightforward. Due to the low nucleophilicity of anilines **29**, caused by the electron-withdrawing fluorine substituents, three equivalents of anilines **29** were needed to obtain an acceptable conversion toward the corresponding imines. After the reduction step, this excess of anilines **29** needed to be separated from amines **289**. However, all attempts to separate this mixture *via* column chromatography (SiO_2) using a PE/EtOAc mixture as the eluent failed since compounds **29** and **289** eluted simultaneously. Only *via* preparative TLC the separation could be achieved after several runs of the TLC plate. However, preparative TLC can only be used on a small scale. Fortunately, the automated flash system (Reveleris Flash Forward), resulted in a very good separation when reversed phase conditions were applied using a CH_3CN/H_2O mixture as the eluent.

3.6.2.2 Protection of anilines **289**

Having anilines **289** in hand, different reaction conditions for their conversion into methanesulfonamides **30** were evaluated (Table 27). However, reaction of aniline **289b** with one or two equivalents methanesulfonyl chloride in pyridine at 0 °C or reflux temperature did not lead to the formation of the corresponding methanesulfonamide **30b** (Table 27, entry 1). Also, upon use of the solvent mixture pyridine/CH_2Cl_2 1/1 at reflux temperature for three hours, no conversion of aniline **289b** was observed (Table 27, entry 2).[148b] Similar reaction conditions were also applied to aniline **289e**, but again no reaction

was observed. (Table 27, entry 3). In a next attempt, aniline **289b** first reacted with NaH in THF for 15 minutes, after which MsCl was added and the reaction mixture was stirred at reflux temperature for 17 h (Table 27, entry 4).[153] But again, no conversion of the starting material was observed. Following these bad results, it was decided to try to protect the amino function as a trifluoromethanesulfonamide group. As such, aniline **289b** reacted with two equivalents *N*-phenyl-bis(trifluoromethanesulfinimide) in dichloromethane, but again no reaction was observed (Table 27, entry 5).[154] Finally, treatment of aniline **289b** with two equivalents of triflic anhydride in the presence of NaH in dichloromethane did lead to the formation of trifluoromethanesulfonamide **292b**, which was isolated in a low yield of 24% (Table 27, entry 6).[155] Applying these reaction conditions to amines **289c** and **289a** also gave rise to the formation of the corresponding trifluoromethanesulfonamides **292c**,**a** which were isolated in slightly higher yields (50-52%) (Table 27, entries 7-8).

Table 27: Protection of anilines 289



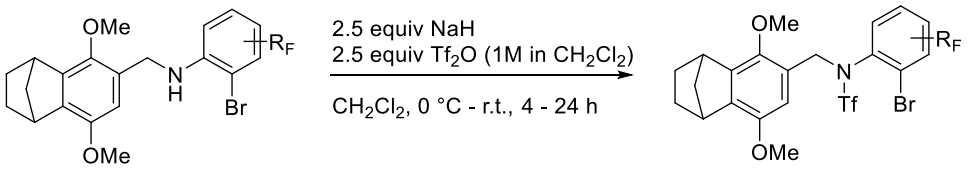
289

30 (PG = Ms)
292 (PG = Tf)

Entry	Substrate	Reaction conditions	Result
1	**289b** (5-F)	1-2 equiv MsCl, pyridine, 0 °C - Δ, 17 h	No reaction
2	**289b** (5-F)	1.3 equiv MsCl, pyridine/CH_2Cl_2 1/1, Δ, 3 h	No reaction
3	**289e** (5-CF_3)	2 equiv MsCl, pyridine/CH_2Cl_2 1/1, Δ, 17 h	No reaction
4	**289b** (5-F)	1) 1.2 equiv NaH, THF, r.t., 15 min 2) 1.2 equiv MsCl, Δ, 17 h	No reaction
5	**289b** (5-F)	2 equiv *N*-phenyl-bis(trifluoromethanesulfinimide), 2 equiv Et_3N, CH_2Cl_2, r.t. - Δ, 3 h	No reaction
6	**289b** (5-F)	2.5 equiv NaH, 2 equiv Tf_2O, CH_2Cl_2, 0 °C - r.t., 3 h	24% **292b**[a]
7	**289c** (6-F)	2.5 equiv NaH, 2 equiv Tf_2O, CH_2Cl_2, 0 °C - r.t., 3 h	50% **292c**[a]
8	**289a** (4-F)	2.5 equiv NaH, 2 equiv Tf_2O, CH_2Cl_2, 0 °C - r.t., 3 h	52% **292a**[a]

[a] Isolated yield.

In an attempt to synthesize *N*-triflyl amides **292** in a higher yield, anilines **289** reacted with triflic anhydride in CH_2Cl_2 instead of using pure triflic anhydride. Satisfyingly, under these reaction conditions, trifluoromethanesulfonamides **292a-e** were formed and isolated in 60-71% yield (Scheme 86).



289

292a (R_F = 4-F, 61%)
292b (R_F = 5-F, 71%)
292c (R_F = 6-F, 61%)
292d (R_F = 4-CF_3, 62%)
292e (R_F = 5-CF_3, 60%)

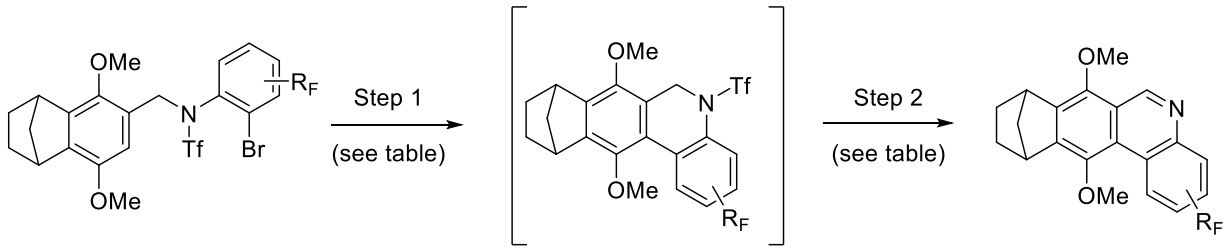
Scheme 86

3.6.2.3 Palladium-catalyzed ring closure towards phenanthridines **288**

The next step in the reaction sequence toward fluorinated 8,9,10,11-tetrahydro-8,11-methanobenzo[*j*]-phenanthridine-7,12-diones was the palladium-catalyzed ring closure of trifluoromethanesulfonamides **292**. To this end, trifluoromethanesulfonamide **292a** was reacted with 12 mol% $Pd(OAc)_2$ using 36 mol% triphenylphosphine as the ligand and two equivalents potassium carbonate in toluene at 100 °C under nitrogen atmosphere. Follow-up using ^{1}H NMR showed a slow progress of the reaction with only 53% conversion of the starting material after 46 hours. Thus, extra $Pd(OAc)_2$ (12 mol%) and PPh_3 (36 mol%) were added and stirring was continued for another nine hours, after which a conversion of 74% was achieved. Again extra $Pd(OAc)_2$ (6 mol%) and PPh_3 (18 mol%) were added and the stirring was continued for another four days, leading to a conversion of 88%. At this point, the reaction was stopped, leading to compound **293a** as the end product. Apparently, the aromatization toward phenanthridine **288a** did not occur under these reaction conditions. In the next step, compound **293a** was used without purification and treated with KO*t*Bu, leading to the desired aromatization toward phenanthridine **288a**, which was isolated in 42% yield (Table 28, entry 1). The reaction time and the amount of catalyst used in the first step could be strongly reduced by performing the Heck coupling under microwave irradiation, although this only led to a slight improvement of the yield (51% over two steps) (Table 28, entry 2). Upon use of trifluoromethanesulfonamide **292c** as the substrate, again a big catalyst load (24 mol% $PdOAc_2$) and extended reaction time in the microwave of 46 hours were necessary to achieve a full conversion (Table 28, entry 3). After aromatization, phenanthridine **288c** was isolated in 43% yield. Finally, the Heck coupling of substrate **292b** gave no conversion when it was performed under microwave irradiation (Table 28, entry

4), but full conversion was achieved in batch (Table 28, entry 5), and eventually phenanthridine **288b** was isolated in 39% yield. It can be concluded that the conversion of monofluorinated trifluoromethanesulfonamides **292a-c** into phenanthridines **288a-c** proceeds sluggishly and needs further optimization.

Table 28: Synthesis of phenanthridines 288



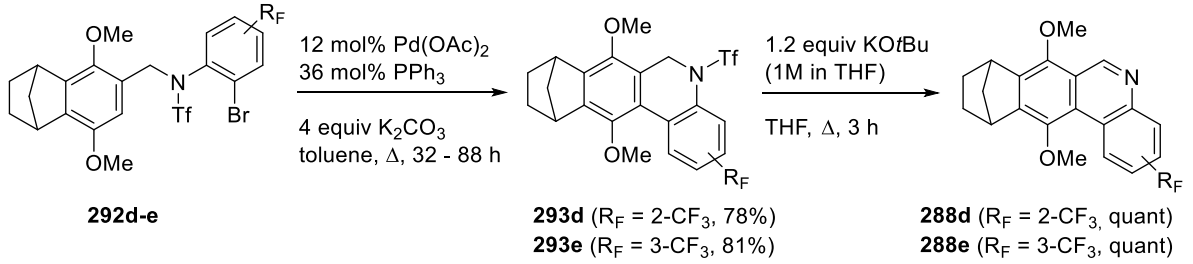
292 **293** **288**

Entry	Substrate	Reaction conditions Step 1	Reaction conditions Step 2	Yield[a]
1	**292a** (4-F)	0.3 equiv $Pd(OAc)_2$, 0.9 equiv PPh_3, 2 equiv K_2CO_3, toluene, 100 °C, 7 d	2 equiv KO*t*Bu[b], Δ, 2 h	42% **288a**
2	**292a** (4-F)	0.06 equiv $Pd(OAc)_2$, 0.18 equiv PPh_3, 2 equiv K_2CO_3, toluene, MW, 125 °C, 3 h	2 equiv KO*t*Bu[b], Δ, 2 h	51% **288a**
3	**292c** (6-F)	0.24 equiv $Pd(OAc)_2$, 0.72 equiv PPh_3, 2 equiv K_2CO_3, toluene, MW, 125 °C, 46 h	2 equiv KO*t*Bu[b], Δ, 3.5 h	43% **288c**
4	**292b** (5-F)	0.06 equiv $Pd(OAc)_2$, 0.18 equiv PPh_3, 2 equiv K_2CO_3, toluene, MW, 125 °C, 2 h	-[c]	-[c]
5	**292b** (5-F)	0.12 equiv $Pd(OAc)_2$, 0.36 equiv PPh_3, 4 equiv K_2CO_3, toluene, Δ, 38 h	3 equiv KO*t*Bu[b], Δ, 3 h	39% **288b**

[a] Yield over two steps, starting from substrate trifluoromethanesulfonamides **292**. [b] 1M in THF. [c] No reaction in step 1.

In an attempt to achieve a higher yield over the two steps, it was decided to isolate intermediates **293d-e**, synthesized *via* the Heck coupling of compounds **292d-e**, before performing the aromatization step. Thus, trifluoromethanesulfonamide **292d** was treated with 6 mol% $Pd(OAc)_2$ in the presence of 18 mol% PPh_3 and 2 equiv K_2CO_3. After 63 hours of stirring in toluene at reflux temperature, no further progress of the

reaction could be noticed and extra $Pd(OAc)_2$ (6 mol%), PPh_3 (18 mol%) and K_2CO_3 (2 equiv) were added. After stirring this mixture for another 24 hours, full consumption of the starting compound was achieved and tetracyclic compound **293d** was isolated in 78% yield. Analogously, intramolecular Heck coupling of trifluoromethanesulfonamide **292e** led to the formation of compound **293e**, in 81% yield. In the next step, aromatization by reaction with KO*t*Bu in THF under reflux conditions, led to phenanthridines **288d**,**e** in quantitative yield (Scheme 87).



292d-e

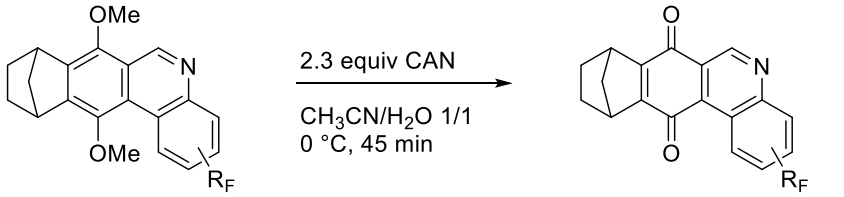
293d (R_F = 2-CF_3, 78%)
293e (R_F = 3-CF_3, 81%)

288d (R_F = 2-CF_3, quant)
288e (R_F = 3-CF_3, quant)

Scheme 87

3.6.2.4 CAN-mediated oxidation toward compounds **31**

The last step in the reaction sequence comprised the oxidative demethylation of compounds **288a-e**, which was achieved by treatment with 2.3 equivalents CAN in an acetonitrile/water mixture (1/1) for 45 minutes at 0 °C. Finally, fluorinated 8,9,10,11-tetrahydro-8,11-methanobenzo[*j*]phenanthridine-7,12-diones **31a-e** were isolated in moderate to good yields (37-76%).



288a-e

31a (R_F = 4-F, 62%)
31b (R_F = 3-F, 50%)
31c (R_F = 2-F, 37%)
31d (R_F = 3-CF_3, 45%)
31e (R_F = 2-CF_3, 76%)

Scheme 88

3.6.3 Conclusion

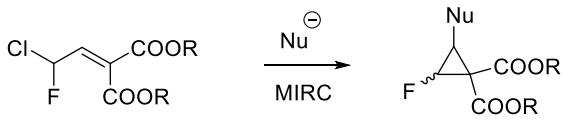
In conclusion, the synthesis of five fluorinated 8,9,10,11-tetrahydro-8,11-methanobenzo[*j*]-phenanthridine-7,12-diones **31** was developed using 5,8-dimethoxy-1,2,3,4-tetrahydro-1,4-

methanonaphthalene-6-carboxaldehyde and various fluorinated 2-bromoanilines as building blocks. Due to the low nucleophilicity of these fluorinated anilines, optimization of the reductive amination was necessary. After triflation of the resulting amines, Pd-catalyzed ring closure and aromatization, oxidative demethylation using CAN led to the formation of the envisaged 8,9,10,11-tetrahydro-8,11-methanobenzo[*j*]phenanthridine-7,12-diones. These compounds will be tested for their activity against *M. tuberculosis* in collaboration with the University of Antwerp.

4 Perspectives

In the literature overview it was shown that only a few examples of ring fluorinated β-ACC derivatives or fluorinated azetidine-2-carboxylates were reported to date. Therefore, in this PhD thesis, the (attempted) synthesis of fluorinated analogues of these compounds is described. However, this proved to be not straightforward and further research concerning the chemistry of these strained fluorinated amino acids derivatives is necessary.

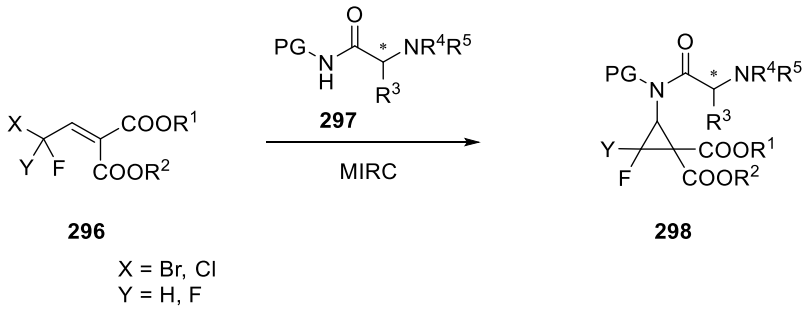
The synthesis of difluorinated β-ACC derivatives **184** demonstrated the negative impact of the two fluorine atoms on the stability of these compounds. Therefore, it is useful to evaluate the synthesis of monofluorinated derivatives **295**, via the MIRC reaction of dialkyl 2-(2-chloro-2-fluoroethylidene)malonates **294** (Scheme 89). In this reaction, the diastereoselective outcome should also be evaluated.



294 **295**

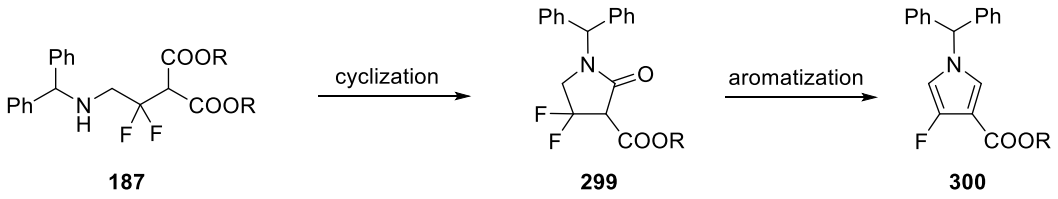
Scheme 89

Furthermore, the incorporation of fluorinated β-ACC derivatives in peptides is of importance to get insight on the influence of these amino acids on the secondary conformation of peptides. However, due to the instability of β-ACC derivatives **184**, their incorporation in peptides will be a major challenge. A possible pathway toward dipeptides incorporating the β-ACC unit is the use of amino acid derivatives **297** as nucleophiles in the MIRC reaction. Michael addition of nitrogen nucleophiles **297** across dialkyl 2-(2-haloethylidene)malonates **296** could lead to the formation of dipeptides **298** after ring closure (Scheme 90).



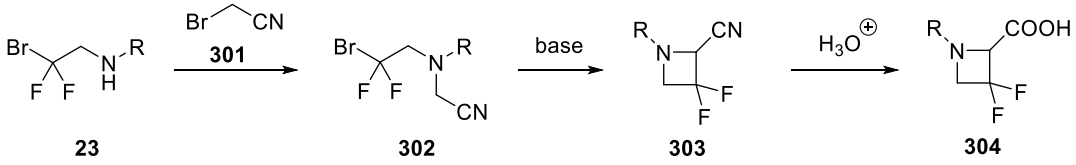
Scheme 90

In this PhD thesis it was also shown that the reduction of pyrrolines **185** resulted in the formation of acyclic amino esters **187**, which proved to be unstable. It should be useful to try to convert acyclic amino esters **187** into 2-pyrrolidinones **299** *via* ring closure, which are possibly more stable (Scheme 91). Further aromatization[156] could lead to the formation of fluorinated pyrroles **300**, which have only been studied to a very limited extent.[157]



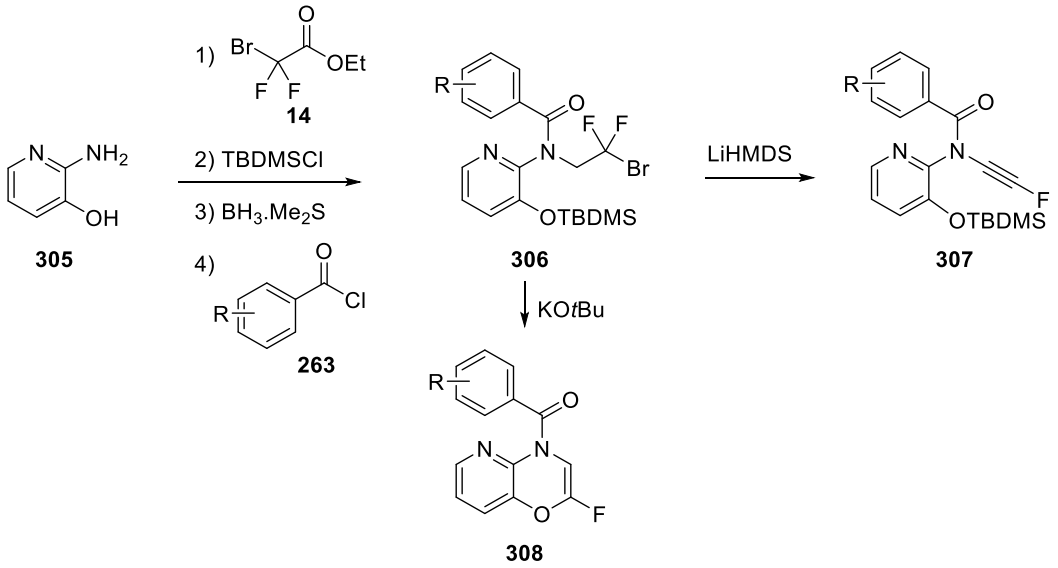
Scheme 91

In the fourth chapter of this PhD thesis, the synthesis of fluorinated azetidine-2-carboxylates was attempted. Unfortunately, this goal could not be achieved. However, there are still some options to be explored which could lead to the formation of these constrained fluorinated amino acid derivatives. For example, the condensation of amines **23** with bromoacetonitrile **301** should lead to amino nitriles **302** (Scheme 92). The deprotonation of these compounds **302** should be easier than the deprotonation of the corresponding esters, and could possibly be followed by ring closure to give azetidines **303**. Subsequent hydrolysis of the nitrile moiety could lead to azetidine-2-carboxylic acids **304**.



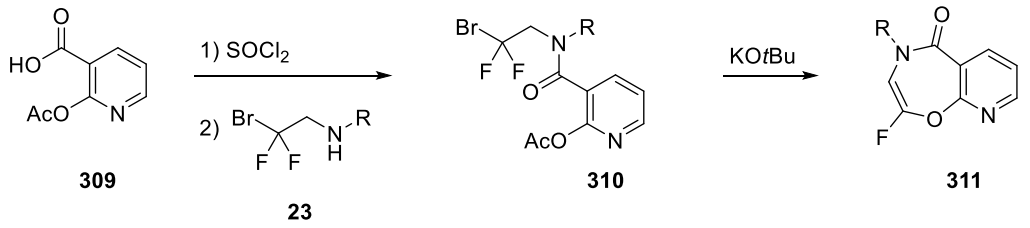
Scheme 92

In another part of this PhD thesis, the efficient synthesis of various 2-fluoro-1,4-benzoxazines **267** and elusive β-fluoroynamides **266** was developed starting from 2-aminophenols **258**. These fluorinated compounds are interesting scaffolds with potential applications in medicinal chemistry. As an expansion of this work, it should be useful to synthesize analogues of 2-fluoro-1,4-benzoxazines **267** incorporating an extra nitrogen atom in the aromatic ring. Thus, applying the same reaction sequence to for example 2-amino-3-hydroxypyridine **305** should give rise to β-fluoroynamides **307** and 2-fluoropyrido[3,2-*b*][1,4]-oxazines **308** (Scheme 93). Although these pyrido[3,2-*b*][1,4]oxazines are interesting scaffolds, they have only been studied to a limited extent,[129e,158] while fluorinated analogues have not been described to date.



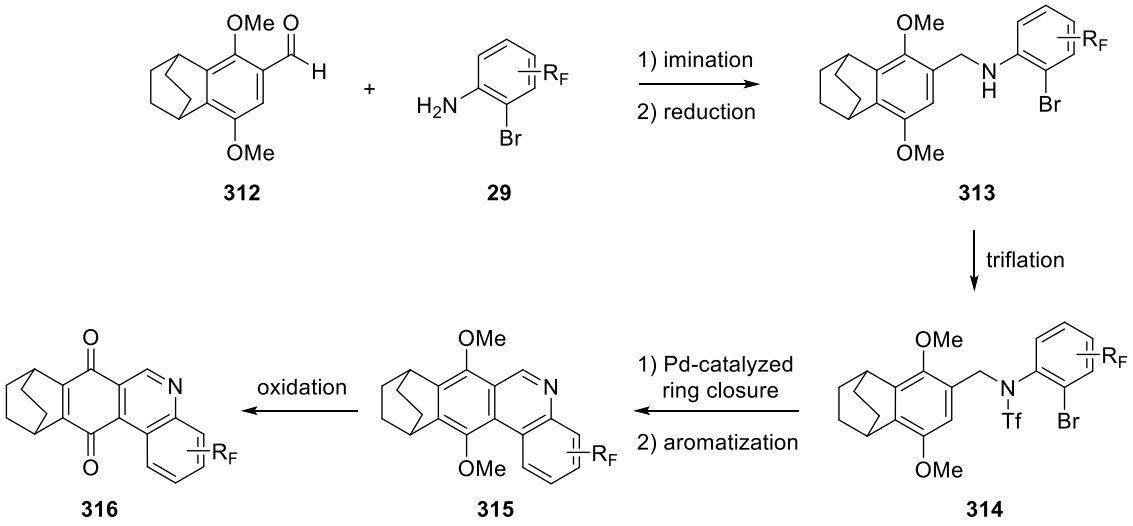
Scheme 93

In addition, the synthesis of 2-fluoro-1,4-benzoxazepin-5-ones **279** could also be expanded to the synthesis of derivatives incorporating an extra nitrogen atom in the aromatic ring. For example, treatment of 2-acetoxypyridine-3-carboxylic acid **309** with thionyl chloride should lead to the formation of the corresponding acid chloride, which could be coupled with fluorinated amines **23** resulting in the formation of amides **310**. Subsequent treatment with KO*t*Bu should give rise to the formation of unprecedented 2-fluoropyrido[3,2-*f*]-1,4-oxazepin-5-ones **311** (Scheme 94). Pyrido[3,2-*f*]-1,4-oxazepin-5-ones, which are not annelated to another aromatic ring, have never been described in the literature before.



Scheme 94

In the final part of this PhD thesis, 8,9,10,11-tetrahydro-8,11-methanobenzo[*j*]phenanthridine-7,12-diones **31** were synthesized as potential anti-mycobacterial compounds. However, these methano-bridged benzo[*j*]phenanthridines are chiral compounds and they were synthesized as a racemic mixture. In addition of this research, the synthesis of the non-chiral ethano-bridged derivatives should be evaluated, which should proceed *via* the beforementioned methodology, starting from ethano-bridged aldehyde **312** (Scheme 95). Reductive amination with fluorinated 2-bromoanilines **29**, followed by triflation of the amine nitrogen atom should afford trifluoromethanesulfonamides **134**. Palladium-catalyzed ring closure and subsequent aromatization should give compounds **315**, which should be converted into fluorinated 8,9,10,11-tetrahydro-8,11-ethanobenzo[*j*]phenanthridine-7,12-diones **316** by CAN-mediated oxidation.



Scheme 95

5 Experimental section

5.1 General methods

Solvents

Dry dichloromethane was obtained via distillation over calcium hydride. Dry tetrahydrofuran, dry diethyl ether and dry toluene were freshly distilled over sodium/benzophenone ketyl before use. Other solvents were used as received from the supplier, unless specified otherwise.

Microwave irradiation

All microwave reactions were performed in a *CEM Focused Microwave™ Synthesis System, Model Discover* with a continuous power output from 0 to 300 W and a self-adjusting, single mode microwave cavity. Reactions were performed in 10 mL thick-walled Pyrex reaction vials, closed with a snap-cap and equipped with a small magnetic stirring bar. The temperature was increased from room temperature to the desired temperature using a ramp time of maximum 5 minutes. The desired temperature was maintained during the course of the reaction. The temperature control system used an external 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 W 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 bottom of the microwave cavity. After the desired reaction time, the vial was cooled down by a stream of air which decreased the temperature of the vial from approximately 150 °C to 40 °C in less than 120 s.

Column chromatography

The purification of reaction mixtures was performed by column chromatography using a glass column filled with silica gel (Acros, particle size 35-70 µm, pore diameter ca. 6 nm). Solvent systems were determined *via* initial TLC analysis on glass plates, coated with silica gel (Merck, Kieselgel 60 F254, precoated 0.25 mm) using UV light (254 nm and 366 nm), iodine vapor or $KMnO_4$ oxidation as detection methods. Automated flash chromatography was performed on a Reveleris® X2 Flash Chromatography System.

Liquid chromatography

LC and LC-MS analyses were performed on an Agilent 1200 Series liquid chromatograph using a reversed phase column (Eclipse plus C18 column, 50 x 4.6 mm, particle size 3.5 µm, or a Supelco Ascentis Express C18 column, 30 x 4.6 mm, particle size 2.7 µm) with an UV-VIS detector and an Agilent 1100 series LC/MSD type SL mass spectrometer (ESI, 70 eV) using a mass selective single quadrupole detector. Gradient elution was used (30% acetonitrile in water to 100% acetonitrile over 6 minutes).

NMR spectroscopy

^{1}H NMR spectra were recorded at 300 MHz (JEOL ECLIPSE+) or 400 MHz (Bruker Avance III) with $CDCl_3$ as solvent and tetramethylsilane as internal standard. ^{13}C NMR spectra were recorded at 75 MHz (JEOL ECLIPSE+) or 100.6 MHz (Bruker Advance III) with $CDCl_3$ as solvent and tetramethylsilane as internal standard. ^{19}F NMR spectra were recorded at 282 MHz (JEOL ECLIPSE+) or 376.5 MHz (Bruker Advance III) with $CDCl_3$ as solvent and $CFCl_3$ as internal standard. Peak assignments were obtained with the aid of HSQC and/or HMBC spectra.

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. Only selected absorbances (ν_{max}, cm^{-1}) were reported.

Mass spectrometry

Low resolution mass spectra were recorded via direct injection on an Agilent 1100 Series LC/MSD type SL mass spectrometer with Electron Spray Ionisation Geometry (ESI 70 eV) and using a Mass Selective Detector (quadrupole). High resolution mass spectra were obtained with an Agilent Technologies 6210 Time-of-Flight Mass Spectrometer (TOFMS), equipped with ESI/APCI-multimode source.

Elementary 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.

Optical rotation

Optical rotations were determined using a JASCO P-2000 Series Polarimeter at a wavelength of 589 nm.

5.2 Safety

General safety aspects

The work in the laboratory of the SynBioC Research group (Department of Sustainable Organic Chemistry and Technology) was conducted in full compliance with the 'Internal Safety Guidelines'. Furthermore, upon use of chemicals, the internal safety document 'Safety instructions: how to work with chemicals', was consulted.

Specific safety aspects

A list of the risks associated with each chemical is available in the corresponding material safety data sheet (MSDS), which can be found on the website of the supplier. Therein, a classification of the hazards was made according to the European Regulation (EC) No 1272/2008 [EU-GHS/CLP], which combines the Globally Harmonized System of Classification and Labeling of Chemicals (GHS) and Classification, Labelling and Packaging regulations (CLP). A brief overview of the chemicals employed in this work classified as category 1, the most severe category, of the respective hazard class will be given below, along with the GHS hazards and precautions.

Acid chlorides (acetyl chloride, 4-methoxybenzoyl chloride, 4-chlorobenzoyl chloride, 2-acetylsalicyloyl chloride, oxalyl chloride): Causes severe skin burns and eye damage. Wear protective gloves/ eye protection/ face protection. **Benzoyl chloride**: Causes severe skin burns and eye damage. May cause an allergic skin reaction. Wear protective gloves/ eye protection/ face protection.

$AlCl_3$: Causes severe skin burns and eye damage. Causes damage to organs through prolonged or repeated exposure if inhaled. Wear protective gloves/ protective clothing/ eye protection/ face protection.

Allyl bromide: Causes severe skin burns and eye damage. May cause genetic defects. May cause cancer. Very toxic to aquatic life. Obtain special instructions before use. Avoid release to the environment. Wear protective gloves/ protective clothing/ eye protection/ face protection.

Amines (propylamine, benzylamine, 4-methoxybenzylamine, ethanolamine): Causes severe skin burns and eye damage. Wear protective gloves/ eye protection/ face protection.

Fluorinated 2-bromoanilines, aniline: May cause an allergic skin reaction. Causes serious eye damage. Causes damage to organs (blood) through prolonged or repeated exposure. Very toxic to aquatic life with long lasting effects. Avoid release to the environment. Wear protective gloves/eye protection/face protection. **3-Amino-4-bromobenzotrifluoride**: Causes severe skin burns and eye damage. Wear protective gloves/eye protection/face protection.

$BF_3.Et_2O$: Causes severe skin burns and eye damage. Causes damage to organs through prolonged or repeated exposure if inhaled. Wear protective gloves/protective clothing/eye protection/face protection.

Borane dimethylsulfide complex: Causes serious eye damage. Wear protective gloves/eye protection/face protection.

Bromoacetates: Causes severe skin burns and eye damage. Wear protective gloves/eye protection/face protection.

Butyllithium: Catches fire spontaneously if exposed to air. May be fatal if swallowed and enters airways. Causes severe skin burns and eye damage. Do not allow contact with air. Handle under inert gas. Protect from moisture.

Cyanides (KCN, NaCN): May be corrosive to metals. Fatal if swallowed, in contact with skin or if inhaled. Causes damage to organs (heart, testes, brain) if swallowed. Causes damage to organs (thyroid) through prolonged or repeated exposure. Very toxic to aquatic life with long lasting effects. Do not breathe dust/fume/gas/mist/vapours/spray. Avoid release to the environment. Wear protective gloves/protective clothing.

Diisobutylaluminium hydride: Highly flammable liquid and vapour. Catches fire spontaneously if exposed to air. Causes severe skin burns and eye damage. Keep away from heat/sparks/open flames/hot surfaces. No smoking. Do not allow contact with air. Wear protective gloves/ protective clothing/eye protection/face protection.

EDC.HCl: Causes serious eye damage. Wear protective gloves/eye protection/face protection.

Ethyl bromodifluoroacetate, ethyl chlorofluoroacetate: Causes severe skin burns and eye damage. Wear protective gloves/eye protection/face protection.

HMPA: May cause genetic defects. May cause cancer. Obtain special instructions before use.

Imidazole: Causes severe skin burns and eye damage. May damage the unborn child. Wear protective gloves/eye protection/face protection.

Inorganic acids (HCl): May be corrosive to metals. Causes severe skin burns and eye damage. Avoid breathing vapours. Wear protective gloves/eye protection/face protection.

Inorganic bases (NaOH, KOH): May be corrosive to metals. Causes severe skin burns and eye damage. Wear protective gloves/protective clothing/eye protection/face protection. **Sodium hydride**: In contact with water releases flammable gases which may ignite spontaneously. Do not allow contact with water.

Iodine: Causes damage to organs (thyroid) through prolonged or repeated exposure if swallowed. Very toxic to aquatic life. Avoid breathing dust. Avoid release to the environment

Isobutyl chloroformate: Causes severe skin burns and eye damage. Wear protective gloves/protective clothing/eye protection/face protection.

$NaBH_4$: In contact with water releases flammable gases which may ignite spontaneously. Causes severe skin burns and eye damage. Wear protective gloves/protective clothing/eye protection/face protection. Do not allow contact with water.

$NaCNBH_3$: Flammable solid. Causes severe skin burns and eye damage. Very toxic to aquatic life with long lasting effects. Keep away from heat, hot surfaces, sparks, open flames and other ignition sources. No smoking. Avoid release to the environment. Wear protective gloves/protective clothing/eye protection/face protection.

N-Bromosuccinimide: Causes severe skin burns and eye damage. Wear protective gloves/protective clothing/eye protection/face protection.

N-methylmorpholine: Causes severe skin burns and eye damage. Wear protective gloves/protective clothing/eye protection/face protection.

Organic acids (HOAc): Causes severe skin burns and eye damage. Wear protective gloves/protective clothing/eye protection/face protection.

Organic bases (KHMDS, LiHMDS, KO*t*Bu, LiO*t*Bu): Causes severe skin burns and eye damage. Wear protective gloves/protective clothing/eye protection/face protection. **NaOMe**: Self-heating: may catch fire. Causes severe skin burns and eye damage. Keep cool. Protect from sunlight. Wear protective gloves/protective clothing/eye protection/face protection.

$Pd(OAc)_2$: Causes serious eye damage. Wear protective gloves/eye protection/face protection.

Phenol: Causes severe skin burns and eye damage. Wear protective gloves/protective clothing/eye protection/face protection.

Phenylacetylene: May be fatal if swallowed and enters airways.

***p*-Toluenesulfonyl chloride, *p*-nitrobenzenesulfonyl chloride, methanesulfonyl chloride**: Causes severe skin burns and eye damage. Wear protective gloves/protective clothing/eye protection/face protection.

Tetrachloromethane: May cause an allergic skin reaction. Causes damage to organs through prolonged or repeated exposure. Harms public health and the environment by destroying ozone in the upper atmosphere. Avoid release to the environment. Wear protective gloves/protective clothing/eye protection/face protection.

$TiCl_4$: Causes severe skin burns and eye damage. Causes damage to organs through prolonged or repeated exposure. Do not breathe dust/fume/gas/mist/vapours/spray. Wear protective gloves/protective clothing/eye protection/face protection.

TMSCl, TBDMSCl: Causes severe skin burns and eye damage. Wear protective gloves/protective clothing/eye protection/face protection.

Thiophenol: Fatal if swallowed, in contact with skin or if inhaled. Causes serious eye damage. Do not breathe dust/fume/gas/mist/vapours/spray. Wear protective gloves/eye protection/face protection.

Thionyl chloride: Causes severe skin burns and eye damage. Wear protective gloves/protective clothing/eye protection/face protection.

Triethylamine: Causes severe skin burns and eye damage. Wear protective gloves/protective clothing/eye protection/face protection.

Triflic anhydride: Causes severe skin burns and eye damage. Wear protective gloves/protective clothing/eye protection/face protection.

Triphenylphosphine: May cause an allergic skin reaction. Wear protective gloves.

5.3 Stereoselective synthesis of both enantiomers of *trans*-2-(diphenylmethylideneamino)cyclopropanecarboxylic acid using a chiral pool approach and their incorporation in dipeptides

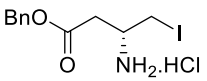
5.3.1 Synthesis of (*R*)-benzyl 4-iodo-3-*N*-(*tert*-butoxycarbonyl)butanoate (*R*)-166

(*R*)-4-Iodobutanoate (*R*)-**166** was synthesized in two steps following a slightly modified literature procedure starting from (*R*)-β-benzyl *N*-(*tert*-butoxycarbonyl)aspartate using PPh_3 instead of polymer bound triphenylphosphine.[67-68]

5.3.2 Synthesis of (*R*)-benzyl 3-amino-4-iodobutanoate hydrochloride (*R*)-167

(*R*)-Benzyl 4-iodo-3-*N*-(*tert*-butoxycarbonyl)butanoate (*R*)-**166** (0.89 g, 2.12 mmol) was dissolved in 10 mL of a saturated solution of HCl in Et_2O at 0 °C and stirred for 6 hours at 0 °C. After stirring the reaction mixture for another 16 hours at room temperature, the solvent was evaporated *in vacuo*. Subsequently, dry Et_2O (20 mL) was added and the solution was filtered. After washing the filter cake with dry Et_2O (20 mL), (*R*)-benzyl 3-amino-4-iodobutanoate hydrochloride (*R*)-**167** (0.39 g, 1.42 mmol) was obtained as white crystals in 76% yield.

(*R*)-Benzyl 3-amino-4-iodobutanoate hydrochloride (*R*)-167



White crystals. Melting point: 129-130 °C. Yield: 76%. **^{1}H NMR** (300 MHz, DMSO-d_6): δ 2.77-2.92 (2H, m, CH_2C=O), 3.46-3.61 (3H, m, CH_2I and CH), 5.15 (2H, s, CH_2O), 7.32-7.43 (5H, m, CH_{arom}), 8.51 (3H, br s, NH_3). **^{13}C NMR** (75 MHz, DMSO-d_6): δ 6.3 (CH_2I), 37.3 ($\underline{C}H_2C$=O), 47.6 (CH), 66.2 (CH_2O), 128.0, 128.1 and 128.4 (5x CH_{arom}), 135.5 ($C_{arom,quat}$), 169.0 (C=O). **IR** (ATR, cm^{-1}): ν_{NH3} = 3028, $\nu_{C=O}$ = 1731, ν_{max} = 1402, 1173, 1154, 1133, 748, 696. **MS** (ES^+): *m*/*z* (%): 320 ($M + H^+$ - HCl, 100), 192 ($M + H^+$ - HCl - HI, 46).

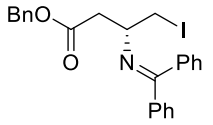
Optical rotation could not be determined due to instability of the HCl salt in MeOH.

5.3.3 Synthesis of (*R*)-benzyl 3-(diphenylmethylideneamino)-4-iodobutanoate (*R*)-164

To a solution of (*R*)-benzyl 3-amino-4-iodobutanoate hydrochloride (*R*)-**167** (0.53 g, 1.5 mmol) in CH_2Cl_2 (20 mL) was added diphenylmethylideneamine **12** (1 equiv, 0.27 g, 1.5 mmol). After stirring the reaction mixture for 20 hours at room temperature, the solvent was evaporated *in vacuo* and the residue was

redissolved in dry Et_2O (20 mL). Filtration of the solids and subsequent removal of the solvent *in vacuo* afforded (*R*)-benzyl 3-(diphenylmethylideneamino)-4-iodobutanoate (*R*)-**164** in 85% yield (0.61 g, 1.27 mmol).

(*R*)-Benzyl 3-(diphenylmethylideneamino)-4-iodobutanoate (*R*)-164



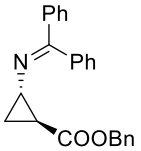
Yellow crystals. Melting point: 82-83 °C. $[\alpha]_D$ -40 ± 1 (c 0.8, CH_2Cl_2). Yield: 85%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 2.76 (1H, dd, *J* = 15.2 Hz, 7.2 Hz, C<u>H</u>(H)C=O), 2.81 (1H, dd, *J* = 15.2 Hz, 5.5 Hz, CH(<u>H</u>)C=O), 3.26 (1H, dd, *J* = 9.9 Hz, 6.1 Hz, C<u>H</u>(H)I), 3.32 (1H, dd, *J* = 9.6 Hz, 6.1 Hz, CH(<u>H</u>)I), 3.84-3.92 (1H, m, CH), 5.06 (1H, d, *J* = 12.4 Hz, C<u>H</u>(H)O), 5.10 (1H, d, *J* = 12.4 Hz, CH(<u>H</u>)O), 7.15-7.20 (2H, m, 2x CH_{arom}), 7.25-7.51 (11H, m, 11x CH_{arom}), 7.57-7.62 (2H, m, 2x CH_{arom}). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 10.9 (CH_2I), 41.2 (<u>C</u>H_2C=O), 58.5 (CH), 66.1 (CH_2O), 127.5, 127.9, 128.0, 128.3, 128.5, 128.7 and 130.3 (15x CH_{arom}), 135.6, 136.0 and 139.3 (3x $C_{arom,quat}$), 169.6 and 170.6 (C=N and C=O). **IR** (ATR, cm^{-1}): $\nu_{C=O}$ = 1737, $\nu_{C=N}$ = 1616, ν_{max} = 1292, 1173, 1155, 1131, 695. **MS** (ES^+): *m/z* (%): 484 ($M + H^+$, 100). **HRMS** (ES^+): calcd for $C_{24}H_{23}INO_2^+$: 484.0768, found 484.0764.

5.3.4 Synthesis of (1*S*,2*S*)-benzyl 2-(diphenylmethylideneamino)cyclopropane-carboxylate (1*S*,2*S*)-8

A solution of (*R*)-benzyl 3-(diphenylmethylideneamino)-4-iodobutanoate (*R*)-**164** (0.15 g, 0.3 mmol, 1 equiv) in THF (3 mL) was cooled to -78 °C and KHMDS (1M in THF) (1.1 equiv, 0.33 mmol, 0.33 mL) was added dropwise. Subsequently, the reaction mixture was stirred for one hour at -78 °C, after which it was quenched with 1 mL $NH_4Cl_{(aq, sat)}$. The mixture was poured in 10 mL NaOH (2M in H_2O), extracted with Et_2O (3x 10 mL) and the organic layers were dried with $MgSO_4$. After removal of the drying agent and evaporation of the solvent *in vacuo*, a mixture of *trans*- and *cis*-benzyl 2-(diphenylmethylideneamino)-cyclopropanecarboxylate (1*S*,2*S*)-**8** and (1*R*,2*S*)-**8** was obtained (dr 97:3) from which (1*S*,2*S*)-benzyl 2-(diphenylmethylideneamino)cyclopropanecarboxylate (1*S*,2*S*)-**8** was isolated in 75% yield (0.080 g, 0.23 mmol) (dr > 99:1) after recrystallization from hexane.

The diastereomeric ratio was determined based on the well-resolved signal of the benzylic protons in the ^{1}H NMR spectrum.

(1*S*,2*S*)-Benzyl 2-(diphenylmethylideneamino)cyclopropanecarboxylate (1*S*,2*S*)-8

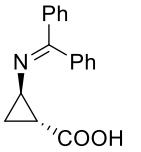


White crystals. Melting point: 102-103 °C. $[\alpha]_D$ 206 (c 1.6, CH_2Cl_2). Yield: 75%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.52-1.63 (2H, m, CH_2), 2.29 (1H, ddd, *J* = 8.6 Hz, 6.1 Hz, 2.5 Hz, CHC=O), 3.37 (1H, ddd, *J* = 7.4 Hz, 4.8 Hz, 2.5 Hz, CHN), 5.08 (2H, s, CH_2O), 7.20-7.55 (15H, m, 15x CH_{arom}). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 18.6 (CH_2), 25.2 (<u>C</u>HC=O), 45.7 (CHN), 66.4 (CH_2O), 128.2, 128.3, 128.40, 128.43, 128.7, 128.9 and 130.1 (10x CH_{arom}), 136.1, 136.4 and 139.6 (3x $C_{arom,quat}$), 169.2 and 172.8 (C=N and C=O). **IR** (ATR, cm^{-1}): $\nu_{C=O}$ = 1714, $\nu_{C=N}$ 1612, ν_{max} = 1400, 1164, 618. **MS** (ES^+): *m*/*z* (%): 356 ($M + H^+$, 100). **HRMS** (ES^+): calcd for $C_{24}H_{22}NO_2^+$: 356.1645, found 356.1644.

5.3.5 Synthesis of (1*R*,2*R*)-2-(diphenylmethylideneamino)cyclopropanecarboxylic acid (1*R*,2*R*)-9

To an ice-cooled solution of (1*R*,2*R*)-benzyl 2-(diphenylmethylideneamino)cyclopropanecarboxylate (1*R*,2*R*)-**8** (0.21 g, 0.6 mmol, 1 equiv) in MeOH/H_2O 5/1 (6 mL), aqueous 2M NaOH (5 equiv, 3 mmol, 1.5 ml) was added. The reaction mixture was stirred at room temperature for 20 hours. The organic solvent was evaporated under reduced pressure and the residual aqueous phase was washed with Et_2O (2x 10 mL). Subsequently, the aqueous layer was carefully acidified with a solution of 2M HCl in H_2O to pH 6, followed by an extraction with CH_2Cl_2 (3x 10 mL). After drying ($MgSO_4$), filtration and evaporation, the pure carboxylic acid (1*R*,2*R*)-**9** was obtained in 61% yield and dr > 99:1 (0.097 g, 0.37 mmol).

(1*R*,2*R*)-2-(Diphenylmethylideneamino)cyclopropanecarboxylic acid (1*R*,2*R*)-9



White crystals. Melting point: 194-195 °C. $[\alpha]_D$ -256 (c 0.5, MeOH). Yield 61%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.55 (1H, ddd, *J* = 7.4 Hz, 5.8 Hz, 4.4 Hz, C<u>H</u>(H)), 1.63 (1H, ddd, *J* = 8.8 Hz, 4.5 Hz, 4.4 Hz, CH(<u>H</u>)), 2.23 (1H, ddd, *J* = 8.5 Hz, 6.1 Hz, 2.5 Hz, CHC=O), 3.38 (1H, ddd, *J* = 7.3 Hz, 4.8 Hz, 2.3 Hz, CHN), 7.24-7.55 (10H, m, 10x CH_{arom}). OH: not visible **^{13}C NMR** (75 MHz, CD_3OD): δ 17.7 (CH_2), 24.6 (<u>C</u>HC=O), 45.4 (CHN), 128.3, 128.5, 128.6, 129.0 and 130.5 (10x CH_{arom}), 136.9 and 139.8 (2x $C_{arom,quat}$), 170.7 and 175.6 (C=N and C=O). **IR** (ATR, cm^{-1}): ν_{OH} = 2850, $\nu_{C=O}$ = 1698, $\nu_{C=N}$ = 1613, ν_{max} = 1209, 1186, 936, 698. **MS** (ES^+): *m*/*z* (%): 266 ($M + H^+$, 100). **HRMS** (ES^+): calcd for $C_{17}H_{16}NO_2^+$: 266.1176, found 266.1176.

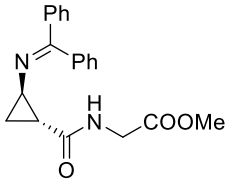
(1*S*,2*S*)-2-(Diphenylmethylideneamino)cyclopropanecarboxylic acid (1*S*,2*S*)-9

$[\alpha]_D$ 247 (c 0.4, MeOH).

5.3.6 Synthesis of (1'*R*,2'*R*)-methyl [(2'-diphenylmethylideneaminocyclopropane)-carbonyl]aminoacetate (1'*R*,2'*R*)-171

To a stirred solution of (1*R*,2*R*)-2-(diphenylmethylideneamino)cyclopropanecarboxylic acid (1*R*,2*R*)-**9** (0.053 g, 0.2 mmol) and methyl glycinate hydrochloride **170a** (1 equiv, 0.025 g, 0.2 mmol) in dry CH_2Cl_2 (5 mL) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC.HCl) (1 equiv, 0.038 g, 0.2 mmol) and *N*-methylmorpholine (3 equiv, 0.061 g, 0.6 mmol), and the reaction mixture was stirred at room temperature for three hours. The reaction mixture was poured into water (10 mL) and extracted with CH_2Cl_2 (3x 5 mL). The combined organic layers were dried with $MgSO_4$. The drying agent was removed by filtration and the filtrate was concentrated *in vacuo* to afford pure (1'*R*,2'*R*)-methyl [(2'-diphenylmethylideneaminocyclopropane)carbonyl]aminoacetate (1'*R*,2'*R*)-**171** (58% yield, 0.039 g, 0.12 mmol) after column chromatography on silica gel (petroleum ether/EtOAc 1/1).

(1'*R*,2'*R*)-Methyl [(2'-diphenylmethylideneaminocyclopropane)carbonyl]aminoacetate (1'*R*,2'*R*)-171



Viscous oil. $[\alpha]_D$ -168 ± 3 (c 0.1, CH_2Cl_2). Yield: 58%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.49 (1H, ddd, *J* = 8.8 Hz, 4.4 Hz, 4.4 Hz, C<u>H</u>(H)), 1.56 (1H, ddd, *J* = 7.4 Hz, 5.8 Hz, 4.4 Hz, CH(<u>H</u>)), 2.11 (1H, ddd, *J* = 8.5 Hz, 5.9 Hz, 3.0 Hz, CHC=O), 3.36 (1H, ddd, *J* = 7.2 Hz, 4.8 Hz, 2.2 Hz, CHN), 3.75 (3H, s, CH_3), 4.03 (2H, d, *J* = 5.0 Hz, C<u>H</u>$_2$NH), 6.28 (1H, t, *J* = 5.0 Hz, NH), 7.23-7.55 (10H, m, 10x CH_{arom}). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 17.5 (<u>C</u>H_2CHN), 26.9 (<u>C</u>HC=O), 41.3 (CH_2N), 44.8 (CHN), 52.4 (CH_3), 128.1, 128.3, 128.4, 128.6, 128.8 and 129.9 (10x CH_{arom}), 136.3 and 139.7 (2x $C_{arom,quat}$), 168.7, 170.5 and 171.6 (C=N and 2x C=O). **IR** (ATR, cm^{-1}): ν_{NH} = 3299, $\nu_{C=O}$ = 1752, $\nu_{C=O}$ = 1648, ν_{max} = 1542, 1207, 1180, 695. **MS** (ES^+): *m/z* (%): 337 (M + H^+, 100). **HRMS** (ES^+): calcd for $C_{20}H_{21}N_2O_3^+$: 337.1547, found 337.1548.

(1'*S*,2'*S*)-Methyl [(2'-diphenylmethylideneaminocyclopropane)carbonyl]aminoacetate (1'*S*,2'*S*)-171

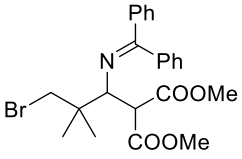
$[\alpha]_D$ 151 ± 1 (c 0.3, CH_2Cl_2).

5.4 Synthesis of novel β-aminocyclobutanecarboxylic acid derivatives by a solvent-free aza-Michael addition and subsequent ring closure

5.4.1 Synthesis of dialkyl 2-[3-halo-2,2-dimethyl-1-(diphenylmethylideneamino)-propyl]malonates 174

As a representative example, the synthesis of dimethyl 2-[3-bromo-2,2-dimethyl-1-(diphenylmethylideneamino)propyl]malonate **174a** is described here. In a flame-dried flask, triethylamine (1.05 equiv, 0.180 g, 1.86 mmol) was added to a mixture of dimethyl 2-(3-bromo-2,2-dimethylpropylidene)malonate **11a** (1 equiv, 0.520 g, 1.86 mmol) and diphenylmethylideneamine **12** (1.05 equiv, 0.350 g, 1.96 mmol). This mixture was stirred at 60 °C under solvent-free conditions for four hours. Subsequently, dry diethyl ether was added, the solution was filtered and the filtrate was concentrated *in vacuo*. Pure dimethyl 2-[3-bromo-2,2-dimethyl-1-(diphenylmethylideneamino)propyl]malonate **174a** was obtained after recrystallization from diethyl ether in 79% yield.

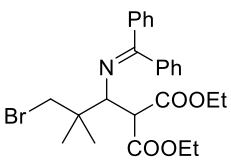
Dimethyl 2-[3-bromo-2,2-dimethyl-1-(diphenylmethylideneamino)propyl]malonate 174a



White crystals. Melting point: 140.6-142.1 °C. Yield: 79%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 0.94 (3H, s, CH_3), 1.05 (3H, s, CH_3), 3.30 (1H, d, *J* = 9.9 Hz, C<u>H</u>(H)Br), 3.42 (1H, d, *J* = 9.9 Hz, CH(<u>H</u>)Br), 3.52 (3H, s, OCH_3), 3.70 (3H, s, OCH_3), 4.02 (1H, d, *J* = 6.1 Hz, <u>C</u>H(COOMe)$_2$), 4.36 (1H, d, *J* = 6.1 Hz, CHN), 7.27-7.60 (10H, m, 10x CH_{arom}). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 22.1 (C<u>C</u>H$_3$(CH$_3$)), 23.4 (CCH$_3$(<u>C</u>H$_3$)), 40.7 (<u>C</u>(CH$_3$)$_2$), 44.2 (BrCH$_2$), 52.4 (OCH_3), 52.7 (OCH_3), 53.9 (<u>C</u>H(COOMe)$_2$), 66.0 (CHN), 128.0, 128.1, 128.6, 128.7 and 130.3 (10x CH_{arom}), 135.5 ($C_{arom,quat}$), 139.6 ($C_{arom,quat}$), 168.4, 168.6 and 169.5 (2x C=O and C=N). **IR** (ATR, cm^{-1}): $\nu_{C=O}$ = 1732, $\nu_{C=N}$ = 1626, ν_{max} = 1224, 1204, 1170, 705, 697. **MS** (ES^+): *m/z* (%): 460/62 ($M + H^+$, 100). **El. Anal.** Calcd for $C_{23}H_{26}BrNO_4$: C 60.01, H 5.69, N 3.04, found C 59.83, H 5.58, N 3.27.

Diethyl 2-[3-bromo-2,2-dimethyl-1-(diphenylmethylideneamino)propyl]malonate 174c

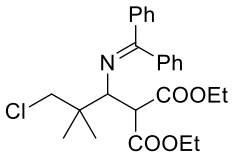
Prepared at room temperature instead of 60 °C.



White crystals. Melting point: 96.9-97.4 °C. Yield: 76%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 0.93 (3H, s, CH_3), 1.04 (3H, t, *J* = 7.2 Hz, $CH_2C\underline{H}_3$), 1.05 (3H, s, CH_3), 1.23 (3H, t, *J* = 7.2 Hz, $CH_2C\underline{H}_3$), 3.31 (1H, d, *J* = 10.2 Hz, C<u>H</u>(H)Br), 3.43 (1H, d, *J* = 10.2 Hz, CH(<u>H</u>)Br), 3.88-4.04 (2H, m, OCH_2), 3.98 (1H, d, *J* = 6.6 Hz, <u>C</u>H(COOEt)$_2$), 4.16 (2H, q, *J* = 7.2 Hz, OCH_2),

4.38 (1H, d, *J* = 6.6 Hz, CHN), 7.26-7.60 (10H, m, 10x CH_{arom}). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 13.9 ($CH_2\underline{C}H_3$), 14.0 ($CH_2\underline{C}H_3$), 22.0 ($C\underline{C}H_3(CH_3)$), 23.4 ($CCH_3(\underline{C}H_3)$), 40.8 ($\underline{C}(CH_3)_2$), 44.3 (CH_2Br), 54.3 ($\underline{C}H(COOEt)_2$), 61.4 ($O\underline{C}H_2$), 61.6 ($O\underline{C}H_2$), 65.9 (CHN), 127.9, 128.1, 128.6, 128.76, 128.82 and 130.2 (10x CH_{arom}), 135.6 ($C_{arom,quat}$), 139.7 ($C_{arom,quat}$), 167.9, 168.2 and 169.3 (2x C=O and C=N). **IR** (ATR, cm^{-1}): $\nu_{C=O}$ = 1727, $\nu_{C=N}$ = 1626, ν_{max} = 1290, 1222, 1178, 1030, 699. **MS** (ES^+): *m/z* (%): 488/90 (M + H^+, 100). **El. Anal.** Calcd for $C_{25}H_{30}BrNO_4$: C 61.48, H 6.19, N 2.87, found C 61.39, H 6.06, N 2.88.

Diethyl 2-[3-chloro-2,2-dimethyl-1-(diphenylmethylideneamino)propyl]malonate 174d



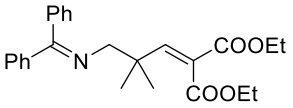
White crystals. Melting point: 83.9-84.1 °C. Yield: 67%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 0.91 (3H, s, CH_3), 1.04 (3H, t, *J* = 6.9 Hz, $CH_2C\underline{H}_3$), 1.04 (3H, s, CH_3), 1.23 (3H, t, *J* = 6.9 Hz, $CH_2C\underline{H}_3$), 3.36 (1H, d, *J* = 11.0 Hz, $C\underline{H}(H)Cl$), 3.47 (1H, d, *J* = 11.0 Hz, $CH(\underline{H})Cl$), 3.94 (2H, q, *J* = 6.9 Hz, OCH_2), 3.99 (1H, d, *J* = 6.3 Hz, $C\underline{H}(COOEt)_2$), 4.16 (2H, q, *J* = 6.9 Hz, OCH_2), 4.36 (1H, d, *J* = 6.3 Hz, CHN), 7.26-7.59 (10H, m, 10x CH_{arom}). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 13.9 ($CH_2C\underline{H}_3$), 14.0 ($CH_2C\underline{H}_3$), 21.0 ($C\underline{C}H_3(CH_3)$), 22.3 ($CCH_3(\underline{C}H_3)$), 41.4 ($\underline{C}(CH_3)_2$), 53.4 (CH_2Cl), 54.2 ($\underline{C}H(COOEt)_2$), 61.4 (OCH_2), 61.6 (OCH_2), 65.8 (CHN), 127.9, 128.0, 128.6, 128.77, 128.85 and 130.2 (10x CH_{arom}), 135.6 ($C_{arom,quat}$), 139.8 ($C_{arom,quat}$), 168.0, 168.2 and 169.3 (2x C=O and C=N). **IR** (ATR, cm^{-1}): $\nu_{C=O}$ = 1723, $\nu_{C=N}$ = 1627, ν_{max} = 1282, 1221, 1180, 1030, 700. **MS** (ES^+): *m/z* (%): 444/46 (M + H^+, 100). **El. Anal.** Calcd for $C_{25}H_{30}ClNO_4$: C 67.63, H 6.81, N 3.15, found C 67.59, H 6.85, N 3.17.

The spectral data of dimethyl 2-[3-chloro-2,2-dimethyl-1-(diphenylmethylideneamino)propyl]malonate **174b** were in accordance with the data reported in a previous Master thesis.[13]

5.4.2 Synthesis of diethyl 2-[2,2-dimethyl-3-(diphenylmethylideneamino)-propylidene]malonate 175b

In a flame-dried flask, triethylamine (1.05 equiv, 0.17 g, 1.7 mmol) was added to a mixture of diethyl 2-(3-bromo-2,2-dimethylpropylidene)malonate **11c** (1 equiv, 0.50 g, 1.63 mmol) and diphenylmethylideneamine (1.05 equiv, 0.31 g, 1.71 mmol). The reaction mixture was stirred at 60 °C under solvent-free conditions for 20 hours. Subsequently, dry diethyl ether was added, the solution was filtered and the solvent was removed *in vacuo*. Pure diethyl 2-[2,2-dimethyl-3-(diphenylmethylideneamino)propylidene]malonate **175b** was obtained after recrystallization from diethyl ether in a yield of 38%.

Diethyl 2-[2,2-dimethyl-3-(diphenylmethylideneamino)propylidene]malonate 175b

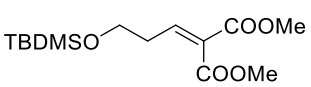


White crystals. Melting point: 75.6-77.0 °C. Yield: 38%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.18 (6H, s, $C(C\underline{H}_3)_2$), 1.28 (3H, t, *J* = 7.2 Hz, $CH_2C\underline{H}_3$), 1.31 (3H, t, *J* = 7.2 Hz, $CH_2C\underline{H}_3$), 3.31 (2H, s, NCH_2), 4.22 (2H, q, *J* = 7.2 Hz, OCH_2), 4.24 (2H, q, *J* = 7.2 Hz, OCH_2), 7.07 (1H, s, CH=C), 7.11-7.15 (2H, m, 2x CH_{arom}), 7.29-7.50 (6H, m, 6x CH_{arom}), 7.61-7.65 (2H, m, 2x CH_{arom}). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 14.0 ($CH_2C\underline{H}_3$), 14.1 ($CH_2C\underline{H}_3$), 24.7 ($C(\underline{C}H_3)_2$), 39.4 ($\underline{C}(CH_3)_2$), 61.26 (OCH_2), 61.35 (OCH_2), 64.2 (NCH_2), 126.4 ($\underline{C}$=CH), 127.8, 128.0, 128.4, 128.5, 128.6 and 130.0 (10x CH_{arom}), 136.8 ($C_{arom,quat}$), 139.8 ($C_{arom,quat}$), 153.7 (C=$\underline{C}$H), 164.5, 167.0 and 168.7 (2x C=O and C=N). **IR** (ATR, cm^{-1}): $\nu_{C=O}$ = 1725, $\nu_{C=C}$ = 1646, $\nu_{C=N}$ = 1626, ν_{max} = 1226, 1204, 1027, 707, 700. **MS** (ES^+): *m/z* (%): 408 ($M + H^+$, 100). **El. Anal.** Calcd for $C_{25}H_{29}NO_4$: C 73.69, H 7.17, N 3.44, found C 73.28, H 7.17, N 3.41.

5.4.3 Synthesis of dimethyl 2-{[(3-*tert*-butyldimethylsilyl)oxy]-propylidene}malonate 179

Dimethyl 2-{[(3-*tert*-butyldimethylsilyl)oxy]propylidene}malonate **179** was synthesized following a literature procedure.[79a]

Dimethyl 2-[(3-*tert*-butyldimethylsilyl)oxy]propylidenemalonate 179



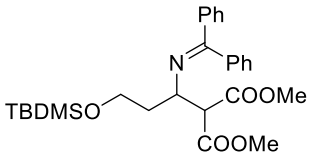
Colorless oil. R_f 0.13 (petroleum ether/EtOAc 10/1). Yield: 60%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 0.05 (6H, s, 2x $SiCH_3$), 0.89 (9H, s, $SiC(CH_3)_3$), 2.54 (2H, dt, *J* = 7.6 Hz, 6.3 Hz, $OCH_2C\underline{H}_2$), 3.74 (2H, t, *J* = 6.3 Hz, OCH_2), 3.79 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 7.14 (1H, t, *J* = 7.6 Hz, CH=C). **^{13}C NMR** (75 MHz, ref = $CDCl_3$): δ -5.3 (2x $SiCH_3$), 18.3 ($Si\underline{C}(CH_3)_3$), 25.9 ($SiC(\underline{C}H_3)_3$), 33.4 ($OCH_2\underline{C}H_2$), 52.3 (OCH_3), 52.4 (OCH_3), 61.3 (OCH_2), 129.1 (CH=$\underline{C}$), 147.7 ($\underline{C}$H=C), 164.3 (C=O), 165.8 (C=O). **IR** (ATR, cm^{-1}): $\nu_{C=O}$ = 1728, $\nu_{C=C}$ = 1649, ν_{max} = 1250, 1212, 1096, 832, 775. **MS** (ES^+): *m/z* (%): 303 ($M + H^+$, 100). **HRMS** (ES^+): calcd. for $C_{14}H_{27}O_5Si^+$ ($M + H^+$): 303.1622, found 303.1610.

5.4.4 Synthesis of dimethyl 2-{1-(diphenylmethylideneamino)-3-[(*tert*-butyldimethylsilyl)oxy]propyl}malonate 181

To a solution of dimethyl 2-{[(3-*tert*-butyldimethylsilyl)oxy]propylidene}malonate **179** (1.00 g, 3.3 mmol) in CH_2Cl_2 (30 mL), diphenylmethylideneamine (2 equiv, 1.20 g, 6.6 mmol) and Et_3N (2 equiv, 0.67 g, 6.6 mmol) were added and this mixture was stirred at reflux temperature for 30 hours. The solvent was removed *in vacuo* and 30 mL of dry Et_2O was added. After filtration of the solids, the solvent was

evaporated, affording crude malonate **181** as yellow crystals. After recrystallisation from hexane, pure malonate **181** (1.01 g, 2.1 mmol) was obtained as white crystals.

Dimethyl 2-{1-(diphenylmethylideneamino)-3-[(*tert*-butyldimethylsilyl)oxy]propyl}malonate 181



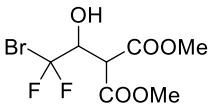
White crystals. Yield: 64%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 0.01 (3H, s, $SiCH_3$), 0.02 (3H, s, $SiCH_3$), 0.85 (9H, s, $SiC(CH_3)_3$), 1.86-1.93 (2H, m, $OCH_2C\underline{H}_2$), 3.49-3.57 (2H, m, OCH_2), 3.69 (3H, s, OCH_3), 3.71 (3H, s, OCH_3), 3.94 (1H, d, *J* = 7.7 Hz, $CH(COOMe)_2$), 4.22-4.29 (1H, m, CHN), 7.28-7.59 (10H, m, 10x CH_{arom}). **^{13}C NMR** (75 MHz, $CDCl_3$): δ -5.4 (2x $SiCH_3$), 18.2 ($SiC(CH_3)_3$), 25.9 ($SiC(\underline{C}H_3)_3$), 37.1 ($OCH_2\underline{C}H_2$), 52.3 (2x OCH_3), 56.8 ($\underline{C}H(COOMe)_2$), 58.4 (CHN), 59.8 (OCH_2), 127.9, 128.1 and 128.3 (6x CH_{arom}), 128.5 (CH_{arom}), 128.6 (2x CH_{arom}), 130.0 (CH_{arom}), 136.2 ($C_{arom,quat}$), 140.1 ($C_{arom,quat}$), 168.4, 168.5 and 168.7 (2x C=O and C=N). **IR** (ATR, cm^{-1}): $\nu_{C=O}$ = 1742, $\nu_{C=O}$ = 1721, $\nu_{C=N}$ = 1627, ν_{max} = 1264, 1253, 1156, 1083, 839, 780, 694. **MS** (ES^+): *m*/*z* (%): 484 ($M + H^+$, 100).

5.5 Synthesis of 2-amino-3,3-difluorocyclopropane-1,1-dicarboxylates

5.5.1 Synthesis of 2-(2-bromo-2,2-difluoro-1-hydroxyethyl)malonates 182

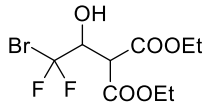
The synthesis of dimethyl 2-(2-bromo-2,2-difluoro-1-hydroxyethyl)malonate **182a** is described as representative. To a solution of ethyl bromodifluoroacetate (3.00 g, 14.8 mmol) in dry dichloromethane (50 mL), was added a solution of DIBAL (1.2M in toluene, 1.1 equiv, 13.6 mL, 16.3 mmol) at -78 °C under nitrogen atmosphere and this mixture was stirred for two hours at the same temperature. In another flask, dimethyl malonate (3 equiv, 5.85 g, 44.3 mmol) was dissolved in dry THF (50 mL) and NaH (3.3 equiv, 1.17 g, 48.8 mmol) was added at 0 °C. This mixture was stirred at 0 °C for 30 minutes and was then transferred into the former reaction mixture. Stirring was continued for one hour while the mixture was allowed to warm to room temperature, after which HCl (2M in H_2O) was added until pH 6 was reached. After filtration over Celite® and extraction with EtOAc (3x 40 mL), the combined organic phases were washed with brine (40 mL). After drying ($MgSO_4$), filtration and evaporation of the organic phase *in vacuo*, crude malonate **182a** was purified by means of column chromatography (petroleum ether/EtOAc 9/1) affording pure dimethyl 2-(2-bromo-2,2-difluoro-1-hydroxyethyl)malonate **182a** (2.63 g, 9.03 mmol).

Dimethyl 2-(2-bromo-2,2-difluoro-1-hydroxyethyl)malonate 182a



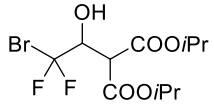
Pale yellow oil. R_f 0.03 (petroleum ether/EtOAc 9/1). Yield: 61%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 3.82 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 3.90 (1H, d, *J* = 3.3 Hz, $CH(COOMe)_2$), 4.62-4.70 (2H, m, C<u>H</u>O<u>H</u>). **^{13}C NMR** (75 MHz, ref = $CDCl_3$): δ 51.6 (<u>C</u>H(COOMe)$_2$), 53.3 (OCH_3), 53.4 (OCH_3), 75.3 (t, *J* = 26.0 Hz, CHOH), 122.9 (t, *J* = 309.8 Hz, CF_2Br), 160.1 and 167.9 (2x C=O). **^{19}F NMR** (282 MHz, $CDCl_3$, ref = $CFCl_3$): δ -57.01 (1F, dd, *J* = 166.7 Hz, $J_{H,F}$ = 7.2 Hz, C<u>F</u>(F)Br), -59.75 (1F, dd, *J* = 166.7 Hz, $J_{H,F}$ = 10.5 Hz, CF(<u>F</u>)Br). **IR** (ATR, cm^{-1}): ν_{OH} = 3458, $\nu_{C=O}$ = 1736, ν_{max} = 1197, 1159, 1100, 1023, 925. **MS** (ES^+): *m/z* (%): 308/10 (M + NH_4^+, 100). **HRMS** (ES^-): calcd. for $C_7H_8BrF_2O_5^-$ (M - H^+): 288.9529, found 288.9528.

Diethyl 2-(2-bromo-2,2-difluoro-1-hydroxyethyl)malonate 182b



Pale yellow oil. R_f 0.14 (petroleum ether/EtOAc 9/1). Yield: 62%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.30 (3H, t, *J* = 7.0 Hz, $CH_2C\underline{H}_3$), 1.31 (3H, t, *J* = 7.0 Hz, $CH_2C\underline{H}_3$), 3.85 (1H, d, *J* = 3.9 Hz, $CH(COOEt)_2$), 4.28 (2H, q, *J* = 7.0 Hz, $OC\underline{H}_2CH_3$), 4.30 (2H, q, *J* = 7.2 Hz, $OC\underline{H}_2CH_3$), 4.66 (1H, dddd, $J_{H,F}$ = 11.1 Hz, *J* = 9.1 Hz, $J_{H,F}$ = 7.9 Hz, *J* = 3.9 Hz, C<u>H</u>OH), 4.78 (1H, d, *J* = 9.1 Hz, OH). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 13.88 and 13.93 (2x CH_3), 51.0 (<u>C</u>H(COOEt)$_2$), 62.7 and 62.8 (2x OCH_2), 75.9 (dd, *J* = 26.0 Hz, 24.7 Hz, CHOH), 122.8 (t, *J* = 310.6 Hz, CF_2Br), 165.6 and 168.1 (2x C=O). **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ -57.15 (1F, dd, *J* = 166.5 Hz, $J_{H,F}$ = 7.9 Hz, C<u>F</u>(F)Br), -59.57 (1F, dd, *J* = 166.5 Hz, $J_{H,F}$ = 11.1 Hz, CF(<u>F</u>)Br). **IR** (ATR, cm^{-1}): ν_{OH} = 3456, $\nu_{C=O}$ = 1736, ν_{max} = 1301, 1177, 1096, 1024, 927. **MS** (ES^+): *m/z* (%): 319/21 (M + H^+, 40). **HRMS** (ES^+): calcd for $C_9H_{14}BrF_2O_5^+$: 318.9987, found 318.9988.

Diisopropyl 2-(2-bromo-2,2-difluoro-1-hydroxyethyl)malonate 182c

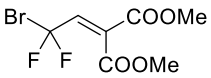


Pale yellow oil. R_f 0.12 (petroleum ether/EtOAc 9/1). Yield: 59%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.27 (6H, d, *J* = 6.1 Hz, $CH(C\underline{H}_3)_2$), 1.30 (6H, d, *J* = 6.1 Hz, $CH(C\underline{H}_3)_2$), 3.85 (1H, d, *J* = 3.9 Hz, $CH(COO\textit{i}Pr)_2$), 4.64 (1H, dddd, $J_{H,F}$ = 11.3 Hz, *J* = 8.7 Hz, $J_{H,F}$ = 8.1 Hz, *J* = 3.9 Hz, C<u>H</u>OH), 4.92 (1H, d, *J* = 8.7 Hz, OH), 5.15 (2H, septet, *J* = 6.4 Hz, 2x $C\underline{H}(CH_3)_2$). **^{13}C NMR** (75 MHz, ref = $CDCl_3$): δ 21.4, 21.48, 21.51 and 21.7 (4x CH_3), 51.5 (<u>C</u>H(COO*i*Pr)$_2$), 70.6 and 70.7 (2x <u>C</u>H$(CH_3)_2$), 75.8 (t, *J* = 25.4 Hz, CHOH), 123.1 (t, *J* = 310.4 Hz, CF_2Br), 165.2 and 167.7 (2x C=O). **^{19}F NMR** (282 MHz, $CDCl_3$, ref = $CFCl_3$): δ -57.02 (1F, dd, *J* = 166.1 Hz, $J_{H,F}$ = 8.1 Hz, C<u>F</u>(F)Br), -59.75 (1F, dd, *J* = 166.1 Hz, $J_{H,F}$ = 11.3 Hz, CF(<u>F</u>)Br). **IR** (ATR, cm^{-1}): ν_{OH} = 3458, $\nu_{C=O}$ = 1737, ν_{max} = 1288, 1179, 1095, 1021, 904. **MS** (ES^+): *m/z* (%): 347/49 (M + H^+, 40), 364/66 (M + NH_4^+, 100). **HRMS** (ES^-): calcd for $C_{11}H_{16}BrF_2O_5^-$ (M - H^+): 345.0155, found 345.

5.5.2 Synthesis of 2-(2-bromo-2,2-difluoroethylidene)malonates 16

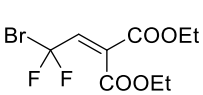
The synthesis of dimethyl 2-(2-bromo-2,2-difluoroethylidene)malonate **16a** is described as representative. Dimethyl 2-(2-bromo-2,2-difluoro-1-hydroxyethyl)malonate **182a** (2.91 g, 10 mmol) was dissolved in dry CH_2Cl_2 (50 mL) and acetyl chloride (2.2 equiv, 1.73 g, 22.0 mmol) and Et_3N (4.5 equiv, 4.55 g, 45.0 mmol) were added dropwise at 0 °C. After stirring at 0 °C for an additional five minutes, the reaction mixture was stirred at reflux temperature for 2.5 hours. A saturated aqueous solution of NH_4Cl (40 mL) was added, the mixture was extracted with CH_2Cl_2 (3x 30 mL) and the combined organic phases were dried over $MgSO_4$. After removal of the drying agent through filtration, the solvent was evaporated under reduced pressure affording crude ethylidenemalonate **16a**. After column chromatography, pure dimethyl 2-(2-bromo-2,2-difluoroethylidene)malonate **16a** (2.20 g, 8.1 mmol) was obtained as a colorless oil.

Dimethyl 2-(2-bromo-2,2-difluoroethylidene)malonate 16a



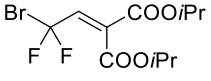
Colorless oil. R_f 0.29 (petroleum ether/EtOAc 9/1). Yield: 81%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 3.87 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 7.00 (1H, t, $J_{H,F}$ = 11.6 Hz, CH). **^{13}C NMR** (75 MHz, ref = $CDCl_3$): δ 53.2 (OCH_3), 53.6 (OCH_3), 113.8 (t, J = 302.3 Hz, $CBrF_2$), 129.3 ($\underline{C}(COOMe)_2$), 134.9 (t, J = 26.5 Hz, CH), 162.2 and 163.2 (2x C=O). **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ -49.50 (2F, d, $J_{H,F}$ = 11.3 Hz, CF_2Br). **IR** (ATR, cm^{-1}): $\nu_{C=O}$ = 1737, $\nu_{C=C}$ = 1665, ν_{max} = 1259, 1220, 1114, 946, 932. **MS** (ES^+): *m*/*z* (%): 290/92 ($M + NH_4^+$, 100). **HRMS**: the mother ion ($M + H^+$) could not be detected.

Diethyl 2-(2-bromo-2,2-difluoroethylidene)malonate 16b



Colorless oil. R_f 0.20 (petroleum ether/EtOAc 8/2). Yield: 76%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.33 (3H, t, J = 7.2 Hz, $OCH_2C\underline{H}_3$), 1.35 (3H, t, J = 7.2 Hz, $OCH_2C\underline{H}_3$), 4.32 (2H, q, J = 7.2 Hz, $OC\underline{H}_2CH_3$), 4.36 (2H, q, J = 7.2 Hz, $OC\underline{H}_2CH_3$), 6.97 (1H, t, $J_{H,F}$ = 11.8 Hz, CH). **^{13}C NMR** (75 MHz, ref = $CDCl_3$): δ 11.5 (2x $OCH_2\underline{C}H_3$), 59.9 ($O\underline{C}H_2CH_3$), 60.5 ($O\underline{C}H_2CH_3$), 111.8 (t, J = 302.3 Hz, CF_2Br), 128.0 ($\underline{C}(COOEt)_2$), 131.6 (t, J = 26.5 Hz, CH), 159.2 and 160.2 (2x C=O). **^{19}F NMR** (282 MHz, $CDCl_3$, ref = $CFCl_3$): δ -48.85 (2F, d, $J_{H,F}$ = 11.8 Hz, CF_2Br). **IR** (ATR, cm^{-1}): $\nu_{C=O}$ = 1736, $\nu_{C=C}$ = 1666, ν_{max} = 1251, 1218, 1111, 947. **MS** (ES^+): *m*/*z* (%) = 301/3 ($M + H^+$, 10), 318/20 ($M + NH_4^+$, 15). **HRMS** (ES^+) calcd for $C_9H_{15}BrF_2NO_4^+$ 318.0147 ($M + NH_4^+$), found 318.0144.

Diisopropyl 2-(2-bromo-2,2-difluoroethylidene)malonate 16c



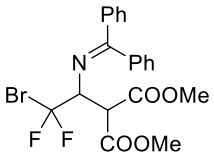
Colorless oil. R_f 0.34 (petroleum ether/EtOAc 95/5). Yield: 71%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.30 (6H, d, J = 6.1 Hz, $CH(C\underline{H}_3)_2$), 1.33 (6H, d, J = 6.1 Hz, $CH(C\underline{H}_3)_2$), 5.13 (1H,

septet, *J* = 6.1 Hz, C<u>H</u>(CH$_3$)$_2$), 5.23 (1H, septet, *J* = 6.1 Hz, C<u>H</u>(CH$_3$)$_2$), 6.92 (1H, t, $J_{H,F}$ = 11.8 Hz, CH). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 21.5 (CH(<u>C</u>H$_3$)$_2$), 21.6 (CH(<u>C</u>H$_3$)$_2$), 70.3 (<u>C</u>H(CH$_3$)$_2$), 70.9 (<u>C</u>H(CH$_3$)$_2$), 114.1 (t, *J* = 302.3 Hz, CF_2Br), 130.8 (t, *J* = 4.6 Hz, <u>C</u>(COO*i*Pr)$_2$), 133.6 (t, *J* = 12.6 Hz, CH), 161.3 and 162.3 (2x C=O). **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ -48.36 (2F, d, $J_{H,F}$ = 11.9 Hz, CF_2Br). **IR** (ATR, cm^{-1}): $\nu_{C=O}$ = 1730, $\nu_{C=C}$ = 1666, ν_{max} = 1257, 1225, 1096, 952. **MS** (ES$^+$): *m/z* (%): 329/31 (M + H$^+$, 40). **HRMS** (ES$^+$): calcd for $C_{11}H_{16}BrF_2O_4^+$: 329.0195, found 329.0194.

5.5.3 Synthesis of 2-[2-bromo-2,2-difluoro-1-(diphenylmethylideneamino)ethyl]-malonates 183

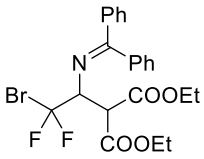
The synthesis of dimethyl 2-[2-bromo-2,2-difluoro-1-(diphenylmethylideneamino)ethyl]malonate **183a** is described as representative. Diphenylmethylideneamine (1.05 equiv, 0.14 g, 0.77 mmol) was added to dimethyl 2-(2-bromo-2,2-difluoroethylidene)malonate **16a** (0.20 g, 0.73 mmol) and this mixture was stirred for one hour at room temperature. After recrystallization from MeOH, pure dimethyl 2-[2-bromo-2,2-difluoro-1-(diphenylmethylideneamino)ethyl]malonate **183a** (0.30 g, 0.66 mmol) was obtained as white crystals.

Dimethyl 2-[2-bromo-2,2-difluoro-1-(diphenylmethylideneamino)ethyl]malonate 183a



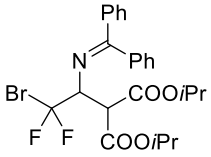
White crystals. Melting point: 69.7-70.7 °C. Yield: 90%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 3.67 (3H, s, OCH_3), 3.72 (3H, s, OCH_3), 4.27 (1H, d, *J* = 8.3 Hz, CH(COOMe)$_2$), 4.77 (1H, ddd, *J* = 8.3 Hz, $J_{H,F}$ = 7.9 Hz, 5.9 Hz, CHN), 7.31-7.65 (10H, m, 10x CH_{arom}). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 52.9 (OCH_3), 53.0 (OCH_3), 54.4 (d, *J* = 3.5 Hz, <u>C</u>H(COOMe)$_2$), 67.6 (t, *J* = 23.1 Hz, CHN), 123.4 (t, *J* = 309.2 Hz, CF_2Br), 128.1 (2x CH_{arom}), 128.3 (2x CH_{arom}), 128.4 (2x CH_{arom}), 129.1 (CH_{arom}), 129.3 (2x CH_{arom}), 131.1 (CH_{arom}), 135.2 ($C_{arom,quat}$), 139.2 ($C_{arom,quat}$), 166.3 and 166.5 (2x C=O), 175.0 (C=N). **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ -50.63 (1F, dd, *J* = 164.9 Hz, $J_{H,F}$ = 7.9 Hz, C<u>F</u>(F)Br), -53.01 (1F, dd, *J* = 164.9 Hz, $J_{H,F}$ = 5.9 Hz, CF(<u>F</u>)Br). **IR** (ATR, cm^{-1}): $\nu_{C=O}$ = 1736, $\nu_{C=N}$ = 1626, ν_{max} = 1284, 1160, 707, 700. **MS** (ES$^+$): *m/z* (%): 454/56 (M + H$^+$, 100). **HRMS** (ES$^+$): calcd for $C_{20}H_{19}BrF_2NO_4^+$: 454.0460, found 454.0442.

Diethyl 2-[2-bromo-2,2-difluoro-1-(diphenylmethylideneamino)ethyl]malonate 183b



White crystals. Melting point: 62-63 °C. R_f 0.30 (petroleum ether/EtOAc 9/1). Yield: 92%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.16 (3H, t, *J* = 7.1 Hz, $OCH_2C\underline{H}_3$), 1.23 (3H, t, *J* = 7.1 Hz, $OCH_2C\underline{H}_3$), 4.04-4.21 (4H, m, 2x OCH_2CH_3), 4.22 (1H, d, *J* = 8.6 Hz, $CH(COOEt)_2$), 4.79 (1H, ddd, *J* = 8.6 Hz, $J_{H,F}$ = 8.1 Hz, 6.4 Hz, CHN), 7.31-7.37 (4H, m, 4x CH_{arom}), 7.39-7.44 (1H, m, CH_{arom}), 7.46-7.52 (3H, m, 3x CH_{arom}), 7.63-7.65 (2H, m, 2x CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 13.9 (CH_3), 14.0 (CH_3), 54.7 (d, *J* = 3.2 Hz, $\underline{C}H(COOEt)_2$), 61.9 (OCH_2), 62.1 (OCH_2), 67.6 (t, *J* = 23.0 Hz, CHN), 123.5 (t, *J* = 309.1 Hz, CF_2Br), 128.0 (2x CH_{arom}), 128.28 (2x CH_{arom}), 128.32 (2x CH_{arom}), 129.0 (CH_{arom}), 129.3 (2x CH_{arom}), 131.0 (CH_{arom}), 135.2 ($C_{arom,quat}$), 139.2 ($C_{arom,quat}$), 165.9 and 166.1 (2x C=O), 174.7 (C=N). **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ -50.60 (1F, dd, *J* = 164.4 Hz, $J_{H,F}$ = 8.1 Hz, $C\underline{F}(F)Br$), -52.97 (1F, dd, *J* = 164.4 Hz, $J_{H,F}$ = 6.4 Hz, $CF(\underline{F})Br$). **IR** (ATR, cm^{-1}): $\nu_{C=O}$ = 1759, $\nu_{C=N}$ = 1625, ν_{max} = 1299, 1270, 1030, 1016, 697. **MS** (ES^+): *m/z* (%): 482/84 (M + H^+, 100). **HRMS** (ES^+): calcd for $C_{22}H_{23}BrF_2NO_4^+$: 482.0773, found 482.0789. **El. Anal.** Calcd for $C_{22}H_{22}BrF_2NO_4$: C 54.79, H 4.60, N 2.90, found C 55.11, H 4.57, N 2.60.

Diisopropyl 2-[2-bromo-2,2-difluoro-1-(diphenylmethylideneamino)ethyl]malonate 183c



White crystals. Melting point: 87-88 °C. Yield: 86%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.13 (6H, d, *J* = 6.6 Hz, $CH(C\underline{H}_3)_2$), 1.20 (3H, d, *J* = 6.6 Hz, $CH(C\underline{H}_3)(CH_3)$), 1.23 (3H, d, *J* = 6.6 Hz, $CH(CH_3)(C\underline{H}_3)$), 4.15 (1H, d, *J* = 8.3 Hz, $CH(COO\textit{i}Pr)_2$), 4.81 (1H, ddd, *J* = 8.3 Hz, $J_{H,F}$ = 8.1 Hz, 6.3 Hz, CHN). **^{13}C NMR** (75 MHz, ref = $CDCl_3$): 21.55 (CH_3), 21.63 (2x CH_3), 21.8 (CH_3), 55.2 ($\underline{C}H(COO\textit{i}Pr)_2$), 67.6 (t, *J* = 23.1 Hz, CHN), 69.7 ($\underline{C}H(CH_3)_2$), 69.8 ($\underline{C}H(CH_3)_2$), 123.7 (t, *J* = 309.2 Hz, CF_2Br), 128.1 (2x CH_{arom}), 128.4 (2x CH_{arom}), 128.5 (2x CH_{arom}), 129.1 (CH_{arom}), 129.5 (2x CH_{arom}), 131.1 (CH_{arom}), 135.4 ($C_{arom,quat}$), 139.4 ($C_{arom,quat}$), 165.7 and 165.9 (2x C=O), 174.6 (C=N). **^{19}F NMR** (282 MHz, $CDCl_3$, ref = $CFCl_3$): δ -50.69 (1F, dd, *J* = 163.8 Hz, $J_{H,F}$ = 8.1 Hz, $C\underline{F}(F)Br$), -53.06 (1F, dd, *J* = 163.8 Hz, $J_{H,F}$ = 6.3 Hz, $CF(\underline{F})Br$). **IR** (ATR, cm^{-1}): $\nu_{C=O}$ = 1754, $\nu_{C=N}$ = 1626, ν_{max} = 1286, 1269, 1094, 1033, 692. **MS** (ES^+): *m/z* (%) = 510/12 (M + H^+, 100). **HRMS** (ES^+) calcd for $C_{24}H_{27}BrF_2NO_4^+$: 510.1086, found 510.1085. **El. Anal.** Calcd for $C_{24}H_{26}BrF_2NO_4$: C 56.48, H 5.14, N 2.74, found C 56.58, H 4.96, N 2.69.

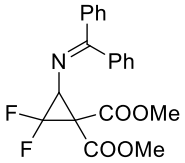
5.5.4 Synthesis of 2,2-difluoro-3-(diphenylmethylideneamino)cyclopropane-1,1-dicarboxylates 184

The synthesis of dimethyl 2,2-difluoro-3-(diphenylmethylideneamino)cyclopropane-1,1-dicarboxylate **184a** is described as representative. Dimethyl 2-[2-bromo-2,2-difluoro-1-(diphenylmethylideneamino)-

ethyl]malonate **183a** (0.28 g, 1.03 mmol) was dissolved in dry THF (5 mL) and KO*t*Bu (1M in THF, 1.1 equiv, 1.13 mmol, 1.13 mL) was added. This mixture was stirred at reflux temperature for one hour after which it was poured in H_2O (5 mL) and extracted with EtOAc (3x 5 mL). The organic fractions were dried ($MgSO_4$), filtered and evaporated *in vacuo*. After flash column chromatography, pure dimethyl 2,2-difluoro-3-(diphenylmethylideneamino)cyclopropane-1,1-dicarboxylate **184a** (0.077 g, 0.22 mmol) was obtained.

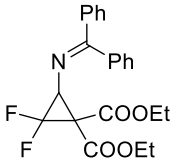
Due to the instability of cyclopropanes **184**, no full characterization could be obtained.

Dimethyl 2,2-difluoro-3-(diphenylmethylideneamino)cyclopropane-1,1-dicarboxylate 184a



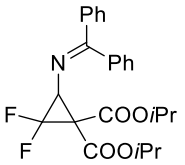
Yellow oil. R_f 0.14 (petroleum ether/EtOAc 8/2). Yield: 20%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.75 (3H, s, OCH_3), 4.09 (3H, s, OCH_3), 5.64 (1H, dd, $J_{H,F}$ = 15.1 Hz, 2.7 Hz, CHN), 7.28-7.31 (2H, m, 2x CH_{arom}), 7.36-7.40 (2H, m, 2x CH_{arom}), 7.46-7.48 (1H, m, 1x CH_{arom}), 7.49-7.52 (3H, m, 3x CH_{arom}), 7.70-7.72 (2H, m, 2x CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 50.9 (OCH_3), 57.2 (OCH_3), 95.7 (dd, *J* = 41.4 Hz, 22.6 Hz, CHN), 125.0 (dd, *J* = 248.8 Hz, 240.8 Hz, CF_2), 129.9 (2x CH_{arom}), 128.3 (2x CH_{arom}), 128.7 (2x CH_{arom}), 129.6 (2x CH_{arom}), 129.8 (CH_{arom}), 131.8 (CH_{arom}), 135.1 ($C_{arom,quat}$), 138.0 ($C_{arom,quat}$), 162.7 (t, *J* = 3.6 Hz, C=O), 170.6 (dd, *J* = 9.0 Hz, 6.2 Hz, C=O), 175.1 (C=N). $\underline{C}(COOMe)_2$: not visible. **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ -81.57 (1F, dd, *J* = 237.0 Hz, $J_{H,F}$ = 15.1 Hz, C$\underline{F}$(F)), -95.55 (1F, dd, *J* = 237.0 Hz, $J_{H,F}$ = 2.7 Hz, CF($\underline{F}$)). **LC-MS** (ES^+): *m/z* (%) = 374 ($M + H^+$, 100).

Diethyl 2,2-difluoro-3-(diphenylmethylideneamino)cyclopropane-1,1-dicarboxylate 184b



Yellow oil. R_f 0.36 (petroleum ether/EtOAc 7/3). Yield: 22%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.27 (3H, t, *J* = 7.2 Hz, CH_3), 1.46 (3H, t, *J* = 7.2 Hz, CH_3), 4.19-4.26 (2H, m, OCH_2), 4.41-4.54 (2H, m, OCH_2), 5.61 (1H, dd, $J_{H,F}$ = 15.3 Hz, 2.2 Hz, CHN), 7.26-7.51 (8H, m, 8x CH_{arom}), 7.69-7.71 (2H, m, 2x CH_{arom}). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 14.5 (CH_3), 14.8 (CH_3), 59.5 (OCH_2), 67.1 (OCH_2), 95.5 (dd, *J* = 41.5 Hz, 23.1 Hz, CHN), 125.1 (dd, *J* = 246.9 Hz, 240.0 Hz, CF_2), 128.0 (2x CH_{arom}), 128.3 (2x CH_{arom}), 128.7 (2x CH_{arom}), 129.6 (2x CH_{arom}), 129.8 (CH_{arom}), 131.7 (CH_{arom}), 135.2 ($C_{arom,quat}$), 138.2 ($C_{arom,quat}$), 162.5 (C=O), 170.4 (dd, *J* = 8.7 Hz, 6.3 Hz, C=O), 174.9 (C=N). $\underline{C}(COOEt)_2$: not visible. **^{19}F NMR** (282 MHz, $CDCl_3$, ref = $CFCl_3$): δ -80.83 (1F, dd, *J* = 238.1 Hz, $J_{H,F}$ = 15.3 Hz, C$\underline{F}$(F)), -95.42 (1F, d, *J* = 238.1 Hz, CF($\underline{F}$)). **LC-MS** (ES^+): *m/z* (%) = 402 ($M + H^+$, 100).

Diisopropyl 2,2-difluoro-3-(diphenylmethylideneamino)cyclopropane-1,1-dicarboxylate 184c

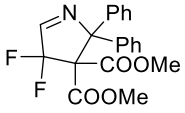


Yellow oil. R_f 0.15 (petroleum ether/EtOAc 93/7). Yield: 56%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.25 (3H, d, *J* = 6.2 Hz, CH(C<u>H</u>$_3$)(CH$_3$)), 1.26 (3H, d, *J* = 6.2 Hz, CH(CH$_3$)(C<u>H</u>$_3$)), 1.41 (3H, d, *J* = 6.2 Hz, CH(C<u>H</u>$_3$)(CH$_3$)), 1.49 (3H, d, *J* = 6.2 Hz, CH(CH$_3$)(C<u>H</u>$_3$)), 5.05-5.16 (2H, m, 2x C<u>H</u>(CH$_3$)$_2$), 5.58 (1H, dd, $J_{H,F}$ = 15.0 Hz, 2.2 Hz, CHN), 7.29-7.32 (2H, m, 2x CH$_{arom}$), 7.34-7.39 (2H, m, 2x CH$_{arom}$), 7.45-7.46 (1H, m, CH$_{arom}$), 7.50-7.51 (3H, m, 3x CH$_{arom}$), 7.68-7.71 (2H, m, 2x CH$_{arom}$). **^{13}C NMR** (100.6 MHz, ref = $CDCl_3$): δ 22.00, 22.04, 22.3 and 22.4 (4x CH$_3$), 66.6 (OCH), 76.0 (OCH), 95.3 (dd, *J* = 41.3 Hz, 22.5 Hz, CHN), 125.2 (dd, *J* = 249.8 Hz, 242.5 Hz, CF$_2$), 128.1 (2x CH$_{arom}$), 128.3 (2x CH$_{arom}$), 128.7 (2x CH$_{arom}$), 129.6 (2x CH$_{arom}$), 129.8 (CH$_{arom}$), 131.6 (CH$_{arom}$), 135.1 (C$_{arom,quat}$), 138.2 (C$_{arom,quat}$), 162.2 (t, *J* = 3.4 Hz, C=O), 170.0 (dd, *J* = 8.9 Hz, 6.0 Hz, C=O), 174.6 (C=N). <u>C</u>(COO*i*Pr)$_2$: not visible. **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ -81.41 (1F, dd, *J* = 238.4 Hz, 15.0 Hz, C<u>F</u>(F)), -96.58 (1F, d, *J* = 238.4 Hz, CF(<u>F</u>)). **IR** (ATR, cm^{-1}): $\nu_{C=O}$ = 1709, $\nu_{C=N}$ = 1617, ν_{max} = 1430, 1321, 1069, 983, 697. **LC-MS** (ES$^+$): *m/z* (%) = 430 (M + H$^+$, 100).

5.5.5 Synthesis of 3,3-difluoro-5,5-diphenyl-1-pyrroline-4,4-dicarboxylates 185

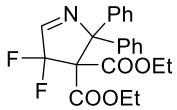
The synthesis of dimethyl 3,3-difluoro-5,5-diphenyl-1-pyrroline-4,4-dicarboxylate **185a** is described as representative. Dimethyl 2-[2-bromo-2,2-difluoro-1-(diphenylmethylideneamino)ethyl]malonate **183a** (0.50 g, 1.85 mmol) was dissolved in dry THF (20 mL) and KO*t*Bu (1M in THF, 1.1 equiv, 2.04 mmol, 2.04 mL) was added. This mixture was stirred at reflux temperature for five hours after which it was poured in H_2O (20 mL) and extracted with EtOAc (3x 20 mL). The organic fractions were dried ($MgSO_4$), filtered and evaporated *in vacuo*. After flash column chromatography, pure dimethyl 3,3-difluoro-5,5-diphenyl-1-pyrroline-4,4-dicarboxylate **185a** (0.49 g, 1.18 mmol) was obtained.

Dimethyl 3,3-difluoro-5,5-diphenyl-1-pyrroline-4,4-dicarboxylate 185a



Pale yellow crystals. Melting point: 93-94 °C. R_f 0.27 (petroleum ether/EtOAc 95/5). Yield: 73%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.47 (6H, s, 2x OCH$_3$), 7.22-7.32 (6H, m, 6x CH$_{arom}$), 7.42-7.44 (4H, m, 4x CH$_{arom}$), 8.01 (1H, t, $J_{H,F}$ = 1.8 Hz, HC=N). **^{13}C NMR** (100.6 MHz, ref = $CDCl_3$): δ 53.1 (2x OCH$_3$), 73.1 (t, *J* = 18.6 Hz, <u>C</u>(COOMe)$_2$), 88.7 (C(Ph)$_2$), 126.0 (t, *J* = 261.8 Hz, CF$_2$), 128.0 (2x CH$_{arom}$), 128.1 (4x CH$_{arom}$), 128.5 (4x CH$_{arom}$), 140.4 (2x C$_{arom,quat}$), 156.2 (t, *J* = 27.3 Hz, HC=N), 165.1 (2x C=O). **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): not visible. **IR** (ATR, cm^{-1}): $\nu_{C=O}$ = 1754, $\nu_{C=O}$ = 1732, ν_{max} = 1255, 1175, 1100, 1068, 759, 694. **MS** (ES$^+$): *m/z* (%): 374 (M + H$^+$, 100). **HRMS** (ES$^+$): calcd. for $C_{20}H_{18}F_2NO_4^+$: 374.1198, found 374.1199.

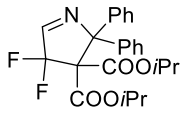
Diethyl 3,3-difluoro-5,5-diphenyl-1-pyrroline-4,4-dicarboxylate 185b



Pale yellow crystals. Melting point: 63-64 °C. R_f 0.42 (petroleum ether/EtOAc 7/3). Yield: 39%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.00 (6H, t, *J* = 7.2 Hz, 2x CH_3), 3.82-4.01 (4H, m, 2x OCH_2), 7.23-7.46 (10H, m, 10x CH_{arom}), 8.01 (1H, t, $J_{H,F}$ = 1.9 Hz, HC=N). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 13.4 (2x CH_3), 62.4 (2x OCH_2), 72.9 (t, *J* = 18.5 Hz, $\underline{C}(COOEt)_2$), 88.4 ($C(Ph)_2$), 126.0 (t, *J* = 261.9 Hz, CF_2), 127.8 (2x CH_{arom}), 127.9 (4x CH_{arom}), 128.5 (4x CH_{arom}), 140.5 (2x $C_{arom,quat}$), 156.2 (t, *J* = 28.3 Hz, HC=N), 164.4 (2x C=O). **^{19}F NMR** (282 MHz, $CDCl_3$). not visible. **IR** (ATR, cm^{-1}): $\nu_{C=O}$ = 1734, ν_{max} = 1244, 761, 698. **MS** (ES^+): *m/z* (%): 402 ($M + H^+$, 100). **HRMS** (ES^+): calcd. for $C_{22}H_{22}F_2NO_4^+$: 402.1511, found 402.1510.

Diisopropyl 3,3-difluoro-5,5-diphenyl-1-pyrroline-4,4-dicarboxylate 185c

This compound was obtained in 66% purity (mixture with benzophenone)

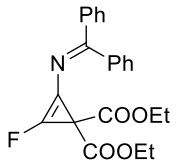


Yellow oil. R_f 0.35 (petroleum ether/EtOAc 9/1). Crude yield: 45% (66% purity). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.90 (6H, br s, $CH(C\underline{H}_3)_2$), 1.04 (2H, d, *J* = 6.3 Hz, $CH(C\underline{H}_3)_2$), 4.74-4.83 (2H, m, 2x $C\underline{H}(CH_3)_2$), 7.24-7.29 (6H, m, 6x CH_{arom}), 7.41-7.48 (4H, m, 4x CH_{arom}), 8.00 (1H, br s, HC=N). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 20.9 ($CH(\underline{C}H_3)_2$), 21.0 ($CH(\underline{C}H_3)_2$), 70.5 (2x $\underline{C}H(CH_3)_2$), 72.7 (t, *J* = 17.8 Hz, $\underline{C}(COO\textit{i}Pr)_2$), 88.2 ($C(Ph)_2$), 126.0 (t, *J* = 261.4 Hz, CF_2), 127.7 (2x CH_{arom}), 127.9 (4x CH_{arom}), 128.5 (4x CH_{arom}), 140.7 (2x $C_{arom,quat}$), 156.3 (t, *J* = 28.2 Hz, HC=N), 163.8 (2x C=O). **^{19}F NMR** (376.5 MHz, $CDCl_3$). not visible.

5.5.6 Synthesis of 2-fluoro-3-(diphenylmethylideneamino)cycloprop-2-ene-1,1-dicarboxylates 186

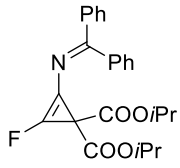
The synthesis of diethyl 2-fluoro-3-(diphenylmethylideneamino)cycloprop-2-ene-1,1-dicarboxylate **186b** is described as representative. To a solution of diethyl 2-[2-bromo-2,2-difluoro-1-(diphenylmethylideneamino)ethyl]malonate **183b** (0.67 g, 1.38 mmol) in dry THF (30 mL), was added KO*t*Bu (1M in THF, 1.1 equiv, 1.52 mmol, 1.52 mL). This mixture was stirred at reflux temperature for one hour after which it was poured in H_2O (20 mL) and extracted with EtOAc (3x 20 mL). The organic fractions were dried ($MgSO_4$), filtered and evaporated *in vacuo*. After flash column chromatography, pure dimethyl 2-(diphenylmethylideneamino)-3-fluorocycloprop-2-ene-1,1-dicarboxylate **186b** (53 mg, 0.14 mmol) was obtained.

Diethyl 2-fluoro-3-(diphenylmethylideneamino)cycloprop-2-ene-1,1-dicarboxylate 186b



White crystals. R_f 0.25 (petroleum ether/EtOAc 9/1). Yield: 10%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.09 (3H, t, *J* = 7.1 Hz, CH_3), 1.31 (3H, t, *J* = 7.1 Hz, CH_3), 3.66 (2H, q, *J* = 7.1 Hz, OCH_2), 4.27 (2H, q, *J* = 7.1 Hz, OCH_2), 7.28-7.48 (8H, m, 8x CH_{arom}), 7.65-7.72 (2H, m, 2x CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 14.3 (CH_3), 14.8 (CH_3), 60.1 (OCH_2), 66.4 (OCH_2), 86.4 (d, *J* = 15.8 Hz, $\underline{C}(COOEt)_2$) 128.2, 128.4 and 130.0 (10x CH_{arom}), 129.6 (d, *J* = 18.3 Hz, $\underline{C}$=CF), 139.5 (2x $C_{arom,quat}$), 143.5 (d, *J* = 269.2 Hz, CF), 154.5 (d, *J* = 5.9 Hz, C=N), 156.9 (d, *J* = 10.2 Hz, C=O), 161.1 (d, *J* = 4.2 Hz, C=O). **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ -151.97 (1F, s, CF). **IR** (ATR, cm^{-1}) $\nu_{C=O}$ = 1698, $\nu_{C=N}$ = 1637, ν_{max} = 1489, 1463, 1109, 1067, 776, 694. **MS** (ES^+): *m/z* (%): 382 (M + H^+, 100). **HRMS** (ES^+): calcd. for $C_{22}H_{21}FNO_4^+$: 382.1449, found 382.1453.

Diisopropyl 2-fluoro-3-(diphenylmethylideneamino)cycloprop-2-ene-1,1-dicarboxylate 186c



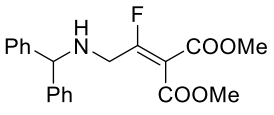
White crystals. R_f 0.32 (petroleum ether/EtOAc 93/7). Yield: 10%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.06 (6H, d, *J* = 6.2 Hz, $CH(C\underline{H}_3)_2$), 1.29 (6H, d, *J* = 6.2 Hz, $CH(C\underline{H}_3)_2$), 3.96 (1H, septet, *J* = 6.2 Hz, CH), 5.13 (1H, septet, *J* = 6.2 Hz, CH), 7.28-7.47 (8H, m, 8x CH_{arom}), 7.65-7.71 (2H, m, 2x CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 21.9 ($C(\underline{C}H_3)_2$), 22.3 ($C(\underline{C}H_3)_2$), 67.5 ($\underline{C}H(CH_3)_2$), 75.5 ($\underline{C}H(CH_3)_2$), 87.5 (d, *J* = 15.3 Hz, $\underline{C}(COOEt)_2$) 128.2, 128.4 and 139.9 (10x CH_{arom}), 129.5 (d, *J* = 17.9 Hz, $\underline{C}$=CF), 139.6 (2x $C_{arom,quat}$), 143.7 (d, *J* = 269.1 Hz, CF), 154.1 (d, *J* = 5.9 Hz, C=N), 156.5 (d, *J* = 10.3 Hz, C=O), 160.7 (d, *J* = 4.1 Hz, C=O). **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ -152.00 (1F, s, CF). **IR** (ATR, cm^{-1}) $\nu_{C=O}$ = 1708, $\nu_{C=N}$ = 1633, ν_{max} = 1450, 1276, 1229, 1100, 1063, 694. **MS** (ES^+): *m/z* (%): 410 (M + H^+, 100). **HRMS** (ES^+): calcd. for $C_{24}H_{25}FNO_4^+$: 410.1762, found 410.1774.

5.5.7 Synthesis of dimethyl 2-[2-(diphenylmethyleneamino)-1-fluoroethylidene]-malonate 188a and diisopropyl 2-[2-(diphenylmethyleneamino)-1,1-difluoroethyl]-malonate 187c

The synthesis of dimethyl 2-[2-(diphenylmethyleneamino)-1-fluoroethylidene]malonate **188a** is described as representative. To a mixture of pyrroline **185a** (69 mg, 0.19 mmol) in acetonitrile (5 mL) was added $NaCNBH_3$ (2 equiv, 23 mg, 0.37 mmol), acetic acid (2 equiv, 24 mg, 0.37 mmol) and acetyl chloride (2 equiv, 29 mg, 0.37 mmol), and this mixture was stirred at 0 °C for 20 minutes. Subsequently, it was quenched with Na_2CO_3 (5 mL), extracted with EtOAc (3x 5 mL) and the combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure. After column chromatography (SiO_2, PE/EtOAc 9/1), pure

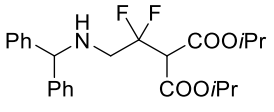
dimethyl 2-[2-(diphenylmethyleneamino)-1-fluoroethylidene]malonate **188a** (19 mg, 0.055 mmol) was obtained.

Dimethyl 2-[2-(diphenylmethyleneamino)-1-fluoroethylidene]malonate 188a



Yellow oil. R_f 0.21 (petroleum ether/EtOAc 9/1). Yield: 29%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.20 (1H, br s, NH), 3.61 (3H, s, CH_3), 3.77 (2H, d, $J_{H,F}$ = 21.4 Hz, CH_2), 3.84 (3H, s, CH_3), 4.89 (1H, s, CH), 7.19-7.24 (2H, m, 2x CH_{arom}), 7.26-7.31 (4H, m, 4x CH_{arom}), 7.39-7.41 (4H, m, 4x CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 45.6 (d, J = 23.3 Hz, $\underline{C}H_2CF$), 52.5 (CH_3), 52.8 (CH_3), 66.0 (CH), 112.3 (d, J = 19.1 Hz, CF=$\underline{C}$), 127.3, 127.4 and 128.6 (10x CH_{arom}), 142.9 (2x $C_{arom,quat}$), 162.9 (d, J = 2.2 Hz, C=O), 163.3 (C=O), 172.3 (d, J = 286.5 Hz, CF). **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ -81.66 (1F, t, $J_{H,F}$ = 21.4 Hz, CF). **IR**, **MS** and **HRMS** data could not be obtained due to instability of compound **184**.

Diisopropyl 2-[2-(diphenylmethyleneamino)-1,1-difluoroethyl]malonate 187c

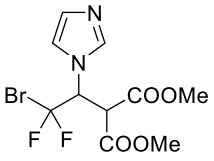


Yellow oil. R_f 0.12 (petroleum ether/EtOAc 95/5). Yield: 18%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.21 (6H, d, J = 6.6 Hz, 2x $CHC\underline{H}_3(CH_3)$), 1.23 (6H, d, J = 6.6 Hz, 2x $CHCH_3(C\underline{H}_3)$), 1.92 (1H, s, NH), 3.23 (2H, t, $J_{H,F}$ = 14.6 Hz, CH_2), 4.28 (1H, t, $J_{H,F}$ = 13.2 Hz, $CHCF_2$), 4.88 (1H, s, $CHPh_2$), 5.06 (2H, septet, J = 6.3 Hz, 2x $C\underline{H}(CH_3)_2$), 7.16-7.36 (10H, m, 10x CH_{arom}). **^{19}F NMR** (282 MHz, $CDCl_3$): δ -102.15 (2F, q, $J_{H,F}$ = 14.0 Hz, CF_2). **IR**, **MS** and **HRMS** data could not be obtained due to instability of compound **187c**.

5.5.8 Synthesis of 2-[2-bromo-2,2-difluoro-1-(1*H*-imidazol-1-yl)ethyl]malonates 192

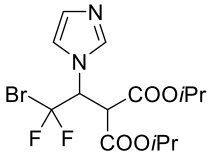
The synthesis of dimethyl 2-[2-bromo-2,2-difluoro-1-(1*H*-imidazol-1-yl)ethyl]malonate **192a** is described as representative. To a solution of dimethyl 2-bromo-2,2-difluoroethylidenemalonate **16a** (0.48 g, 1.76 mmol) in *tert*-butanol (25 mL) were added imidazole (1 equiv, 0.12 g, 1.76 mmol) and triethylamine (1 equiv, 0.18 g, 1.76 mmol), and this mixture was stirred at reflux temperature for three hours. After removal of the solvent *in vacuo*, dichloromethane (20 mL) was added and this mixture was washed with brine (20 mL). The organic layer was dried with $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was recrystallized from Et_2O, affording pure dimethyl 2-[2-bromo-2,2-difluoro-1-(1*H*-imidazol-1-yl)ethyl]malonate **192a** (0.40 g, 1.18 mmol).

Dimethyl 2-[2-bromo-2,2-difluoro-1-(1*H*-imidazol-1-yl)ethyl]malonate 192a



Pale yellow crystals. Melting point: 88-89 °C. Yield: 67%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 3.56 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 4.24 (1H, d, *J* = 10.5 Hz, C<u>H</u>$(COOMe)_2$), 5.49 (1H, ddd, $J_{H,F}$ = 15.9 Hz, *J* = 10.5 Hz, $J_{H,F}$ = 3.6 Hz, CHN), 7.01 (1H, d, *J* = 1.1 Hz, CH_{arom}), 7.10 (1H, s, CH_{arom}), 7.63 (1H, s, CH_{arom}). **^{13}C NMR** (75 MHz, ref = $CDCl_3$): δ 52.5 (<u>C</u>$(COOMe)_2$), 53.7 (OCH_3), 54.0 (OCH_3), 64.3 (dd, *J* = 28.3 Hz, 23.7 Hz, <u>C</u>HCF_2Br), 118.6 (CH_{arom}), 120.4 (t, *J* = 310.4 Hz, CF_2Br), 130.4 (CH_{arom}), 138.7 (CH_{arom}), 164.4 (C=O), 165.2 (C=O). **^{19}F NMR** (282 MHz, $CDCl_3$): δ -52.30 (1F, dd, *J* = 173.6 Hz, $J_{H,F}$ = 3.6 Hz, C<u>F</u>(F)Br), -56.33 (1F, dd, *J* = 173.6 Hz, $J_{H,F}$ = 15.9 Hz, CF(<u>F</u>)Br). **IR** (ATR, cm^{-1}): $\nu_{C=O}$ = 1743, ν_{max} = 1285, 1251, 1230. **MS** (ES^+): *m/z* (%): 341/43 (M + H^+, 100). **HRMS** (ES^+): calcd. for $C_{10}H_{12}BrF_2N_2O_4^+$: 340.9943, found 340.9933. **El. Anal.** Calcd for $C_{10}H_{11}BrF_2N_2O_4$: C 35.21, H 3.25, N 8.21, found C 35.19, H 3.10, N 8.12.

Diisopropyl 2-[2-bromo-2,2-difluoro-1-(1*H*-imidazol-1-yl)ethyl]malonate 192b



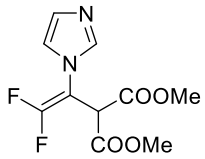
White crystals. Melting point: 76-77 °C. Yield: 57%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.05 (3H, d, *J* = 6.3 Hz, CHC<u>H</u>$_3$(CH_3)), 1.08 (3H, d, *J* = 6.3 Hz, $CHCH_3$(C<u>H</u>$_3$)), 1.28 (3H, d, *J* = 6.3 Hz, CHC<u>H</u>$_3$(CH_3)), 1.30 (3H, d, *J* = 6.3 Hz, $CHCH_3$(C<u>H</u>$_3$)), 4.14 (1H, d, *J* = 10.5 Hz, CH$(COOiPr)_2$), 4.83 (1H, septet, *J* = 6.3 Hz, C<u>H</u>$(CH_3)_2$), 5.12 (1H, septet, *J* = 6.3 Hz, C<u>H</u>$(CH_3)_2$), 5.46 (1H, ddd, $J_{H,F}$ = 15.8 Hz, *J* = 10.5 Hz, $J_{H,F}$ = 3.2 Hz, CHN), 7.02 (1H, s, CH_{arom}), 7.09 (1H, s, CH_{arom}), 7.63 (1H, s, CH_{arom}). **^{13}C NMR** (100.6 MHz, ref = $CDCl_3$): δ 21.1 (CH<u>C</u>H$_3$(CH_3)), 21.2 ($CHCH_3$(<u>C</u>H$_3$)), 21.39 (CH<u>C</u>H$_3$(CH_3)), 21.43 ($CHCH_3$(<u>C</u>H$_3$)), 53.3 (<u>C</u>H$(COOiPr)_2$), 64.0 (dd, *J* = 27.9 Hz, 24.2 Hz, CHN), 70.9 (<u>C</u>H$(CH_3)_2$), 71.1 (<u>C</u>H$(CH_3)_2$), 118.6 (d, *J* = 1.5 Hz, CH_{arom}), 120.6 (dd, *J* = 311.1 Hz, 309.8 Hz, CF_2Br), 130.1 (CH_{arom}), 138.6 (CH_{arom}), 163.3 (C=O), 164.1 (C=O). **^{19}F NMR** (282 MHz, $CDCl_3$): δ -51.75 (1F, dd, *J* = 172.7 Hz, $J_{H,F}$ = 3.2 Hz, C<u>F</u>(F)Br), -56.02 (1F, dd, *J* = 172.7 Hz, $J_{H,F}$ = 15.8 Hz, CF(<u>F</u>)Br). **IR** (ATR, cm^{-1}): $\nu_{C=O}$ = 1723, ν_{max} = 1228, 1182, 936, 787, 644. **MS** (ES^+): *m/z* (%): 397/99 (M + H^+, 100). **HRMS** (ES^+): calcd. for $C_{14}H_{20}BrF_2N_2O_4^+$: 397.0569, found 397.0563. **El. Anal.** Calcd for $C_{14}H_{19}BrF_2N_2O_4$: C 42.33, H 4.82, N 7.05, found C 42.43, H 4.77, N 7.23.

5.5.9 Synthesis of 2-[2,2-difluoro-1-(1*H*-imidazol-1-yl)vinyl]malonates 194

The synthesis of dimethyl 2-[2,2-difluoro-1-(1*H*-imidazol-1-yl)vinyl]malonate **194a** is described as representative. To a solution of dimethyl 2-[2-bromo-2,2-difluoro-1-(1*H*-imidazol-1-yl)ethyl]malonate **192a** (0.138 g, 0.41 mmol) in dry THF (5 mL) was added KO*t*Bu (1M in THF, 1.5 equiv, 0.61 mmol, 0.61 mL). This mixture was stirred at reflux temperature for one hour, after which extra KO*t*Bu (1M in THF, 1.5 equiv,

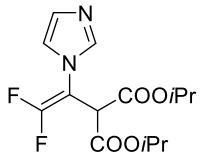
0.61 mmol, 0.61 mL) was added and the stirring was continued for another two hours. The reaction mixture was poured in a saturated aqueous solution of NH_4Cl (10 mL) and extracted with EtOAc (3x 10 mL). After drying of the combined organic layers with $MgSO_4$, the drying agent was filtered off and the solvent was removed *in vacuo*. Purification using preparative TLC afforded dimethyl 2-[2,2-difluoro-1-(1*H*-imidazol-1-yl)vinyl]malonate **194a** (30 mg, 0. 12 mmol) as a colorless oil.

Dimethyl 2-[2,2-difluoro-1-(1*H*-imidazol-1-yl)vinyl]malonate 194a



Colorless oil. R_f 0.35 (petroleum ether/EtOAc 1/1). Yield: 29%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.76 (6H, s, 2x OCH_3), 4.54 (1H, d, $J_{H,F}$ = 1.8 Hz, $CH(COOMe)_2$), 7.03 (1H, s, CH_{arom}), 7.10 (1H, s, CH_{arom}), 7.57 (1H, s, CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 51.2 (d, J = 2.4 Hz, $\underline{C}H(COOMe)_2$), 53.5 (2x OCH_3), 91.3 (dd, J = 38.8 Hz, 19.9 Hz, $\underline{C}CF_2$), 120.7 (CH_{arom}), 129.8 (CH_{arom}), 138.7 (CH_{arom}), 156.6 (dd, J = 298.0 Hz, 294.0 Hz, CF_2), 165.7 (t, J = 2.8 Hz, 2x C=O). **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ -85.54 (1F, d, J = 23.2 Hz, $C\underline{F}(F)$), -90.33 (1F, dd, J = 23.2 Hz, $J_{H,F}$ = 1.8 Hz, $CF(\underline{F})$). **IR** (ATR, cm^{-1}): $\nu_{C=O}$ = 1737, ν_{max} = 1233, 1155, 1078.

Diisopropyl 2-[2,2-difluoro-1-(1*H*-imidazol-1-yl)vinyl]malonate 194c



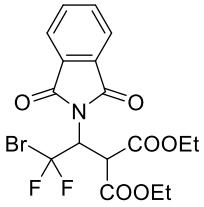
Colorless oil. R_f 0.15 (petroleum ether/EtOAc 8/2). Yield: 49%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.18 (6H, d, J = 6.3 Hz, 2x $CHC\underline{H}_3(CH_3)$), 1.22 (6H, d, J = 6.3 Hz, 2x $CHCH_3(C\underline{H}_3)$), 4.45 (1H, d, $J_{H,F}$ = 2.1 Hz, $CH(COO$*i*$Pr)_2$), 5.04 (2H, septet, J = 6.3 Hz, 2x $C\underline{H}(CH_3)_2$), 7.09 (2H, s, 2x CH_{arom}), 7.60 (1H, s, CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 21.4 (2x $CH\underline{C}H_3(CH_3)$), 21.5 (2x $CHCH_3(\underline{C}H_3)$), 52.0 (d, J = 2.2 Hz, $\underline{C}H(COO$*i*$Pr)_2$), 70.8 (2x $\underline{C}H(CH_3)_2$), 91.6 (dd, J = 39.0 Hz, 19.1 Hz, $\underline{C}CF_2$), 120.9 (CH_{arom}), 129.5 (CH_{arom}), 138.8 (CH_{arom}), 156.4 (dd, J = 297.5 Hz, 293.3 Hz, CF_2), 164.9 (t, J = 2.9 Hz, 2x C=O). **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ -86.32 (1F, d, J = 23.1 Hz, $C\underline{F}(F)$), -91.04 (1F, d, J = 23.1 Hz, $CF(\underline{F})$). **IR** (ATR, cm^{-1}): $\nu_{C=O}$ = 1728, ν_{max} = 1296, 1240, 1096, 960. **MS** (ES^+): *m/z* (%): 317 ($M + H^+$, 100). **HRMS** (ES^+): calcd. for $C_{14}H_{19}F_2N_2O_4^+$: 317.1307, found 317.1317.

5.5.10 Synthesis of 2-[(2-bromo-2,2-difluoro-1-phthalimido)ethyl]malonates 196

The synthesis of diisopropyl 2-[(2-bromo-2,2-difluoro-1-phthalimido)ethyl]malonate **196c** is described as representative. To a solution of diisopropyl 2-bromo-2,2-difluoroethylidenemalonate **16c** (0.25 g, 0.76 mmol) in *tert*-butanol (20 mL) were added potassium phthalimide (1.1 equiv, 0.16 g, 0.84 mmol) and tetramethylammonium bromide (0.05 equiv, 5.8 mg, 0.038 mmol) and this mixture was stirred at reflux temperature for three hours. After evaporation of the solvent under reduced pressure, EtOAc (20 mL) was

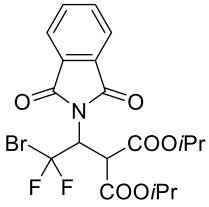
added and this mixture was washed with H_2O (3x 20 mL). The organic layer was dried with $MgSO_4$ and after filtration, evaporation of the solvent *in vacuo* afforded crude malonate **196c**. Purification *via* column chromatography afforded pure diisopropyl 2-[(2-bromo-2,2-difluoro-1-phthalimido)ethyl]malonate **196c** (0.25 mmol, 0.12 g).

Diethyl 2-(2-bromo-2,2-difluoro-1-phthalimidoethyl)malonate 196b



Colorless oil. R_f 0.38 (petroleum ether/EtOAc 9/1). Yield: 28%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.10 (3H, t, *J* = 7.1 Hz, CH_3), 1.33 (3H, t, *J* = 7.1 Hz, CH_3), 3.99-4.13 (2H, m, OCH_2), 4.25-4.36 (2H, m, OCH_2), 4.92 (1H, d, *J* = 11.4 Hz, $CH(COOEt)_2$), 5.62 (1H, ddd, $J_{H,F}$ = 15.9 Hz, *J* = 11.4 Hz, $J_{H,F}$ = 4.2 Hz, CHN), 7.78-7.80 (2H, m, 2x CH_{arom}), 7.86-7.98 (2H, m, 2x CH_{arom}).**^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 13.7 (CH_3), 13.9 (CH_3), 49.4 ($\underline{C}H(COOEt)_2$), 57.7 (dd, *J* = 28.2 Hz, 24.9 Hz, CHN), 62.4 (OCH_2), 62.7 (OCH_2), 121.0 (dd, *J* = 315.6 Hz, 310.2 Hz, CF_2Br), 123.9 (CH_{arom}), 124.2 (2x CH_{arom}), 131.1 ($C_{arom,quat}$), 131.4 ($C_{arom,quat}$), 134.7 (2x CH_{arom}), 165.0 and 165.6 (2x OC=O), 166.5 and 166.8 (2x NC=O) **^{19}F NMR** (376.5 MHz, $CDCl_3$): δ -49.01 (1F, dd, *J* = 167.8 Hz, $J_{H,F}$ = 4.2 Hz, $C\underline{F}(F)$), -50.27 (1F, dd, *J* = 167.8 Hz, $J_{H,F}$ = 15.9 Hz $CF(\underline{F})$). **IR** (ATR, cm^{-1}): $\nu_{C=O}$ = 1726, ν_{max} = 1371, 1281, 1214, 1072, 1020, 718. **MS** (ES^+): *m/z* (%): 465/67 ($M + NH_4^+$, 100). **HRMS** (ES^+): calcd. for $C_{17}H_{20}BrF_2N_2O_6^+$ ($M + NH_4^+$): 465.0467, found 465.0465.

Diisopropyl 2-[(2-bromo-2,2-difluoro-1-phthalimido)ethyl]malonate 196c



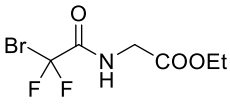
Yellow oil. R_f 0.05 (petroleum ether/EtOAc 9/1). Yield: 33%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.05 (3H, d, *J* = 6.3 Hz, $CHC\underline{H}_3(CH_3)$), 1.10 (3H, d, *J* = 6.3 Hz, $CHCH_3(C\underline{H}_3)$), 1.30 (6H, d, *J* = 6.3 Hz, $CH(C\underline{H}_3)_2$), 4.85 (1H, d, *J* = 11.6 Hz, $CH(COO\textit{i}Pr)_2$), 4.86 (1H, septet, *J* = 6.3 Hz, $C\underline{H}(CH_3)_2$), 5.13 (1H, septet, *J* = 6.3 Hz, $C\underline{H}(CH_3)_2$), 5.60 (1H, ddd, $J_{H,F}$ = 15.6 Hz, *J* = 11.6 Hz, $J_{H,F}$ = 4.3 Hz, CHN), 7.76-7.81 (2H, m, 2x CH_{arom}), 7.86-7.97 (2H, m, 2x CH_{arom}).**^{13}C NMR** (100.6 MHz, ref = $CDCl_3$): δ 21.3 ($CH\underline{C}H_3(CH_3)$), 21.4 ($CHCH_3(\underline{C}H_3)$), 23.5 ($CH(\underline{C}H_3)_2$), 50.0 ($\underline{C}H(COO\textit{i}Pr)_2$), 57.7 (dd, *J* = 28.6 Hz, 25.3 Hz, CHN), 70.2 ($\underline{C}H(CH_3)_2$), 70.6 ($\underline{C}H(CH_3)_2$), 121.2 (dd, *J* = 315.2 Hz, 310.1 Hz, CF_2Br), 123.9 and 124.2 (2x CH_{arom}), 131.2 ($C_{arom,quat}$), 131.6 ($C_{arom,quat}$), 134.8 (2x CH_{arom}), 164.6 and 165.2 (2x OC=O), 166.6 and 167.0 (2x NC=O). **^{19}F NMR** (282 MHz, $CDCl_3$): δ -48.69 (1F, dd, *J* = 167.1 Hz, $J_{H,F}$ = 4.3 Hz, $C\underline{F}(F)$), -50.07 (1F, dd, *J* = 167.1 Hz, $J_{H,F}$ = 15.6 Hz, $CF(\underline{F})$). **IR** (ATR, cm^{-1}): $\nu_{C=O}$ = 1726, ν_{max} = 1375, 1285, 1097, 717. **MS** (ES^+): *m/z* (%): 493/95 ($M + NH_4^+$, 100), 476/78 ($M + H^+$, 20). **HRMS** (ES^+): calcd. for $C_{19}H_{24}BrF_2N_2O_6^+$ ($M + NH_4^+$): 493.0780, found 493.0761.

5.6 Attempted synthesis of 3-fluoro- and 3,3-difluoroazetidine-2-carboxylates

5.6.1 Synthesis of *N*-(2-bromo-2,2-difluoroacetyl)glycinates 200

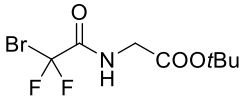
The synthesis of ethyl *N*-(2-bromo-2,2-difluoroacetyl)glycinate **200a** is described as representative. To a solution of ethyl bromodifluoroacetate (2.00 g, 9.9 mmol) in CH_2Cl_2 (50 mL), the hydrochloric acid salt of ethyl glycinate (1 equiv, 1.38 g, 9.9 mmol) and Et_3N (1 equiv, 1.00 g, 9.9 mmol) were added. This mixture was stirred for 17 hours at room temperature after which the solvent was evaporated. Subsequently, Et_2O (50 mL) was added and the solids were filtered off. After removal of the solvent *in vacuo*, the crude reaction product was purified *via* column chromatography affording 1.96 g (7.52 mmol) glycinate **200a**.

Ethyl *N*-(2-bromo-2,2-difluoroacetyl)glycinate 200a



Yellow oil. R_f 0.30 (petroleum ether/EtOAc 6/4). Yield: 76%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.32 (3H, t, *J* = 7.1 Hz, CH_3), 4.12 (2H, d, *J* = 5.0 Hz, NCH_2), 4.12 (2H, q, *J* = 7.1 Hz, OCH_2), 6.78 (1H, br s, NH). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 14.1 (CH_3), 41.6 (NCH_2), 62.2 (OCH_2), 111.3 (t, *J* = 315.0 Hz, CF_2Br), 160.3 (t, *J* = 28.3 Hz, $CF_2Br\underline{C}$=O), 168.5 (C=O). **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ -61.29 (2F, s, CF_2Br). **IR** (ATR, cm^{-1}): ν_{NH} = 3333, $\nu_{C=O}$ = 1747, $\nu_{C=O}$ = 1709, ν_{max} = 1543, 1213, 1175, 1137, 1018, 918. **MS** (ES^+): *m/z* (%): 277/79 (M + NH_4^+, 30). **HRMS** (ES^-): calcd. for $C_6H_7BrF_2NO_3^-$: 257.9583, found 257.9586.

***Tert*-butyl *N*-(2-bromo-2,2-difluoroacetyl)glycinate 200b**



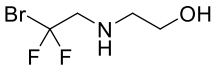
Yellow oil. R_f 0.15 (petroleum ether/EtOAc 9/1). Yield: 88%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.50 (9H, s, $C(CH_3)_3$), 4.07 (2H, d, *J* = 4.9 Hz, NCH_2), 6.74 (1H, br s, NH). **^{13}C NMR** (100.6 MHz, ref = $CDCl_3$): δ 28.0 ($C(\underline{C}H_3)_3$), 42.3 (CH_2), 83.2 ($\underline{C}(CH_3)_3$), 111.6 (t, *J* = 315.5 Hz, CF_2Br), 160.3 (t, *J* = 27.9 Hz, $CF_2Br\underline{C}$=O), 167.6 (C=O). **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ -61.10 (2F, s, CF_2Br). **IR** (ATR, cm^{-1}): ν_{NH} = 3323, $\nu_{C=O}$ = 1708, ν_{max} = 1369, 1231, 1137, 1018, 914. **MS** (ES^+): 305/7 (M + NH_4^+, 100).

5.6.2 Synthesis of 2-(2-bromo-2,2-difluoroethyl)amino-1-ethanol 201

To a solution of ethyl *N*-(2-bromo-2,2-difluoroacetyl)glycinate **200a** (0.50 g, 1.9 mmol) in dry CH_2Cl_2 (10 mL) $BH_3.Me_2S$ (6 equiv, 0.88 g, 11.2 mmol) was added and this mixture was stirred at reflux temperature for 76 hours. Subsequently, it was slowly quenched with a mixture of H_2O and MeOH (1/1, 15 mL) and extracted with CH_2Cl_2 (3x 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and

evaporated *in vacuo*. The crude reaction product was purified using column chromatography affording 0.12 g (0.59 mmol) 2-(2-bromo-2,2-difluoroethyl)amino-1-ethanol **201**.

2-(2-Bromo-2,2-difluoroethyl)amino-1-ethanol 201

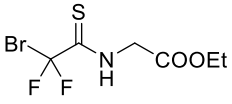


Yellow oil. R_f 0.03 (petroleum ether/EtOAc 9/2). Yield: 31%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.08 (2H, br s, OH and NH), 2.96 (2H, t, J = 5.1 Hz, $CH_2\underline{C}H_2NH$), 3.43 (2H, t, $J_{H,F}$ = 12.5 Hz, CH_2CF_2Br), 3.67 (2H, t, J = 5.1 Hz, $C\underline{H}_2OH$). **^{13}C NMR** (100.6 MHz, ref = $CDCl_3$): δ 50.7 ($CH_2\underline{C}H_2NH$), 59.06 (t, J = 23.7 Hz, $\underline{C}H_2CF_2Br$), 61.2 (OCH_2), 123.4 (t, J = 308.8 Hz, CF_2Br). **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ -51.98 (2F, t, $J_{H,F}$ = 12.5 Hz, CF_2Br). **IR** (ATR, cm^{-1}): ν_{NH} and ν_{OH} = 3347, ν_{max} = 1200, 1131, 1079, 913. **MS** (ES^+): *m/z* (%): 204/6 ($M + H^+$, 100). **HRMS** (ES^+): calcd. for $C_4H_9BrF_2NO^+$: 203.9830, found 203.9829.

5.6.3 Synthesis of ethyl (2-bromo-2,2-difluorothioacetyl)glycinate 202

To a solution of ethyl *N*-(2-bromo-2,2-difluoroacetyl)glycinate **200a** (3.00 g, 1.15 mmol) in dry toluene (50 mL) was added Lawesson's reagent (1.2 equiv, 5.60 g, 13.8 mmol) and this mixture was stirred at reflux temperature for two hours. Subsequently, the solvent was removed under reduced pressure and the residue was purified using column chromatography (PE/EtOAc 9/1), affording pure ethyl (2-bromo-2,2-difluorothioacetyl)glycinate **202** (2.22 g, 8.1 mmol).

Ethyl (2-bromo-2,2-difluorothioacetyl)glycinate 202



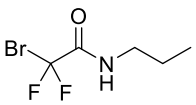
Yellow oil. R_f 0.08 (petroleum ether/EtOAc 9/1). Yield: 70%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.34 (3H, t, J = 7.1 Hz, CH_3), 4.32 (2H, q, J = 7.1 Hz, OCH_2), 4.35 (d, J = 4.3 Hz, CH_2N), 8.38 (1H, s, NH). **^{13}C NMR** (100.6 MHz, ref = $CDCl_3$): δ 14.1 (CH_3), 47.2 (OCH_2), 62.6 (CH_2N), 113.2 (t, J = 309.6 Hz, CF_2Br), 167.8 (C=O), 188.1 (t, J = 27.6 Hz, C=S). **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ -52.59 (2F, s, CF_2Br). **IR** (ATR, cm^{-1}): ν_{NH} = 3303, $\nu_{C=O}$ = 1732, $\nu_{C=S}$ = 1201, ν_{max} = 1092, 1007, 977, 846. **MS**, **HRMS**: M^+ could not be detected.

5.6.4 Synthesis of 2-bromo-2,2-difluoroacetamides 205

The synthesis of *N*-propyl-2-bromo-2,2-difluoroacetamide **205b** is described as representative. To an ice-cooled solution of ethyl bromodifluoroacetate **14** (5.07 g, 25 mmol) in CH_2Cl_2 (40 mL), was added a solution of propylamine (1.77 g, 30 mmol, 1.2 equiv) in CH_2Cl_2 (20 mL). This mixture was allowed to warm to room temperature and after stirring for 15 hours at this temperature, the solvent and excess propylamine were

removed *in vacuo*, affording *N*-propyl-2-bromo-2,2-difluoroacetamide **205b** (5.39 g, 24.8 mmol) in 99% yield.

***N*-Propyl-2-bromo-2,2-difluoroacetamide 205b**



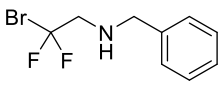
Colorless oil. Yield: 99%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 0.97 (3H, t, *J* = 7.2 Hz, CH_3), 1.63 (2H, sextet, *J* = 7.2 Hz, $CH_2\underline{C}H_2CH_3$), 3.34 (2H, q, *J* = 6.8 Hz, NCH_2), 6.31 (1H, br s, NH). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 11.1 (CH_3), 22.3 ($\underline{C}H_2CH_3$), 41.9 (NCH_2), 111.9 (t, *J* = 316.1 Hz, CF_2Br), 160.3 (t, *J* = 27.1 Hz, C=O). **^{19}F NMR** (282 MHz, $CDCl_3$): δ -60.40 (2F, s, CF_2Br). **IR** (ATR, cm^{-1}): ν_{NH} = 3304, $\nu_{C=O}$ = 1698, ν_{max} = 1542, 1130. **MS** (ES^-): *m/z* (%): 214/16 (M - H^+, 100).

The spectral data of *N*-benzyl-2-bromo-2,2-difluoroacetamide **205a** were in accordance with those reported in the literature.[159]

5.6.5 Synthesis of amines 23

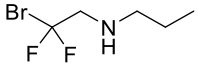
2-Bromo-2,2-difluoroethylamines **23** were synthesized following a literature procedure.[15]

***N*-Benzyl-2-bromo-2,2-difluoroethylamine 23a**



Yellow oil. R_f 0.42 (petroleum ether/EtOAc 9/1). Yield: 85%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.86 (1H, br s, NH), 3.36 (2H, t, $J_{H,F}$ = 12.5 Hz, CH_2CF_2Br), 3.95 (2H, s, $C_{arom,quat}CH_2$), 7.27-7.37 (5H, m, 5x CH_{arom}). **^{13}C NMR** (100.6 MHz, ref = $CDCl_3$): δ 52.8 ($C_{arom,quat}\underline{C}H_2$), 58.3 (t, *J* = 23.5 Hz, $\underline{C}H_2CF_2Br$), 123.7 (t, *J* = 308.9 Hz, CF_2Br), 127.4 (CH_{arom}), 128.1 and 128.6 (4x CH_{arom}), 139.3 ($C_{arom,quat}$). **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ -51.34 (2F, t, $J_{H,F}$ = 12.5 Hz, CF_2Br). **IR** (ATR, cm^{-1}): ν_{NH} = 3360, ν_{max} = 1117, 909, 889, 697. **MS** (ES^+): *m/z* (%): 250/52 (M + H^+, 20), 150 (100). **HRMS** (ES^+): calcd. for $C_9H_{11}BrF_2N^+$: 250.0037, found 250.0036.

***N*-Propyl-2-bromo-2,2-difluoroethylamine 23b**

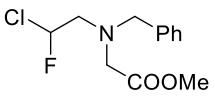


Colorless oil. Yield: 89%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.93 (3H, t, *J* = 7.3 Hz, CH_3), 1.47 (1H, br s, NH), 1.50 (2H, sextet, *J* = 7.3 Hz, $CH_2\underline{C}H_2CH_3$), 2.72 (2H, t, *J* = 7.3 Hz, $N\underline{C}H_2CH_2$), 3.36 (2H, t, $J_{H,F}$ = 12.6 Hz, CH_2CF_2Br). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 11.5 (CH_3), 23.4 ($\underline{C}H_2CH_3$), 51.2 ($N\underline{C}H_2CH_2$), 59.4 (t, *J* = 23.3 Hz, $\underline{C}H_2CF_2Br$), 123.9 (t, *J* = 309.1 Hz, CF_2Br). **^{19}F NMR** (376.5 MHz, $CDCl_3$): δ -51.15 (2F, t, $J_{H,F}$ = 12.6 Hz, CF_2Br). **IR** (ATR, cm^{-1}): ν_{NH} = 3216, ν_{max} = 1462, 1195, 1094, 904. **MS** (ES^+): *m/z* (%): 202/4 (M + H^+, 100). **HRMS** (ES^+): calcd. for $C_5H_{11}BrF_2N^+$: 202.0037, found 202.0033.

5.6.6 Synthesis of amino esters 209 and 198

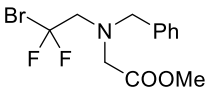
The synthesis of methyl *N*-benzyl-*N*-(2-chloro-2-fluoroethyl)glycinate **209a** is described as representative. To a mixture of *N*-(2-chloro-2-fluoroethyl)benzylamine **208a** (5.00 g, 26.6 mmol) and methyl bromoacetate **207a** (7 equiv, 28.5 g, 187 mmol), was added LiHMDS (1M in THF, 1.1 equiv, 29.3 mL, 29.3 mmol) at 0 °C. This mixture was stirred at room temperature for 23 hours, after which dichloromethane (50 mL) and H_2O (50 mL) were added. After extraction with dichloromethane (2x 30 mL), drying ($MgSO_4$), filtration and evaporation of the solvent under reduced pressure, a mixture of methyl *N*-benzyl-*N*-(2-chloro-2-fluoroethyl)glycinate **209a** and methyl bromoacetate **207a** was obtained. After separation of this mixture (Reveleris Flash Forward, reversed phase chromatography, CH_3CN/H_2O. Gradient: during 2 CV: 20% CH_3CN, during 3 CV: 20 -> 50% CH_3CN, during 8 CV: 50 -> 70% CH_3CN, during 1 CV: 70 -> 100% CH_3CN, during 2 CV: 100% CH_3CN), pure methyl *N*-benzyl-*N*-(2-chloro-2-fluoroethyl)glycinate **209a** (5.46 g, 21.0 mmol) was obtained as a yellow oil.

Methyl *N*-benzyl-*N*-(2-chloro-2-fluoroethyl)glycinate 209a



Yellow oil. Yield: 79%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.21 (1H, ddd, $J_{H,F}$ = 26.2 Hz, J = 15.0 Hz, 3.4 Hz, C<u>H</u>(H)CHClF), 3.37 (1H, ddd, J = 15.0 Hz, $J_{H,F}$ = 14.3 Hz, J = 7.1 Hz, CH(<u>H</u>)CHClF), 3.50 (2H, s, CH_2C=O), 3.71 (3H, s, OCH_3), 3.95 (2H, s, $CH_2C_{arom,quat}$), 6.09 (1H, ddd, $J_{H,F}$ = 51.6 Hz, J = 7.1 Hz, 3.4 Hz, CHClF), 7.27-7.33 (5H, m, 5x CH_{arom}). **^{13}C NMR** (100.6 MHz, ref = $CDCl_3$): δ 51.6 (OCH_3), 54.9 (<u>C</u>H_2C=O), 59.2 (<u>C</u>$H_2C_{arom,quat}$), 61.0 (d, J = 21.4 Hz, <u>C</u>H_2CHClF), 101.6 (d, J = 244.3 Hz, CHClF), 127.7 (CH_{arom}), 128.7 (2x CH_{arom}), 128.9 (2x CH_{arom}), 138.5 ($C_{arom,quat}$), 171.9 (C=O). **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ -137.31 (1F, ddd, $J_{H,F}$ = 51.6 Hz, 26.2 Hz, 14.3 Hz, CHClF). **IR** (ATR, cm^{-1}): $\nu_{C=O}$ = 1739, ν_{max} = 1202, 1164, 1037, 699. **MS** (ES^+): *m/z* (%): 260 ($M + H^+$, 100). **HRMS** (ES^+): calcd. for $C_{12}H_{16}ClFNO_2^+$: 260.0848, found 260.0848.

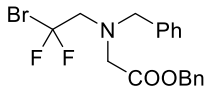
Methyl *N*-benzyl-*N*-(2-bromo-2,2-difluoroethyl)glycinate 198a



Yellow oil. R_f 0.27 (petroleum ether/EtOAc 95/5). Yield: 70%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.47 (2H, s, CH_2C=O), 3.59 (2H, t, $J_{H,F}$ = 12.6 Hz, CH_2CBrF_2), 3.69 (3H, s, OCH_3), 4.03 (2H, s, $CH_2C_{arom,quat}$), 7.23-7.35 (5H, m, 5x CH_{arom}). **^{13}C NMR** (100.6 MHz, ref = $CDCl_3$): δ 51.7 (OCH_3), 53.4 (<u>C</u>H_2C=O), 59.1 (<u>C</u>$H_2C_{arom,quat}$), 64.0 (t, J = 23.1 Hz, <u>C</u>H_2CBrF_2), 123.8 (t, J = 309.2 Hz, $CBrF_2$), 127.7 (CH_{arom}), 128.7 (2x CH_{arom}), 128.9 (2x CH_{arom}), 138.2 ($C_{arom,quat}$), 171.8 (C=O). **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ -52.47 (2F, t, $J_{H,F}$ = 12.6 Hz, $CBrF_2$). **IR** (ATR, cm^{-1}): $\nu_{C=O}$ = 1737, ν_{max} = 1202, 1165,

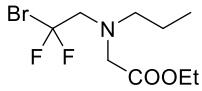
1084, 1022, 924, 698. **MS** (ES^+): *m/z* (%): 322/24 ($M + H^+$, 20), 117 (100). **HRMS** (ES^+): calcd. for $C_{12}H_{15}BrF_2NO_2^+$: 322.0249, found 322.0261.

Benzyl *N*-benzyl-*N*-(2-bromo-2,2-difluoroethyl)glycinate 198c



Yellow oil. R_f 0.48 (petroleum ether/EtOAc 9/1). Yield: 40%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.52 (2H, s, $CH_2C{=}O$), 3.61 (2H, t, $J_{H,F}$ = 12.6 Hz, CH_2CBrF_2), 4.04 (2H, s, $NCH_2C_{arom,quat}$), 5.15 (2H, s, $C{=}OCH_2C_{arom,quat}$), 7.30-7.40 (10H, m, 10x CH_{arom}). **^{13}C NMR** (100.6 MHz, ref = $CDCl_3$): δ 53.4 ($\underline{C}H_2C{=}O$), 58.7 ($N\underline{C}H_2C_{arom,quat}$), 63.6 (t, *J* = 23.1 Hz, $\underline{C}H_2CBrF_2$), 66.2 ($C{=}O\underline{C}H_2C_{arom,quat}$), 123.6 (t, *J* = 309.1 Hz, $CBrF_2$), 128.2, 128.4, 128.5, 128.7 (8x CH_{arom}), 128.9 (CH_{arom}), 129.6 (CH_{arom}), 134.3 ($C_{arom,quat}$), 135.5 ($C_{arom,quat}$), 137.8 ($C_{arom,quat}$), 170.8 (C=O). **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ -52.38 (2F, t, $J_{H,F}$ = 12.6 Hz, $CBrF_2$). **IR** (ATR, cm^{-1}): $\nu_{C=O}$ = 1738, ν_{max} = 1194, 1088, 1023, 697. **MS** (ES^+): *m/z* (%): 398/400 ($M + H^+$, 100). **HRMS** (ES^+): calcd. for $C_{18}H_{19}BrF_2NO_2^+$: 398.0562, found 398.0549.

Ethyl *N*-propyl-*N*-(2-bromo-2,2-difluoroethyl)glycinate 198d



Yellow oil. R_f 0.38 (petroleum ether/EtOAc 9/1). Yield: 64%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.89 (3H, t, *J* = 7.4 Hz, $CH_2CH_2C\underline{H}_3$), 1.28 (3H, t, *J* = 7.1 Hz, $OCH_2C\underline{H}_3$), 1.48 (2H, sextet, *J* = 7.4 Hz, $CH_2C\underline{H}_2CH_3$), 2.76 (2H, t, *J* = 7.4 Hz, $C\underline{H}_2CH_2CH_3$), 3.50 (2H, t, $J_{H,F}$ = 13.1 Hz, CH_2CF_2Br), 3.56 (2H, s, CH2C=O), 4.17 (2H, q, *J* = 7.1 Hz, $OC\underline{H}_2CH_3$). **^{13}C NMR** (100.6 MHz, ref = $CDCl_3$): δ 11.4 ($CH_2CH_2\underline{C}H_3$), 14.4 ($OCH_2\underline{C}H_3$), 21.7 ($CH_2\underline{C}H_2CH_3$), 55.0 ($\underline{C}H_2C{=}O$), 57.4 ($\underline{C}H_2CH_2CH_3$), 60.6 (OCH_2), 64.5 (t, *J* = 22.7 Hz, $\underline{C}H_2CF_2Br$), 123.9 (t, *J* = 309.1 Hz, CF_2Br), 171.5 (C=O). **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ -52.76 (2F, t, $J_{H,F}$ = 13.1 Hz, $CBrF_2$). **IR** (ATR, cm^{-1}): $\nu_{C=O}$ = 1736, ν_{max} = 1188, 1088, 1016, 926, 903. **MS** (ES^+): *m/z* (%): 288/90 ($M + H^+$, 100).

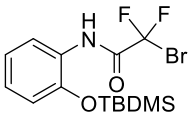
5.7 Synthesis of fluorinated heterocycles by exploring the nucleophilic vinylic substitution (S_NV) reaction of *gem*-difluoroenamides

5.7.1 Synthesis of silyl ethers 260

The synthesis of silyl ether **260a** is given as representative. To a mixture of amide **261a** (2.00 g, 7.5 mmol) and imidazole (1.02 g, 15.0 mmol, 2 equiv) in anhydrous CH_2Cl_2 (40 mL) under N_2 atmosphere, TBDMSCl (1.19 g, 7.9 mmol, 1.05 equiv) was added at room temperature. This mixture was stirred for 17 hours at room temperature. Subsequently, H_2O (40 mL) was added and an extraction was performed with CH_2Cl_2

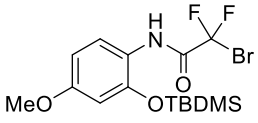
(3x 30 mL). After drying of the combined organic phases ($MgSO_4$), filtration and evaporation of the solvent under reduced pressure, acetamide **260a** was obtained as orange crystals in 95% yield (2.71 g, 7.1 mmol).

***N*-{2-[(*Tert*-butyldimethylsilyl)oxy]phenyl}-2-bromo-2,2-difluoroacetamide 260a**



Orange crystals. Melting point: 56-57 °C. Yield: 95%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 0.30 (6H, s, 2x $SiCH_3$), 1.03 (9H, s, $SiC(CH_3)_3$), 6.88 (1H, dd, *J* = 7.7 Hz, 1.7 Hz, CH_{arom}), 7.01 (1H, ddd, *J* = 7.7 Hz, 7.7 Hz, 1.7 Hz, CH_{arom}), 7.71 (1H, ddd, *J* = 7.7 Hz, 7.7 Hz, 2.2 Hz, CH_{arom}), 8.30 (1H, dd, *J* = 7.7 Hz, 2.2 Hz, CH_{arom}), 8.55 (1H, br s, NH). **^{13}C NMR** (75 MHz, $CDCl_3$): δ -4.4 (2x $SiCH_3$), 18.1 ($SiC(CH_3)_3$), 25.6 ($SiC(CH_3)_3$), 111.6 (t, *J* = 316.1 Hz, CF_2Br), 117.5, 120.2, 121.9 and 125.7 (4x CH_{arom}), 127.3 and 144.7 (2x $C_{arom,quat}$), 156.8 (t, *J* = 27.7 Hz, C=O). **^{19}F NMR** (282 MHz, $CDCl_3$, ref = $CFCl_3$): δ -60.87 (2F, s, CF_2Br). **IR** (ATR, cm^{-1}): ν_{NH} = 3398, $\nu_{C=O}$ = 1717, ν_{max} = 1458, 1100, 783, 752. **MS** (ES^+): *m/z* (%): 380/82 (M + H^+, 100). **HRMS** (ES^+): calcd. for $C_{14}H_{21}BrF_2NO_2Si^+$: 380.0488, found 380.0478.

***N*-{4-Methoxy-2-[(*tert*-butyldimethylsilyl)oxy]phenyl}-2-bromo-2,2-difluoroacetamide 260b**

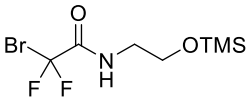


Brown crystals. Melting point: 69-70 °C. R_f 0.36 (petroleum ether/EtOAc 9/1). Yield: 74%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.30 (6H, s, 2x $SiCH_3$), 1.03 (9H, s, $SiC(CH_3)_3$), 3.79 (3H, s, OCH_3), 6.45 (1H, d, *J* = 2.7 Hz, CH_{arom}), 6.55 (1H, dd, *J* = 9.0 Hz, 2.7 Hz, CH_{arom}), 8.30 (1H, d, *J* = 9.0 Hz, CH_{arom}), 8.36 (1H, br s, NH). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ -4.4 (2x $SiCH_3$), 18.1 ($SiC(CH_3)_3$), 25.6 ($SiC(CH_3)_3$), 55.5 (OCH_3), 105.1 and 105.5 (2x CH_{arom}), 111.7 (t, *J* = 316.8 Hz, CF_2Br), 120.8 ($C_{arom,quat}$), 120.9 (CH_{arom}), 145.9 ($C_{arom,quat}$), 156.5 (t, *J* = 27.2 Hz, C=O), 157.4 ($C_{arom,quat}$). **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ -60.61 (2F, s, CF_2Br). **IR** (ATR, cm^{-1}): ν_{NH} = 3404, $\nu_{C=O}$ = 1717, ν_{max} = 1530, 1109, 834. **MS** (ES^+): *m/z* (%): 410/12 (M + H^+, 100). **El. Anal.** Calcd for $C_{15}H_{22}BrF_2NO_3Si$: C 43.91, H 5.40, N 3.41, found C 44.02, H 5.74, N 3.35.

5.7.2 Synthesis of amides 239 and 242

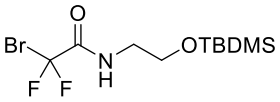
The synthesis of *N*-{2-[(trimethylsilyl)oxy]ethyl}-2-bromo-2,2-difluoroacetamide **239** is described as representative. To a solution of ethyl bromodifluoroacetate **14** (6.92 g, 34.1 mmol) in dry CH_2Cl_2 (170 mL) was added a solution of 2-[(trimethylsilyl)oxy]ethylamine **238** (1.1 equiv, 5.00 g, 37.5 mmol) in dry CH_2Cl_2 (20 mL) at 0 °C. After stirring this reaction mixture at room temperature for 16 hours, the solvent was removed under reduced pressure, affording *N*-{2-[(trimethylsilyl)oxy]ethyl}-2-bromo-2,2-difluoroacetamide **239** (9.51 g, 32.7 mmol).

***N*-{2-[(Trimethylsilyl)oxy]ethyl}-2-bromo-2,2-difluoroacetamide 239**



Yellow oil. Yield: 96%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 0. 14 (9H, s, $Si(CH_3)_3$), 3.49 (2H, q, *J* = 5.3 Hz, CH_2NH), 3.71 (2H, t, *J* = 5.3 Hz, CH_2O), 6.62 (1H, br s, NH). **^{13}C NMR** (100.6 MHz, ref = $CDCl_3$): δ -0.6 ($SiCH_3)_3$), 42.2 (CH_2NH), 60.3 (CH_2O), 111.9 (t, *J* = 315.9 Hz, CF_2Br), 160.7 (t, *J* = 27.1 Hz, C=O). **^{19}F NMR** (282 MHz, $CDCl_3$): δ -60.37 (2F, s, CF_2Br). **IR** (ATR, cm^{-1}): ν_{NH} = 3307, $\nu_{C=O}$ = 1702, ν_{max} = 1542, 1252, 1135, 1099, 933, 838. **MS** (ES^+): *m/z* (%): 290/92 (M + H^+, 10), 102 (100).

***N*-{2-[(*Tert*-butyldimethylsilyl)oxy]ethyl}-2-bromo-2,2-difluoroacetamide 242**

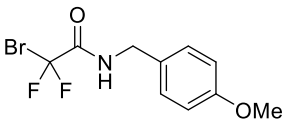


Colorless oil. Yield: 65%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 0.08 (6H, s, 2x $SiCH_3$), 0.90 (9H, s, $SiC(CH_3)_3$), 3.49 (2H, q, *J* = 5.3 Hz, CH_2NH), 3.75 (2H, t, *J* = 5.3 Hz, CH_2O), 6.63 (1H, br s, NH). **^{13}C NMR** (75 MHz, $CDCl_3$): δ -5.5 (2x $SiCH_3$), 18.2 ($SiC(CH_3)_3$), 25.8 ($SiC(\underline{C}H_3)_3$), 42.2 (CH_2NH), 60.8 (CH_2O), 111.9 (t, *J* = 315.6 Hz, CF_2Br), 160.1 (t, *J* = 27.7 Hz, C=O).**^{19}F NMR** (282 MHz, $CDCl_3$): δ -60.34 (2F, s, CF_2Br). **IR** (ATR, cm^{-1}): ν_{NH} = 3313, $\nu_{C=O}$ = 1703, ν_{max} = 1104, 935, 831, 776.

5.7.3 Synthesis of amides 205c, 261 and 269

The synthesis of *N*-(4-methoxybenzyl)-2-bromo-2,2-difluoroacetamide **205c** is given as a representative example. To a solution of ethyl bromodifluoroacetate **14** (2.23 g, 11 mmol) in EtOAc (50 mL), 4-methoxybenzylamine (1.51 g, 11 mmol, 1 equiv) and Et_3N (1.11 g, 11 mmol, 1 equiv) were added, after which the mixture was stirred at reflux temperature for four hours. Subsequently, H_2O (30 mL) was added and an extraction with EtOAc (3 x 30 mL) was performed. After drying of the organic layer ($MgSO_4$), filtration and evaporation of the solvent, yellow crystals were obtained, which were recrystallized from Et_2O affording pure amide **205c** as white crystals in 75% yield.

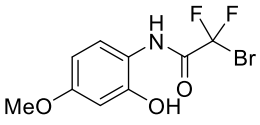
***N*-(4-Methoxybenzyl)-2-bromo-2,2-difluoroacetamide 205c**



White crystals. Melting point: 89-90 °C. R_f 0.05 (petroleum ether/EtOAc 9/1). Yield: 75%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.78 (3H, s, OCH_3), 4.42 (2H, d, *J* = 5.8 Hz, CH_2), 6.79 (1H, br s, NH), 6.87 (2H, d, *J* = 8.7 Hz, 2x CH_{arom}), 7.21 (2H, d, *J* = 8.7 Hz, 2x CH_{arom}). **^{13}C NMR** (100.6 MHz, ref = $CDCl_3$): δ 43.7 (CH_2NH), 55.4 (OCH_3), 111.9 (t, *J* = 316.1 Hz, CF_2Br), 114.4 (2x CH_{arom}), 128.3 ($C_{arom,quat}$), 129.4 (2x CH_{arom}), 159.6 ($C_{arom,quat}$), 160.0 (t, *J* = 27.5 Hz, C=O). **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ -60.99 (2F, s, CF_2Br). **IR** (ATR, cm^{-1}): ν_{NH} = 3233, $\nu_{C=O}$ = 1695, ν_{max} =

1514, 1169, 1125, 820. **MS** (ES^+): *m/z* (%): 311/13 (M + NH_4^+, 20), 221 (100). **HRMS** (ES^-): calcd. for $C_{10}H_9BrF_2NO_2^-$: 291.9790, found 291.9790.

***N*-(2-Hydroxy-4-methoxyphenyl)-2-bromo-2,2-difluoroacetamide 261b**



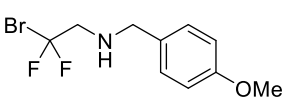
Brown crystals. Melting point: 159-160 °C. Yield: 40%. **^{1}H NMR** (400 MHz, CD_3CN): δ 3.79 (3H, s, OCH_3), 6.53 (1H, dd, *J* = 8.6 Hz, 2.6 Hz, CH_{arom}), 6.56 (1H, d, *J* = 2.6 Hz, CH_{arom}), 7.52 (1H, d, *J* = 8.6 Hz, CH_{arom}), 7.60 (1H, br s, NH or OH), 8.62 (1H, br s, NH or OH). **^{13}C NMR** (100.6 MHz, acetone-d6): δ 55.6 (OCH_3), 102.8 and 105.6 (2x CH_{arom}), 112.9 (t, *J* = 315.5 Hz, CF_2Br), 117.6 ($C_{arom,quat}$), 124.9 (CH_{arom}), 150.9 ($C_{arom,quat}$), 158.5 (t, *J* = 27.1 Hz, C=O), 159.7 ($C_{arom,quat}$). **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ -60.53 (2F, s, CF_2Br). **IR** (ATR, cm^{-1}): ν_{NH} = 3386, ν_{OH} = 3244, $\nu_{C=O}$ = 1685, ν_{max} = 1547, 1151, 1110. **MS** (ES^+): *m/z* (%): 296/98 (M + H^+, 30), 313/15 (M + NH_4^+, 20). **HRMS** (ES^-): calcd. for $C_9H_7BrF_2NO_3^-$: 293.9583, found 293.9572. **El. Anal.** Calcd for $C_9H_8BrF_2NO_3$: C 36.51, H 2.72, N 4.73, found C 36.86, H 2.68, N 4.57.

The spectral data of *N*-(2-hydroxyphenyl)-2-bromo-2,2-difluoroacetamide **261a**[160] and *N*-phenyl-2-bromo-2,2-difluoroacetamide **269**[135] were in accordance with those reported in the literature.

5.7.4 Synthesis of amines 23c, 243, 262 and 270

The synthesis of amine **23c** is given as a representative example. To a solution of *N*-(4-methoxybenzyl)-2-bromo-2,2-difluoroacetamide **205c** (1.94 g, 6.9 mmol) in anhydrous THF (40 mL), borane dimethylsulfide complex (1.58 g, 21 mmol, 3 equiv) was added with a syringe. Subsequently, this mixture was stirred at reflux temperature for 17 hours after which it was slowly quenched with a mixture of water and methanol (H_2O/MeOH : 1/1, 50 mL). After extraction with EtOAc (3x 50 mL), drying ($MgSO_4$), filtration and evaporation of the solvent, the residue was redissolved in MeOH and stirred in the presence of Pd/C (0.05 equiv, 0.35 mmol) at room temperature for two hours. After filtration, the crude amine **23c** was purified by column chromatography (SiO_2, PE/EtOAc 92/8) and obtained in 73% yield (1.41 g, 5.0 mmol).

***N*-(4-Methoxybenzyl)-2-bromo-2,2-difluoroethylamine 23c**

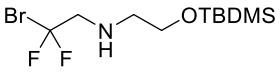


Colorless oil. R_f 0.12 (petroleum ether/EtOAc 92/8). Yield: 73%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.78 (1H, br s, NH), 3.34 (2H, t, $J_{H,F}$ = 12.6 Hz, CH_2CF_2Br), 3.81 (3H, s, OCH_3), 3.88 (2H, s, $C_{arom,quat}CH_2$), 6.88 (2H, d, *J* = 8.8 Hz, 2x CH_{arom}), 7.25 (2H, d, *J* = 8.8 Hz, 2x CH_{arom}). **^{13}C NMR** (100.6 MHz, ref = $CDCl_3$): δ 52.2 ($C_{arom,quat}\underline{C}H_2$), 55.2 ($OCH_3$), 58.1 (t, *J* = 23.5 Hz, $\underline{C}H_2CF_2Br$), 113.9 (2x CH_{arom}), 123.8 (t, *J* = 308.8 Hz, CF_2Br), 129.3 (2x CH_{arom}), 131.3 and 158.9 (2x $C_{arom,quat}$). **^{19}F NMR** (376.5 MHz,

$CDCl_3$, ref = $CFCl_3$): δ -51.23 (2F, t, $J_{H,F}$ = 12.7 Hz, CF_2Br). **IR** (ATR, cm^{-1}): ν_{NH} = 3362, ν_{max} = 1512, 1246, 1033. **MS** (ES^+): *m/z* (%): 121 (100).

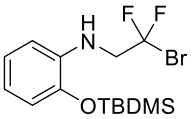
***N*-{2-[(*Tert*-butyldimethylsilyl)oxy]ethyl}-2-bromo-2,2-difluoroethylamine 243**

This compound was synthesized using 6 equivalents $BH_3.Me_2S$ (2nd portion of three equivalents was added after 24 hours) in CH_2Cl_2 for 44 hours.



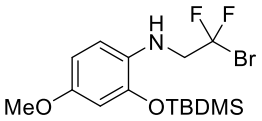
Colorless oil. Yield: 89%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.07 (6H, s, 2x $SiCH_3$), 0.90 (9H, s, $SiC(CH_3)_3$), 1.90 (1H, br s, NH), 2.86 (2H, *t*, *J* = 5.2 Hz, CH_2NH), 3.39 (2H, t, $J_{H,F}$ = 12.6 Hz, CH_2CF_2), 3.70 (2H, t, *J* = 5.2 Hz, CH_2O). **^{13}C NMR** (100.6 MHz, ref = $CDCl_3$): δ -5.3 (2x $SiCH_3$), 18.3 ($SiC(CH_3)_3$), 25.9 ($SiC(CH_3)_3$), 51.1 (CH_2NH), 59.4 (t, *J* = 23.5 Hz, CH_2CF_2), 62.6 (CH_2O), 123.8 (t, *J* = 308.8 Hz, CF_2Br). **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ -51.59 (2F, t, $J_{H,F}$ = 12.6 Hz, CF_2Br). **IR** (ATR, cm^{-1}): ν_{NH} = 3365, ν_{max} = 1088, 906, 830, 773. **MS** (ES^+): *m/z* (%): 318/20 (M + H^+, 100). **HRMS** (ES^+): calcd. for $C_{10}H_{23}BrF_2NOSi^+$ (M + H^+): 318.0695, found 318.0683.

***N*-{2-[(*Tert*-butyldimethylsilyl)oxy]phenyl}-2-bromo-2,2-difluoroethylamine 262a**



Yellow oil. R_f 0.14 (petroleum ether/EtOAc 99/1). Yield: 90%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 0.25 (6H, s, 2x $SiCH_3$), 1.02 (9H, s, $SiC(CH_3)_3$), 3.95 (2H, td, $J_{H,F}$ = 11.8 Hz, *J* = 3.4 Hz, CH_2), 4.65 (1H, br s, NH), 6.65 (1H, ddd, *J* = 7.8 Hz, 7.4 Hz, 1.5 Hz, CH_{arom}), 6.70 (1H, d, *J* = 7.9 Hz, CH_{arom}), 6.77 (1H, dd, *J* = 7.8 Hz, 1.4 Hz, CH_{arom}), 6.87 (1H, ddd, *J* = 7.9 Hz, 7.4 Hz, 1.4 Hz, CH_{arom}). **^{13}C NMR** (75 MHz, ref = $CDCl_3$): δ -4.2 (2x $SiCH_3$), 18.3 ($SiC(CH_3)_3$), 25.9 ($SiC(CH_3)_3$), 54.3 (t, *J* = 25.4 Hz, CH_2CF_2Br), 110.9, 118.0, 118.3 and 122.0 (4x CH_{arom}), 122.6 (t, *J* = 309.2 Hz, CF_2Br), 138.0 and 142.7 (2x $C_{arom,quat}$). **^{19}F NMR** (282 MHz, $CDCl_3$, ref = $CFCl_3$): δ -53.30 (t, $J_{H,F}$ = 11.8 Hz, CF_2Br). **IR** (ATR, cm^{-1}): ν_{NH} = 3446, ν_{max} = 1514, 1254, 916, 781. **MS** (ES^+): *m/z* (%): 366/68 (M + H^+, 100). **HRMS** (ES^+): calcd. for $C_{14}H_{23}BrF_2NOSi^+$: 366.0695, found 366.0702.

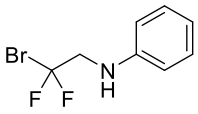
***N*-{4-Methoxy-2-[(*tert*-butyldimethylsilyl)oxy]phenyl}-2-bromo-2,2-difluoroethylamine 262b**



Yellow oil. R_f 0.57 (petroleum ether/EtOAc 9/1). Yield: 95%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.26 (6H, s, 2x $SiCH_3$), 1.02 (9H, s, $SiC(CH_3)_3$), 3.73 (3H, s, OCH_3), 3.89 (2H, td, $J_{H,F}$ = 12.1 Hz, *J* = 7.2 Hz, CH_2), 4.33 (1H, t, *J* = 7.2 Hz, NH), 6.42 (1H, d, *J* = 2.8 Hz, CH_{arom}), 6.44 (1H, dd, *J* = 8.4 Hz, 2.8 Hz, CH_{arom}), 6.62 (1H, d, *J* = 8.4 Hz, CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ -4.3 (2x $SiCH_3$), 18.2 ($SiC(CH_3)_3$), 25.8 ($SiC(CH_3)_3$), 55.1 (t, *J* = 24.9 Hz, CH_2CF_2Br), 55.6 (OCH_3), 105.5, 106.2 and 111.5 (3x CH_{arom}), 122.6 (t, *J* = 309.2 Hz, CF_2Br), 132.1, 143.6 and 152.5 (3x $C_{arom,quat}$). **^{19}F NMR** (376.5

MHz, $CDCl_3$, ref = $CFCl_3$): δ -53.13 (2F, t, $J_{H,F}$ = 12.1 Hz, CF_2Br). **IR** (ATR, cm^{-1}): ν_{NH} = 3442, ν_{max} = 1518, 1163, 837, 780. **MS** (ES^+): *m/z* (%): 396/98 ($M + H^+$, 100). **HRMS** (ES^+): calcd. for $C_{15}H_{25}BrF_2NO_2Si^+$: 396.0801, found 396.0813.

***N*-(2-Bromo-2,2-difluoroethyl)aniline 270**

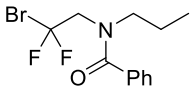


Colorless oil. R_f 0.35 (petroleum ether/EtOAc 95/5). Yield: 46%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.91-3.99 (2H, m, CH_2), 4.10 (1H, s, NH), 6.71 (2H, d, *J* = 7.7 Hz, 2x CH_{arom}), 6.80 (1H, tt, *J* = 7.4 Hz, 1.0 Hz, CH_{arom}), 7.19-7.24 (2H, m, 2x CH_{arom}). **^{13}C NMR** (100.6 MHz, ref = $CDCl_3$): δ 54.5 (t, *J* = 25.1 Hz, CH_2), 113.2 (2x CH_{arom}), 119.1 (CH_{arom}), 122.6 (t, *J* = 309.4 Hz, CF_2Br), 129.5 (2x CH_{arom}), 146.1 ($C_{arom,quat}$). **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ -53.33 (2F, t, $J_{H,F}$ = 11.9 Hz, CF_2Br). **IR** (ATR, cm^{-1}): ν_{NH} = 3416, ν_{max} = 1602, 1511, 1100, 909, 747, 690.

5.7.5 Synthesis of *N*-(2-bromo-2,2-difluoroethyl)benzamides 217, 249, 264 and 271

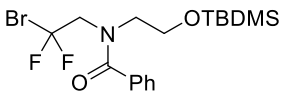
The synthesis of *N*-(2-bromo-2,2-difluoroethyl)-*N*-propylbenzamide **217** is described as representative. To a mixture of *N*-propyl-2-bromo-2,2-difluoroethylamine **23b** (0.33 g, 1.7 mmol) and Et_3N (0.84 g, 8.3 mmol, 5 equiv) in anhydrous CH_2Cl_2 (20 mL), a solution of benzoyl chloride (0.23 g, 1.7 mmol, 1 equiv) in anhydrous CH_2Cl_2 (5 mL) was added slowly at 0 °C. After stirring at room temperature for 20 hours, the reaction mixture was washed with an aqueous solution of HCl (5%, 10 mL) and $NaHCO_3$ (aq, sat). After drying ($MgSO_4$) and filtration, the solvent was evaporated *in vacuo*. Column chromatography (SiO_2, PE/EtOAc 8/2) afforded pure benzamide **217** in 90% yield (0.41 g, 1.5 mmol).

***N*-(2-Bromo-2,2-difluoroethyl)-*N*-propylbenzamide 217**



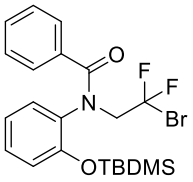
Yellow oil. R_f 0.34 (petroleum ether/EtOAc 8/2). Yield: 90%. **^{1}H NMR** (400 MHz, $CDCl_3$, 50 °C): δ 0.79 (3H, t, *J* = 7.2 Hz, $CH_2C\underline{H}_3$), 1.52-1.58 (2H, m, $CH_2C\underline{H}_2CH_3$), 3.45 (2H, t, *J* = 6.8 Hz, $NC\underline{H}_2CH_2$), 4.33 (2H, t, $J_{H,F}$ = 11.2 Hz, $CF_2BrC\underline{H}_2$), 7.39-7.46 (5H, m, 5x CH_{arom}). **^{13}C NMR** (100.6 MHz, ref = $CDCl_3$): δ 10.8 ($CH_2\underline{C}H_3$), 21.1 ($\underline{C}H_2CH_3$), 51.3 ($N\underline{C}H_2CH_2$), 52.1 ($\underline{C}H_2CF_2Br$), 121.2 (t, *J* = 308.8 Hz, CF_2Br), 126.8 (2x CH_{arom}), 128.6 (2x CH_{arom}), 129.9 (CH_{arom}), 135.6 ($C_{arom,\ quat}$), 172.8 (C=O). **^{19}F NMR** (376.5 MHz, $CDCl_3$): δ -50.02 (2F, br s, CF_2Br). **IR** (ATR, cm^{-1}): $\nu_{C=O}$ = 1647, ν_{max} = 1407, 1089, 1021, 935, 699. **MS** (ES^+): *m/z* (%): 306/8 ($M + H^+$, 100). **HRMS** (ES^+): calcd. for $C_{12}H_{15}BrF_2NO^+$: 306.0300, found 306.0295.

_N_-(2-Bromo-2,2-difluoroethyl)-_N_-{2-[(_tert_-butyldimethylsilyl)oxy]ethyl}benzamine 249



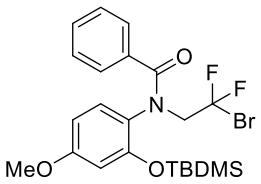
Colorless oil. R_f 0.07 (petroleum ether/EtOAc 97/3). Yield: 71%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 0.01 (3H, s, $SiCH_3$), 0.32 (3H, s, $SiCH_3$), 0.87 (9H, s, $SiC(CH_3)_3$), 3.44-3.90 (4H, m, CH_2CH_2), 4.24-4.66 (2H, m, CH_2CF_2), 7.35-7.40 (5H, m, 5x CH_{arom}). **^{13}C NMR** (75 MHz, $CDCl_3$): δ -5.5 (2x $SiCH_3$), 18.1 ($SiC(CH_3)_3$), 25.8 ($SiC(CH_3)_3$), 51.4 (CH_2N), 53.2 (m, CH_2CF_2), 61.5 (CH_2O), 121.2 (t, J = 309.9 Hz, CF_2Br), 127.0 (2x CH_{arom}), 128.6 (2x CH_{arom}), 129.9 (CH_{arom}), 135.5 ($C_{arom,quat}$), 172.8 (C=O). **^{19}F NMR** (282 MHz, $CDCl_3$, ref = $CFCl_3$): δ -50.56 (2F, br s, CF_2Br). **IR** (ATR, cm^{-1}): $\nu_{C=O}$ = 1655, ν_{max} = 1090, 1071, 930, 834, 777. **MS** (ES^+): *m/z* (%): 422/24 ($M + H^+$, 100). **HRMS** (ES^+): calcd. for $C_{17}H_{27}BrF_2NO_2Si^+$: 422.0957, found 422.0965.

_N_-(2-Bromo-2,2-difluoroethyl)-_N_-{2-[(_tert_-butyldimethylsilyl)oxy]phenyl}benzamide 264a



White crystals. Melting point: 89-90 °C. R_f 0.23 (petroleum ether/EtOAc 9/1). Yield: 98%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.26 (3H, s, $SiCH_3$), 0.32 (3H, s, $SiCH_3$), 1.02 (9H, s, $SiC(CH_3)_3$), 4.00 (1H, ddd, $J_{H,F}$ = 18.5 Hz, J = 14.9 Hz, $J_{H,F}$ = 4.2 Hz, $CH(H)CF_2Br$), 5.44 (1H, ddd, $J_{H,F}$ = 18.9 Hz, J = 14.9 Hz, $J_{H,F}$ = 10.3 Hz, $CH(H)CF_2Br$), 6.74-6.77 (2H, m, 2x CH_{arom}), 7.06-7.15 (4H, m, 4x CH_{arom}), 7.21-7.22 (1H, m, CH_{arom}), 7.28-7.30 (2H, m, 2x CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ -4.4 ($SiCH_3$), -3.9 ($SiCH_3$), 18.2 ($SiC(CH_3)_3$), 25.7 ($SiC(CH_3)_3$), 56.4 (dd, J = 25.0 Hz, 22.4 Hz, CH_2CF_2Br), 118.6 (CH_{arom}), 120.7 (dd, J = 311.4 Hz, 308.4 Hz, CF_2Br), 121.0 (CH_{arom}), 127.5 (2x CH_{arom}), 128.0 (2x CH_{arom}), 129.3, 129.9 and 131.7 (3x CH_{arom}), 132.9, 134.9 and 150.7 (3x $C_{arom,quat}$), 171.3 (C=O). **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ -49.08 (1F, ddd, J = 154.5 Hz, $J_{H,F}$ = 18.9 Hz, 4.2 Hz, $CF(F)Br$), -50.75 (1F, ddd, J = 154.5, $J_{H,F}$ = 18.5 Hz, 10.3 Hz, $CF(F)Br$). **IR** (ATR, cm^{-1}): $\nu_{C=O}$ = 1658, ν_{max} = 1285, 909, 783. **MS** (ES^+): *m/z* (%): 470/72 ($M + H^+$, 100). **HRMS** (ES^+): calcd. for $C_{21}H_{27}BrF_2NO_2Si^+$: 470.0957, found 470.0957. **El. Anal.** Calcd for $C_{21}H_{26}BrF_2NO_2Si$: C 53.62, H 5.57, N 2.98, found C 53.53, H 5.90, N 2.91.

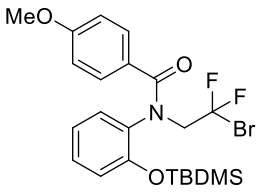
_N_-(2-Bromo-2,2-difluoroethyl)-_N_-{4-methoxy-2-[(_tert_-butyldimethylsilyl)oxy]phenyl}benzamide 264b



White crystals. Melting point: 119-120 °C. R_f 0.13 (petroleum ether/EtOAc 9/1). Yield: 52%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.26 (3H, s, $SiCH_3$), 0.31 (3H, s, $SiCH_3$), 1.02 (9H, s, $SiC(CH_3)_3$), 3.70 (3H, s, OCH_3), 4.91 (1H, ddd, $J_{H,F}$ = 18.4 Hz, J = 14.9 Hz, $J_{H,F}$ = 4.3 Hz, $CH(H)CF_2Br$), 5.43 (1H, ddd, $J_{H,F}$ = 18.7 Hz, J = 14.9 Hz, $J_{H,F}$ = 10.5 Hz, $CH(H)CF_2Br$), 6.28-6.31 (2H, m, 2x CH_{arom}), 6.99-7.01 (1H, m, CH_{arom}), 7.13-7.17 (2H, m, 2x CH_{arom}), 7.21-7.24 (1H, m, CH_{arom}), 7.29-7.31 (2H, m, 2x CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ -4.4 ($SiCH_3$), -3.9 ($SiCH_3$), 18.2 ($SiC(CH_3)_3$), 25.7 ($SiC(CH_3)_3$), 55.3 (OCH_3), 56.6 (dd, J = 24.9 Hz, 22.4 Hz, CH_2CF_2Br), 105.1 and 105.3 (2x

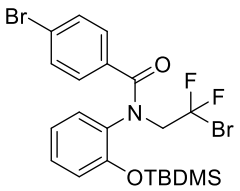
CH_{arom}), 120.9 (dd, *J* = 311.3 Hz, 308.3 Hz, CF_2Br), 126.2 ($C_{arom,quat}$), 127.5 (2x CH_{arom}), 127.9 (2x CH_{arom}), 129.8 and 132.0 (2x CH_{arom}), 135.1, 151.6 and 160.0 (3x $C_{arom,quat}$), 171.6 (C=O). **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ -49.12 (1F, ddd, *J* = 154.5 Hz, $J_{H,F}$ = 18.7 Hz, 4.3 Hz, C<u>F</u>(F)Br), -50.71 (1F, ddd, *J* = 154.5, $J_{H,F}$ = 18.4 Hz, 10.5 Hz, CF(<u>F</u>)Br). **IR** (ATR, cm^{-1}): $\nu_{C=O}$ = 1652, ν_{max} = 1509, 1171, 833. **MS** (ES^+): *m/z* (%): 500/2 (M + H^+, 100). **HRMS** (ES^+): calcd. for $C_{22}H_{29}BrF_2NO_3Si^+$: 500.1063, found 500.1067.

***N*-(2-Bromo-2,2-difluoroethyl)-*N*-{2-[(*tert*-butyldimethylsilyl)oxy]phenyl}-4-methoxybenzamide 264c**



Colorless oil. R_f 0.29 (petroleum ether/EtOAc 95/5). Yield: 76%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.19 (3H, s, $SiCH_3$), 0.27 (3H, s, $SiCH_3$), 0.97 (9H, s, $SiC(CH_3)_3$), 3.60 (3H, s, OCH_3), 4.00 (1H, ddd, $J_{H,F}$ = 19.0 Hz, *J* = 15.0 Hz, $J_{H,F}$ = 3.8 Hz, C<u>H</u>(H)CF_2Br), 5.40 (1H, ddd, $J_{H,F}$ = 19.3 Hz, *J* = 15.0 Hz, $J_{H,F}$ = 9.6 Hz, CH(<u>H</u>)CF_2Br), 6.58 (2H, d, *J* = 8.7 Hz, 2x CH_{arom}), 6.72-6.76 (1H, m, CH_{arom}), 6.76 (1H, d, *J* = 8.2 Hz, CH_{arom}), 7.05 (1H, ddd, *J* = 8.2 Hz, 7.6 Hz, 1.6 Hz, CH_{arom}), 7.11 (1H, d, *J* = 7.6 Hz, CH_{arom}), 7.26 (2H, d, *J* = 8.7 Hz, 2x CH_{arom}). **^{13}C NMR** (100.6 MHz, ref = $CDCl_3$): δ -4.6 ($SiCH_3$), -4.1 ($SiCH_3$), 18.0 ($SiC(CH_3)_3$), 25.5 ($SiC(CH_3)_3$), 54.9 (OCH_3), 56.6 (dd, *J* = 23.7 Hz, 23.1 Hz, CH_2CF_2Br), 112.6 (2x CH_{arom}), 118.7 (CH_{arom}), 120.8 (dd, *J* = 311.1 Hz, 308.9 Hz, CF_2Br), 121.1 (CH_{arom}), 126.6 ($C_{arom,quat}$), 129.1 (CH_{arom}), 130.3 (2x CH_{arom}), 131.2 (CH_{arom}), 133.3, 150.5 and 160.8 (3x $C_{arom,quat}$), 170.4 (C=O). **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ -48.91 (1F, ddd, *J* = 153.2 Hz, $J_{H,F}$ = 19.3 Hz, 3.8 Hz, C<u>F</u>(F)Br), -50.74 (1F, ddd, *J* = 153.2 Hz, $J_{H,F}$ = 19.0 Hz, 9.6 Hz, CF(<u>F</u>)Br). **IR** (ATR, cm^{-1}): $\nu_{C=O}$ = 1657, ν_{max} = 1497, 1253, 909, 782. **MS** (ES^+): *m/z* (%): 500/2 (M + H^+, 100). **HRMS** (ES^+): calcd. for $C_{22}H_{29}BrF_2NO_3Si^+$: 500.1063, found 500.1070.

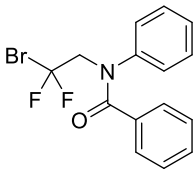
***N*-(2-Bromo-2,2-difluoroethyl)-*N*-{2-[(*tert*-butyldimethylsilyl)oxy]phenyl}-4-bromobenzamide 264d**



White crystals. Melting point: 83-84 °C. R_f 0.57 (petroleum ether/EtOAc 9/1). Yield: 75%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.24 (3H, s, $SiCH_3$), 0.31 (3H, s, $SiCH_3$), 1.01 (9H, s, $SiC(CH_3)_3$), 4.00 (1H, ddd, $J_{H,F}$ = 18.7 Hz, *J* = 15.0 Hz, $J_{H,F}$ = 4.2 Hz, C<u>H</u>(H)CF_2Br), 5.43 (1H, ddd, $J_{H,F}$ = 19.0 Hz, *J* = 15.0 Hz, $J_{H,F}$ = 10.1 Hz, CH(<u>H</u>)CF_2Br), 6.75-6.79 (2H, m, 2x CH_{arom}), 7.07-7.14 (2H, m, 2x CH_{arom}), 7.20 (2H, d, *J* = 8.5 Hz, 2x CH_{arom}), 7.26 (2H, d, *J* = 8.5 Hz, 2x CH_{arom}). **^{13}C NMR** (100.6 MHz, ref = $CDCl_3$): δ -4.4 ($SiCH_3$), -4.0 ($SiCH_3$), 18.0 ($SiC(CH_3)_3$), 25.6 ($SiC(CH_3)_3$), 56.5 (dd, *J* = 24.8 Hz, 22.6 Hz, CH_2CF_2Br), 118.7 (CH_{arom}), 120.5 (dd, *J* = 311.2 Hz, 308.4 Hz, CF_2Br), 121.2 (CH_{arom}), 124.4 ($C_{arom,quat}$), 129.5 (CH_{arom}), 129.7 (2x CH_{arom}), 130.6 (2x CH_{arom}), 131.3 (CH_{arom}), 132.6, 133.6 and 150.6 (3x $C_{arom,quat}$), 171.1 (C=O). **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ -49.27 (1F, ddd, *J* = 154.4 Hz, 19.0 Hz, 4.2 Hz, C<u>F</u>(F)Br), -50.85 (1F, ddd, *J* = 154.4 Hz, 18.7 Hz, 10.1 Hz, CF(<u>F</u>)Br). **IR** (ATR, cm^{-1}): $\nu_{C=O}$ = 1664, ν_{max} = 1479,

1282, 1100, 908, 732. **MS** (ES^+): *m/z* (%): 548/50/52 ($M + H^+$, 100). **HRMS** (ES^+): calcd. for $C_{21}H_{26}Br_2F_2NO_2Si^+$: 548.0062, found 548.0063.

***N*-(2-Bromo-2,2-difluoro)-*N*-phenylbenzamide 271**

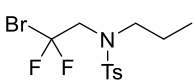


Colorless oil. R_f 0.10 (petroleum ether/EtOAc 9/1). Yield: 63%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.81 (2H, t, $J_{H,F}$ = 12.8 Hz, CH_2), 7.08-7.11 (2H, m, 2x CH_{arom}), 7.14-7.20 (3H, m, 3x CH_{arom}), 7.21-7.25 (3H, m, 3x CH_{arom}), 7.29-3.31 (2H, m, 2x CH_{arom}). **^{13}C NMR** (100.6 MHz, ref = $CDCl_3$): δ 57.9 (t, *J* = 24.0 Hz, CH_2), 120.4 (t, *J* = 310.1 Hz, CF_2), 127.5 (CH_{arom}), 127.77 and 127.79 (4x CH_{arom}), 128.6 (2x CH_{arom}), 129.3 (2x CH_{arom}), 130.1 (CH_{arom}), 134.7 ($C_{arom,quat}$), 142.8 ($C_{arom,quat}$), 171.0 (C=O). **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ -49.97 (2F, t, $J_{H,F}$ = 12.9 Hz, CF_2Br). **IR** (ATR, cm^{-1}): $\nu_{C=O}$ = 1659, ν_{max} = 1370, 1302, 1107, 926, 695. **MS** (ES^+): *m/z* (%): 340/42 ($M + H^+$, 100). **HRMS** (ES^+): calcd. for $C_{15}H_{13}BrF_2NO^+$: 340.0143, found 340.0133.

5.7.6 Synthesis of *N*-(2-bromo-2,2-difluoroethyl)-4-methylbenzenesulfonamides 219 and 244

The synthesis of *N*-(2-bromo-2,2-difluoroethyl)-*N*-propyl-4-methylbenzenesulfonamide **219** is described as representative. To a mixture of *N*-propyl-2-bromo-2,2-difluoroethylamine **23b** (5.00 g, 25 mmol), Et_3N (4.00 g, 21 mmol, 0.8 equiv) and DMAP (0.26 g, 2.1 mmol, 0.08 equiv) in anhydrous CH_2Cl_2 (100 mL), a solution of *p*-toluenesulfonyl chloride (2.12 g, 21 mmol, 0.8 equiv) in anhydrous CH_2Cl_2 (25 mL) was added at 0 °C. The reaction mixture was stirred at reflux temperature for 47 h, poured in 1M HCl (50 mL) and extracted with CH_2Cl_2 (3x 50 mL). After drying of the organic fase ($MgSO_4$), filtration of the drying agent, and evaporation of the solvent *in vacuo*, *N*-(2-bromo-2,2-difluoroethyl)-*N*-propyl-4-methylbenzenesulfonamide **219** was obtained in 78% yield (5.81 g, 19.5 mmol).

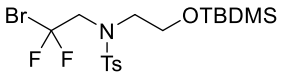
***N*-(2-Bromo-2,2-difluoroethyl)-*N*-propyl-4-methylbenzenesulfonamide 219**



White crystals. Melting point: 56-57 °C. Yield: 78%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.82 (3H, t, *J* = 7.4 Hz, $CH_2C\underline{H}_3$), 1.58 (2H, sextet, *J* = 7.6 Hz, $CH_2C\underline{H}_2CH_3$), 2.43 (3H, s, $CH_3C_{arom,quat}$), 3.18-3.22 (2H, m, $NC\underline{H}_2CH_2$), 4.10 (2H, t, $J_{H,F}$ = 13.3 Hz, $CF_2BrC\underline{H}_2$), 7.31 (2H, d, *J* = 8.1 Hz, 2x CH_{arom}), 7.71 (2H, d, *J* = 8.1 Hz, 2x CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 10.9 ($CH_2\underline{C}H_3$), 20.8 ($\underline{C}H_2CH_3$), 21.5 ($\underline{C}H_3C_{arom,quat}$), 50.9 ($N\underline{C}H_2CH_2$), 56.0 (t, *J* = 24.2 Hz, $\underline{C}H_2CF_2Br$), 120.6 (t, *J* = 309.5 Hz, CF_2Br), 127.3 (2x CH_{arom}), 129.8 (2x CH_{arom}), 136.6 ($C_{arom,\ quat}$), 143.9 ($C_{arom,quat}$). **^{19}F NMR** (376.5 MHz, $CDCl_3$): δ -51.47 (2F, t, $J_{H,F}$ = 13.3

Hz, CF_2Br). **IR** (ATR, cm^{-1}): ν_{max} = 1345, 1154, 942, 732. **MS** (ES^+): *m/z* (%): 373/75 (M + NH_4^+, 100), 356/58 (M + H^+, 80). **HRMS** (ES^+): calcd. for $C_{12}H_{17}BrF_2NO_2S^+$: 356.0126, found 356.0125.

***N*-(2-Bromo-2,2-difluoroethyl)-*N*-{2-[(*tert*-butyldimethylsilyl)oxy]ethyl}-4-methylbenzenesulfonamide 244**

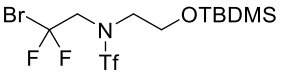


Yellow oil. R_f 0.17 (petroleum ether/EtOAc 17/0.6). Yield: 25%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 0.01 (6H, s, 2x $SiCH_3$), 0.85 (9H, s, $SiC(CH_3)_3$), 2.39 (3H, s, $CH_3C_{arom,quat}$), 3.40 (2H, t, *J* = 5.5 Hz, NCH_2), 3.73 (2H, t, *J* = 5.5 Hz, OCH_2), 4.36 (2H, t, $J_{H,F}$ = 14.0 Hz, CH_2CF_2), 7.28 (2H, d, *J* = 8.0 Hz, 2x CH_{arom}), 7.66 (2H, d, *J* = 8.0 Hz, 2x CH_{arom}). **^{13}C NMR** (75 MHz, $CDCl_3$): δ -5.2 (2x $SiCH_3$), 18.3 ($SiC(CH_3)_3$), 21.5 ($CH_3C_{arom,quat}$), 25.9 ($SiC(CH_3)_3$), 50.6 (NCH_2), 57.2 (t, *J* = 23.5 Hz, CH_2CF_2), 62.4 (CH_2O), 120.9 (t, *J* = 307.5 Hz, CF_2Br), 127.4 (2x CH_{arom}), 129.8 (2x CH_{arom}), 137.0 ($C_{arom,quat}$), 143.9 ($C_{arom,quat}$). **^{19}F NMR** (282 MHz, $CDCl_3$): δ -51.89 (2F, t, $J_{H,F}$ = 14.0 Hz, CF_2Br). **IR** (ATR, cm^{-1}): ν_{max} = 1158, 1091, 994, 938, 840, 813, 775, 731. **MS** (ES^+): *m/z* (%): 472/74 (M + H^+, 100). **HRMS** (ES^+): calcd. for $C_{17}H_{29}BrF_2NO_3SSi^+$: 472.0783, found 472.0781.

5.7.7 Synthesis of *N*-(2-bromo-2,2-difluoroethyl)-*N*-{2-[(*tert*-butyldimethylsilyl)oxy]-ethyl}-1,1,1-trifluoromethanesulfonamide 248

To a solution of *N*-{2-[(*tert*-butyldimethylsilyl)oxy]ethyl}-2-bromo-2,2-difluoroethylamine **243** (1.50 g, 4.72 mmol) and triethylamine (1.2 equiv, 0.57 g, 5.66 mmol) in dry CH_2Cl_2 (40 mL) was added triflic anhydride (1.1 equiv, 0.87 mL, 2.19 mmol) at 0 °C. Subsequently, this reaction mixture was stirred at room temperature for 17 hours, after which the mixture was washed with aqueous HCl (1M) and the organic phase was dried ($MgSO_4$), filtered and evaporated under reduced pressure. After purification using column chromatography, pure *N*-(2-bromo-2,2-difluoroethyl)-*N*-{2-[(*tert*-butyldimethylsilyl)oxy]ethyl}-1,1,1-trifluoromethanesulfonamide **248** was obtained (1.59 g, 3.54 mmol).

***N*-(2-Bromo-2,2-difluoroethyl)-*N*-{2-[(*tert*-butyldimethylsilyl)oxy]ethyl}-1,1,1-trifluoromethane-sulfonamide 248**



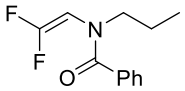
Colorless oil. R_f 0.47 (petroleum ether/EtOAc 20/1). Yield: 75%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 0.09 (6H, s, 2x $SiCH_3$), 0.91 (9H, s, $SiC(CH_3)_3$), 3.68 (2H, t, *J* = 5.0 Hz, NCH_2), 3.88 (2H, t, *J* = 5.0 Hz, OCH_2), 4.46 (2H, t, $J_{H,F}$ = 13.2 Hz, CH_2CF_2). **^{13}C NMR** (75 MHz, $CDCl_3$): δ -2.7 ($SiCH_3$), 2.9 ($SiCH_3$), 21.0 ($SiC(CH_3)_3$), 28.7 ($SiC(CH_3)_3$), 53.3 (CH_2N), 59.8 (t, *J* = 23.7 Hz, CH_2CF_2), 65.0 (CH_2O), 122.1 (t, *J* = 308.6 Hz, CF_2Br), 122.6 (q, *J* = 322.7 Hz, CF_3). **^{19}F NMR** (282 MHz, $CDCl_3$): δ -52.76 (2F, m, CF_2Br),

-74.87 (3F, t, *J* = 5.3 Hz, CF_3). **IR** (ATR, cm^{-1}): ν_{max} = 1192, 1126, 1014, 936, 778. **MS** (ES^+): *m/z* (%): 450/52 ($M + H^+$, 100).

5.7.8 Synthesis of β,β-difluorinated enamides 218, 220, 245, 250, 251 and 272

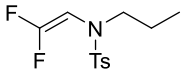
The synthesis of benzamide **218** is given as a representative example. To a solution of *N*-2-bromo-2,2-difluoroethyl-*N*-propylbenzamide **217** (1.29 g, 4.2 mmol) in anhydrous THF (40 mL), a solution of LiHMDS in THF (1M, 4.4 mL, 1.05 equiv) was added at 0 °C. The reaction mixture was stirred at room temperature for three hours, after which it was quenched with $NaHCO_3$ (aq, sat) and extracted with EtOAc (3x 50 mL). After drying of the combined organic phases ($MgSO_4$), filtration and evaporation of the solvent, crude benzamide **218** was obtained, which was purified *via* column chromatography (SiO_2, PE/EtOAc 9/1) affording pure amide **218** in 85% yield (0.80 g, 3.6 mmol).

***N*-(2,2-Difluorovinyl)-*N*-propylbenzamide 218**



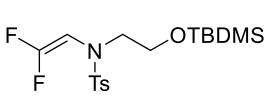
Yellow oil. R_f 0.23 (petroleum ether/EtOAc 9/1). Yield: 85%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.94 (3H, br s, $CH_2C\underline{H}_3$), 1.62-1.68 (2H, m, $CH_2C\underline{H}_2CH_3$), 3.57 (2H, br s, $NC\underline{H}_2CH_2$), 5.42 (1H, br s, $CH=CF_2$), 7.36-7.46 (5H, m, 5x CH_{arom}). **^{13}C NMR** (100.6 MHz, ref = $CDCl_3$): δ 11.2 ($CH_2\underline{C}H_3$), 20.9 ($\underline{C}H_2CH_3$), 49.4 ($N\underline{C}H_2CH_2$), 89.0-89.5 (m, $\underline{C}H=CF_2$), 127.5 (2x CH_{arom}), 128.3 (2x CH_{arom}), 130.3 (CH_{arom}), 135.7 ($C_{arom,\ quat}$), 155.5 (t, *J* = 289.9 Hz, $CH=\underline{C}F_2$), 171.1 (C=O). **^{19}F NMR** (376.5 MHz, $CDCl_3$): δ -87.75 (1F, dd, *J* = 38.9 Hz, $J_{H,F}$ = 18.2 Hz, $C\underline{F}(F)$), -100.56 (1F, d, *J* = 38.9 Hz, $CF(\underline{F})$). **IR** (ATR, cm^{-1}): $\nu_{C=O}$ = 1647, ν_{max} = 1407, 1089, 1021, 935, 699. **MS** (ES^+): *m/z* (%): 226 ($M + H^+$, 100). **HRMS** (ES^+): calcd. for $C_{12}H_{14}F_2NO^+$: 226.1038, found 226.1038.

***N*-(2,2-Difluorovinyl)-*N*-propyl-4-methylbenzenesulfonamide 220**



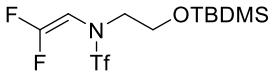
Yellow crystals. Melting point: 51-52 °C. R_f 0.30 (petroleum ether/EtOAc 10/1). Yield: 82%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 0.92 (3H, t, *J* = 7.2 Hz, $CH_2C\underline{H}_3$), 1.54 (2H, sextet, *J* = 7.2 Hz, $CH_2C\underline{H}_2CH_3$), 2.44 (3H, s, $CH_3C_{arom,quat}$), 3.10 (2H, t, *J* = 7.2 Hz, $NC\underline{H}_2CH_2$), 4.87 (1H, dd, $J_{H,F}$ = 18.3 Hz, 2.8 Hz, $CH=CF_2$), 7.33 (2H, d, *J* = 8.3 Hz, 2x CH_{arom}), 7.68 (2H, d, *J* = 8.3 Hz, 2x CH_{arom}). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 10.9 ($CH_2\underline{C}H_3$), 21.4 ($\underline{C}H_2CH_3$), 21.6 ($\underline{C}H_3C_{arom,quat}$), 51.6 ($N\underline{C}H_2CH_2$), 84.9 (dd, *J* = 49.6 Hz, 13.9 Hz, $\underline{C}H=CF_2$), 127.4 (2x CH_{arom}), 129.8 (2x CH_{arom}), 134.8 ($C_{arom,quat}$), 143.9 ($C_{arom,quat}$), 159.5 (dd, *J* = 300.0 Hz, 289.6 Hz, $CH=\underline{C}F_2$). **^{19}F NMR** (282 MHz, $CDCl_3$): δ -83.20 (1F, dd, *J* = 28.3 Hz, $J_{H,F}$ = 18.3 Hz, $C\underline{F}(F)$), -93.38 (1F, d, *J* = 28.3 Hz, $CF(\underline{F})$). **IR** (ATR, cm^{-1}): ν_{max} = 1749, 1341, 1240, 1164. **MS** (ES^+): *m/z* (%): 276 ($M + H^+$, 100), 293 ($M + NH_4^+$, 33). **HRMS** (ES^+): calcd. for $C_{12}H_{16}F_2NO_2S^+$: 276.0864, found 276.0863.

***N*-{2-[(*Tert*-butyldimethylsilyl)oxy]ethyl}-*N*-(2,2-difluorovinyl)-4-methylbenzenesulfonamine 245**



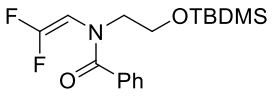
Colorless oil. R_f 0.37 (petroleum ether/EtOAc 9/1). Yield: 70%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.01 (6H, s, 2x $SiCH_3$), 0.84 (9H, s, $SiC(CH_3)_3$), 2.41 (3H, s, CH_3), 3.29 (2H, t, *J* = 6.0 Hz, CH_2N), 3.72 (2H, t, *J* = 6.0 Hz, CH_2O), 5.04 (1H, dd, $J_{H,F}$ = 18.3 Hz, 2.7 Hz, $CH=CF_2$), 7.29 (2H, d, *J* = 8.2 Hz, 2x CH_{arom}), 7.67 (2H, d, *J* = 8.2 Hz, 2x CH_{arom}). **^{13}C NMR** (100.6 MHz, ref = $CDCl_3$): δ -5.5 (2x $SiCH_3$), 18.3 ($SiC(CH_3)_3$), 21.6 ($CH_3C_{arom,quat}$), 25.9 ($SiC(CH_3)_3$), 52.3 (CH_2N), 61.7 (CH_2O), 86.3 (dd, *J* = 50.0 Hz, 13.8 Hz, $CH=CF_2$), 127.5 (2x CH_{arom}), 129.9 (2x CH_{arom}), 135.3 ($C_{arom,quat}$), 144.1 ($C_{arom,quat}$), 159.1 (dd, *J* = 299.6 Hz, 289.1 Hz, CF_2). **^{19}F NMR** (376.5 MHz, $CDCl_3$): δ -83.40 (1F, dd, *J* = 29.0 Hz, $J_{H,F}$ = 18.3 Hz, $CF(F)$), -94.60 (1F, d, *J* = 29.0 Hz, $CF(F)$). **IR** (ATR, cm^{-1}): ν_{max} = 1165, 1090, 883, 812, 776, 659. **MS** (ES^+): *m/z* (%): 392 ($M + H^+$, 100).

***N*-{2-[(*Tert*-butyldimethylsilyl)oxy]ethyl}-*N*-(2,2-difluorovinyl)-1,1,1-trifluoromethanesulfonamide 250**



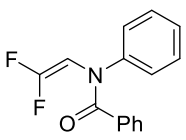
Yellow oil. R_f 0.20 (petroleum ether/EtOAc 9/1). Yield: 65%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.07 (6H, s, 2x $SiCH_3$), 0.89 (9H, s, $SiC(CH_3)_3$), 3.60 (2H, t, *J* = 5.3 Hz, CH_2N), 3.79 (2H, t, *J* = 5.3 Hz, CH_2O), 5.39 (1H, dd, $J_{H,F}$ = 17.9 Hz, 3.3 Hz, $CH=CF_2$). **^{13}C NMR** (75 MHz, $CDCl_3$): δ -5.6 (2x $SiCH_3$), 18.2 ($SiC(CH_3)_3$), 25.7 ($SiC(CH_3)_3$), 54.0 (CH_2N), 60.8 (CH_2O), 85.2 (dd, *J* = 51.9 Hz, 15.0 Hz, $CH=CF_2$), 119.9 (q, *J* = 323.8 Hz, CF_3), 159.4 (dd, *J* = 300.0 Hz, 293.1 Hz, CF_2). **^{19}F NMR** (376.5 MHz, $CDCl_3$): δ -75.06 (3F, s, CF_3), -80.75 to -80.87 (1F, m, $CF(F)$), -92.43 to -92.50 (1F, m, $CF(F)$). **IR** (ATR, cm^{-1}): ν_{max} = 1226, 1191, 1116, 836, 777. **MS** (ES^+): *m/z* (%): 370 ($M + H^+$, 55), 361 (100). **HRMS**: $M + H^+$ could not be detected.

***N*-(2,2-Difluorovinyl)-*N*-{2-[(*tert*-butyldimethylsilyl)oxy]ethyl}benzamide 251**



Yellow oil. R_f 0.20 (petroleum ether/EtOAc 9/1). Yield: 35%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 0.08 (6H, s, $SiCH_3$), 0.91 (9H, s, 2x $SiC(CH_3)_3$), 3.62-3.87 (4H, m, CH_2CH_2), 5.52-5.56 (1H, m, $CH=CF_2$), 7.39-7.50 (5H, m, 5x CH_{arom}). **^{13}C NMR** (75 MHz, $CDCl_3$): δ -5.4 (2x $SiCH_3$), 18.2 ($SiC(CH_3)_3$), 25.9 ($SiC(CH_3)_3$), 50.5 (CH_2N), 60.7 (CH_2O), 90.3-91.2 (m, $CH=CF_2$), 127.6 (2x CH_{arom}), 128.2 (2x CH_{arom}), 130.3 (CH_{arom}), 135.6 ($C_{arom,quat}$), 159.4 (t, *J* = 298.6 Hz, CF_2), 171.2 (C=O). **^{19}F NMR** (282 MHz, $CDCl_3$, ref = $CFCl_3$): δ -85.59 (1F, br s, $CF(F)$), -101.06 (1F, d, *J* = 42.1 Hz, $CF(F)$).

***N*-(2,2-Difluorovinyl)-*N*-phenylbenzamide 272**



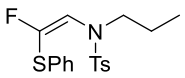
Yellow oil. R_f 0.28 (petroleum ether/EtOAc 85/15). Yield: 63%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.02 (1H, d, $J_{H,F}$ = 19.5 Hz, $CH=CF_2$), 7.12 (2H, d, *J* = 7.7 Hz, 2x CH_{arom}), 7.17-7.33 (6H, m, 6x CH_{arom}), 7.38 (2H, d, *J* = 7.5 Hz, 2x CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 89.9 (dd, *J* =

49.9 Hz, 11.6 Hz, CH=CF_2), 126.7 (2x CH_{arom}), 127.1 (CH_{arom}), 128.0 (2x CH_{arom}), 128.8 (2x CH_{arom}), 129.2 (2x CH_{arom}), 130.5 (CH_{arom}), 134.7 ($C_{arom,quat}$), 141.6 ($C_{arom,quat}$), 155.7 (dd, *J* = 296.3 Hz, 285.0 Hz, CF_2), 169.9 (C=O). **^{19}F NMR** (282 MHz, $CDCl_3$): δ -86.01 (1F, dd, *J* = 41.6 Hz, $J_{H,F}$ = 19.5 Hz, CF(F)), -99.89 (1F, d, *J* = 41.6 Hz, CF(F)). **IR** (ATR, cm^{-1}): $\nu_{C=O}$ = 1660, ν_{max} = 1333, 1305, 1282, 1228, 693. **MS** (ES^+): *m/z* (%): 260 ($M + H^+$, 100). **HRMS** (ES^+): calcd. for $C_{15}H_{12}F_2NO^+$: 260.0881, found 260.0878.

5.7.9 Synthesis of enamides 221a, 221b and 222b, amine 223b and glycinate 224b

The synthesis of enamide **221a** is described as a representative example. *N*-(2,2-Difluorovinyl)-*N*-propyl-4-methylbenzenesulfonamide **220** (0.21 g, 0.78 mmol) was dissolved in acetonitrile (5 mL) and subsequently, thiophenol (0.103 g, 0.93 mmol, 1.2 equiv) and KOH (0.052 g, 0.93 mmol, 1.2 equiv) were added. After stirring the reaction mixture for 20 hours at reflux temperature, an aqueous solution of HCl (1N, 10 mL) was added and an extraction with EtOAc (3x 10 mL) was performed. The combined organic layers were dried ($MgSO_4$), filtered and the solvent was removed *in vacuo*. After column chromatography (SiO_2, PE/EtOAc 24/1), enamide **221a** was isolated in 69% yield (0.20 g, 0.54 mmol).

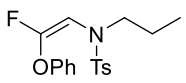
(*Z*)-*N*-[2-Fluoro-2-(phenylthio)vinyl]-*N*-propyl-4-methylbenzenesulfonamide 221a

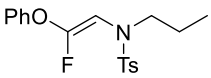


White crystals. Melting point: 85-86 °C. R_f 0.13 (petroleum ether/EtOAc 24/1). Yield: 69%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.96 (3H, t, *J* = 7.4 Hz, CH_2CH_3), 1.58 (2H, sextet, *J* = 7.2 Hz, $CH_2CH_2CH_3$), 2.43 (3H, s, $CH_3C_{arom,quat}$), 3.19 (2H, t, *J* = 7.2 Hz, NCH_2), 5.89 (1H, d, $J_{H,F}$ = 5.5 Hz, CH=CFS), 7.30-7.33 (5H, m, 5x CH_{arom}), 7.38-7.40 (2H, m, 2x CH_{arom}), 7.69 (2H, d, *J* = 8.3 Hz, 2x CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 11.2 (CH_2CH_3), 21.6 (CH_2CH_3 and $CH_3C_{arom,quat}$), 52.0 (NCH_2CH_2), 115.1 (d, *J* = 52.2 Hz, CH=CFS), 127.5 (2x CH_{arom}), 128.2 (CH_{arom}), 129.2 (2x CH_{arom}), 129.77 (2x CH_{arom}), 129.85 ($C_{arom,quat}$), 131.5 (2x CH_{arom}), 134.8 ($C_{arom,quat}$), 143.9 ($C_{arom,quat}$), 158.9 (d, *J* = 297.3 Hz, CH=CFS). **^{19}F NMR** (282 MHz, $CDCl_3$): δ -98.83 (1F, d, $J_{H,F}$ = 5.5 Hz, CH=CFS). **IR** (ATR, cm^{-1}): ν_{max} = 1344, 1161, 1145, 672. **MS** (ES^+): *m/z* (%): 366 ($M + H^+$, 100). **HRMS** (ES^+): calcd. for $C_{18}H_{21}FNO_2S_2^+$: 366.0992, found 366.0989. **El. Anal.** Calcd for $C_{18}H_{20}FNO_2S_2$: C 59.15, H 5.52, N 3.83, found C 59.35, H 5.72, N 3.73.

Enamides **221b** (major) and **222b** (minor) were obtained as an inseparable mixture (ratio **221b** : **222b** = 8 : 2).

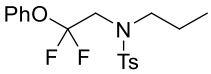
(*E*)-*N*-(2-Fluoro-2-phenoxyvinyl)-*N*-propyl-4-methylbenzenesulfonamide 221b and (*Z*)-*N*-(2-fluoro-2-phenoxyvinyl)-*N*-propyl-4-methylbenzenesulfonamide 222b





Yellow oil. R_f 0.13 (petroleum ether/EtOAc 95/5). Yield: 32%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.87 (2.4H, t, *J* = 7.4 Hz, $CH_2C\underline{H}_3$ (major)), 0.94 (0.6H, t, *J* = 7.4 Hz, $CH_2C\underline{H}_3$ (minor)), 1.56 (2H, sextet, *J* = 7.3 Hz, $CH_2C\underline{H}_2CH_3$), 2.36 (2.4H, s, $CH_3C_{arom,quat}$ (major)), 2.39 (0.6H, s, $CH_3C_{arom,quat}$ (minor)), 3.15 (0.4H, t, *J* = 7.1 Hz, $NC\underline{H}_2CH_2$ (minor)), 3.21 (1.6H, t, *J* = 7.0 Hz, $NC\underline{H}_2CH_2$ (major)), 4.88 (0.2H, d, $J_{H,F}$ = 19.3 Hz, C<u>H</u>=CFO (minor)), 5.33 (0.8H, d, $J_{H,F}$ = 1.0 Hz, C<u>H</u>=CFO (major)), 6.91-6.93 (1.6H, m, 2x CH_{arom} (major)), 7.07-7.37 (4H, m, 5x CH_{arom} (major)), 7.07-7.37 (1.4H, m, 7x CH_{arom} (minor)), 7.64-7.67 (1.6H, m, 2x CH_{arom} (major)), 7.69 (0.4H, d, *J* = 8.4 Hz, 2x CH_{arom} (minor)). **^{13}C NMR** (100.6 MHz, ref = $CDCl_3$): δ 11.0 ($CH_2\underline{C}H_3$), 21.48 ($\underline{C}H_3C_{arom,quat}$ (major)), 21.50 ($\underline{C}H_3C_{arom,quat}$ (minor)), 21.53 ($\underline{C}H_2CH_3$ (major)), 21.6 ($\underline{C}H_2CH_3$ (minor)), 51.5 (NCH_2), 91.9 (d, *J* = 20.7 Hz, <u>C</u>H=CFO (minor)), 92.8 (d, *J* = 60.3 Hz, <u>C</u>H=CFO (major)), 116.8 (2x CH_{arom} (minor)), 116.9 (2x CH_{arom} (major)), 124.5 (CH_{arom} (major)), 124.8 (CH_{arom} (minor)), 127.4 (2x CH_{arom} (major) and 2x CH_{arom} (minor)), 129.60 (2x CH_{arom} (major)), 129.62 (2x CH_{arom} (major)), 129.7 (2x CH_{arom} (minor)), 130.0 (2x CH_{arom} (minor)), 135.1 ($C_{arom,quat}$ (minor)), 135.4 ($C_{arom,quat}$ (major)), 143.6 ($C_{arom,quat}$ (major)), 143.7 ($C_{arom,quat}$ (minor)), 153.5 (d, *J* = 1.2 Hz, $OC_{arom,quat}$ (major)), 154.6 (d, *J* = 1.5 Hz, $OC_{arom,quat}$ (minor)), 156.5 (d, *J* = 283.9 Hz, CH=<u>C</u>FO (major)), 157.5 (d, *J* = 290.0 Hz, CH=<u>C</u>FO (minor)). **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ -84.57 (0.2F, d, $J_{H,F}$ = 19.3 Hz, CH=CFO (minor)), -95.80 (0.8F, s, CH=CFO (major)). **IR** (ATR, cm^{-1}): ν_{max} = 1341, 1190, 1163, 748, 658. **MS** (ES^+): *m/z* (%): 350 ($M + H^+$, 100). **HRMS** (ES^+): calcd. for $C_{18}H_{21}FNO_3S^+$: 350.1221, found 350.1224.

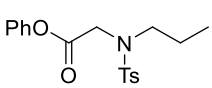
***N*-(2,2-Difluoro-2-phenoxyethyl)-*N*-propyl-4-methylbenzenesulfonamide 223b**



White crystals. Melting point: 77-78 °C. R_f 0.08 (petroleum ether/EtOAc 95/5). Yield: 10%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.86 (3H, t, *J* = 7.4 Hz, $CH_2C\underline{H}_3$), 1.67 (2H, sextet, *J* = 7.5 Hz, $CH_2C\underline{H}_2CH_3$), 2.41 (3H, s, $C\underline{H}_3C_{arom,quat}$), 3.27-3.31 (2H, m, $NC\underline{H}_2CH_2$), 3.96 (2H, t, $J_{H,F}$ = 9.3 Hz, $C\underline{H}_2CF_2O$), 7.03-7.06 (2H, m, 2x CH_{arom}), 7.18-7.22 (1H, m, CH_{arom}), 7.27-7.33 (4H, m, 4x CH_{arom}), 7.76 (2H, d, *J* = 8.3 Hz, 2x CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 11.0 ($CH_2\underline{C}H_3$), 20.9 ($\underline{C}H_2CH_3$), 21.5 ($\underline{C}H_3C_{arom,quat}$), 49.5 (t, *J* = 34.5 Hz, $\underline{C}H_2CF_2$), 50.4 (NCH_2), 121.7 (2x CH_{arom}), 122.2 (t, *J* = 270.2 Hz, $CH_2\underline{C}F_2$), 125.8 (CH_{arom}), 127.4 (2x CH_{arom}), 129.4 (2x CH_{arom}), 129.6 (2x CH_{arom}), 137.3, 143.4 and 149.7 (3x $C_{arom,quat}$). **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ -73.49 (2F, t, $J_{H,F}$ = 9.3 Hz, CF_2). **IR** (ATR, cm^{-1}): ν_{max} = 1336, 1264, 1146, 994. **MS** (ES^+):

m/z (%): 370 (M + H^+, 100), 387 (M + NH_4^+, 12). **HRMS** (ES^+): calcd. for $C_{18}H_{22}F_2NO_3S^+$: 370.1283, found 370.1279. **El. Anal.** Calcd for $C_{18}H_{21}F_2NO_3S$: C 58.52, H 5.73, N 3.79, found C 58.53, H 5.32, N 3.66.

Phenyl *N*-propyl-*N*-tosylglycinate 224b

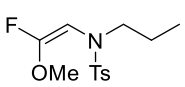


White crystals. Melting point: 88-89 °C. R_f 0.03 (petroleum ether/EtOAc 95/5). Yield: 85%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.89 (3H, t, *J* = 7.4 Hz, $CH_2C\underline{H}_3$), 1.61 (2H, sextet, *J* = 7.4 Hz, $CH_2C\underline{H}_2CH_3$), 2.38 (3H, s, $CH_3C_{arom,quat}$), 3.24-3.28 (2H, m, $NC\underline{H}_2CH_2$), 4.27 (2H, s, $NC\underline{H}_2CO$), 6.98-7.01 (2H, m, 2x CH_{arom}), 7.18-7.22 (1H, m, CH_{arom}), 7.27 (2H, d, *J* = 8.1 Hz, 2x CH_{arom}), 7.31-7.36 (2H, m, 2x CH_{arom}), 7.77 (2H, d, *J* = 8.3 Hz, 2x CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 11.1 ($CH_2\underline{C}H_3$), 21.3 ($\underline{C}H_2CH_3$), 21.5 ($\underline{C}H_3C_{arom,quat}$), 48.1 ($N\underline{C}H_2CO$), 50.2 ($N\underline{C}H_2CH_2$), 121.2 (2x CH_{arom}), 126.1 (CH_{arom}), 127.4 (2x CH_{arom}), 129.4 (2x CH_{arom}) and 129.6 (2x CH_{arom}), 136.6, 143.5 and 150.2 (3x $C_{arom,quat}$), 167.7 (C=O). **IR** (ATR, cm^{-1}): $\nu_{C=O}$ = 1769, ν_{max} = 1334, 1148, 656. **MS** (ES^+): *m/z* (%): 348 (M + H^+, 100), 365 (M + NH_4^+, 58). **HRMS** (ES^+): calcd. for $C_{18}H_{22}NO_4S^+$: 348.1264, found 348.1273.

5.7.10 Synthesis of enamides 221c and 222c.

To a solution of enamide **220** (0.15 g, 0.55 mmol) in anhydrous THF (10 mL), a solution of NaOMe in MeOH (1M, 0.55 mL, 1 equiv) was added. This mixture was stirred for three hours at room temperature. Subsequently, aqueous NH_4Cl (10 mL) was added, followed by an extraction with EtOAc (3x 10 mL). After drying of the combined organic phases ($MgSO_4$), filtration and evaporation of the solvent under reduced pressure, a mixture of two isomers **221c** and **222c** was obtained. After column chromatography (SiO_2, PE/EtOAc 9/1), enamides **221c** and **222c** were isolated in 57% (0.090 g, 0.31 mmol) and 15% (0.024 g, 0.08 mmol) yield, respectively.

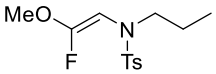
(*E*)-*N*-(2-Fluoro-2-methoxyvinyl)-*N*-propyl-4-methylbenzenesulfonamide 221c



Yellow oil. R_f 0.31 (petroleum ether/EtOAc 9/1). Yield: 57%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.91 (3H, t, *J* = 7.4 Hz, $CH_2C\underline{H}_3$), 1.53 (2H, sextet, *J* = 7.3 Hz, $CH_2C\underline{H}_2CH_3$), 2.42 (3H, s, $CH_3C_{arom,quat}$), 3.10 (2H, td, *J* = 7.2 Hz, 0.8 Hz, $NC\underline{H}_2CH_2$), 3.71 (3H, d, *J* = 1.0 Hz, OCH_3), 4.63 (1H, d, $J_{H,F}$ = 0.7 Hz, CH=CFO), 7.30 (2H, d, *J* = 8.1 Hz, 2x CH_{arom}), 7.68 (2H, d, *J* = 8.1 Hz, 2x CH_{arom}). **^{13}C NMR** (100.6 MHz, ref = $CDCl_3$): δ 10.9 ($CH_2\underline{C}H_3$), 21.3 and 21.4 ($\underline{C}H_2CH_3$ and $\underline{C}H_3C_{arom,quat}$), 51.9 (d, *J* = 1.2 Hz, $N\underline{C}H_2CH_2$), 57.4 (d, *J* = 6.0 Hz, OCH_3), 86.5 (d, *J* = 64.1 Hz, $\underline{C}H$=CFO), 127.4 (2x CH_{arom}), 129.4 (2x CH_{arom}), 135.1 and 143.4 (2x $C_{arom,quat}$), 161.7 (d, *J* = 280.1 Hz, CH=$\underline{C}$FO). **^{19}F NMR** (282 MHz, $CDCl_3$): δ -97.22 (1F, s, CH=CFO). **IR** (ATR,

cm^{-1}): ν_{max} = 1339, 1161, 732. **MS** (ES^+): *m/z* (%): 288 ($M + H^+$, 25). **HRMS** (ES^+): calcd. for $C_{13}H_{19}FNO_3S^+$: 288.1064, found 288.1068.

(*Z*)-*N*-(2-Fluoro-2-methoxyvinyl)-*N*-propyl-4-methylbenzenesulfonamide 222c

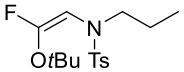


Yellow oil. R_f 0.12 (petroleum ether/EtOAc 9/1). Yield: 15%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.92 (3H, t, *J* = 7.4 Hz, $CH_2\underline{C}H_3$), 1.54 (2H, sextet, *J* = 7.4 Hz, $CH_2\underline{C}H_2CH_3$), 2.42 (3H, s, $CH_3C_{arom,quat}$), 3.14 (2H, t, *J* = 7.2 Hz, $NCH_2\underline{C}H_2$), 3.69 (3H, s, OCH_3), 4.39 (1H, d, $J_{H,F}$ = 21.6 Hz, CH=CFO), 7.29 (2H, d, *J* = 8.3 Hz, 2x CH_{arom}), 7.69 (2H, d, *J* = 8.3 Hz, 2x CH_{arom}). **^{13}C NMR** (100.6 MHz, ref = $CDCl_3$): δ 11.0 ($CH_2\underline{C}H_3$), 21.4 and 21.5 ($\underline{C}H_2CH_3$ and $\underline{C}H_3C_{arom,quat}$), 52.1 (d, *J* = 1.8 Hz, $NCH_2\underline{C}H_2$), 57.0 (d, *J* = 3.6 Hz, OCH_3), 81.6 (d, *J* = 20.4 Hz, $\underline{C}$H=CFO), 127.4 (2x CH_{arom}), 129.5 (2x CH_{arom}), 135.4 ($C_{arom,quat}$), 143.4 ($C_{arom,quat}$) 162.5 (d, *J* = 268.9 Hz, CH=$\underline{C}$FOCH_3). **^{19}F NMR** (282 MHz, $CDCl_3$): δ -85.13 (1F, d, $J_{H,F}$ = 21.6 Hz, CH=CFO). **IR** (ATR, cm^{-1}): ν_{max} = 1348, 1166, 998, 665. **MS** (ES^+): *m/z* (%): 288 ($M + H^+$, 25). **HRMS** (ES^+): calcd. for $C_{13}H_{19}FNO_3S^+$: 288.1064, found 288.1059.

5.7.11 Synthesis of enamide 221d

To a solution of enamide **220** (0.36 g, 1.3 mmol) in anhydrous THF (20 mL), a solution of KO*t*Bu in THF (1M, 1.44 mL, 1.1 equiv) was added at 0 °C. After stirring this reaction mixture for two hours at room temperature, a saturated solution of NH_4Cl in H_2O (20 mL) was added. Upon subsequent extraction with EtOAc (3x 20 mL), drying of the organic layers ($MgSO_4$), filtration and evaporation of the solvent *in vacuo*, a mixture of enamides **221d** and **222d** was obtained (**221d** : **222d** = 8 : 2), from which enamide **221d** was isolated in 46% (0.20 g, 0.60 mmol) yield *via* column chromatography (SiO_2, PE/EtOAc 97/3).

(*E*)-*N*-[2-Fluoro-2-(*tert*-butoxy)vinyl]-*N*-propyl-4-methylbenzenesulfonamide 221d

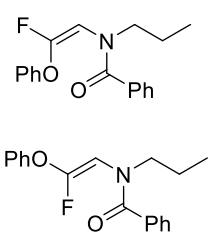


White crystals. Melting point: 91-92 °C. R_f 0.24 (petroleum ether/EtOAc 97/3). Yield: 46%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.89 (3H, t, *J* = 7.4 Hz, $CH_2\underline{C}H_3$), 1.34 (9H, d, *J* = 0.8 Hz, $C(CH_3)_3$), 1.52 (2H, sextet, *J* = 7.3 Hz, $CH_2\underline{C}H_2CH_3$), 2.42 (3H, s, $CH_3C_{arom,quat}$), 3.14 (2H, td, *J* = 7.2 Hz, $J_{H,F}$ = 0.8 Hz, $NCH_2\underline{C}H_2$), 4.88 (1H, d, $J_{H,F}$ = 1.2 Hz, $\underline{C}$H=CFO), 7.29 (2H, d, *J* = 8.1 Hz, 2x CH_{arom}), 7.69 (2H, d, *J* = 8.1 Hz, 2x CH_{arom}). **^{13}C NMR** (100.6 MHz, ref = $CDCl_3$) δ 11.2 ($CH_2\underline{C}H_3$), 21.3 and 21.5 ($\underline{C}H_2CH_3$ and $\underline{C}H_3C_{arom,quat}$), 28.6 ($C(\underline{C}H_3)_3$), 51.8 ($N\underline{C}H_2CH_2$), 84.7 ($O\underline{C}(CH_3)_3$), 90.2 (d, *J* = 69.9 Hz, $\underline{C}$H=CFO), 127.5 (2x CH_{arom}), 129.5 (2x CH_{arom}), 135.8 and 143.3 (2x $C_{arom,quat}$), 159.3 (d, *J* = 284.9 Hz, CH=$\underline{C}$FO). **^{19}F NMR** (282 MHz, $CDCl_3$): δ -85.62 (1F, s, CH=CFO). **IR** (ATR, cm^{-1}): ν_{max} = 1343, 1165, 1151, 1137, 660. **MS** (ES^+): *m/z* (%): 352 ($M + Na^+$, 10). **HRMS** (ES^+): calcd for $C_{16}H_{25}FNO_3S^+$: 330.1534, found 330.1542.

5.7.12 Synthesis of enamides 226 and 227

To a solution of enamide **218** (0.045 g, 0.20 mmol) in acetonitrile (5 mL) were added phenol (0.023 g, 0.24 mmol, 1.2 equiv) and KOH (0.013 g, 0.24 mmol, 1.2 equiv). After stirring this reaction mixture for four hours at reflux temperature, a saturated solution of NH_4Cl in H_2O (5 mL) was added. Upon subsequent extraction with EtOAc (3x 10 mL), drying of the organic layers ($MgSO_4$), filtration and evaporation of the solvent *in vacuo*, enamides **226** and **227** were isolated as a mixture (ratio **226** : **227** = 4 : 1) in 80% yield (0.048 g, 0.16 mmol) after preparative TLC (SiO_2, PE/EtOAc 9/1).

(*E*)-*N*-(2-Fluoro-2-phenoxyvinyl)-*N*-propylbenzamide 226 and (*Z*)-(2-fluoro-2-phenoxyvinyl)-*N*-propylbenzamide 227



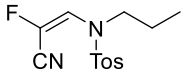
Yellow oil. R_f 0.18 (petroleum ether/EtOAc 9/1). Yield: 80%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.94 (3H, br s, $CH_2C\underline{H}_3$), 1.70 (2H, br s, $CH_2C\underline{H}_2CH_3$), 3.63 (2H, br s, NCH_2), 5.43 (0.2H, d, $J_{H,F}$ = 19.9 Hz, CH=CFO (minor)), 5.76 (0.8H, br s, C<u>H</u>=CFO (major)), 6.81-6.91 (3H, m, 3x CH_{arom}), 7.13-7.56 (7H, m, 7x CH_{arom}). **^{13}C NMR** (100.6 MHz, ref = $CDCl_3$): δ 11.2 ($CH_2\underline{C}H_3$), 20.8 ($\underline{C}H_2CH_3$), 49.4 ($N\underline{C}H_2CH_2$), 96.8 (<u>C</u>H=CFO (minor)), 97.4 (d, J = 57.0 Hz, <u>C</u>H=CFO (major)), 115.4, 116.4, 120.0, 124.4, 127.6, 127.9, 128.1, 128.3, 129.4, 129.8, 130.2 and 130.3 (10x CH_{arom} (major + minor)), 135.8 ($C_{arom,quat}$), 152.8 (d, J = 281.0 Hz, CH=<u>C</u>FO (minor)), 154.7 (d, J = 323.4 Hz, CH=<u>C</u>FO (major)), 171.3 (C=O). **^{19}F NMR** (282 MHz, $CDCl_3$): δ -87.11 (1F, d, $J_{H,F}$ = 19.9 Hz, CH=CFO (minor)), -100.96 (1F, s, CHCFO (major)). **IR** (ATR, cm^{-1}): ν_{max} = 1627, 1191, 1164, 751, 691. **MS** (ES^+): *m/z* (%): 300 ($M + H^+$, 100). **HRMS** (ES^+): calcd for $C_{18}H_{19}FNO_2^+$: 300.1394, found 300.1408.

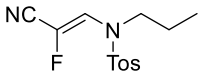
5.7.13 Synthesis of enamides 229 and 230

To a solution of enamide **220** (0.152 g, 0.55 mmol) and triethylamine (2 equiv, 0.112 g, 1.10 mmol) in DMF (10 mL) was added KCN (2 equiv, 0.072 g, 1.10 mmol) and this mixture was stirred for 23 hours at 40 °C. After adding EtOAc (10 mL), the mixture was washed with brine (3x 10 mL). Drying of the organic phase ($MgSO_4$), filtration and evaporation of the solvent afforded the crude reaction mixture from which a mixture of enamides **229** and **230** was isolated in a ratio of **229** : **230** = 3 : 2 (0.048 g, 0.17 mmol).

Enamides **229** (major) and **230** (minor) were obtained as an inseparable mixture (ratio **229** : **230** = 3 : 2).

(*E*)-*N*-(2-Cyano-2-fluorovinyl)-*N*-propyl-4-methylbenzenesulfonamide 229 and (*Z*)-(2-cyano-2-fluorovinyl)-*N*-propyl-4-methylbenzenesulfonamide 230



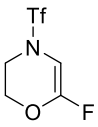


Yellow oil. R_f 0.26 (petroleum ether/EtOAc 10/1). Yield: 30%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.87 (1.1H, t, *J* = 7.4 Hz, $CH_2C\underline{H}_3$ (minor)), 0.92 (1.9H, t, *J* = 7.4 Hz, $CH_2C\underline{H}_3$ (major)), 1.56 (0.7H, sextet, *J* = 7.8 Hz, $CH_2C\underline{H}_2CH_3$ (minor)), 1.65 (1.3H, sextet, *J* = 7.6 Hz, $CH_2C\underline{H}_2CH_3$ (major)), 2.46 (3H, s, $CH_3C_{arom,quat}$), 3.45-3.49 (2H, m, CH_2N), 6.92 (0.4H, d, $J_{H,F}$ = 26.6 Hz, CH=CFCN (minor)), 7.38 (2H, d, *J* = 8.1 Hz, 2x CH_{arom}), 7.66-7.72 (2.6H, m, CH=CFCN (major) and 2x CH_{arom}). **^{13}C NMR** (100.6 MHz, ref = $CDCl_3$): δ 10.0 ($CH_2\underline{C}H_3$ (major)), 10.8 ($CH_2\underline{C}H_3$ (minor)), 21.4 ($\underline{C}H_2CH_3$ (major)), 21.8 ($\underline{C}H_3C_{arom,quat}$), 22.4 (d, *J* = 4.0 Hz, $\underline{C}H_2CH_3$ (minor)), 48.1 (CH_2N (major)), 49.3 (d, *J* = 6.9 Hz, CH_2N (minor)), 112.2 (d, *J* = 42.2 Hz, CN (major)), 113.6 (d, *J* = 41.4 Hz, CN (minor)), 118.1 (d, *J* = 237.1 Hz, CF (minor)), 121.0 (d, *J* = 213.3 Hz, CF (major)), 121.5 ($\underline{C}H$=CFCN (minor)), 127.3 (2x CH_{arom}), 128.1 (d, *J* = 48.8 Hz, $\underline{C}H$=CFCN (major)), 129.9 (d, *J* = 13.3 Hz, $C_{arom,quat}$ (major or minor)), 130.5 (2x CH_{arom}), 134.9 (d, *J* = 20.6 Hz, $C_{arom,quat}$ (major or minor)), 145.5 ($C_{arom,quat}$). **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ -153.87 (0.4F, d, $J_{H,F}$ = 26.6 Hz, CH=CFCN (minor)), -159.87 (0.6F, d, $J_{H,F}$ = 13.9 Hz, CH=CFCN (major)). **IR** (ATR, cm^{-1}): ν_{CN} = 2217, ν_{max} = 1346, 1166, 1137, 990, 813, 662. **MS** (ES^+): *m/z* (%): 300 ($M + NH_4^+$, 100).

5.7.14 Synthesis of 6-fluoro-4-(trifluoromethanesulfonyl)-3,4-dihydro-2*H*-1,4-oxazine 252

To a solution of *N*-{2-[(*tert*-butyldimethylsilyl)oxy]ethyl}-*N*-(2,2-difluorovinyl)-1,1,1-trifluoromethanesulfonamine **250** (0.144 g, 0.39 mmol) in dry THF (5 mL) was added TBAF (1M in THF, 0.2 equiv, 0.08 mmol) at 0 °C. After stirring the reaction mixture at room temperature for 17 hours, it was quenched with H_2O (5 mL) and extracted with EtOAc (3x 5 mL). The combined organic phases were dried ($MgSO_4$), filtered and evaporated *in vacuo*. After purification using column chromatography, pure 6-fluoro-4-(trifluoromethanesulfonyl)-3,4-dihydro-2*H*-1,4-oxazine **252** (9 mg, 0.039 mmol) was obtained.

6-Fluoro-4-(trifluoromethanesulfonyl)-3,4-dihydro-2*H*-1,4-oxazine 252



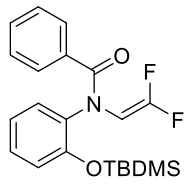
Colorless oil. R_f 0.20 (petroleum ether/EtOAc 9/1). Yield: 10%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 3.77 (2H, t, *J* = 4.4 Hz, CH_2N), 4.36 (2H, t, *J* = 4.4 Hz, CH_2O), 5.88 (1H, s, CH=CF). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 43.5 (CH_2N), 65.9 (CH_2O), 83.4 (d, *J* = 51.9 Hz, $\underline{C}H$=CF), 119.9 (q, *J* = 325.0 Hz, CF_3), 153.6

(d, *J* = 248.1 Hz, CH=CF). **^{19}F NMR** (282 MHz, $CDCl_3$): δ -73.71 (3F, s, CF_3), -107.43 (1F, s, CH=CF). **IR** (ATR, cm^{-1}): ν_{max} = 1396, 1304, 1186, 1148, 1088, 1017, 629.

5.7.15 Synthesis of enamide 265a

To a solution of benzamide **264a** (0.11 g, 0.24 mmol) in anhydrous THF (10 mL), a solution of LiO*t*Bu in THF (1M, 0.24 mL, 1 equiv) was added. After stirring this reaction mixture at room temperature for 1.5 hours, a saturated solution of NH_4Cl in H_2O (10 mL) was added. After extraction with EtOAc (3x 10 mL), drying ($MgSO_4$), filtration and evaporation of the solvent *in vacuo*, crude enamide **265a** was obtained. Purification *via* preparative TLC (SiO_2, PE/EtOAc 95/5) afforded pure enamide **265a** in 73% yield (0.067 g, 0.18 mmol).

***N*-{2-[(*Tert*-butyldimethylsilyl)oxy]phenyl}-*N*-(2,2-difluorovinyl)benzamide 265a**

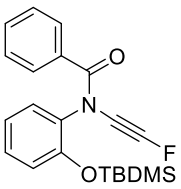


Colorless oil. R_f 0.43 (petroleum ether/EtOAc 9/1). Yield: 73%. **^{1}H NMR** (400 MHz, $CDCl_3$, 50 °C): δ 0.23 (6H, s, 2x $SiCH_3$), 0.99 (9H, s, $SiC(CH_3)_3$), 6.22 (1H, br s, $CH=CF_2$), 6.75 (1H, d, *J* = 7.4 Hz, CH_{arom}), 6.83 (1H, t, *J* = 7.5 Hz, CH_{arom}), 7.08-7.18 (4H, m, 4x CH_{arom}), 7.24-7.28 (1H, m, CH_{arom}), 7.34-7.42 (2H, m, 2x CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ -4.3 (2x $SiCH_3$), 18.2 ($SiC(CH_3)_3$), 25.7 ($SiC(CH_3)_3$), 89.3 (d, *J* = 53.8 Hz, $CH=CF_2$), 119.1 and 121.2 (2x CH_{arom}), 127.5 (2x CH_{arom}), 128.3 (2x CH_{arom}), 129.2, 130.0 and 130.2 (3x CH_{arom}), 132.0, 134.7 and 151.2 (3x $C_{arom,quat}$), 154.6 (dd, *J* = 297.3 Hz, 280.2 Hz, $CH=CF_2$), 169.9 (C=O). **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ -89.07 (1F, dd, *J* = 52.2 Hz, $J_{H,F}$ = 18.2 Hz, CF(F)), -103.03 (1F, d, *J* = 52.2 Hz, CF(F)). **IR** (ATR, cm^{-1}): $\nu_{C=O}$ = 1663, ν_{max} = 1327, 1284, 913, 781, 714, 695. **MS** (ES^+): *m/z* (%): 390 ($M + H^+$, 100). **HRMS** (ES^+): calcd. for $C_{21}H_{26}F_2NO_2Si^+$: 390.1695, found 390.1693.

5.7.16 Synthesis of ynamides 266a,c,d

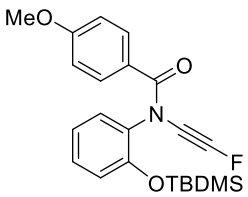
The synthesis of *N*-{2-[(*tert*-butyldimethylsilyl)oxy]phenyl}-*N*-(2-fluoroethynyl)benzamide **266a** is given as representative. To a solution of benzamide **264a** (0.30 g, 0.64 mmol) in anhydrous THF (30 mL), a solution of LiHMDS in THF (1M, 1.40 mL, 2.2 equiv) was added at 0 °C. The reaction mixture was allowed to warm to room temperature and was stirred at that temperature for 2.5 hours. Subsequently, aqueous NH_4Cl (30 mL) was added and this mixture was extracted with EtOAc (3x 20 mL). Drying of the combined organic layers ($MgSO_4$), filtration and evaporation of the solvent under reduced pressure, afforded ynamide **266a** (0.23 g, 0.62 mmol), which was purified *via* column chromatography (SiO_2, PE/EtOAc 95/5).

***N*-{2-[(*Tert*-butyldimethylsilyl)oxy]phenyl}-*N*-(2-fluoroethynyl)benzamide 266a**



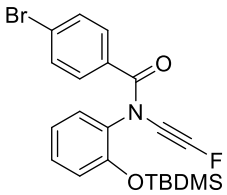
Pale yellow crystals. Melting point: 72-73 °C. R_f 0.21 (petroleum ether/EtOAc 95/5). Yield: 97%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 0.18 (6H, s, 2x $SiCH_3$), 0.94 (9H, s, $SiC(CH_3)_3$), 6.68-6.80 (1H, m, CH_{arom}), 6.83-6.92 (1H, m, CH_{arom}), 7.11-7.13 (2H, m, 2x CH_{arom}), 7.24-7.41 (5H, m, 5x CH_{arom}). **^{13}C NMR** (75 MHz, ref = $CDCl_3$): δ -4.6 (2x $SiCH_3$), 18.4 ($SiC(CH_3)_3$), 27.5 ($SiC(CH_3)_3$), 98.5 (d, *J* = 55.4 Hz, C≡CF), 116.4, 124.5, 125.0 and 126.6 (4x CH_{arom}), 128.1 (2x CH_{arom}), 128.4 (2x CH_{arom}), 129.8 ($C_{arom,quat}$), 130.3 (CH_{arom}), 135.3 and 150.8 (2x $C_{arom,quat}$), 162.5 (d, *J* = 274.6 Hz, C≡CF), 169.5 (C=O). **^{19}F NMR** (282 MHz, $CDCl_3$, ref = $CFCl_3$): δ -89.78 (1F, s, C≡CF). **IR** (ATR, cm^{-1}): $\nu_{C=O}$ = 1657, ν_{max} = 1491, 1347, 1244. $\nu_{C\equiv C}$: not visible. **MS** (ES^+): *m/z* (%): 370 (M + H^+, 100). **HRMS** (ES^+): calcd. for $C_{21}H_{25}FNO_2Si^+$: 370.1633, found 370.1643.

***N*-{2-[(*Tert*-butyldimethylsilyl)oxy]phenyl}-*N*-(2-fluoroethynyl)-4-methoxybenzamide 266c**



Yellow oil. R_f 0.63 (petroleum ether/EtOAc 9/1). Yield: 94%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.14 (6H, s, 2x $SiCH_3$), 0.92 (9H, s, $SiC(CH_3)_3$), 3.77 (3H, s, OCH_3), 6.77 (2H, d, *J* = 8.5 Hz, 2x CH_{arom}), 6.90-6.94 (2H, m, 2x CH_{arom}), 7.09-7.12 (2H, m, 2x CH_{arom}), 7.32 (2H, d, *J* = 8.5 Hz, 2x CH_{arom}). **^{13}C NMR** (100.6 MHz, ref = $CDCl_3$): δ -4.70 ($SiCH_3$), -4.67 ($SiCH_3$), 18.3 ($SiC(CH_3)_3$), 27.3 ($SiC(CH_3)_3$), 55.2 (OCH_3), 98.7 (d, *J* = 54.3 Hz, C≡CF), 113.2 (2x CH_{arom}), 116.2, 124.5, 125.0 and 126.3 (4x CH_{arom}), 127.4 and 130.2 (2x $C_{arom,quat}$), 130.6 (2x CH_{arom}), 150.8 and 161.1 (2x $C_{arom,quat}$), 162.4 (d, *J* = 274.3 Hz, C≡CF), 168.7 (C=O). **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ -89.92 (1F, s, C≡CF). **IR** (ATR, cm^{-1}): $\nu_{C\equiv C}$ = 2244, $\nu_{C=O}$ = 1649, ν_{max} = 1245, 732. **MS** (ES^+): *m/z* (%): 400 (M + H^+, 100). **HRMS** (ES^+): calcd. for $C_{22}H_{27}FNO_3Si^+$: 400.1739, found 400.1748.

***N*-{2-[(*Tert*-butyldimethylsilyl)oxy]phenyl}-*N*-(2-fluoroethynyl)-4-bromobenzamide 266d**



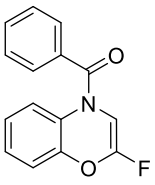
Yellow crystals. Melting point: 87-88 °C. R_f 0.63 (petroleum ether/EtOAc 9/1). Yield: 83%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.18 (6H, s, 2x $SiCH_3$), 0.93 (9H, s, $SiC(CH_3)_3$), 6.73 (1H, br s, CH_{arom}), 6.91 (1H, ddd, *J* = 8.0 Hz, 6.5 Hz, 2.1 Hz, CH_{arom}), 7.11-7.17 (4H, m, 4x CH_{arom}), 7.41 (2H, d, *J* = 8.5 Hz, 2x CH_{arom}). **^{13}C NMR** (100.6 MHz, ref = $CDCl_3$): δ -4.6 ($SiCH_3$), -4.5 ($SiCH_3$), 18.4 ($SiC(CH_3)_3$), 27.4 ($SiC(CH_3)_3$), 89.5 (d, *J* = 54.9 Hz, C≡CF), 116.6 and 124.7 (2x CH_{arom}), 124.8 ($C_{arom,quat}$), 124.9 and 126.8 (2x CH_{arom}), 129.5 ($C_{arom,quat}$), 130.1 (2x CH_{arom}), 131.3 (2x CH_{arom}), 134.1 and 150.7 (2x $C_{arom,quat}$), 162.5 (d, *J* = 274.1 Hz, C≡CF), 168.2 (C=O). **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ -89.49 (1F, s, C≡CF). **IR** (ATR, cm^{-1}): $\nu_{C\equiv C}$ = 2247, $\nu_{C=O}$ = 1651, ν_{max} = 1247, 730. **MS** (ES^+): *m/z* (%):

448/50 (M + H^+, 100). **HRMS** (ES^+): calcd. for $C_{21}H_{24}BrFNO_2Si^+$: 448.0738, found 448.0734. **El. Anal.** Calcd for $C_{21}H_{23}BrFNO_2Si$: C 56.25, H 5.17, N 3.12, found C 56.30, H 4.73, N 3.02.

5.7.17 Synthesis of benzoxazines 267a-c

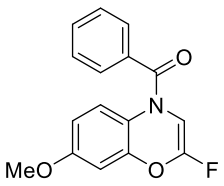
The synthesis of benzoxazine **267a** is described as a representative example. To a solution of benzamide **264a** (0.10 g, 0.21 mmol) in anhydrous THF (10 mL), a solution of KO*t*Bu in THF (1M, 0.21 mL, 1 equiv) was added. After stirring this reaction mixture at room temperature for two hours, saturated aqueous NH_4Cl (10 mL) was added. After extraction with EtOAc (3x 10 mL), drying ($MgSO_4$), filtration and evaporation of the solvent *in vacuo*, crude benzoxazine **267a** was obtained. Purification *via* preparative TLC (SiO_2, PE/EtOAc 95/5) afforded pure benzoxazine **267a** in 80% yield (0.043 g, 0.17 mmol).

4-Benzoyl-2-fluorobenzo[*b*][1,4]oxazine 267a



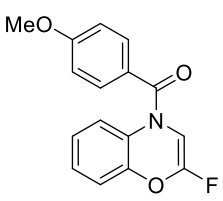
Yellow oil. R_f 0.33 (petroleum ether/EtOAc 9/1). Yield: 80%. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 6.16 (1H, br s, CH=CFO), 6.98-7.14 (3H, m, 3x CH_{arom}), 7.40-7.56 (6H, m, 6x CH_{arom}). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 89.4 (d, *J* = 48.5 Hz, <u>C</u>H=CF), 117.1, 123.2, 125.0 and 126.7 (4x CH_{arom}), 127.7 ($C_{arom,quat}$), 128.1 (2x CH_{arom}), 128.8 (2x CH_{arom}), 131.1 (CH_{arom}), 134.7 and 147.2 (2x $C_{arom,quat}$), 153.1 (d, *J* = 259.6 Hz, CH=<u>C</u>F), 167.5 (C=O). **^{19}F NMR** (282 MHz, $CDCl_3$, ref = $CFCl_3$): δ -112.33 (1F, br s, CH=CF). **IR** (ATR, cm^{-1}): $\nu_{C=O}$ = 1657, ν_{max} = 1490, 1340, 1243, 748, 697. **MS** (ES^+): *m/z* (%): 256 (M + H^+, 30). **HRMS** (ES^+): calcd. for $C_{15}H_{11}FNO_2^+$: 256.0768, found 256.0780.

4-Benzoyl-2-fluoro-7-methoxybenzo[*b*][1,4]oxazine 267b



Yellow oil. R_f 0.22 (petroleum ether/EtOAc 9/1). Yield: 82%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.78 (3H, s, OCH_3), 6.12 (1H, br s, CH=CF), 6.57-6.58 (2H, m, 2x CH_{arom}), 7.40-7.54 (6H, m, 6x CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 55.8 (OCH_3), 89.5 (d, *J* = 47.2 Hz, <u>C</u>H=CF), 103.0 and 110.1 (2x CH_{arom}), 120.7 ($C_{arom,quat}$), 123.7 (CH_{arom}), 128.0 (2x CH_{arom}), 128.7 (2x CH_{arom}), 130.8 (CH_{arom}), 135.1 and 147.9 (2x $C_{arom,quat}$), 152.8 (d, *J* = 258.7 Hz, CH=<u>C</u>F), 158.2 ($C_{arom,quat}$), 167.2 (C=O). **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ -113.34 (1F, br s, CH=CF). **IR** (ATR, cm^{-1}): $\nu_{C=O}$ = 1651, ν_{max} = 1503, 1307, 1246, 699. **MS** (ES^+): *m/z* (%): 286 (M + H^+, 100). **HRMS** (ES^+): calcd. for $C_{16}H_{13}FNO_3^+$: 286.0874, found 286.0879.

4-(4-Methoxybenzoyl)-2-fluorobenzo[*b*][1,4]oxazine 267c

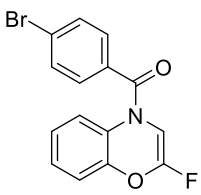


Yellow crystals. Melting point: 68-69 °C. R_f 0.06 (petroleum ether/EtOAc 9/1). Yield: 70%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.84 (3H, s, OCH_3), 6.22 (1H, d, $J_{H,F}$ = 2.7 Hz, CH=CF), 6.90 (2H, d, *J* = 8.9 Hz, 2x CH_{arom}), 6.98 (1H, ddd, *J* = 9.6 Hz, 7.1 Hz, 1.6 Hz, CH_{arom}), 6.98-7.00 (1H, m, CH_{arom}), 7.08 (1H, ddd, *J* = 8.4 Hz, 7.1 Hz, 1.4 Hz, CH_{arom}), 7.51-7.55 (3H, m, 3x CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 55.4 (OCH_3), 89.5 (d, *J* = 47.6 Hz, CH=CF), 113.8 (2x CH_{arom}), 117.0, 123.0, 124.8 and 126.3 (4x CH_{arom}), 126.5 and 128.1 (2x $C_{arom,quat}$), 130.3 (2x CH_{arom}), 147.1 ($C_{arom,quat}$), 153.0 (d, *J* = 261.6 Hz, CH=CF), 161.8 ($C_{arom,quat}$), 169.9 (C=O). **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ -113.01 (1F, d, $J_{H,F}$ = 2.7 Hz, CH=CF). **IR** (ATR, cm^{-1}): $\nu_{C=O}$ = 1652, ν_{max} = 1605, 1238, 1180, 756. **MS** (ES^+): *m/z* (%): 286 ($M + H^+$, 100). **HRMS** (ES^+): calcd. for $C_{16}H_{13}FNO_3^+$: 286.0874, found 286.0880.

Synthesis of benzoxazine 267d

N-{2-[(*Tert*-butyldimethylsilyl)oxy]phenyl}-*N*-(2-fluoroethynyl)-4-bromobenzamide **266d** (0.11 g, 0.23 mmol) was dissolved in anhydrous THF (10 mL) at 0 °C and a solution of TBAF in THF (1M, 0.23 mL, 1 equiv) was added. Stirring was continued for one hour at the same temperature. Subsequently, the reaction mixture was quenched with H_2O (10 mL) and extracted with EtOAc (3x 10 mL). After drying of the organic layers ($MgSO_4$), filtration and evaporation of the solvent, crude benzoxazine **267d** was obtained. Purification by means of preparative TLC (SiO_2, PE/EtOAc 9/1) afforded benzoxazine **267d** in 86% yield (0.067 g, 0.20 mmol).

4-(4-Bromobenzoyl)-2-fluorobenzo[*b*][1,4]oxazine 267d

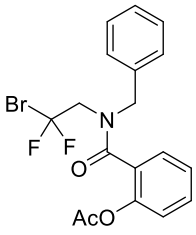


Yellow oil. R_f 0.40 (petroleum ether/EtOAc 9/1). Yield: 86%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.14 (1H, br s, CH=CF), 7.00-7.03 (2H, m, 2x CH_{arom}), 7.13 (1H, ddd, *J* = 8.1 Hz, 7.4 Hz, 1.4 Hz, CH_{arom}), 7.41-7.58 (5H, m, 5x CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 89.1 (d, *J* = 47.7 Hz, CH=CF), 117.1, 123.0 and 124.9 (3x CH_{arom}), 125.6 ($C_{arom,quat}$), 126.8 (CH_{arom}), 127.4 ($C_{arom,quat}$), 129.7 (2x CH_{arom}), 131.9 (2x CH_{arom}), 133.4 and 147.1 (2x $C_{arom,quat}$), 153.2 (d, *J* = 263.2 Hz, CH=CF), 166.1 (C=O). **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ -111.80 (1F, d, $J_{H,F}$ = 2.6 Hz, CH=CF). **IR** (ATR, cm^{-1}): $\nu_{C=O}$ = 1654, ν_{max} = 1489, 1345, 1242, 750. **MS** (ES^+): *m/z* (%): 334/36 ($M + H^+$, 100). **HRMS** (ES^+): calcd. for $C_{15}H_{10}BrFNO_2^+$: 333.9873, found 333.9875.

5.7.18 Synthesis of benzamides 276a-c

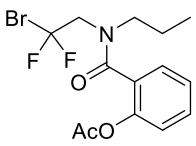
The synthesis of benzamide **276b** is described as representative example. To a mixture of *N*-propyl-2-bromo-2,2-difluoroethylamine **23b** (0.54 g, 2.7 mmol) and *O*-acetylsalicyloyl chloride **275a** (0.53 g, 2.7 mmol, 1 equiv) in THF (30 mL), triethylamine (1.35 g, 13 mmol, 5 equiv) was slowly added at room temperature. After stirring this reaction mixture at the same temperature for two hours, aqueous HCl (1M, 30 mL) was added and an extraction with Et_2O (3x 20 mL) was performed. After drying ($MgSO_4$), filtration and evaporation of the solvent, benzamide **276b** was purified *via* column chromatography (SiO_2, PE/EtOAc 85/15) and obtained in 55% yield (0.53 g, 1.49 mmol).

2-Acetoxy-*N*-(2-bromo-2,2-difluoroethyl)-*N*-(benzyl)benzamide 276a



Yellow oil. R_f 0.15 (petroleum ether/EtOAc 85/15). Yield: 95%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.03 (0.7H, s, $CH_3C=O$ (minor)), 2.32 (2.3H, s, $CH_3C=O$ (major)), 3.57-4.43 (2H, br s, CH_2CF_2), 4.57 (2H, s, CH_2N), 7.12 (2H, d, J = 6.8 Hz, 2x CH_{arom}), 7.21-7.46 (7H, m, 7x CH_{arom}). **^{13}C NMR** (100.6 MHz, ref = $CDCl_3$): δ 20.6 ($\underline{C}H_3C=O$ (minor)), 20.8 ($\underline{C}H_3C=O$ (major)), 47.9 ($\underline{C}H_2C_{arom,quat}$ (minor)), 51.5 (t, J = 23.6 Hz, $\underline{C}H_2CF_2Br$ (major)), 53.0 ($\underline{C}H_2C_{arom,quat}$ (major)), 56.0 (t, J = 23.9 Hz, $\underline{C}H_2CF_2Br$ (minor)), 120.4 (t, J = 309.5 Hz, CF_2Br), 123.0 (CH_{arom} (minor)), 123.3 (CH_{arom} (major)), 126.2 (CH_{arom}), 127.3 (2x CH_{arom}), 127.5 and 128.2 (2x CH_{arom}), 128.4 ($C_{arom,quat}$ (minor)), 128.5 ($C_{arom,quat}$ (major)), 128.9 (2x CH_{arom} (minor)), 129.1 (2x CH_{arom} (major)), 130.8 (CH_{arom}), 135.2 and 147.0 (2x $C_{arom,quat}$ (major)), 135.8 and 146.5 (2x $C_{arom,quat}$ (minor)), 168.81, 168.85, 168.9 and 169.1 (NC=O (major and minor) and OC=O (major and minor)). **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ -49.11 to -52.76 (2F, m, CF_2Br). **IR** (ATR, cm^{-1}): $\nu_{C=O}$ = 1767, $\nu_{C=O}$ = 1656, ν_{max} = 1190, 1076, 910, 730. **MS** (ES^+): *m/z* (%): 412/14 (M + H^+, 100). **HRMS** (ES^+): calcd. for $C_{18}H_{17}BrF_2NO_3^+$: 412.0354, found 412.0361.

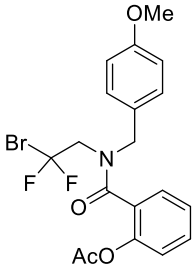
2-Acetoxy-*N*-(2-bromo-2,2-difluoroethyl)-*N*-(propyl)benzamide 276b



Colorless oil. R_f 0.29 (petroleum ether/EtOAc 85/15). Yield: 55%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.74 (2.3H, t, J = 7.4 Hz, $CH_2C\underline{H}_3$ (major)), 0.98 (0.7H, t, J = 7.3 Hz, $CH_2C\underline{H}_3$ (minor)), 1.50 (1.5H, sextet, J = 7.4 Hz, $C\underline{H}_2CH_3$ (major)), 1.68 (0.5H, sextet, J = 7.3 Hz, $C\underline{H}_2CH_3$ (minor)), 2.26 (3H, s, $CH_3C=O$), 3.28 (2H, t, J = 7.6 Hz, $NC\underline{H}_2CH_2$), 3.83-4.62 (2H, m, CH_2CF_2Br), 7.20 (1H, d, J = 8.2 Hz, CH_{arom}), 7.30 (1H, d, J = 7.0 Hz, CH_{arom}), 7.33 (1H, ddd, J = 7.3 Hz, 7.0 Hz, 1.8 Hz, CH_{arom}), 7.45 (1H, ddd, J = 8.2 Hz, 7.3 Hz, 1.8 Hz, CH_{arom}).**^{13}C NMR** (100.6 MHz, ref = $CDCl_3$, 50 °C): δ 10.6 ($CH_2\underline{C}H_3$ (major)), 11.2 ($CH_2\underline{C}H_3$ (minor)), 19.8 ($\underline{C}H_2CH_3$ (minor)), 20.7 ($\underline{C}H_3C=O$), 20.9 ($\underline{C}H_2CH_3$ (major)), 47.7 ($N\underline{C}H_2CH_2$ (minor)), 50.6 ($N\underline{C}H_2CH_2$ (major)), 51.8 (t, J = 23.7 Hz, $\underline{C}H_2CF_2Br$ (major)), 57.7 (t, J = 23.3 Hz,

$\underline{C}H_2CF_2Br$ (minor)), 120.5 (t, *J* = 309.6 Hz, CF_2Br), 123.1, 125.9, 127.4 and 130.4 (4x CH_{arom} (major)), 122.9, 126.0, 128.0 and 130.6 (4x CH_{arom} (minor)), 128.7 ($C_{arom,quat}$ (minor)), 128.8 ($C_{arom,quat}$ (major)), 146.6 ($C_{arom,quat}$), 168.6, 168.7 and 168.9 (NC=O (major and minor) and OC=O). **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ -50.86 (2F, br s, CF_2Br). **IR** (ATR, cm^{-1}): $\nu_{C=O}$ = 1767, $\nu_{C=O}$ = 1651, ν_{max} = 1192, 1177, 1078. **MS** (ES^+): *m/z* (%): 364/66 (M + H^+, 100). **HRMS** (ES^+): calcd. for $C_{14}H_{17}BrF_2NO_3^+$: 364.0354, found 364.0355.

2-Acetoxy-*N*-(2-bromo-2,2-difluoroethyl)-*N*-(4-methoxybenzyl)benzamide 276c



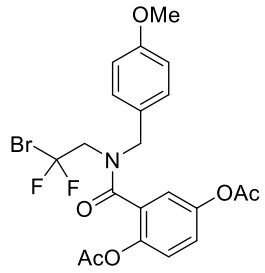
White crystals. Melting point: 109-110 °C. R_f 0.11 (petroleum ether/EtOAc 9/2). Yield: 78%. **^{1}H NMR** (400 MHz, $CDCl_3$, 50 °C): δ 2.04 (0.6H, s, CH_3C=O (minor)), 2.30 (2.4H, s, CH_3C=O (major)), 3.80 (3H, s, OCH_3), 3.89 (0.4H, br s, CH_2CF_2 (minor)), 4.30 (1.6H, br s, CH_2CF_2 (major)), 4.49 (2H, s, $CH_2C_{arom,quat}$), 6.86-6.88 (2H, m, 2x CH_{arom}), 7.02-7.04 (2H, m, 2x CH_{arom}), 7.20-7.27 (2H, m, 2x CH_{arom}), 7.38-7.45 (2H, m, 2x CH_{arom}). **^{13}C NMR** (100.6 MHz, ref = $CDCl_3$): δ 20.6 ($\underline{C}H_3C$=O (minor)), 20.8 ($\underline{C}H_3C$=O (major)), 47.2 ($\underline{C}H_2C_{arom,quat}$ (minor)), 51.0 (t, *J* = 23.7 Hz, $\underline{C}H_2CF_2Br$ (major)), 52.4 ($CH_2C_{arom,quat}$ (major)), 55.2 (OCH_3), 55.8 (t, *J* = 23.5 Hz, $\underline{C}H_2CF_2Br$ (minor)), 114.2 (2x CH_{arom} (minor)), 114.4 (2x CH_{arom} (major)), 120.5 (t, *J* = 309.5 Hz, CF_2Br), 123.0 (CH_{arom} (minor)), 123.2 (CH_{arom} (major)), 126.2 (CH_{arom}), 126.8 ($C_{arom,quat}$), 127.6 (CH_{arom} (major)), 127.8 (CH_{arom} (minor)), 128.26 ($C_{arom,quat}$ (minor)), 128.33 (2x CH_{arom} (minor)), 128.5 ($C_{arom,quat}$ (major)), 128.8 (2x CH_{arom} (major)), 130.4 (CH_{arom} (minor)), 130.8 (CH_{arom} (major)), 146.4 ($C_{arom,quat}$ (minor)), 146.9 ($C_{arom,quat}$ (major)), 159.5 ($C_{arom,quat}$), 168.7, 168.8 and 168.9 (NC=O (major and minor) and OC=O). **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ -48.54 to -52.33 (2F, m, CF_2Br). **IR** (ATR, cm^{-1}): $\nu_{C=O}$ = 1765, $\nu_{C=O}$ = 1654, ν_{max} = 1188, 1080, 925, 790. **MS** (ES^+): *m/z* (%): 442/44 (M + H^+, 100). **HRMS** (ES^+): calcd. for $C_{19}H_{19}BrF_2NO_4^+$: 442.0460, found 442.0458.

5.7.19 Synthesis of benzamides 276d-e

The synthesis of benzamide **276d** is described as representative example. 2,5-Diacetoxybenzoic acid (0.22 g, 0.94 mmol) was dissolved in $SOCl_2$ (distilled, 1 mL) and stirred at reflux temperature for 15 minutes. Subsequently, the residual $SOCl_2$ was evaporated under reduced pressure. The resulting acid chloride **275b** was used without purification and redissolved in anhydrous THF (20 mL) and *N*-(4-methoxybenzyl)-2-bromo-2,2-difluoroethylamine **23c** (0.26 g, 1 equiv) and Et_3N (0.19 g, 2 equiv) were added at 0 °C. Subsequently, the reaction mixture was stirred at room temperature for 22 hours, after which H_2O (20 mL) was added and an extraction was performed with EtOAc (3x 20 mL). The combined organic layers were

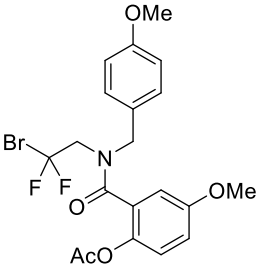
dried ($MgSO_4$), filtered and the solvent was removed *in vacuo*. Purification *via* flash chromatography (SiO_2, PE/EtOAc 7/3) afforded benzamide **276d** in 72% yield (0.34 g, 0.68 mmol).

2,5-Diacetoxy-*N*-(2-bromo-2,2-difluoroethyl)-*N*-(4-methoxybenzyl)benzamide 276d



Yellow oil. R_f 0.17 (petroleum ether/EtOAc 7/3). Yield: 72%. **^{1}H NMR** (400 MHz, $CDCl_3$, 50 °C): δ 2.03 (0.9H, br s, CH_3C=O (minor)), 2.27 (3H, s, CH_3C=O), 2.29 (2.1H, br s, CH_3C=O (major)), 3.80 (3H, s, OCH_3), 3.89 (0.6H, br s, CH_2CF_2 (minor)), 4.27 (1.4H, br s, CH_2CF_2 (major)), 4.50 (2H, br s, $CH_2C_{arom,quat}$), 6.86-6.88 (2H, m, 2x CH_{arom}), 7.03-7.05 (2H, m, 2x CH_{arom}), 7.15-7.25 (3H, m, 3x CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 20.6 ($\underline{C}H_3C$=O (minor)), 20.8 ($\underline{C}H_3C$=O (major)), 21.0 ($\underline{C}H_3C$=O), 47.4 ($\underline{C}H_2C_{arom,quat}$ (minor)), 51.0 (t, *J* = 23.6 Hz, $\underline{C}H_2CF_2Br$ (major)), 52.6 ($CH_2C_{arom,quat}$ (major)), 55.3 (OCH_3), 55.8 (t, *J* = 24.0 Hz, $\underline{C}H_2CF_2Br$ (minor)), 114.3 (2x CH_{arom} (minor)), 114.5 (2x CH_{arom} (major)), 120.5 (t, *J* = 309.3 Hz, CF_2Br), 120.9 (CH_{arom} (major)), 121.6 (CH_{arom} (minor)), 123.9 (CH_{arom}), 124.0 (CH_{arom} (minor)), 124.2 (CH_{arom} (major)), 126.6 ($C_{arom,quat}$), 129.17 (2x CH_{arom} (major)), 129.24 (2x CH_{arom} (minor)), 130.5 ($C_{arom,quat}$), 143.8 ($C_{arom,quat}$ (minor)), 144.2 ($C_{arom,quat}$ (major)), 148.0 ($C_{arom,quat}$), 159.5 ($C_{arom,quat}$ (minor)), 159.6 ($C_{arom,quat}$ (major)), 167.6 (NC=O (minor)), 167.8 (NC=O (major)), 168.8 (2x OC=O)). **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ -48.49 to -51.32 (2F, m, CF_2Br). **IR** (ATR, cm^{-1}): $\nu_{C=O}$ = 1763, $\nu_{C=O}$ = 1655, ν_{max} = 1201, 1163. **MS** (ES^+): *m/z* (%): 517/19 (M + NH_4^+, 100), 500/2 (M + H^+, 98). **HRMS** (ES^+): calcd. for $C_{21}H_{21}BrF_2NO_6^+$: 500.0515, found 500.0496.

2-Acetoxy-5-methoxy-*N*-(2-bromo-2,2-difluoroethyl)-*N*-(4-methoxybenzyl)benzamide 276e



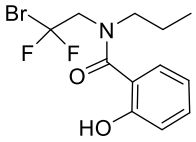
White crystals. Melting point: 94-95 °C. R_f 0.12 (petroleum ether/EtOAc 9/2). Yield: 67%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.02 (0.7H, s, CH_3C=O (minor)), 2.29 (2.3H, s, CH_3C=O (major)), 3.75 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 3.81 (2H, br s, CH_2CF_2), 4.51 (2H, br s, $CH_2C_{arom,quat}$), 6.86-6.88 (3H, m, 3x CH_{arom}), 6.95 (1H, dd, *J* = 9.0 Hz, 2.9 Hz, CH_{arom}), 7.04 (2H, d, *J* = 8.6 Hz, 2x CH_{arom}), 7.12 (1H, d, *J* = 9.0 Hz, CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 18.8 ($\underline{C}H_3C$=O (minor)), 19.0 ($\underline{C}H_3C$=O (major)), 49.4 (t, *J* = 23.1 Hz, $\underline{C}H_2CF_2Br$), 50.7 ($\underline{C}H_2C_{arom,quat}$), 53.5 ($OCH_3$), 53.9 ($OCH_3$), 110.5 ($CH_{arom}$ (major)), 110.9 (CH_{arom} (minor)), 112.4 (2x CH_{arom} (minor)), 112.6 (2x CH_{arom} (major)), 114.4 (CH_{arom} (major)), 114.8 (CH_{arom} (minor)), 118.6 (t, *J* = 309.6 Hz, CF_2Br), 122.2 (CH_{arom} (minor)), 122.4 (CH_{arom} (major)), 125.1 ($C_{arom,quat}$ (major)), 125.9 ($C_{arom,quat}$ (minor)), 127.0 (2x CH_{arom} (major)), 127.4 (2x CH_{arom} (minor)), 128.7 ($C_{arom,quat}$), 137.9 ($C_{arom,quat}$ (minor)), 138.4 ($C_{arom,quat}$ (major)), 155.4 and 157.7 (2x $C_{arom,quat}$), 166.7 (NC=O (minor)), 166.9 (NC=O

(major)), 167.4 (OC=O (minor)), 167.5 (OC=O (major)). **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ -48.56 to -52.09 (2F, m, CF_2Br). **IR** (ATR, cm^{-1}): $\nu_{C=O}$ = 1762, $\nu_{C=O}$ = 1650, ν_{max} = 1188, 1110, 1029. **MS** (ES^+): *m/z* (%): 472/74 (M + H^+, 100). **HRMS** (ES^+): calcd. for $C_{20}H_{21}BrF_2NO_5^+$: 472.0566, found 472.0557. **El. Anal.** Calcd for $C_{20}H_{20}BrF_2NO_5$: C 50.86, H 4.27, N 2.97, found C 50.73, H 4.21, N 2.92.

5.7.20 Synthesis of benzamide 277b, enamide 278b and 2-fluoro-1,4-benzoxazepin-5-one 279b

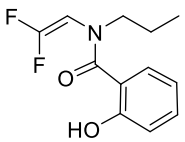
To an ice-cooled solution of benzamide **276b** (0.086 g, 0.24 mmol) in anhydrous THF (5 mL), a solution of LiHMDS in THF (1M, 0.52 mL, 2.2 equiv) was added, and the resulting mixture was stirred at room temperature for 5 hours. Subsequently, the reaction mixture was poured into saturated aqueous NH_4Cl (5 mL) and extracted with EtOAc (3x 10 mL). Drying ($MgSO_4$), filtration of the drying agent and removal of the solvent afforded benzamide **277b**, enamide **278b** and 2-fluoro-1,4-benzoxazepin-5-one **279b**, which were further purified in 30% (0.024 g, 0.072 mmol), 17% (0.010 g, 0.041 mmol,) and 31% (0.0.16 g, 0.074 mmol) yield, respectively, by preparative TLC (PE/EtOAc 9/1).

***N*-2-Bromo-2,2-difluoroethyl-*N*-propyl-(2-hydroxy)benzamide 277b**



Yellow oil. R_f 0.04 (petroleum ether/EtOAc 9/1). Yield: 30%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.82 (3H, t, *J* = 7.4 Hz, CH_3), 1.60 (2H, sextet, *J* = 7.4 Hz, $C\underline{H}_2CH_3$), 3.64 (2H, t, *J* = 7.4 Hz, $NC\underline{H}_2CH_2$), 4.40 (2H, t, $J_{H,F}$ = 12.3 Hz, CH_2CF_2Br), 6.91 (1H, ddd, *J* = 7.8 Hz, 7.3 Hz, 0.9 Hz, CH_{arom}), 7.03 (1H, dd, *J* = 8.3 Hz, 0.9 Hz, CH_{arom}), 7.33 (1H, dd, *J* = 7.8 Hz, 1.6 Hz, CH_{arom}), 7.37 (1H, ddd, *J* = 8.3 Hz, 7.3 Hz, 1.6 Hz, CH_{arom}), 8.76 (1H, br s, OH). **^{13}C NMR** (100.6 MHz, ref = $CDCl_3$): δ 10.9 (CH_3), 21.1 ($\underline{C}H_2CH_3$), 51.6 ($\underline{C}H_2CF_2Br$), 53.9 ($\underline{C}H_2N$), 117.8 (CH_{arom}), 118.7 ($C_{arom,quat}$), 119.4 (CH_{arom}), 120.9 (t, *J* = 309.5 Hz, CF_2Br), 128.1 and 132.6 (2x CH_{arom}), 157.0 ($C_{arom,quat}$), 173.4 (C=O). **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ -50.47 (2H, t, $J_{H,F}$ = 12.3 Hz, CF_2Br). **IR** (ATR, cm^{-1}): ν_{OH} = 3174, $\nu_{C=O}$ = 1620, ν_{max} = 1595, 1083, 751. **MS** (ES^+): *m/z* (%): 322/24 (M + H^+, 100). **HRMS** (ES^+): calcd. for $C_{12}H_{15}BrF_2NO_2^+$: 322.0249, found 322.0247.

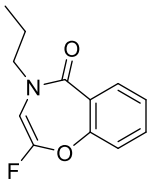
***N*-2,2-Difluorovinyl-*N*-propyl-(2-hydroxy)benzamide 278b**



White powder. Melting point: 59-60 °C. R_f 0.11 (petroleum ether/EtOAc 9/1). Yield: 17%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.96 (3H, t, *J* = 7.5 Hz, CH_3), 1.69 (2H, sextet, *J* = 7.5 Hz, $C\underline{H}_2CH_3$), 3.60 (2H, t, *J* = 7.5 Hz, NCH_2), 5.61 (1H, dd, $J_{H,F}$ = 19.3 Hz, 2.1 Hz, $CH{=}CF_2$), 6.83 (1H, ddd, *J* = 7.9 Hz, 7.3 Hz, 1.0 Hz, CH_{arom}), 7.00 (1H, dd, *J* = 8.3 Hz, 1.0 Hz, CH_{arom}), 7.35 (1H, ddd, *J* = 8.3 Hz, 7.3 Hz, 1.5 Hz, CH_{arom}), 7.43 (1H, dd, *J* = 7.9 Hz, 1.5 Hz, CH_{arom}), 9.95 (1H, br s, OH). **^{13}C NMR** (100.6 MHz,

$CDCl_3$): δ 11.2 (CH_3), 20.6 ($\underline{C}H_2CH_3$), 50.3 (NCH_2), 89.6 (dd, *J* = 49.4 Hz, 13.3 Hz, $\underline{C}HCF_2$), 116.3 ($C_{arom,quat}$), 118.1, 118.3, 128.7 and 133.5 (4x CH_{arom}), 155.4 (dd, *J* = 295.9 Hz, 287.7 Hz, $CH\underline{C}F_2$), 159.8 ($C_{arom,quat}$), 171.6 (C=O). **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ -87.33 (1F, dd, *J* = 40.8 Hz, $J_{H,F}$ = 19.3 Hz, CH=C$\underline{F}$(F), -99.90 (1F, d, *J* = 40.8 Hz, CH=CF($\underline{F}$)). **IR** (ATR, cm^{-1}): ν_{OH} = 3159, $\nu_{C=O}$ = 1616, ν_{max} = 1233, 760. **MS** (ES^+): *m/z* (%): 242 (M + H^+, 100). **HRMS** (ES^+): calcd. for $C_{12}H_{14}F_2NO_2^+$: 242.0987, found 242.0987.

2-Fluoro-4-propylbenzo[*f*][1,4]oxazepin-5-one 279b

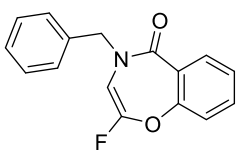


Pale yellow oil. R_f 0.17 (petroleum ether/EtOAc 9/1). Yield: 31% (67% yield was obtained following the procedure described below). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.97 (3H, t, *J* = 7.4 Hz, $CH_2C\underline{H}_3$), 1.70 (2H, sextet, *J* = 7.4 Hz, $C\underline{H}_2CH_3$), 3.57-3.61 (2H, m, CH_2N), 5.50 (1H, d, $J_{H,F}$ = 3.7 Hz, CH=CF), 7.11 (1H, dd, *J* = 8.2 Hz, 1.1 Hz, CH_{arom}), 7.29 (1H, ddd, *J* = 7.8 Hz, 7.4 Hz, 1.1 Hz, CH_{arom}), 7.48 (1H, ddd, *J* = 8.2 Hz, 7.4 Hz, 1.8 Hz, CH_{arom}), 7.92 (1H, dd, *J* = 7.8 Hz, 1.8 Hz, CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 11.1 (CH_3), 21.1 ($\underline{C}H_2CH_3$), 49.9 (NCH_2), 95.8 (d, *J* = 57.7 Hz, $\underline{C}$H=CF), 119.4 (CH_{arom}), 125.98 ($C_{arom,quat}$), 126.02, 132.6 and 133.3 (3x CH_{arom}), 156.8 (d, *J* = 279.7 Hz, CH=$\underline{C}$F), 159.7 (d, *J* = 4.3 Hz, $C_{arom,quat}$), 165.1 (C=O). **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ -99.24 (1F, d, $J_{H,F}$ = 3.7 Hz, CF). **IR** (ATR, cm^{-1}): $\nu_{C=O}$ = 1639, ν_{max} = 1453, 1411, 1192, 759. **MS** (ES^+): *m/z* (%): 222 (M + H^+, 100). **HRMS** (ES^+): calcd. for $C_{12}H_{13}FNO_2^+$: 222.0925, found 222.0930.

5.7.21 Synthesis of benzo[*f*][1,4]oxazepin-5-ones 279a-e

As a representative example, the synthesis of 2-fluoro-4-(4-methoxybenzyl)benzo[*f*][1,4]oxazepin-5-one **279c** is described here. To a solution of benzamide **276c** (1.15 g, 2.6 mmol) in anhydrous THF (30 mL), a solution of KO*t*Bu in THF (1M, 5.2 mL, 2 equiv) was added at room temperature. After stirring the reaction mixture at reflux temperature for three hours, saturated aqueous NH_4Cl (30 mL) was added. After extraction (3x 30 mL EtOAc), drying with $MgSO_4$, filtration of the drying agent and evaporation of the solvent, crude oxazepin-5-one **279c** was obtained. Purification by means of column chromatography (SiO_2, PE/EtOAc 9/1) afforded pure oxazepin-5-one **279c** in 77% yield (0.60 g, 2.0 mmol).

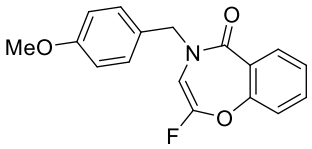
4-Benzyl-2-fluorobenzo[*f*][1,4]oxazepin-5-one 279a



White crystals. Melting point: 65-66 °C. R_f 0.19 (petroleum ether/EtOAc 9/1). Yield: 62%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.85 (2H, s, CH_2N), 5.49 (1H, d, $J_{H,F}$ = 3.7 Hz, CH=CF), 7.11 (1H, dd, *J* = 8.2 Hz, 1.1 Hz, CH_{arom}), 7.28-7.38 (5H, m, 5x CH_{arom}), 7.49 (1H, ddd, *J* = 8.2 Hz, 7.4 Hz, 1.8 Hz, CH_{arom}), 7.99 (1H, dd, *J* = 7.8 Hz, 1.8 Hz, CH_{arom}). **^{13}C NMR**

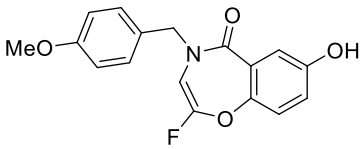
(100.6 MHz, $CDCl_3$): δ 51.5 (NCH_2), 95.3 (d, *J* = 58.1 Hz, <u>C</u>H=CF), 119.5 (CH_{arom}), 125.6 (d, *J* = 2.1 Hz, $C_{arom,quat}$), 126.1 and 127.8 (2x CH_{arom}), 128.0 (2x CH_{arom}), 128.8 (2x CH_{arom}), 132.8 and 133.6 (2x CH_{arom}), 136.0 ($C_{arom,quat}$), 156.9 (d, *J* = 280.1 Hz, CH=<u>C</u>F), 159.7 (d, *J* = 4.4 Hz, $C_{arom,quat}$), 165.3 (C=O). **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ -98.64 (1F, d, $J_{H,F}$ = 3.7 Hz, CF). **IR** (ATR, cm^{-1}): $\nu_{C=O}$ = 1627, ν_{max} = 1451, 1420, 1196, 692. **MS** (ES^+): *m/z* (%): 270 ($M + H^+$, 100). **HRMS** (ES^+): calcd. for $C_{16}H_{13}FNO_2^+$: 270.0925, found 270.0921.

2-Fluoro-4-(4-methoxybenzyl)benzo[*f*][1,4]oxazepin-5-one 279c



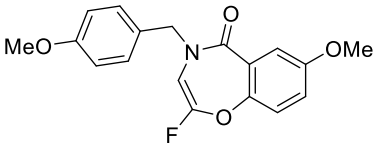
Yellow oil. R_f 0.12 (petroleum ether/EtOAc 9/1). Yield: 77%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.80 (3H, s, OCH_3), 4.78 (2H, s, NCH_2), 5.48 (1H, d, $J_{H,F}$ = 3.7 Hz, CH=CF), 6.88 (2H, d, *J* = 8.6 Hz, 2x CH_{arom}), 7.11 (1H, dd, *J* = 8.2 Hz, 1.0 Hz, CH_{arom}), 7.27 (2H, d, *J* = 8.6 Hz, 2x CH_{arom}), 7.31 (1H, ddd, *J* = 7.8 Hz, 7.4 Hz, 1.0 Hz, CH_{arom}), 7.49 (1H, ddd, *J* = 8.2 Hz, 7.4 Hz, 1.8 Hz, CH_{arom}), 7.98 (1H, dd, *J* = 7.8 Hz, 1.8 Hz, CH_{arom}). **^{13}C NMR** (100.6 MHz, ref = $CDCl_3$): δ 50.8 (NCH_2), 55.0 (OCH_3), 95.2 (d, *J* = 58.1 Hz, <u>C</u>H=CF), 114.0 (2x CH_{arom}), 119.3 (CH_{arom}), 125.5 (d, *J* = 2.1 Hz, $C_{arom,quat}$), 125.9 (CH_{arom}), 128.0 ($C_{arom,quat}$), 129.3 (2x CH_{arom}), 132.6 and 133.4 (2x CH_{arom}), 156.6 (d, *J* = 279.9 Hz, CH=<u>C</u>F), 159.2 ($C_{arom,quat}$), 159.5 (d, *J* = 4.3 Hz, $C_{arom,quat}$), 165.0 (C=O). **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ -98.67 (1F, d, $J_{H,F}$ = 3.7 Hz, CF). **IR** (ATR, cm^{-1}): $\nu_{C=O}$ = 1640, ν_{max} = 1246, 1218, 1200, 1137, 760. **MS** (ES^+): *m/z* (%): 300 ($M + H^+$, 100). **HRMS** (ES^+): calcd. for $C_{17}H_{15}FNO_3^+$: 300.1030, found 300.1023.

2-Fluoro-7-hydroxy-4-(4-methoxybenzyl)benzo[*f*][1,4]oxazepin-5-one 279d



Brown crystals. Melting point: 108-109 °C. Yield: 86%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.80 (3H, s, OCH_3), 4.77 (2H, s, NCH_2), 5.39 (1H, br s, OH), 5.44 (1H, d, $J_{H,F}$ = 3.8 Hz, CH=CF), 6.88 (2H, d, *J* = 8.7 Hz, 2x CH_{arom}), 6.94-7.00 (2H, m, 2x CH_{arom}), 7.24-7.26 (2H, m, 2x CH_{arom}), 7.44 (1H, d, *J* = 2.9 Hz, CH_{arom}). **^{13}C NMR** (100.6 MHz, ref = $CDCl_3$): δ 51.5 (NCH_2), 55.4 (OCH_3), 94.9 (d, *J* = 60.2 Hz, <u>C</u>H=CF), 114.3 (2x CH_{arom}), 118.2, 120.7 and 121.4 (3x CH_{arom}), 125.5 and 127.6 (2x $C_{arom,quat}$), 129.5 (2x CH_{arom}), 153.1 (d, *J* = 4.4 Hz, $C_{arom,quat}$), 154.8 ($C_{arom,quat}$), 157.4 (d, *J* = 282.4 Hz, CH=<u>C</u>F), 159.4 ($C_{arom,quat}$), 166.1 (C=O). **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ -97.96 (1F, s, CF). **IR** (ATR, cm^{-1}): ν_{OH} = 3336, $\nu_{C=O}$ = 1634, ν_{max} = 1454, 1219, 1174, 813. **MS** (ES^+): *m/z* (%): 316 ($M + H^+$, 100). **HRMS** (ES^+): calcd. for $C_{17}H_{15}FNO_4^+$: 316.0980, found 316.0975.

2-Fluoro-7-methoxy-4-(4-methoxybenzyl)benzo[*f*][1,4]oxazepin-5-one 279e

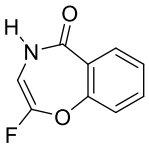


Yellow oil. R_f 0.17 (petroleum ether/EtOAc 8/2). Yield: 88%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.80 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 4.78 (2H, s, NCH_2), 5.44 (1H, d, $J_{H,F}$ = 3.8 Hz, CH=CF), 6.88 (2H, d, J = 8.8 Hz, 2x CH_{arom}), 7.00-7.01 (2H, m, 2x CH_{arom}), 7.27 (2H, d, J = 8.8 Hz, 2x CH_{arom}), 7.44 (1H, dd, J = 2.4 Hz, 1.0 Hz, CH_{arom}). **^{13}C NMR** (100.6 MHz, ref = $CDCl_3$): δ 51.2 (NCH_2), 55.3 (OCH_3), 55.9 (OCH_3), 95.0 (d, J = 58.5 Hz, CH=CF), 114.3 (2x CH_{arom}), 115.4, 120.3 and 120.5 (3x CH_{arom}), 126.2 (d, J = 2.2 Hz, $C_{arom,quat}$), 128.1 ($C_{arom,quat}$), 129.5 (2x CH_{arom}), 153.6 (d, J = 4.4 Hz, $C_{arom,quat}$), 157.26 ($C_{arom,quat}$), 157.28 (d, J = 281.1 Hz, CH=CF), 159.4 ($C_{arom,quat}$), 165.2 (C=O). **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ -98.49 (1F, d, $J_{H,F}$ = 3.8 Hz, CF). **IR** (ATR, cm^{-1}): $\nu_{C=O}$ = 1640, ν_{max} = 1429, 1244, 1214, 1174, 1032. **MS** (ES^+): *m/z* (%): 330 ($M + H^+$, 100). **HRMS** (ES^+): calcd. for $C_{18}H_{17}FNO_4^+$: 330.1136, found 330.1137.

5.7.22 Synthesis of benzo[*f*][1,4]oxazepin-5-ones 280a-b

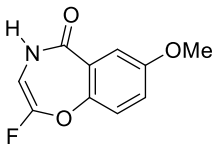
The synthesis of 2-fluorobenzo[*f*][1,4]oxazepin-5-one **280a** is described as representative example. 2-Fluoro-4-(4-methoxybenzyl)benzo[*f*][1,4]oxazepin-5-one **279c** (0.12 g, 0.38 mmol) was dissolved in $BF_3.OEt_2$ (0.27 g, 5 equiv, 0.24 mL) and this mixture was stirred at 128 °C for 6 hours. Subsequently, Et_2O (10 mL) and $NaHCO_3$ (10 mL) were added and an extraction was performed with EtOAc (3x 10 mL). After drying ($MgSO_4$), filtration and evaporation of the organic phase *in vacuo*, Et_2O (10 mL) was added and the precipitate was filtered off. After evaporation, crude benzoxazepinone **280a** was obtained and recrystallized from Et_2O, affording pure benzoxazepinone **280a** in 51% yield (0.035 g, 0.19 mmol).

2-Fluorobenzo[*f*][1,4]oxazepin-5-one 280a



White crystals. Yield: 51%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.60 (1H, t, $J_{H,F}$ = 4.0 Hz, CH=CF), 6.46 (1H, br s, NH), 7.15 (1H, d, J = 8.1 Hz, CH_{arom}), 7.32 (1H, ddd, J = 7.8 Hz, 7.4 Hz, 0.7 Hz, CH_{arom}), 7.55 (1H, ddd, J = 8.1 Hz, 7.4 Hz, 1.7 Hz, CH_{arom}), 7.95 (1H, dd, J = 7.8 Hz, 1.7 Hz, CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 90.6 (d, J = 58.9 Hz, CH=CF), 120.2 (CH_{arom}), 124.6 (d, J = 2.2 Hz, $C_{arom,quat}$), 126.1, 132.4 and 134.4 (3x CH_{arom}), 156.0 (d, J = 275.8 Hz, CH=CF), 158.7 ($C_{arom,quat}$), 166.3 (C=O). **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): -100.91 (1F, br s, CH=CF). **IR** (ATR, cm^{-1}): $\nu_{C=O}$ = 1675, ν_{max} = 1223, 1180, 786, 752. **MS** (ES^+): *m/z* (%): 180 ($M + H^+$, 100). **HRMS** (ES^+): calcd. for $C_9H_7FNO_2^+$: 180.0455, found 180.0454.

2-Fluoro-7-methoxybenzo[*f*][1,4]oxazepin-5-one 280b



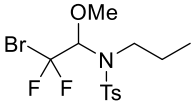
White crystals. Yield: 54%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.83 (3H, s, OCH_3), 5.56 (1H, t, $J_{H,F}$ = 4.1 Hz, CH=CF), 6.50 (1H, br s, NH), 7.05-7.06 (2H, m, 2x CH_{arom}), 7.39-7.40 (1H, m, CH_{arom}). **^{13}C NMR** (100.6 MHz, ref = $CDCl_3$): δ 56.0 (OCH_3), 90.6 (d, *J* = 58.9 Hz, CH=CF), 115.0, 121.2 and 121.3 (3x CH_{arom}), 125.3 (d, *J* = 2.3 Hz, $C_{arom,quat}$), 152.7 (d, *J* = 3.7 Hz, $C_{arom,quat}$), 156.4 (d, *J* = 277.7 Hz, CH=CF), 157.3 ($C_{arom,quat}$), 167.1 (C=O). **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ -100.65 (1F, d, $J_{H,F}$ = 4.1 Hz, CF). **IR** (ATR, cm^{-1}): $\nu_{C=O}$ = 1673, ν_{max} = 1487, 1432, 1216, 1186, 768. **MS** (ES^+): *m/z* (%): 210 ($M + H^+$, 100). **HRMS** (ES^+): calcd. for $C_{10}H_9FNO_3^+$: 210.0561, found 210.0558.

5.7.23 Reactivity of β,β-difluoroenamide 220 toward electrophiles

Synthesis of *N*-(2-bromo-2,2-difluoro-1-methoxyethyl)-*N*-propyl-4-methyl-benzenesulfonamide 281

To a solution of enamide **220** (0.250 g, 0.91 mmol) in methanol (5 mL) was added NBS (1 equiv, 0.160 g, 0.97 mmol) and this mixture was stirred at room temperature for four hours. The solvent was evaporated under reduced pressure after which CCl_4 was added and the solids were filtered off. This afforded pure *N*-(2-bromo-2,2-difluoro-1-methoxyethyl)-*N*-propyl-4-methylbenzenesulfonamide **281** (0.210 g, 0.545 mmol).

***N*-(2-Bromo-2,2-difluoro-1-methoxyethyl)-*N*-propyl-4-methylbenzenesulfonamide 281**



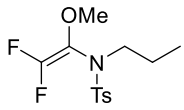
Yellow oil. Yield: 60%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.78 (2H, t, *J* = 7.4 Hz, CH_2CH_3), 1.49-1.65 (2H, m, CH_2CH_3), 2.44 (3H, s, $CH_3C_{arom,quat}$), 3.17 (2H, t, *J* = 8.3 Hz, NCH_2), 3.46 (3H, s, OCH_3), 5.47 (1H, dd, $J_{H,F}$ = 11.5 Hz, 4.5 Hz, CH), 7.31 (2H, d, *J* = 8.2 Hz, 2x CH_{arom}), 7.75 (2H, d, *J* = 8.2 Hz, 2x CH_{arom}). **^{13}C NMR** (100.6 MHz, ref = $CDCl_3$): δ 11.4 (CH_2CH_3), 21.6 ($CH_3C_{arom,quat}$), 22.6 (CH_2CH_3), 45.0 (NCH_2), 57.4 (OCH_3), 89.9 (dd, *J* = 28.8 Hz, 23.4 Hz, CH), 119.6 (dd, *J* = 316.2 Hz, 309.4 Hz, CF_2Br), 127.7 (2x CH_{arom}), 129.7 (2x CH_{arom}), 137.0 ($C_{arom,quat}$), 144.2 ($C_{arom,quat}$). **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ -56.84 (1F, dd, *J* = 164.9 Hz, $J_{H,F}$ = 4.5 Hz, CF(F)Br), -61.10 (1F, dd, *J* = 164.9 Hz, $J_{H,F}$ = 11.5 Hz, CF(F)Br). **IR** (ATR, cm^{-1}): ν_{max} = 1164, 1135, 1095, 946, 659. **MS** (ES^+): *m/z* (%): 403/5 ($M + NH_4^+$, 80), 386/88 ($M + H^+$, 100).

Synthesis of *N*-(2,2-difluoro-1-methoxyvinyl)-*N*-propyl-4-methylbenzenesulfonamide 282

To a solution of *N*-(2-bromo-2,2-difluoro-1-methoxyethyl)-*N*-propyl-4-methylbenzenesulfonamide **281** (0.050 g, 0.129 mmol) in dry THF (2 mL) was added LiHMDS (1M in THF, 2 equiv, 0.259 mL, 0.259 mmol) at 0 °C. Subsequently, this mixture was stirred at reflux temperature for one hour, after which another

equivalent of LiHMDS (1M in THF, 0.129 mL, 0.129 mmol) was added and the stirring was continued for another two hours. The reaction mixture was poured into aqueous NH_4Cl (5 mL) and extracted with EtOAc (3x 5 mL). After drying ($MgSO_4$), filtration, evaporation and purification using preparative TLC, pure *N*-(2,2-difluoro-1-methoxyvinyl)-*N*-propyl-4-methylbenzenesulfonamide **282** (0.014 g, 0.0453 mmol) was obtained.

***N*-(2,2-Difluoro-1-methoxyvinyl)-*N*-propyl-4-methylbenzenesulfonamide 282**



Colorless oil. R_f 0.30 (petroleum ether/EtOAc 9/1). Yield: 35%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.79 (2H, t, *J* = 7.4 Hz, $CH_2C\underline{H}_3$), 1.48 (2H, sextet, *J* = 7.4 Hz, $C\underline{H}_2CH_3$), 2.44 (3H, s, $CH_3C_{arom,quat}$), 3.18 (2H, t, *J* = 7.4 Hz, NCH_2), 3.66 (3H, s, OCH_3), 7.31 (2H, d, *J* = 8.1 Hz, 2x CH_{arom}), 7.77 (2H, d, *J* = 8.1 Hz, 2x CH_{arom}). **^{13}C NMR** (100.6 MHz, ref = $CDCl_3$): δ 10.9 ($CH_2\underline{C}H_3$), 21.2 ($\underline{C}H_2CH_3$), 21.6 ($\underline{C}H_3C_{arom,quat}$), 49.2 ($NCH_2$), 59.0 (dd, *J* = 3.9 Hz, 2.5 Hz, OCH_3), 115.7 (dd, *J* = 35.5 Hz, 34.1 Hz, CF_2=$\underline{C}$OMe), 127.8 (2x CH_{arom}), 129.6 (2x CH_{arom}), 136.3 ($C_{arom,quat}$), 144.1 ($C_{arom,quat}$), 153.9 (dd, *J* = 289.8 Hz, 285.4 Hz, CF_2). **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ -102.17 (1F, d, *J* = 55.3 Hz, C$\underline{F}$(F)), -107.63 (1F, d, *J* = 55.3 Hz, CF($\underline{F}$)). **IR** (ATR, cm^{-1}): ν_{max} = 1351, 1289, 1236, 1171, 1154, 669. **MS** (ES^+): *m/z* (%): 323 (M + NH_4^+, 100), 306 (M + H^+, 40).

5.8 Synthesis of fluorinated 8,9,10,11-tetrahydro-8,11-methanobenzo-[*j*]phenanthridine-7,12-diones

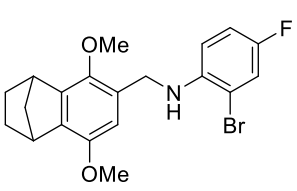
5.8.1 Synthesis of amines 289

Synthesis of 2-bromo-*N*-[(5,8-dimethoxy-1,2,3,4-tetrahydro-1,4-methanonaphthalen-6-yl)methyl]-anilines 289a and 289b

The synthesis of 2-bromo-*N*-[(5,8-dimethoxy-1,2,3,4-tetrahydro-1,4-methanonaphthalen-6-yl)methyl]-4-fluoroaniline **289a** is described as representative. A solution of 5,8-dimethoxy-1,2,3,4-tetrahydro-1,4-methanonaphthalene-6-carbaldehyde **28** (0.22 g, 0.93 mmol), 2-bromo-4-fluoroaniline **29a** (3 equiv, 0.53 g, 2.78 mmol) and $MgSO_4$ (3 equiv, 0.33 g, 2.78 mmol) in 2-methyltetrahydrofuran (4 mL) was stirred under microwave irradiation at 60 °C for 45 minutes. Subsequently, the drying agent was filtered off and the solvent was removed *in vacuo*, affording the corresponding imine, which was used without further purification in the next step. The imine was dissolved in MeOH (10 mL), and $NaCNBH_3$ (2.5 equiv, 0.15 g, 2.32 mmol) and acetic acid (1.2 equiv, 0.069 g, 1.11 mmol) were added. After stirring the reaction mixture

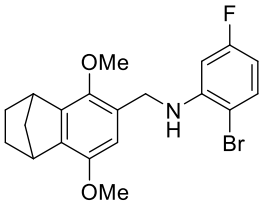
for 17 hours at room temperature, saturated aqueous Na_2CO_3 (15 mL) was added and an extraction with EtOAc was performed (3x 10 mL). After drying of the combined organic phases ($MgSO_4$), filtration and evaporation, crude aniline **289a** was obtained, which was purified by reverse phase automated flash chromatography (0.26 g, 0.62 mmol).

2-Bromo-*N*-[(5,8-dimethoxy-1,2,3,4-tetrahydro-1,4-methanonaphthalen-6-yl)methyl]-4-fluoroaniline 289a



Pale yellow crystals. Melting point: 93-94 °C. R_f 0.03 (petroleum ether/EtOAc 9/1). Gradient used for purification: during 3 CV: 40% CH_3CN, during 30 CV: 40 -> 100% CH_3CN, during 3 CV: 100% CH_3CN. Yield: 67%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.28-1.36 (2H, m, 2x $CH_X\underline{H}_N$), 1.56 (1H, d, J = 8.7 Hz, $C\underline{H}_AH_S$), 1.80 (1H, d, J = 8.7 Hz, $CH_A\underline{H}_S$), 1.94-2.07 (2H, m, 2x $C\underline{H}_XH_N$), 3.66 (1H, br s, CH-1 or CH-4), 3.71 (1H, br s, CH-1 or CH-4), 3.82 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 4.37 (2H, br s, $C\underline{H}_2NH$), 4.60 (1H, br s, NH), 6.69 (1H, s, CH_{arom}), 6.72 (1H, dd, J = 9.0 Hz, $J_{H,F}$ = 5.2 Hz, CH_{arom}), 6.97 (1H, ddd, J = 9.0 Hz, $J_{H,F}$ = 8.1 Hz, J = 2.9 Hz, CH_{arom}), 7.27 (1H, dd, $J_{H,F}$ = 8.0 Hz, J = 2.9 Hz, CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 26.5 and 27.0 (CH_2CH_2), 39.7 (CH-1 or CH-4), 41.3 (CH-1 or CH-4), 44.1 (CH_2NH), 49.1 (CH_2), 55.9 (OCH_3), 61.4 (OCH_3), 108.9 (d, J = 9.8 Hz, $\underline{C}_{arom,quat}$), 109.6 ($CH_{arom}$), 111.7 (d, J = 7.5 Hz, CH_{arom}), 115.0 (d, J = 11.6 Hz, $\underline{C}H_{arom}CF$), 119.3 (d, J = 25.5 Hz, $CH_{arom}CF$), 128.3, 136.5 and 140.5 (3x $C_{arom,quat}$), 142.0 (d, J = 2.1 Hz, $C_{arom,quat}$), 146.1 and 149.1 (2x $C_{arom,quat}$), 154.5 (d, J = 238.8 Hz, CF_{arom}). **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ -127.76 (1F, ddd, $J_{H,F}$ = 8.1 Hz, 8.0 Hz, 5.2 Hz, CF_{arom}). **IR** (ATR, cm^{-1}): ν_{max} = 1506, 1490, 1315, 1023, 848, 796. **MS** (ES^+): *m/z* (%): 217 (100). **HRMS** (ES^+): calcd. for $C_{14}H_{17}O_2^+$ (M - $C_6H_4BrFN^-$): 217.1223, found 217.1224.

2-Bromo-*N*-[(5,8-dimethoxy-1,2,3,4-tetrahydro-1,4-methanonaphthalen-6-yl)methyl]-5-fluoroaniline 289b



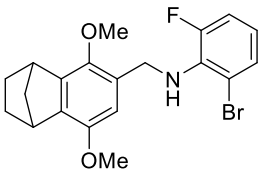
Pale yellow crystals. Melting point: 80-81 °C. Gradient used for purification: during 3 CV: 40% CH_3CN, during 30 CV: 40 -> 100% CH_3CN, during 3 CV: 100% CH_3CN. Yield: 53%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.20-1.28 (2H, m, 2x $CH_X\underline{H}_N$), 1.49 (1H, d, J = 8.8 Hz, $C\underline{H}_AH_S$), 1.70-1.73 (1H, m, $CH_A\underline{H}_S$), 1.87-1.99 (2H, m, 2x $C\underline{H}_XH_N$), 3.56-3.59 (1H, m, CH-1 or CH-4), 3.62-3.64 (1H, m, CH-1 or CH-4), 3.76 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 4.29 (2H, br s, $C\underline{H}_2NH$), 4.78 (1H, br s, NH), 6.28 (1H, ddd, J = 8.5 Hz, $J_{H,F}$ = 8.2 Hz, J = 2.8 Hz, CH_{arom}), 6.44 (1H, dd, $J_{H,F}$ = 11.3 Hz, J = 2.8 Hz, CH_{arom}), 7.32 (1H, dd, J = 8.5 Hz, $J_{H,F}$ = 6.0 Hz, CH_{arom}). **^{13}C NMR** (100.6 MHz, ref = $CDCl_3$): δ 26.5 and 27.1 (CH_2CH_2), 39.8 (CH-1 or CH-4), 41.4 (CH-1 or CH-4), 43.7

(CH_2NH), 49.2 (CH_2), 56.1 (OCH_3), 61.6 (OCH_3), 99.1 (d, *J* = 27.8 Hz, $\underline{C}H_{arom}CF$), 103.7 (d, *J* = 2.5 Hz, $C_{arom,quat}$), 104.3 (1H, d, *J* = 23.1 Hz, $\underline{C}H_{arom}CF$), 109.8 (CH_{arom}), 127.8 ($C_{arom,quat}$), 132.9 (d, *J* = 9.9 Hz, CH_{arom}), 136.8, 140.7 and 146.3 (3x $C_{arom,quat}$), 146.5 (d, *J* = 11.3 Hz, $C_{arom,quat}$), 149.2 ($C_{arom,quat}$), 163.5 (d, *J* = 243.0 Hz, CF_{arom}). **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ -113.62 (1F, ddd, $J_{H,F}$ = 11.3 Hz, 8.2 Hz, 6.0 Hz, CF_{arom}). **IR** (ATR, cm^{-1}): ν_{max} = 1613, 1486, 1308, 1170, 1021, 824. **MS** (ES^+): *m/z* (%): 217 (100). **HRMS** (ES^+): calcd. for $C_{14}H_{17}O_2^+$ (M - $C_6H_4BrFN^-$): 217.1223, found 217.1227.

Synthesis of 2-bromo-*N*-[(5,8-dimethoxy-1,2,3,4-tetrahydro-1,4-methanonaphthalen-6-yl)methyl]-6-fluoroaniline 289c

A mixture of 5,8-dimethoxy-1,2,3,4-tetrahydro-1,4-methanonaphthalene-6-carbaldehyde **28** (0.23 g, 0.97 mmol), 2-bromo-6-fluoroaniline **29c** (1 equiv, 0.18 g, 0.97 mmol), $NaCNBH_3$ (2.5 equiv, 0.15 g, 2.4 mmol) and acetic acid (2 equiv, 0.12 g, 1.9 mmol) in *iso*-propanol (20 mL) was stirred at room temperature for seven days. After this time, a saturated aqueous solution of Na_2CO_3 (15 mL) was added and an extraction with EtOAc was performed (3x 15 mL). After drying of the combined organic phases ($MgSO_4$), filtration and evaporation, crude aniline **289c** was obtained, which was purified by reverse phase automated flash chromatography (0.080 g, 0.19 mmol).

2-Bromo-*N*-[(5,8-dimethoxy-1,2,3,4-tetrahydro-1,4-methanonaphthalen-6-yl)methyl]-6-fluoroaniline 289c

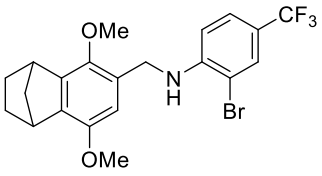


Pale yellow oil. Gradient used for purification: during 3 CV: 40% CH_3CN, during 30 CV: 40 -> 100% CH_3CN, during 3 CV: 100% CH_3CN. Yield: 20%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.17-1.28 (2H, m, 2x $CH_X\underline{H}_N$), 1.48 (1H, ddd, *J* = 8.7 Hz, 1.4 Hz, 1.4 Hz, $C\underline{H}_AH_S$), 1.69-1.72 (1H, m, $CH_A\underline{H}_S$), 1.86-1.98 (2H, m, 2x $C\underline{H}_XH_N$), 3.55-3.57 (1H, m, CH-1 or CH-4), 3.62-3.64 (1H, m, CH-1 or CH-4), 3.76 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 4.38 (1H, br s, NH), 4.47 (2H, d, *J* = 4.4 Hz, $C\underline{H}_2NH$), 6.61 (1H, ddd, *J* = 8.2 Hz, 8.1 Hz, $J_{H,F}$ = 4.9 Hz, CH_{arom}), 6.95 (1H, ddd, $J_{H,F}$ = 12.4 Hz, *J* = 8.2 Hz, 1.4 Hz, CH_{arom}), 7.22 (1H, ddd, *J* = 8.1 Hz, 1.4 Hz, 1.3 Hz, CH_{arom}). **^{13}C NMR** (100.6 MHz, ref = $CDCl_3$): δ 26.6 and 27.1 (CH_2CH_2), 39.7 (CH-1 or CH-4), 41.5 (CH-1 or CH-4), 46.7 (d, *J* = 9.6 Hz, CH_2NH), 49.1 (CH_2), 56.0 (OCH_3), 61.5 (OCH_3), 110.2 (CH_{arom}), 113.9 (d, *J* = 5.5 Hz, $C_{arom,quat}$), 116.0 (d, *J* = 21.3 Hz, $\underline{C}H_{arom}CF$), 119.6 (d, *J* = 8.5 Hz, CH_{arom}), 128.2 (d, *J* = 3.1 Hz, CH_{arom}), 129.5 ($C_{arom,quat}$), 135.4 (d, *J* = 12.0 Hz, $C_{arom,quat}$), 136.5, 140.3, 146.3 and 148.9 (4x $C_{arom,quat}$), 153.4 (d, *J* = 245.0 Hz, CF_{arom}). **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ -124.10 (1F, dd, $J_{H,F}$ = 12.4 Hz, 4.9 Hz, CF_{arom}). **MS** (ES^+): *m/z* (%): 217 (100).

Synthesis of 2-bromo-*N*-[(5,8-dimethoxy-1,2,3,4-tetrahydro-1,4-methanonaphthalen-6-yl)methyl]-anilines 289d and 289e

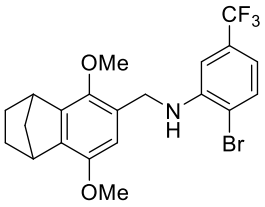
The synthesis of 2-bromo-*N*-[(5,8-dimethoxy-1,2,3,4-tetrahydro-1,4-methanonaphthalen-6-yl)methyl]-5-(trifluoromethyl)aniline **289e** is described as representative. A mixture of 5,8-dimethoxy-1,2,3,4-tetrahydro-1,4-methanonaphthalene-6-carboxaldehyde **28** (0.67 g, 2.88 mmol), 2-bromo-5-trifluoromethylaniline **29e** (3 equiv, 2.07 g, 8.63 mmol) and $MgSO_4$ (3 equiv, 1.04 g, 8.63 mmol) in dry dichloromethane (40 mL) was stirred at reflux temperature for 19 hours. After this time, the drying agent was filtered off and the solvent was removed *in vacuo*, affording the corresponding imine which was used without further purification in the next step. The imine was dissolved in MeOH (30 mL) and $NaCNBH_3$ (2.5 equiv, 0.45 g, 7.2 mmol) and acetic acid (1.2 equiv, 0.21 g, 3.46 mmol) were added. After stirring the reaction mixture for 17 hours at room temperature, saturated aqueous Na_2CO_3 (30 mL) was added and an extraction with EtOAc was performed (3x 20 mL). After drying of the combined organic phases ($MgSO_4$), filtration and evaporation, crude aniline **289e** was obtained, which was purified by reverse phase automated flash chromatography (0.86 g, 1.90 mmol).

2-Bromo-*N*-[(5,8-dimethoxy-1,2,3,4-tetrahydro-1,4-methanonaphthalen-6-yl)methyl]-4-(trifluoromethyl)aniline 289d



Pale yellow oil. Gradient used for purification: during 3 CV: 40% CH_3CN, during 30 CV: 40 -> 100% CH_3CN, during 3 CV: 100% CH_3CN. Yield: 71%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.19-1.29 (2H, m, 2x $CH_X\underline{H}_N$), 1.50 (1H, d, *J* = 8.8 Hz, $C\underline{H}_AH_S$), 1.72 (1H, d, *J* = 8.8 Hz, $CH_A\underline{H}_S$), 1.88-2.00 (2H, m, 2x $C\underline{H}_XH_N$), 3.58 (1H, br s, CH-1 or CH-4), 3.64 (1H, br s, CH-1 or CH-4), 3.76 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 4.36 (2H, d, *J* = 5.5 Hz, $C\underline{H}_2NH$), 5.03 (1H, t, *J* = 5.5 Hz, NH), 6.58 (1H, s, CH_{arom}), 6.73 (1H, d, *J* = 8.5 Hz, CH_{arom}), 7.41 (1H, dd, *J* = 8.5 Hz, 1.2 Hz, CH_{arom}), 7.67 (1H, d, *J* = 1.2 Hz, CH_{arom}). **^{13}C NMR** (100.6 MHz, ref = $CDCl_3$): δ 26.5 and 27.0 (CH_2CH_2), 39.8 (CH-1 or CH-4), 41.5 (CH-1 or CH-4), 43.5 (CH_2NH), 49.2 (CH_2), 56.1 (OCH_3), 61.5 (OCH_3), 108.7 ($C_{arom,quat}$), 109.8 and 110.6 (2x CH_{arom}), 119.2 (q, *J* = 33.3 Hz, $\underline{C}CF_3$), 124.2 (q, *J* = 270.7 Hz, CF_3), 125.9 (q, *J* = 3.6 Hz, $\underline{C}H_{arom}CCF_3$), 127.5 ($C_{arom,quat}$), 129.6 (q, *J* = 3.8 Hz, $\underline{C}H_{arom}CCF_3$), 137.0, 140.7, 146.3, 147.5 and 149.2 (5x $C_{arom,quat}$). **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ -61.48 (1F, s, CF_3). **IR** (ATR, cm^{-1}): ν_{NH} = 3408, ν_{max} = 1610, 1319, 1107, 1076, 1056. **MS** (ES^+): *m/z* (%): 217 (100). **HRMS** (ES^+): calcd. for $C_{14}H_{17}O_2^+$ (M - $C_7H_4BrF_3N^-$): 217.1223, found 217.1222.

2-Bromo-*N*-[(5,8-dimethoxy-1,2,3,4-tetrahydro-1,4-methanonaphthalen-6-yl)methyl]-5-(trifluoromethyl)aniline 289e



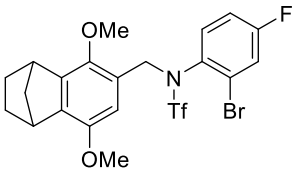
Pale yellow oil. Gradient used for purification: during 3 CV: 40% CH_3CN, during 30 CV: 40 -> 100% CH_3CN, during 3 CV: 100% CH_3CN. Yield: 66%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.19-1.28 (2H, m, 2x $CH_X\underline{H}_N$), 1.50 (1H, d, *J* = 8.8 Hz, $C\underline{H}_AH_S$), 1.71-1.74 (1H, m, $CH_A\underline{H}_S$), 1.88-2.00 (2H, m, 2x $C\underline{H}_XH_N$), 3.58 (1H, br s, CH-1 or CH-4), 3.64 (1H, br s, CH-1 or CH-4), 3.77 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 4.34 (2H, d, *J* = 5.3 Hz, $C\underline{H}_2NH$), 4.89 (1H, t, *J* = 5.3 Hz, NH), 6.61 (1H, s, CH_{arom}), 6.80 (1H, dd, *J* = 8.2 Hz, 1.5 Hz, CH_{arom}), 6.94 (1H, d, *J* = 1.5 Hz, CH_{arom}), 7.51 (1H, d, *J* = 8.2 Hz, CH_{arom}). **^{13}C NMR** (100.6 MHz, ref = $CDCl_3$): δ 26.5 and 27.1 (CH_2CH_2), 39.8 (CH-1 or CH-4), 41.5 (CH-1 or CH-4), 43.8 (CH_2NH), 49.2 (CH_2), 56.1 (OCH_3), 61.6 (OCH_3), 107.9 (q, *J* = 3.9 Hz, $\underline{C}H_{arom}CCF_3$), 110.2 ($CH_{arom}$), 113.0 ($C_{arom,quat}$), 114.0 (q, *J* = 3.9 Hz, $\underline{C}H_{arom}CCF_3$), 124.3 (q, *J* = 272.4 Hz, CF_3), 127.6 ($C_{arom,quat}$), 131.0 (q, *J* = 32.1 Hz, $\underline{C}CF_3$), 132.8 (CH_{arom}), 137.1, 140.7, 145.4, 146.5 and 149.1 (5x $C_{arom,quat}$). **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ -63.36 (1F, s, CF_3). **IR** (ATR, cm^{-1}): ν_{max} = 1165, 1119, 1080, 1054, 1019. **MS** (ES^+): *m/z* (%): 217 (100). **HRMS** (ES^+): calcd. for $C_{14}H_{17}O_2^+$ (M – $C_7H_4BrF_3N^-$): 217.1223, found 217.1227.

5.8.2 Synthesis of trifluoromethanesulfonamides 292

The synthesis of *N*-(2-bromo-5-fluorophenyl)-*N*-[(5,8-dimethoxy-1,2,3,4-tetrahydro-1,4-methano-naphthalen-6-yl)methyl]-1,1,1-trifluoromethanesulfonamide **292b** is described as representative. To a solution of aniline **289b** (0.158 g, 0.39 mmol) in dry CH_2Cl_2 (10 mL), were added NaH (2.5 equiv, 23 mg, 0.97 mmol) and Tf_2O (1M in CH_2Cl_2, 2.5 equiv, 0.97 mL, 0.97 mmol) at 0 °C under N_2 atmosphere. This mixture was stirred at room temperature for seven hours, after which it was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with EtOAc (3x 10 mL). The combined organic phases were dried ($MgSO_4$), filtered and evaporated *in vacuo*. After purification *via* column chromatography, pure trifluoromethanesulfonamide **292b** was obtained in 71% yield (0.149 g, 0.28 mmol).

_N_-(2-Bromo-4-fluorophenyl)-_N_-[(5,8-dimethoxy-1,2,3,4-tetrahydro-1,4-methanonaphthalen-6-yl)methyl]-1,1,1-trifluoromethanesulfonamide 292a

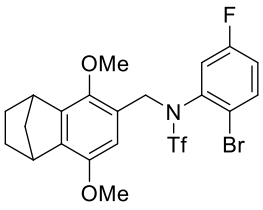
This compound exists as two rotamers in a ratio R1/R2 1/1, due to hindered rotation of the sulfonamide bond.



Viscous oil. R_f 0.27 (petroleum ether/EtOAc 95/5). Yield: 61%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.01-1.14 (2H, m, 2x $CH_X\underline{H}_N$ (R1 and R2)), 1.42-1.45 (1H, m, $C\underline{H}_AH_S$ (R1 and R2)), 1.58-1.62 (1H, m, $CH_A\underline{H}_S$ (R1 and R2)), 1.84-1.93 (2H, m, 2x $C\underline{H}_XH_N$ (R1 and R2)), 3.52 (2H, br s, CH-1 and CH-4 (R1 and R2)), 3.571 and 3.574 (2x 1.5H, 2x s, OCH_3 (R1 and R2)), 3.71 and 3.73 (2x 1.5H, 2x s, OCH_3 (R1 and R2)), 4.88-4.99 (2H, m, CH_2N (R1 and R2)), 6.51 and 6.59 (2x 0.5H, 2x s, CH_{arom} (R1 and R2)), 6.79 and 6.81 (2x 0.5H, 2x ddd, 2x J = 8.8 Hz, 7.2 Hz, 2.8 Hz, CH_{arom} (R1 and R2)), 6.93 and 6.96 (2x 0.5H, 2x dd, 2x J = 8.8 Hz, 5.5 Hz, CH_{arom} (R1 and R2)), 7.31 and 7.32 (2x 0.5H, 2x dd, 2x J = 7.8 Hz, 2.8 Hz, CH_{arom} (R1 and R2)). **^{13}C NMR** (100.6 MHz, ref = $CDCl_3$): δ 26.36, 26.41, 26.9 and 27.0 (CH_2CH_2 (R1 and R2)), 39.7, 39.8, 41.58 and 41.62 (CH-1 and CH-4 (R1 and R2)), 48.8 and 49.0 (CH_2 (R1 and R2)), 51.0 and 51.2 (CH_2N (R1 and R2)), 55.9 (OCH_3 (R1 and R2)), 60.9 and 61.1 (OCH_3 (R1 and R2)), 111.77 and 111.84 (CH_{arom} (R1 and R2)), 114.7 and 114.8 (2x d, 2x J = 22.2 Hz, CH_{arom} (R1 and R2)), 120.2 (q, J = 323.0 Hz, CF_3 (R1 and R2)), 120.8 (d, J = 25.5 Hz, CH_{arom} (R1 and R2)), 122.7 (d, J = 16.5 Hz, $C_{arom,quat}$ (R1 and R2)), 126.0-126.4 (m, $C_{arom,quat}$ (R1 and R2)), 131.8 and 131.9 (2x d, 2x J = 11.9 Hz, $C_{arom,quat}$ (R1 and R2)), 134.15 (d, J = 7.5 Hz, CH_{arom} (R1 and R2)), 138.89 and 138.96 ($C_{arom,quat}$ (R1 and R2)), 139.6 and 139.7 ($C_{arom,quat}$ (R1 and R2)), 147.0 and 147.1 ($C_{arom,quat}$ (R1 and R2)), 148.7 and 148.9 ($C_{arom,quat}$ (R1 and R2)), 162.2 (d, J = 254.5 Hz, CF_{arom} (R1 and R2)). **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ -75.23 (3F, s, CF_3), -109.55 to -109.67 (1F, m, CF_{arom}). **IR** (ATR, cm^{-1}): ν_{max} = 1485, 1392, 1223, 1185, 1142, 1040, 1024, 731. **MS** (ES^+): m/z (%): 217 (100). **HRMS** (ES^+): calcd. for $C_{14}H_{17}O_2^+$ (M - $C_7H_3BrF_4NO_2S^-$): 217.1223, found 217.1216.

_N_-(2-Bromo-5-fluorophenyl)-_N_-[(5,8-dimethoxy-1,2,3,4-tetrahydro-1,4-methanonaphthalen-6-yl)methyl]-1,1,1-trifluoromethanesulfonamide 292b

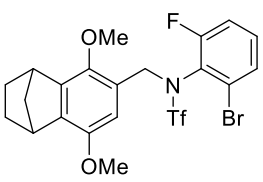
This compound exists as two rotamers in a ratio R1/R2 1/1, due to hindered rotation of the sulfonamide bond.



Viscous oil. R_f 0.28 (petroleum ether/EtOAc 9/1). Yield: 71%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.00-1.18 (2H, m, 2x $CH_X\underline{H}_N$ (R1 and R2)), 1.43 (1H, d, J = 8.6 Hz, $C\underline{H}_AH_S$ (R1 and R2)), 1.58-1.65 (1H, m, $CH_A\underline{H}_S$ (R1 and R2)), 1.85-1.91 (2H, m, 2x $C\underline{H}_XH_N$ (R1 and R2)), 3.52 (2H, br s, CH-1 and CH-4 (R1 and R2)), 3.59 and 3.62 (2x 1.5H, 2x s, OCH_3 (R1 and R2)), 3.708 and 3.711 (2x 1.5H, 2x s, OCH_3 (R1 and R2)), 4.95 (2H, s, CH_2N (R1 and R2)), 6.51 and 6.54 (2x 0.5H, 2x s, CH_{arom} (R1 and R2)), 6.70 and 6.75 (2x 0.5H, 2x dd, 2x J = 8.9 Hz, 2.9 Hz, CH_{arom} (R1 and R2)), 6.87-6.92 (1H, m, CH_{arom} (R1 and R2)), 7.52 and 7.53 (2x 0.5H, 2x dd, 2x J = 8.9 Hz, 5.7 Hz, CH_{arom} (R1 and R2)). **^{13}C NMR** (100.6 MHz, ref = $CDCl_3$): δ 26.3, 26.4, 26.9 and 27.0 (CH_2CH_2 (R1 and R2)), 39.7, 39.8, 41.66 and 41.67 (CH-1 and CH-4 (R1 and R2)), 48.8 and 49.0 (CH_2 (R1 and R2)), 51.0 and 51.3 (CH_2N (R1 and R2)), 56.0 (OCH_3 (R1 and R2)), 60.9 and 61.1 (OCH_3 (R1 and R2)), 111.8 and 112.0 (CH_{arom} (R1 and R2)), 117.99 and 118.04 (2x d, 2x J = 22.1 Hz, CH_{arom} (R1 and R2)), 120.1 ($C_{arom,quat}$ (R1 and R2)), 120.1 (q, J = 313.1 Hz, CF_3 (R1 and R2)), 120.6 (d, J = 21.1 Hz, CH_{arom} (R1 and R2)), 122.5 and 122.6 ($C_{arom,quat}$ (R1 and R2)), 134.1 (d, J = 8.5 Hz, CH_{arom} (R1 and R2)), 136.6 (d, J = 10.6 Hz, CH_{arom} (R1 or R2)), 136.8 (d, J = 11.4 Hz, CH_{arom} (R1 or R2)), 139.06 and 139.11 ($C_{arom,quat}$ (R1 and R2)), 139.6 and 139.7 ($C_{arom,quat}$ (R1 and R2)), 146.99 and 147.00 ($C_{arom,quat}$ (R1 and R2)), 148.7 and 148.8 ($C_{arom,quat}$ (R1 and R2)), 161.1 and 161.2 (2x d, 2x J = 249.7 Hz, CF_{arom} (R1 and R2)). **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ -75.35 (3F, s, CF_3), -113.71 to -113.87 (1F, m, CF_{arom}). **MS** (ES^+) m/z (%): 555/57 ($M + NH_4^+$, 25), 217 (100). **HRMS** (ES^+): calcd. for $C_{14}H_{17}O_2^+$ ($M - C_7H_3BrF_4NO_2S^-$): 217.1223, found 217.1218.

_N_-(2-Bromo-6-fluorophenyl)-_N_-[(5,8-dimethoxy-1,2,3,4-tetrahydro-1,4-methanonaphthalen-6-yl)methyl]-1,1,1-trifluoromethanesulfonamide 292c

This compound exists as two rotamers in a ratio major/minor 0.56/0.44, due to hindered rotation of the sulfonamide bond.

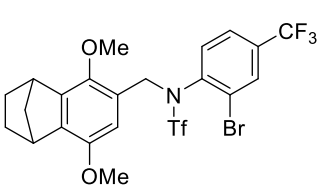


Viscous oil. R_f 0.35 (petroleum ether/EtOAc 9/1). Yield: 61%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.01-1.13 (2H, m, 2x $CH_X\underline{H}_N$), 1.41-1.43 (1H, m, $C\underline{H}_AH_S$), 1.60-1.64 (1H, m, $CH_A\underline{H}_S$), 1.82-1.90 (2H, m, 2x $C\underline{H}_XH_N$), 3.50 (1H, br s, CH-1 or CH-4), 3.52 (1H, br s, CH-1 or CH-4), 3.54 (1.8H, OCH_3 (major)), 3.57 (1.2H, OCH_3 (minor)), 3.68 (1.2H,

OCH_3 (minor)), 3.70 (1.8H, OCH_3 (major)), 4.82 (0.4H, d, *J* = 13.3 Hz, C<u>H</u>(H)N (minor)), 4.85 (0.6H, d, *J* = 13.4 Hz, C<u>H</u>(H)N (major)), 5.03 (0.6H, d, *J* = 13.4 Hz, CH(<u>H</u>)N (major)), 5.07 (0.4H, d, *J* = 13.3 Hz, CH(<u>H</u>)N (minor)), 6.55 (0.4H, s, CH_{arom} (minor)), 6.61 (0.6H, s, CH_{arom} (major)), 6.97-7.03 (1H, m, CH_{arom}), 7.17 (1H, ddd, *J* = 8.2 Hz, 8.2 Hz, 5.5 Hz, CH_{arom}), 7.34-7.37 (1H, m, CH_{arom}). **^{13}C NMR** (100.6 MHz, ref = $CDCl_3$): δ 26.4 and 26.9 (CH_2CH_2 (minor)), 26.5 and 27.0 (CH_2CH_2 (major)), 39.7 (CH-1 or CH-4), 41.68 and 41.71 (CH-1 or CH-4 (minor+major)), 48.8 (CH_2 (major)), 48.9 (CH_2 (minor)), 50.4 (CH_2N (minor)), 50.5 (CH_2N (major)), 55.9 (OCH_3 (minor)), 56.0 (OCH_3 (major)), 61.0 (OCH_3 (major)), 61.1 (OCH_3 (minor)), 112.6 (CH_{arom} (minor)), 112.7 (CH_{arom} (major)), 115.5 (d, *J* = 21.6 Hz, CH_{arom} (minor)), 115.6 (d, *J* = 21.6 Hz, CH_{arom} (major)), 120.0 (q, *J* = 323.3 Hz, CF_3), 122.3 ($C_{arom,quat}$ (minor)), 122.4 ($C_{arom,quat}$ (major)), 124.7 (d, *J* = 15.1 Hz, $C_{arom,quat}$ (minor)), 124.9 (d, *J* = 14.7 Hz, $C_{arom,quat}$ (major)), 127.5 ($C_{arom,quat}$), 129.1 (d, *J* = 3.8 Hz, CH_{arom} (major)), 129.2 (d, *J* = 4.3 Hz, CH_{arom} (minor)), 131.6 (d, *J* = 9.4 Hz, CH_{arom}), 139.0 ($C_{arom,quat}$), 139.1 ($C_{arom,quat}$ (major)), 139.2 ($C_{arom,quat}$ (minor)), 147.2 ($C_{arom,quat}$), 148.5 ($C_{arom,quat}$ (minor)), 148.6 ($C_{arom,quat}$ (major)), 160.79 (d, *J* = 256.1 Hz, CF_{arom} (minor)), 160.83 (d, *J* = 256.3 Hz, CF_{arom} (major)). **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ -75.51 (d, *J* = 11.4 Hz, CF_3 (major or minor)), -75.54 (d, *J* = 15.5 Hz, CF_3 (major or minor), -112.18 (1F, br s, CF_{arom}). **IR** (ATR, cm^{-1}): ν_{max} = 1394, 1187, 1138, 1024, 869, 782. **MS** (ES^+): *m*/*z* (%): 217 (100). **HRMS** (ES^+): calcd. for $C_{14}H_{17}O_2^+$ (M - $C_7H_3BrF_4NO_2S^-$): 217.1223, found 217.1210.

N-[2-Bromo-4-(trifluoromethyl)phenyl]-*N*-[(5,8-dimethoxy-1,2,3,4-tetrahydro-1,4-methanonaphthalen-6-yl)methyl]-1,1,1-trifluoromethanesulfonamide 292d

This compound exists as two rotamers in a ratio R1/R2 1/1, due to hindered rotation of the sulfonamide bond.

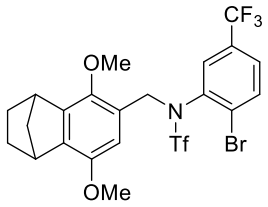


Yellow oil. R_f 0.53 (petroleum ether/EtOAc 9/1). Yield: 62%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.97-1.06 (2H, m, 2x $CH_X\underline{H}_N$ (R1 and R2)), 1.41-1.44 (1H, m, $C\underline{H}_AH_S$ (R1 and R2)), 1.57-1.61 (1H, m, $CH_A\underline{H}_S$ (R1 and R2)), 1.81-1.92 (2H, m, 2x $C\underline{H}_XH_N$ (R1 and R2)), 3.49 and 3.50 (2H, 2x br s, CH-1 and CH-4 (R1 and R2)), 3.55 and 3.57 (2x 1.5H, 2x s, OCH_3 (R1 and R2)), 3.70 and 3.72 (2x 1.5H, 2x s, OCH_3 (R1 and R2)), 4.95 (1H, d, *J* = 13.5 Hz, C<u>H</u>(H)N (R1 and R2)), 5.01 (1H, d, *J* = 13.5 Hz, CH(<u>H</u>)N (R1 and R2)), 6.52 and 6.57 (2x 0.5H, 2x s, CH_{arom} (R1 and R2)), 7.08 and 7.12 (2x 0.5H, 2x d, 2x *J* = 8.3 Hz, CH_{arom} (R1 and R2)), 7.33-7.37 (1H, m, CH_{arom} (R1 and R2)), 7.83-7.85 (1H, m, CH_{arom} (R1 and R2)). **^{13}C NMR** (100.6 MHz, ref = $CDCl_3$): δ 26.3, 26.8 and 26.9 (CH_2CH_2 (R1 and R2)), 39.67, 39.73, 41.6 and 41.7 (CH-1 and CH-4 (R1 and R2)), 48.7 and 48.9 (CH_2 (R1 and R2)), 51.0 and 51.3 (CH_2N (R1 and R2)), 55.9 (OCH_3 (R1 and R2)), 60.7 and 60.9 (OCH_3 (R1 and R2)), 111.8 and 112.0 (CH_{arom} (R1 and R2)), 120.1 (q, *J* = 322.9 Hz, SCF_3 (R1 and R2)), 122.2 and 122.4 (2x $C_{arom,quat}$

(R1 and R2)), 122.7 (q, *J* = 273.1 Hz, $C_{arom}\underline{C}F_3$ (R1 and R2)), 124.4-124.6 (m, CH_{arom} (R1 and R2)), 125.9-126.3 (m, $C_{arom,quat}$ (R1 and R2)), 130.5-130.7 (m, CH_{arom} (R1 and R2)), 132.5 and 132.6 (2x d, 2x *J* = 33.5 Hz, 2x $\underline{C}_{arom}CF_3$), 133.7 (m, CH_{arom} (R1 and R2)), 139.0, 139.1, 139.2, 139.3, 139.4 and 139.4 (3x $C_{arom,quat}$ (R1 and R2)), 147.0 ($C_{arom,quat}$ (R1 and R2)), 148.7 and 148.8 ($C_{arom,quat}$ (R1 and R2)). **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ -63.50 and -63.53 (2x 1.5F, 2x s, 2x SCF_3 (R1 and R2), -75.29 and -75.32 (2x 1.5F, 2x s, 2x $C_{arom}CF_3$ (R1 and R2)). **IR** (ATR, cm^{-1}): ν_{max} = 1394, 1319, 1175, 1134, 1025. **MS** (ES^+): *m/z* (%): 217 (100). **HRMS** (ES^+): calcd. for $C_{14}H_{17}O_2^+$ (M - $C_8H_3BrF_6NO_2S^-$): 217.1223, found 217.1214.

_N_-[2-Bromo-5-(trifluoromethyl)phenyl]-_N_-[(5,8-dimethoxy-1,2,3,4-tetrahydro-1,4-methanonaphthalen-6-yl)methyl]-1,1,1-trifluoromethanesulfonamide 292e

This compound exists as two rotamers in a ratio R1/R2 1/1, due to hindered rotation of the sulfonamide bond.

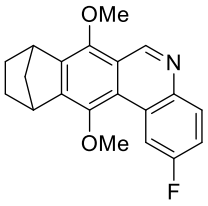


Viscous oil. R_f 0.24 (petroleum ether/EtOAc 9/1). Yield: 60%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.00-1.12 (2H, m, 2x $CH_X\underline{H}_N$ (R1 and R2)), 1.40-1.42 (1H, m, $C\underline{H}_AH_S$ (R1 and R2)), 1.55-1.60 (1H, m , $CH_A\underline{H}_S$ (R1 and R2)), 1.81-1.90 (2H, m, 2x $C\underline{H}_XH_N$ (R1 and R2)), 3.47-3.52 (2H, m, CH-1 and CH-4 (R1 and R2)), 3.577 and 3.580 (2x 1.5H, 2x s, OCH_3 (R1 and R2)), 3.708 and 3.715 (2x 1.5H, 2x s, OCH_3 (R1 and R2)), 4.91-5.01 (2H, m, CH_2N (R1 and R2)), 6.51 and 6.54 (2x 0.5H, 2x s, CH_{arom} (R1 and R2)), 7.12 and 7.18 (2x 0.5H, 2x d, 2x *J* = 1.7 Hz, CH_{arom} (R1 and R2)), 7.36 and 7.40 (2x 0.5H, 2x dd, 2x *J* = 8.6 Hz, 1.7 Hz, CH_{arom} (R1 and R2)), 7.70 and 7.72 (2x 0.5H, 2x d, 2x *J* = 8.6 Hz, CH_{arom} (R1 and R2)). **^{13}C NMR** (100.6 MHz, ref = $CDCl_3$): δ 26.2, 26.3, 26.8 and 26.9 (CH_2CH_2 (R1 and R2)), 39.65, 39.70, 41.68 and 41.70 (CH-1 and CH-4 (R1 and R2)), 48.8 and 48.9 (CH_2 (R1 and R2)), 51.2 and 51.4 (CH_2N (R1 and R2)), 56.01 and 56.03 (OCH_3 (R1 and R2)), 60.7 and 60.8 (OCH_3 (R1 and R2)), 111.8 and 112.0 (CH_{arom} (R1 and R2)), 120.1 (q, *J* = 322.8 Hz, SCF_3 (R1 and R2)), 122.08 and 122.11 (2x $C_{arom,quat}$ (R1 and R2)), 123.0 (q, *J* = 270.2 Hz, $C_{arom}\underline{C}F_3$ (R1 and R2)), 127.0-127.2 (m, CH_{arom} (R1 and R2)), 129.8-130.5 (CH_{arom} and $C_{arom,quat}$ (R1 and R2)), 130.3 and 130.4 (2x d, 2x *J* = 33.6 Hz, 2x $\underline{C}_{arom}CF_3$ (R1 and R2)), 134.1 and 134.2 (CH_{arom} (R1 and R2)), 136.3 and 136.8 ($C_{arom,quat}$ (R1 and R2)), 139.3, 139.4, 139.5 and 139.6 (2x $C_{arom,quat}$ (R1 and R2)), 146.8 and 147.0 ($C_{arom,quat}$ (R1 and R2)), 148.7 and 148.8 ($C_{arom,quat}$ (R1 and R2)). **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ -63.43 and -63.48 (2x 1.5F, 2x s, 2x SCF_3 (R1 and R2)), -75.42 and -75.45 (2x 1.5F, 2x s, 2x $C_{arom}CF_3$ (R1 and R2)). **IR** (ATR, cm^{-1}): ν_{max} = 1395, 1325, 1225, 1189, 1173, 1133. **MS** (ES^+): *m/z* (%): 217 (100).

5.8.3 Synthesis of 7,12-dimethoxy-8,9,10,11-tetrahydro-8,11-methanobenzo[*j*]-phenanthridines 288a-c

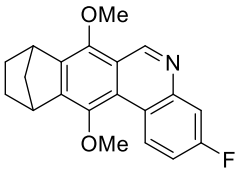
The synthesis of 7,12-dimethoxy-2-fluoro-8,9,10,11-tetrahydro-8,11-methanobenzo[*j*]phenanthridine **288a** is described as representative. To a mixture of *N*-(2-bromo-4-fluorophenyl)-*N*-[(5,8-dimethoxy-1,2,3,4-tetrahydro-1,4-methanonaphthalen-6-yl)methyl]-1,1,1-trifluoromethanesulfonamide **292a** (0.250 g, 0.46 mmol) in dry toluene (4 mL) in a pressure vial under N_2-atmosphere, $Pd(OAc)_2$ (0.06 equiv, 6 mg, 0.027 mmol), triphenylphosphine (0.18 equiv, 22 mg, 0.084 mmol) and K_2CO_3 (2 equiv, 128 mg, 0.93 mmol) were added. This mixture was stirred under microwave irradiation at 125 °C for 3 hours, after which it was quenched with H_2O (4 mL). Subsequently, this mixture was filtered over Celite® and extracted with EtOAc (3x 6 mL). This organic phase was dried ($MgSO_4$), filtered and evaporated *in vacuo*, affording crude 7,12-dimethoxy-2-fluoro-5-(trifluoromethanesulfonyl)-5,6,8,9,10,11-hexahydro-8,11-methanobenzo[*j*]-phenanthridine **293a**, which was not purified but used as such in the following reaction. Therefore, crude **293a** was dissolved in dry THF (10 mL) and two equivalents of KO*t*Bu (1M in THF, 0.92 mL) were added and this mixture was stirred at reflux temperature for two hours. After the addition of a saturated aqueous solution of NH_4Cl (10 mL), an extraction with EtOAc was performed (3x 5 mL) and the combined organic phases were dried ($MgSO_4$), filtered and evaporated under reduced pressure. Purification using preparative TLC afforded pure 7,12-dimethoxy-2-fluoro-8,9,10,11-tetrahydro-8,11-methanobenzo[*j*]phenanthridine **288a** (0.077 g, 0.24 mmol).

7,12-Dimethoxy-2-fluoro-8,9,10,11-tetrahydro-8,11-methanobenzo[*j*]phenanthridine 288a



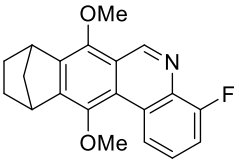
Yellow oil. R_f 0.06 (petroleum ether/EtOAc 9/1). Yield: 51%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.42-1.44 (2H, m, 2x $CH_X\underline{H}_N$), 1.71 (1H, d, *J* = 9.1 Hz, $C\underline{H}_AH_S$), 1.87-1.90 (1H, m, $CH_A\underline{H}_S$), 2.11-2.16 (2H, m, 2x $C\underline{H}_XH_N$), 3.89 (2H, br s, CH-8 and CH-11), 3.96 (3H, s, OCH_3), 4.10 (3H, s, OCH_3), 7.45 (1H, ddd, *J* = 9.0 Hz, 7.7 Hz, 2.8 Hz, CH_{arom}), 8.14 (1H, dd, *J* = 9.0 Hz, 6.1 Hz, CH_{arom}), 9.07 (1H, dd, *J* = 12.3 Hz, 2.8 Hz, CH_{arom}), 9.54 (1H, s, CH_{arom}). **^{13}C NMR** (100.6 MHz, ref = $CDCl_3$): δ 27.21 and 27.23 (CH_2CH_2), 41.0 (CH-8 or CH-11), 41.3 (CH-8 or CH-11), 48.8 (CH_2), 61.0 (OCH_3), 62.2 (OCH_3), 111.6 (d, *J* = 25.6 Hz, CH_{arom}), 116.9 (d, *J* = 24.7 Hz, CH_{arom}), 120.6 ($C_{arom,quat}$), 124.9 (d, *J* = 10.7 Hz, $C_{arom,quat}$), 125.1 (d, *J* = 4.2 Hz, $C_{arom,quat}$), 131.6 (d, *J* = 9.4 Hz, CH_{arom}), 138.0, 142.0, 145.7, 146.7 and 147.0 (5x $C_{arom,quat}$), 147.8 (CH_{arom}), 161.0 (d, *J* = 243.6 Hz, CF_{arom}). **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ -112.89 to -112.96 (1F, m, CF_{arom}). **MS** (ES^+): *m*/*z* (%): 324 ($M + H^+$, 100). **HRMS** (ES^+): calcd. for $C_{20}H_{19}FNO_2^+$: 324.1394, found 324.1408.

7,12-Dimethoxy-3-fluoro-8,9,10,11-tetrahydro-8,11-methanobenzo[*j*]phenanthridine 288b



Yellow oil. R_f 0.07 (petroleum ether/EtOAc 9/1). Yield: 39%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.40-1.44 (2H, m, 2x $CH_X\underline{H}_N$), 1.69 (1H, d, *J* = 9.1 Hz, $C\underline{H}_AH_S$), 1.88 (1H, d, *J* = 9.1 Hz, $CH_A\underline{H}_S$), 2.10-2.15 (2H, m, 2x $C\underline{H}_XH_N$), 3.89 (2H, br s, CH-8 and CH-11), 3.92 (3H, s, OCH_3), 4.10 (3H, s, OCH_3), 7.38 (1H, ddd, *J* = 9.4 Hz, 8.0 Hz, 2.8 Hz, CH_{arom}), 7.79 (1H, dd, *J* = 9.8 Hz, 2.8 Hz, CH_{arom}), 9.41 (1H, dd, *J* = 9.4 Hz, 6.3 Hz, CH_{arom}), 9.59 (1H, s, CH_{arom}). **^{13}C NMR** (100.6 MHz, ref = $CDCl_3$): δ 27.1 and 27.2 (CH_2CH_2), 40.9 (CH-8 or CH-11), 41.2 (CH-8 or CH-11), 48.6 (CH_2), 60.8 (OCH_3), 62.0 (OCH_3), 113.9 (d, *J* = 20.3 Hz, CH_{arom}), 115.7 (d, *J* = 22.7 Hz, CH_{arom}), 120.1 ($C_{arom,quat}$), 120.5 (d, *J* = 2.1 Hz, $C_{arom,quat}$), 125.4 ($C_{arom,quat}$), 128.7 (d, *J* = 8.8 Hz, CH_{arom}), 136.7, 146.0 and 146.3 (3x $C_{arom,quat}$), 146.4 (d, *J* = 11.3 Hz, $C_{arom,quat}$), 147.0 ($C_{arom,quat}$), 149.6 (CH_{arom}), 161.8 (d, *J* = 248.1 Hz, CF_{arom}). **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ -113.31 to -113.38 (1F, m, CF_{arom}). **IR** (ATR, cm^{-1}): ν_{max} = 1450, 1314, 1208, 1049. **MS** (ES^+): *m*/*z* (%): 324 ($M + H^+$, 100). **HRMS** (ES^+): calcd. for $C_{20}H_{19}FNO_2^+$: 324.1394, found 324.1399.

7,12-Dimethoxy-4-fluoro-8,9,10,11-tetrahydro-8,11-methanobenzo[*j*]phenanthridine 288c



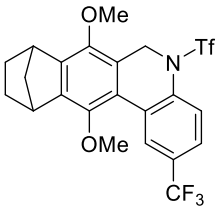
Yellow oil. R_f 0.07 (petroleum ether/EtOAc 9/1). Yield: 43%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.41-1.45 (2H, m, 2x $CH_X\underline{H}_N$), 1.71 (1H, d, *J* = 9.1 Hz, $C\underline{H}_AH_S$), 1.88-1.91 (1H, m, $CH_A\underline{H}_S$), 2.12-2.16 (2H, m, 2x $C\underline{H}_XH_N$), 3.90 (1H, br s, CH-8 or CH-11), 3.91 (1H, br s, CH-8 or CH-11), 3.93 (3H, s, OCH_3), 4.10 (3H, s, OCH_3), 7.42 (1H, ddd, $J_{H,F}$ = 10.0 Hz, *J* = 8.1 Hz, 1.2 Hz, CH_{arom}), 7.56 (1H, ddd, *J* = 8.4 Hz, 8.1 Hz, $J_{H,F}$ = 5.8 Hz, CH_{arom}), 9.18 (1H, d, *J* = 8.4 Hz, CH_{arom}), 9.63 (1H, s, CH_{arom}). **^{13}C NMR** (100.6 MHz, ref = $CDCl_3$): δ 27.06 and 27.10 (CH_2CH_2), 40.9 (CH-8 or CH-11), 41.3 (CH-8 or CH-11), 48.6 (CH_2), 60.9 (OCH_3), 62.1 (OCH_3), 112.9 (d, *J* = 19.3 Hz, CH_{arom}), 120.7 ($C_{arom,quat}$), 122.2 (d, *J* = 4.5 Hz, CH_{arom}), 124.9 (d, *J* = 2.6 Hz, $C_{arom,quat}$), 125.6 ($C_{arom,quat}$), 126.5 (d, *J* = 8.6 Hz, CH_{arom}), 134.8 (d, *J* = 10.3 Hz, $C_{arom,quat}$), 137.7, 146.3, 146.5 and 147.1 (4x $C_{arom,quat}$), 148.7 (d, *J* = 1.3 Hz, CH_{arom}), 158.4 (d, *J* = 252.4 Hz, CF_{arom}). **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ -125.22 (1F, dd, $J_{H,F}$ = 10.0 Hz, 5.8 Hz, CF_{arom}). **IR** (ATR, cm^{-1}): ν_{max} = 1316, 1033, 963, 762. **MS** (ES^+): *m*/*z* (%): 324 ($M + H^+$, 100). **HRMS** (ES^+): calcd. for $C_{20}H_{19}FNO_2^+$: 324.1394, found 324.1406.

5.8.4 Synthesis of 7,12-dimethoxy-5-(trifluoromethanesulfonyl)-5,6,8,9,10,11-hexahydro-8,11-methanobenzo[*j*]phenanthridines 293d-e

The synthesis of 7,12-dimethoxy-2-trifluoromethyl-5-(trifluoromethanesulfonyl)-5,6,8,9,10,11-hexahydro-8,11-methanobenzo[*j*]phenanthridine **293d** is described as representative. To a solution of *N*-

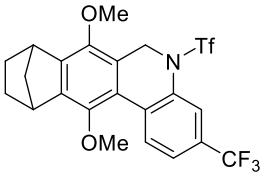
(2-bromo-4-(trifluoromethyl)phenyl)-*N*-(5,8-dimethoxy-1,2,3,4-tetrahydro-1,4-methanonaphthalen-6-yl)methyl)-1,1,1-trifluoromethanesulfonamide **292d** (0.32 g, 0.55 mmol) in THF (10 mL) under nitrogen atmosphere, were added $Pd(OAc)_2$ (0.06 equiv, 7.4 mg, 0.033 mmol), triphenylphosphine (0.18 equiv, 26 mg, 0.099 mmol) and K_2CO_3 (2 equiv, 0.152 g, 1.10 mmol) and this mixture was stirred at reflux temperature for 61 hours. After this time, extra $Pd(OAc)_2$ (0.06 equiv, 7.4 mg, 0.033 mmol), triphenylphosphine (0.18 equiv, 26 mg, 0.099 mmol) and K_2CO_3 (2 equiv, 0.152 g, 1.10 mmol) were added and stirring was continued for another 25 hours. After the addition of H_2O (10 mL), the reaction mixture was filtered over Celite® and extracted with EtOAc (3x 10 mL). After drying of the combined organic phases ($MgSO_4$), filtration and evaporation *in vacuo*, the crude product was purified *via* column chromatography yielding 7,12-dimethoxy-2-trifluoromethyl-5-(trifluoromethanesulfonyl)-5,6,8,9,10,11-hexahydro-8,11-methanobenzo-[*j*]phenanthridine **293d** (0.217 g, 0.43 mmol).

7,12-Dimethoxy-2-trifluoromethyl-5-(trifluoromethanesulfonyl)-5,6,8,9,10,11-hexahydro-8,11-methanobenzo[*j*]phenanthridine 293d



Pale yellow crystals. Melting point: 118-119 °C. R_f 0.38 (petroleum ether/EtOAc 9/1). Yield: 78%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.29-1.34 (2H, m, 2x $CH_X\underline{H}_N$), 1.59 (1H, d, *J* = 9.0 Hz, $C\underline{H}_AH_S$), 1.79 (1H, *J* = 9.0 Hz, $CH_A\underline{H}_S$), 2.02-2.07 (2H, m, 2x $C\underline{H}_XH_N$), 3.63 (3H, s, OCH_3), 3.70 (2H, br s, CH-8 and CH-11), 3.90 (3H, s, OCH_3), 4.66 (1H, br s, $C\underline{H}$(H)N), 4.97 (1H, br s, CH($\underline{H}$)N), 7.57 (1H, dd, *J* = 8.5 Hz, 1.6 Hz, CH_{arom}), 7.72 (1H, d, *J* = 8.5 Hz, CH_{arom}), 8.77 (1H, d, *J* = 1.6 Hz, CH_{arom}). **^{13}C NMR** (100.6 MHz, ref = $CDCl_3$): δ 27.0 (CH_2CH_2), 40.7 (CH-8 or CH-11), 41.7 (CH-8 or CH-11), 45.6 (CH_2NH), 48.9 (CH_2), 60.9 (OCH_3), 61.2 (OCH_3), 120.0 (q, *J* = 324.5 Hz, SCF_3), 120.8 ($C_{arom,quat}$), 124.0 (q, *J* = 272.4 Hz, $C_{arom}\underline{C}F_3$), 124.5 (q, *J* = 3.5 Hz, CH_{arom}), 125.3 ($C_{arom,quat}$), 125.55 (CH_{arom}), 125.61 (q, *J* = 4.0 Hz, CH_{arom}), 129.7 (q, *J* = 32.5 Hz, $\underline{C}_{arom}CF_3$), 130.2, 137.0, 141.2, 142.8, 145.6 and 147.5 (6x $C_{arom,quat}$). **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ -63.19 (3F, s, SCF_3), -75.78 (3F, s, $C_{arom}CF_3$). **IR** (ATR, cm^{-1}): ν_{max} = 1400, 1332, 1195, 1137, 1086. **MS** (ES^+): *m/z* (%): 374 (M - CHF_3SO_3 + H^+, 100). **HRMS** (ES^+): calcd. for $C_{21}H_{19}F_3NO_2^+$ (M - CHF_3SO_3 + H^+): 374.1362, found 374.1378.

7,12-Dimethoxy-3-trifluoromethyl-5-(trifluoromethanesulfonyl)-5,6,8,9,10,11-hexahydro-8,11-methanobenzo[*j*]phenanthridine 293e

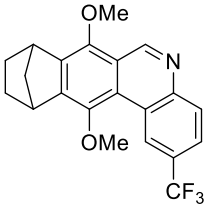


Pale yellow crystals. Melting point: 143-144 °C. R_f 0.42 (petroleum ether/EtOAc 9/1). Yield: 81%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.28-1.35 (2H, m, 2x $CH_X\underline{H}_N$), 1.59 (1H, d, *J* = 9.0 Hz, $C\underline{H}_AH_S$), 1.79 (1H, d, *J* = 9.0 Hz, $CH_A\underline{H}_S$), 2.03-2.07 (2H, m, 2x $C\underline{H}_XH_N$), 3.62 (3H, s, OCH_3), 3.70 (2H, br s, CH-8 and CH-11), 3.90 (3H, s, OCH_3), 4.64 (1H, br s, C<u>H</u>(H)N), 4.99 (1H, br s, CH(<u>H</u>)N), 7.61 (1H, d, *J* = 8.5 Hz, CH_{arom}), 7.83 (1H, s, CH_{arom}), 8.55 (1H, d, *J* = 8.5 Hz, CH_{arom}). **^{13}C NMR** (100.6 MHz, ref = $CDCl_3$): δ 27.0 (CH_2CH_2), 40.7 (CH-8 or CH-11), 41.7 (CH-8 or CH-11), 45.6 (CH_2NH), 48.8 (CH_2), 61.0 (OCH_3), 61.1 (OCH_3), 120.0 (q, *J* = 324.7 Hz, SCF_3), 120.9 ($C_{arom,quat}$), 122.5 (q, *J* = 3.7 Hz, CH_{arom}), 123.7 (q, *J* = 272.3 Hz, $C_{arom}\underline{C}F_3$), 124.3 (q, *J* = 3.5 Hz, CH_{arom}), 125.7 ($C_{arom,quat}$), 128.8 (CH_{arom}), 129.6 (q, *J* = 33.2 Hz, $\underline{C}_{arom}CF_3$), 133.1, 134.5, 141.5, 142.8, 145.7 and 147.7 (6x $C_{arom,quat}$). **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ -63.20 (3F, s, SCF_3), -75.70 (3F, s, $C_{arom}CF_3$). **IR** (ATR, cm^{-1}): ν_{max} = 1398, 1327, 1311, 1193, 1121, 1075. **MS** (ES^+): *m*/*z* (%): 374 (M - CHF_3SO_3 + H^+, 100). **HRMS** (ES^+): calcd. for $C_{21}H_{19}F_3NO_2^+$ (M - CHF_3SO_3 + H^+): 374.1362, found 374.1368.

5.8.5 Synthesis of 7,12-dimethoxy-8,9,10,11-tetrahydro-8,11-methanobenzo[*j*]-phenanthridines 288d,e

The synthesis of 7,12-dimethoxy-2-trifluoromethyl-8,9,10,11-tetrahydro-8,11-methanobenzo[*j*]-phenanthridine **288d** is described as representative. To a solution of 7,12-dimethoxy-2-trifluoromethyl-5-(trifluoromethanesulfonyl)-5,6,8,9,10,11-hexahydro-8,11-methanobenzo[*j*]phenanthridine **293d** (0.155 g, 0.31 mmol) in THF (10 mL), was added KO*t*Bu (1M in THF, 1.2 equiv, 0.37 mmol) and this mixture was stirred at reflux temperature for three hours. After the addition of saturated aqueous NH_4Cl, the reaction mixture was extracted with EtOAc (3x 10 mL), dried ($MgSO_4$), filtered and evaporated under reduced pressure. Without the need for purification, 7,12-dimethoxy-2-trifluoromethyl-8,9,10,11-tetrahydro-8,11-methanobenzo[*j*]phenanthridine **288d** was obtained in quantitative yield (0.113 g, 0.31 mmol).

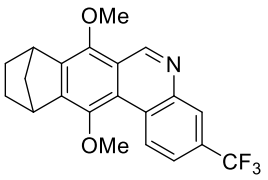
7,12-Dimethoxy-2-trifluoromethyl-8,9,10,11-tetrahydro-8,11-methanobenzo[*j*]phenanthridine 288d



Yellow oil. Yield: quant. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.39-1.44 (2H, m, 2x $CH_X\underline{H}_N$), 1.70 (1H, d, *J* = 9.2 Hz, $C\underline{H}_AH_S$), 1.87-1.90 (1H, m, $CH_A\underline{H}_S$), 2.11-2.16 (2H, m, 2x $C\underline{H}_XH_N$), 3.90 (2H, br s, CH-8 and CH-11), 3.95 (3H, s, OCH_3), 4.11 (3H, s, OCH_3), 7.89 (1H, dd, *J* = 8.5 Hz, 1.8 Hz, CH_{arom}), 8.24 (1H, d, *J* = 8.5 Hz, CH_{arom}), 9.67 (1H, s, CH_{arom}), 9.79 (1H, br s,

CH_{arom}). **^{13}C NMR** (100.6 MHz, ref = $CDCl_3$): δ 27.0 and 27.1 (CH_2CH_2), 41.0 (CH-8 or CH-11), 41.4 (CH-8 or CH-11), 48.7 (CH_2), 60.8 (OCH_3), 62.0 (OCH_3), 120.6 and 123.4 (2x $C_{arom,quat}$), 123.9 (q, *J* = 3.1 Hz, CH_{arom}), 124.6 (q, *J* = 271.2 Hz, CF_3), 124.7 (q, *J* = 4.6 Hz, CH_{arom}), 125.0 ($C_{arom,quat}$), 128.2 (q, *J* = 31.9 Hz, CCF_3), 130.4 (CH_{arom}), 137.9, 146.2, 146.8 and 147.2 (4x $C_{arom,quat}$), 150.6 (CH_{arom}). **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ -62.20 (3F, s, CF_3). **IR** (ATR, cm^{-1}): ν_{max} = 1334, 1320, 1161, 1118, 1087. **MS** (ES^+): *m*/*z* (%): 374 (M + H^+, 100). **HRMS** (ES^+): calcd. for $C_{21}H_{19}F_3NO_2^+$: 374.1362, found 374.1378.

7,12-Dimethoxy-3-trifluoromethyl-8,9,10,11-tetrahydro-8,11-methanobenzo[*j*]phenanthridine 288e

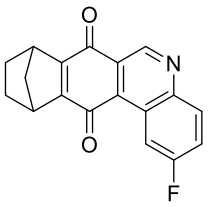


Yellow oil. Yield: quant. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.41-1.46 (2H, m, 2x $CH_X\underline{H}_N$), 1.72 (1H, d, *J* = 9.1 Hz, $C\underline{H}_AH_S$), 1.88-1.92 (1H, m, $CH_A\underline{H}_S$), 2.13-2.18 (2H, m, 2x $C\underline{H}_XH_N$), 3.92 (2H, br s, CH-8 and CH-11), 3.95 (3H, s, OCH_3), 4.12 (3H, s, OCH_3), 7.82 (1H, dd, *J* = 8.9 Hz, 1.9 Hz, CH_{arom}), 8.44 (1H, br s, CH_{arom}), 9.52 (1H, d, *J* = 8.9 Hz, CH_{arom}), 9.66 (1H, s, CH_{arom}). **^{13}C NMR** (100.6 MHz, ref = $CDCl_3$): δ 26.9 and 27.0 (CH_2CH_2), 40.9 (CH-8 or CH-11), 41.4 (CH-8 or CH-11), 48.6 (CH_2), 60.7 (OCH_3), 61.8 (OCH_3), 120.8 ($C_{arom,quat}$), 122.3 (q, *J* = 3.1 Hz, CH_{arom}), 124.2 (q, *J* = 272.2 Hz, CF_3), 125.5 and 126.2 (2x $C_{arom,quat}$), 127.0 (q, *J* = 4.1 Hz, CH_{arom}), 127.7 (CH_{arom}), 129.3 (q, *J* = 32.6 Hz, $\underline{C}CF_3$), 138.2, 144.2, 146.4, 146.6 and 146.9 (5x $C_{arom,quat}$), 149.8 (CH_{arom}). **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ -62.82 (3F, s, CF_3). **IR** (ATR, cm^{-1}): ν_{max} = 1332, 1312, 1174, 1116, 1070, 1050. **MS** (ES^+): *m*/*z* (%): 374 (M + H^+, 100). **HRMS** (ES^+): calcd. for $C_{21}H_{19}F_3NO_2^+$: 374.1362, found 374.1379.

5.8.6 Synthesis of 8,9,10,11-tetrahydro-8,11-methanobenzo[*j*]phenanthridine-7,12-diones 31

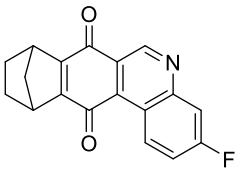
The synthesis of 2-fluoro-8,9,10,11-tetrahydro-8,11-methanobenzo[*j*]phenanthridine-7,12-dione **31a** is described as representative. To a solution of 7,12-dimethoxy-2-fluoro-8,9,10,11-tetrahydro-8,11-methanobenzo[*j*]phenanthridine **288a** (0.030 g, 0.093 mmol) in CH_3CN (2 mL), was added a solution of CAN (2.3 equiv, 0.12 g, 0.21 mmol) in H_2O (2 mL) at 0 °C. This mixture was stirred at this temperature for 45 minutes, after which H_2O (4 mL) was added and an extraction was performed with EtOAc (3x 5 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure affording crude 2-fluoro-8,9,10,11-tetrahydro-8,11-methanobenzo[*j*]phenanthridine-7,12-dione **31a**, which was purified *via* preparative TLC (0.015 g, 0.034 mmol).

2-Fluoro-8,9,10,11-tetrahydro-8,11-methanobenzo[*j*]phenanthridine-7,12-dione 31a



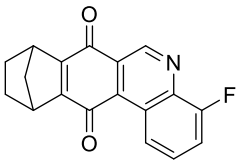
Orange crystals. Melting point: 198-199 °C. R_f 0.13 (petroleum ether/EtOAc 9/1). Yield: 37%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.27-1.34 (2H, m, 2x $CH_X\underline{H}_N$), 1.52 (1H, d, *J* = 9.2 Hz, $C\underline{H}_AH_S$), 1.74-1.77 (1H, m, $CH_A\underline{H}_S$), 2.00-2.08 (2H, m, 2x $C\underline{H}_XH_N$), 3.69 (1H, br s, CH-8 or CH-11), 3.70 (1H, br s, CH-8 or CH-11), 7.62 (1H, ddd, *J* = 9.3 Hz, $J_{H,F}$ = 7.5 Hz, *J* = 2.8 Hz, CH_{arom}), 8.17 (1H, dd, *J* = 9.3 Hz, $J_{H,F}$ = 5.7 Hz, CH_{arom}), 9.15 (1H, dd, $J_{H,F}$ = 11.4 Hz, *J* = 2.8 Hz, CH_{arom}), 9.55 (1H, s, CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 25.2 and 25.3 (CH_2CH_2), 40.9 (CH-8 or CH-11), 41.4 (CH-8 or CH-11), 47.3 (CH_2), 111.3 (d, *J* = 25.8 Hz, CH_{arom}), 122.1 (d, *J* = 26.4 Hz, CH_{arom}), 123.7 (d, *J* = 11.8 Hz, $C_{arom,quat}$), 124.1 ($C_{arom,quat}$), 132.3 (d, *J* = 6.7 Hz, $C_{arom,quat}$), 132.5 (d, *J* = 9.5 Hz, CH_{arom}), 146.7 (d, *J* = 2.8 Hz, CH_{arom}), 149.4, 152.0 and 155.3 (3x $C_{arom,quat}$), 163.1 (d, *J* = 251.1 Hz, CF_{arom}), 182.1 and 185.0 (2x C=O). **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ -107.83 (1F, ddd, $J_{H,F}$ = 11.4 Hz, 7.5 Hz, 5.7 Hz, CF_{arom}). **IR** (ATR, cm^{-1}): $\nu_{C=O}$ = 1645, ν_{max} = 1320, 1271, 1196, 1006. **MS** (ES^+): *m*/*z* (%): 294 ($M + H^+$, 100). **HRMS** (ES^+): calcd. for $C_{18}H_{13}FNO_2^+$: 294.0925, found 294.0931.

3-Fluoro-8,9,10,11-tetrahydro-8,11-methanobenzo[*j*]phenanthridine-7,12-dione 31b



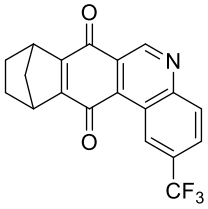
Orange crystals. Melting point: 154-155 °C. R_f 0.29 (petroleum ether/EtOAc 9/1). Yield: 50%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.27-1.34 (2H, m, 2x $CH_X\underline{H}_N$), 1.52 (1H, d, *J* = 9.2 Hz, $C\underline{H}_AH_S$), 1.73-1.77 (1H, m, $CH_A\underline{H}_S$), 2.02-2.08 (2H, m, 2x $C\underline{H}_XH_N$), 3.69 (2H, br s, CH-8 and CH-11), 7.54 (1H, ddd, *J* = 9.6 Hz, 8.0 Hz, 2.6 Hz, CH_{arom}), 7.89 (1H, dd, *J* = 9.4 Hz, 2.6 Hz, CH_{arom}), 9.48 (1H, dd, *J* = 9.6 Hz, 6.2 Hz, CH_{arom}), 9.60 (1H, s, CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 25.3 and 25.4 (CH_2CH_2), 40.9 (CH-8 or CH-11), 41.4 (CH-8 or CH-11), 47.2 (CH_2), 113.8 (d, *J* = 20.2 Hz, CH_{arom}), 119.6 ($C_{arom,quat}$), 120.5 (d, *J* = 24.5 Hz, CH_{arom}), 123.3 (d, *J* = 2.7 Hz, $C_{arom,quat}$), 130.3 (d, *J* = 9.6 Hz, CH_{arom}), 133.0 (d, *J* = 1.8 Hz, $C_{arom,quat}$), 148.7 (CH_{arom}), 152.0 ($C_{arom,quat}$), 153.6 (d, *J* = 12.7 Hz, $C_{arom,quat}$), 155.1 ($C_{arom,quat}$), 164.1 (d, *J* = 256.5 Hz, CF_{arom}), 182.0 and 185.2 (2x C=O). **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ -105.86 (1F, ddd, *J* = 9.4 Hz, 8.0 Hz, 6.2 Hz, CF_{arom}). **IR** (ATR, cm^{-1}): $\nu_{C=O}$ = 1655, ν_{max} = 1620, 1314, 1287. **MS** (ES^+): *m*/*z* (%): 294 ($M + H^+$, 100). **HRMS** (ES^+): calcd. for $C_{18}H_{13}FNO_2^+$ ($M + H^+$): 294.0925, found 294.0927.

4-Fluoro-8,9,10,11-tetrahydro-8,11-methanobenzo[*j*]phenanthridine-7,12-dione 31c



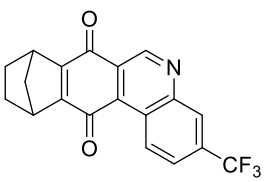
Orange crystals. Melting point: 171-172 °C. Yield: 62%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.30-1.34 (2H, m, 2x $CH_X\underline{H}_N$), 1.53 (1H, d, *J* = 9.2 Hz, $C\underline{H}_AH_S$), 1.75-1.78 (1H, m, $CH_A\underline{H}_S$), 2.04-2.08 (2H, m, 2x $C\underline{H}_XH_N$), 3.70 (2H, br s, CH-8 and CH-11), 7.54 (1H, ddd, $J_{H,F}$ = 9.9 Hz, *J* = 7.8 Hz, 1.2 Hz, CH_{arom}), 7.69 (1H, ddd, *J* = 8.8 Hz, 7.8 Hz, $J_{H,F}$ = 5.4 Hz, CH_{arom}), 9.20 (1H, d, *J* = 8.8 Hz, CH_{arom}), 9.62 (1H, s, CH_{arom}). **^{13}C NMR** (100.6 MHz, $CDCl_3$): δ 25.3 and 25.4 (CH_2CH_2), 41.0 (CH-8 or CH-11), 41.5 (CH-8 or CH-11), 47.2 (CH_2), 115.7 (d, *J* = 18.5 Hz, CH_{arom}), 123.5 (d, *J* = 5.3 Hz, CH_{arom}), 124.2 and 124.4 (2x $C_{arom,quat}$), 129.9 (d, *J* = 8.1 Hz, CH_{arom}), 132.8 (d, *J* = 2.5 Hz, $C_{arom,quat}$), 142.1 (d, *J* = 11.3 Hz, $C_{arom,quat}$), 147.6 (CH_{arom}), 151.9 and 155.4 (2x $C_{arom,quat}$), 157.8 (d, *J* = 257.9 Hz, CF_{arom}), 181.9 and 184.9 (2x C=O). **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ -123.53 (1F, dd, $J_{H,F}$ = 9.9 Hz, 5.4 Hz, CF_{arom}). **IR** (ATR, cm^{-1}): $\nu_{C=O}$ = 1655, ν_{max} = 1326, 1287, 1274, 765. **MS** (ES^+): *m/z* (%): 294 ($M + H^+$, 100). **HRMS** (ES^+): calcd. for $C_{18}H_{13}FNO_2^+$: 294.0925, found 294.0931.

2-Trifluoromethyl-8,9,10,11-tetrahydro-8,11-methanobenzo[*j*]phenanthridine-7,12-dione 31d



Orange crystals. Melting point: 151-152 °C. R_f 0.17 (petroleum ether/EtOAc 9/1). Yield: 76%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.27-1.35 (2H, m, 2x $CH_X\underline{H}_N$), 1.54 (1H, d, *J* = 9.2 Hz, $C\underline{H}_AH_S$), 1.75-1.79 (1H, m, $CH_A\underline{H}_S$), 2.03-2.10 (2H, m, 2x $C\underline{H}_XH_N$), 3.70 (1H, br s, CH-8 or CH-11), 3.71 (1H, br s, CH-8 or CH-11), 8.01 (1H, dd, *J* = 8.9 Hz, 2.0 Hz, CH_{arom}), 8.29 (1H, d, *J* = 8.9 Hz, CH_{arom}), 9.70 (1H, s, CH_{arom}), 9.83 (1H, s, CH_{arom}). **^{13}C NMR** (100.6 MHz, ref = $CDCl_3$): δ 25.3 and 25.5 (CH_2CH_2), 41.1 (CH-8 or CH-11), 41.6 (CH-8 or CH-11), 47.4 (CH_2), 121.9 ($C_{arom,quat}$), 123.9 (q, *J* = 272.9 Hz, CF_3), 124.4 ($C_{arom,quat}$), 126.0 (q, *J* = 4.6 Hz, CH_{arom}), 127.3 (q, *J* = 3.2 Hz, CH_{arom}), 131.4 (CH_{arom}), 131.7 (q, *J* = 32.7 Hz, $\underline{C}CF_3$), 133.4 ($C_{arom,quat}$), 149.7 (CH_{arom}), 152.2, 152.6 and 155.4 (3x $C_{arom,quat}$), 181.8 and 184.9 (2x C=O). **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ -63.16 (3F, s, CF_3). **IR** (ATR, cm^{-1}): $\nu_{C=O}$ = 1657, ν_{max} = 1303, 1287, 1273, 1130. **MS** (ES^+): *m/z* (%): 344 ($M + H^+$, 100). **HRMS** (ES^+): calcd. for $C_{19}H_{13}F_3NO_2^+$: 344.0893, found 344.0897.

3-Trifluoromethyl-8,9,10,11-tetrahydro-8,11-methanobenzo[*j*]phenanthridine-7,12-dione 31e



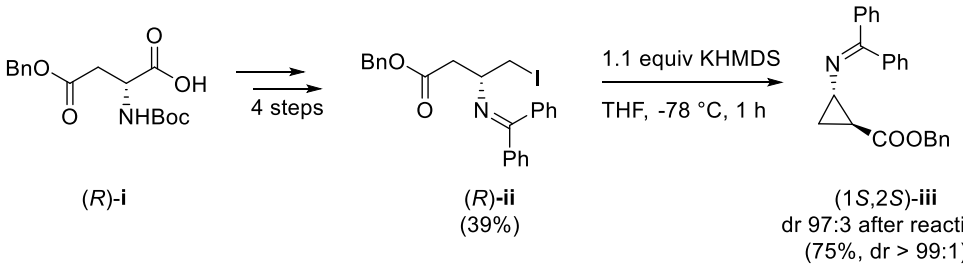
Orange crystals. Melting point: 158-159 °C. Yield: 45%. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.28-1.35 (2H, m, 2x $CH_X\underline{H}_N$), 1.54 (1H, d, *J* = 9.2 Hz, $C\underline{H}_AH_S$), 1.76-1.78 (1H, m, $CH_A\underline{H}_S$), 2.03-2.10 (2H, m, 2x $C\underline{H}_XH_N$), 3.70 (1H, br s, CH-8 or CH-11), 3.71 (1H, br s, CH-8 or CH-11), 7.92 (1H, dd, *J* = 9.1 Hz, 1.7 Hz, CH_{arom}), 8.47 (1H, s, CH_{arom}), 9.58 (1H, d, *J* = 9.1 Hz, CH_{arom}), 9.69 (1H, s, CH_{arom}). **^{13}C NMR** (100.6 MHz, ref = $CDCl_3$): δ 25.2 and 25.3 (CH_2CH_2),

41.0 (CH-8 or CH-11), 41.5 (CH-8 or CH-11), 47.3 (CH_2), 123.4 (q, *J* = 272.9 Hz, CF_3), 124.3 and 124.7 (2x $C_{arom,quat}$), 125.3 (q, *J* = 2.9 Hz, CH_{arom}), 127.6 (q, *J* = 4.4 Hz, CH_{arom}), 129.1 (CH_{arom}), 132.6 ($C_{arom,quat}$), 132.9 (q, *J* = 33.2 Hz, $\underline{C}CF_3$), 148.8 (CH_{arom}), 150.9, 152.0 and 155.4 (3x $C_{arom,quat}$), 181.7 and 184.8 (2x C=O). **^{19}F NMR** (376.5 MHz, $CDCl_3$, ref = $CFCl_3$): δ -63.80 (3F, s, CF_3). **IR** (ATR, cm^{-1}): $\nu_{C=O}$ = 1655, ν_{max} = 1332, 1286, 1163, 1131. **MS** (ES^+): *m*/*z* (%): 344 ($M + H^+$, 100). **HRMS** (ES^+): calcd. for $C_{19}H_{13}F_3NO_2^+$: 344.0893, found 344.0901.

6 Summary

Strained cyclic amino acids, with a small-membered ring as core structure, are of importance as building blocks for novel peptidomimetics. More specifically, strained β-amino acid derivatives increase the conformational stability and rigidity of peptides, and less units are necessary to obtain peptides which adopt a well-defined secondary structure. Therefore, in the first part of this PhD thesis, novel cyclic β-amino acid derivatives were synthesized, containing a cyclopropane or a cyclobutane ring as their core structure.

As such, the synthesis of benzyl 2-(diphenylmethylideneamino)cyclopropanecarboxylate (1*S*,2*S*)-**iii** is described, employing (*R*)-β-benzyl *N*-(*tert*-butoxycarbonyl)aspartate (*R*)-**i** as a chiral building block. To this end, aspartate (*R*)-**i** was converted into γ-iodo-β-amino ester (*R*)-**ii** in four steps in 39% overall yield. The diastereoselective ring closure of precursor (*R*)-**ii** was effectuated by treatment with KHMDS in THF at -78 °C for one hour, leading to a diastereomeric mixture with a diastereomeric ratio *trans*:*cis* = 97:3. After purification, 2-(diphenylmethylideneamino)cyclopropanecarboxylate (1*S*,2*S*)-**iii** was obtained as a single diastereomer in 75% yield (dr > 99:1).

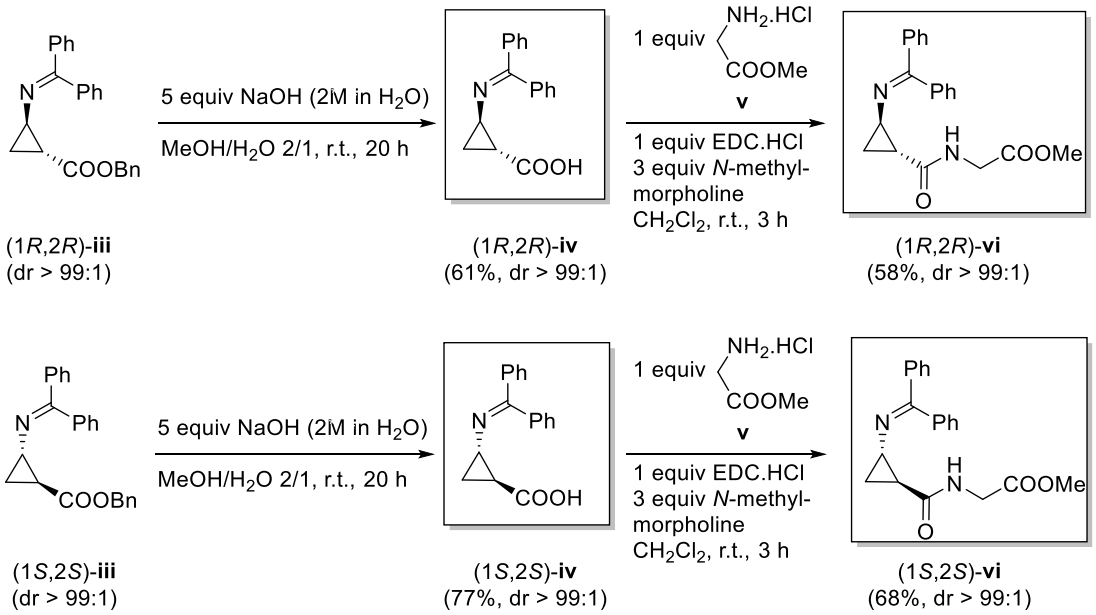


(*R*)-**i**

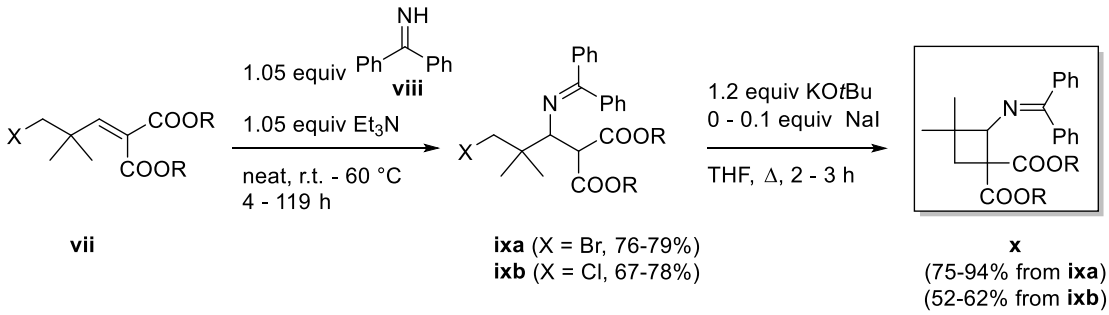
(*R*)-**ii**
(39%)

(1*S*,2*S*)-**iii**
dr 97:3 after reaction
(75%, dr > 99:1)

Subsequently, the saponification of both enantiomers of benzyl cyclopropanecarboxylate **iii** was performed by treatment with five equivalents of NaOH in a MeOH/H_2O mixture for 20 hours at room temperature, leading to the formation of cyclopropanecarboxylic acids (1*R*,2*R*)-**iv** and (1*S*,2*S*)-**iv** in 61% and 77% yield, respectively. The coupling of amino acids **iv** with the hydrochloric salt of methyl glycinate **v** was achieved under standard peptide formation reaction conditions, leading to dipeptides (1*R*,2*R*)-**vi** and (1*S*,2*S*)-**vi** in good yields.

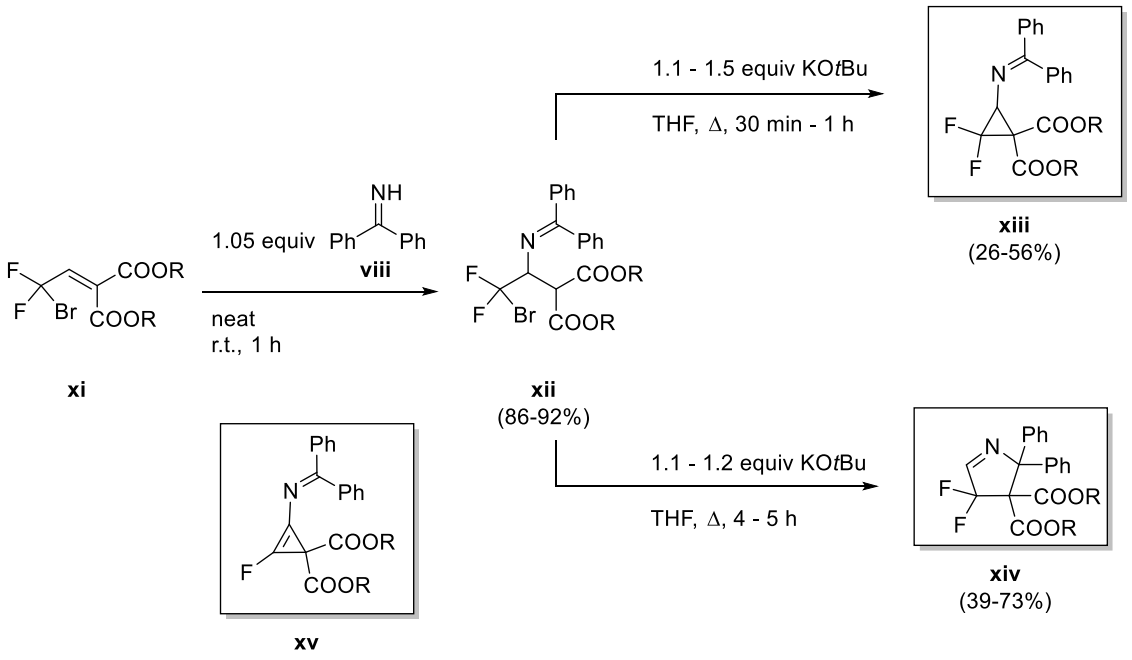


In the second part of this PhD thesis, the synthesis of dialkyl cyclobutane-1,1-dicarboxylates **x** starting from 3-halopropylidenemalonates **vii** was optimized. After screening various reaction conditions, it was found that the addition of diphenylmethylideneamine **viii** across alkylidenemalonates **vii** occured under neat reaction conditions, giving adducts **ix** in good yields after recrystallization. The ring closure of adducts **ix** toward the corresponding cyclobutanes **x** was effectuated by treatment with KO*t*Bu in case of the brominated adducts **ixa**, while a catalytic amount of NaI had to be added to the reaction mixture to achieve ring closure of the chlorinated derivatives **ixb**.



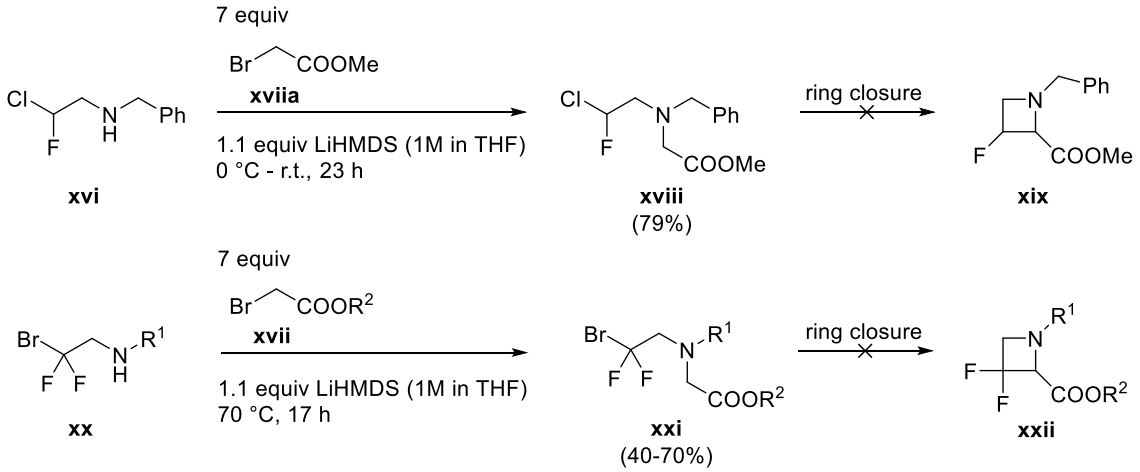
The following parts of this PhD thesis focused on the synthesis of fluorinated compounds. Due to fluorine's unique properties (strong electronegativity, small van der Waals radius), its introduction in organic compounds can induce significant changes in their chemical and pharmacological properties. Therefore, in the pharmaceutical industry, there is a great interest in the synthesis of fluorinated compounds.

The synthesis of fluorinated β-aminocyclopropane-1,1-dicarboxylates **xiii** was envisaged *via* the same methodology as described above for the synthesis of cyclobutane-,1,-dicarboxylates **x**, using bromodifluorinated ethylidenemalonates **xi** as Michael acceptors. Michael-type addition of diphenylmethylideneamine **viii** was achieved under neat reaction conditions and afforded adducts **xii** in very good yields. Subsequently, the ring closure of Michael adducts **xii** toward the envisaged fluorinated β-aminocyclopropane-1,1-dicarboxylates **xiii** was investigated. However, treatment of adducts **xii** with base led to the formation of reaction mixtures containing starting material **xii**, cyclopropanes **xiii**, pyrrolines **xiv**, which are the result of a ring transformation of cyclopropanes **xiii**, and fluorinated cyclopropenes **xv** in varying ratios depending on the reaction conditions. Furthermore, this ring closure proved to be sluggish and poorly reproducible due to the instability of the reaction products. Cyclopropanes **xiii** were formed as the major reaction products upon treatment of adducts **xii** with 1.1-1.5 equivalents of KO*t*Bu for a short reaction time of 30 minutes to one hour. The synthesis of pyrrolines **xiv** was achieved using a longer reaction time of 4-5 hours, to enable the ring transformation of cyclopropanes **xiii** toward pyrrolines **xiv**. Under all reaction conditions which were evaluated, fluorinated cyclopropenedicarboxylates **xv** were formed as side products and were isolated in low yields.

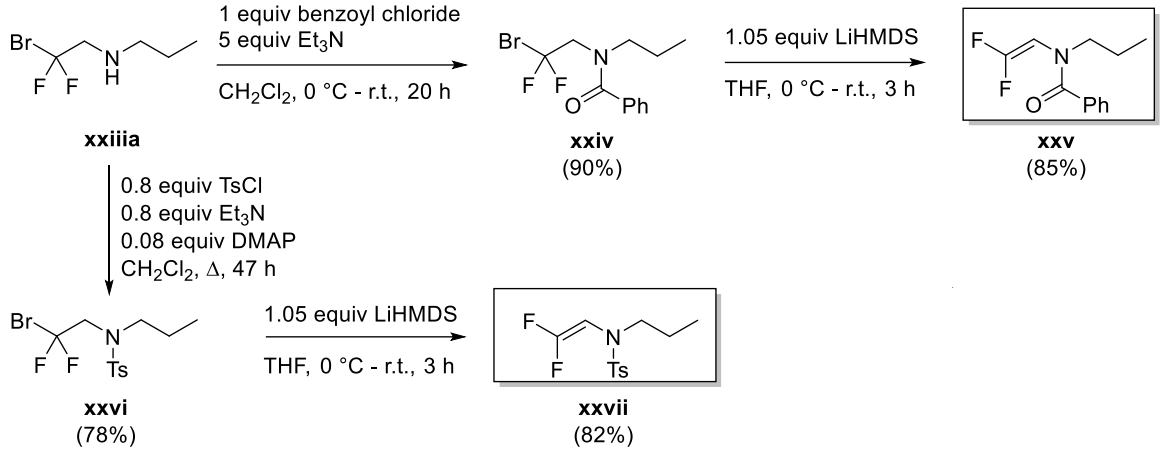


The reduction of pyrrolines **xiv** was evaluated by treatment with $NaCNBH_3$ and led to the formation of acyclic amino esters, which proved to be unstable and could not be fully characterized.

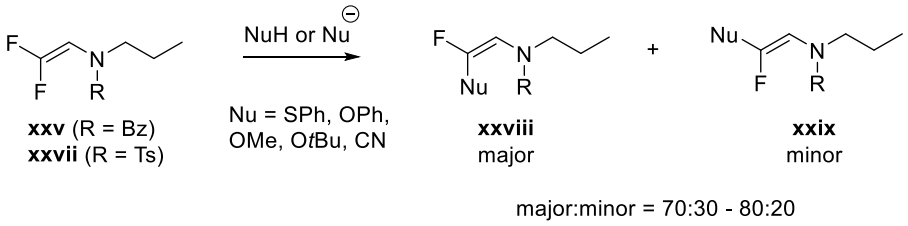
Furthermore, the synthesis of another class of constrained fluorinated amino acids was envisaged, more specifically fluorinated azetidine-2-carboxylates **xix** and **xxii**. To this end, several routes toward precursors **xviii** and **xxi** were evaluated and finally these compounds were synthesized by reacting amines **xvi** and **xx** with an excess of bromoacetates **xvii** in the presence of LiHMDS (1M in THF) for 17-23 hours at room temperature or 70 °C. However, all attempts to convert amino esters **xviii** and **xxi** into the corresponding azetidines failed. While treatment with KO*t*Bu and BuLi led to a nucleophilic addition across the ester moiety, the use of NaH and KMHDS gave no reaction and only resulted in recovery of the starting material. Finally, when amino esters **xviii** and **xxi** were treated with LiHMDS, a peculiar reaction was observed, i.e. removal of the methoxycarbonylmethyl group, leading to the formation of amines **xvi** and **xx**, respectively.



In the next part of this PhD thesis, the synthesis of β,β-difluoroenamides **xxv** and **xxvii** was described, as new building blocks for the synthesis of azaheterocyclic compounds. Protection of secondary amine **xxiiia** by reaction with benzoyl chloride followed by treatment with LiHMDS led to the formation of enamide **xxv**, while the protection of amine **xxiiia** as tosylamide **xxvi** resulted in the formation of enamide **xxvii** after treatment with base.

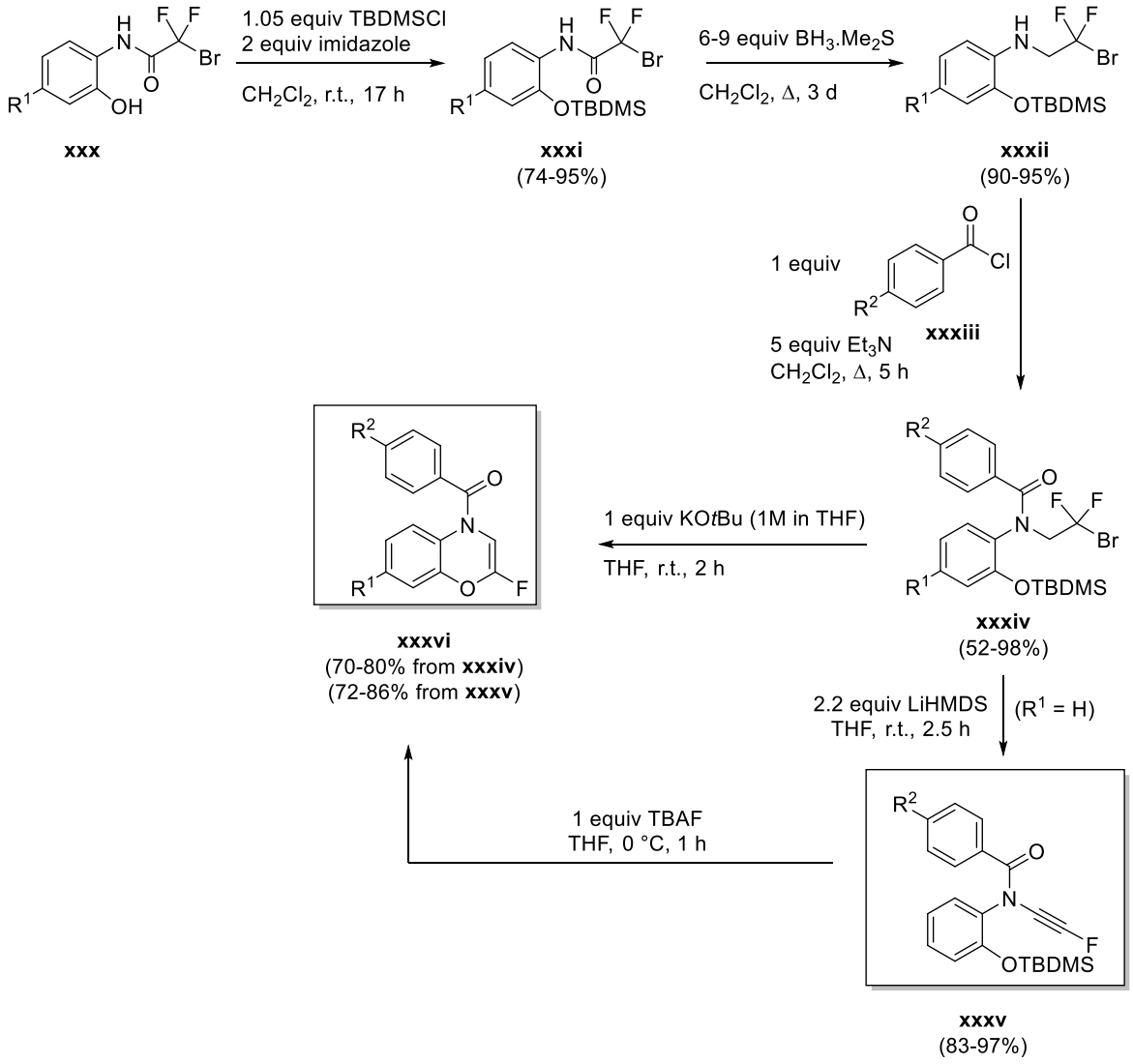


Due to the presence of the electron-withdrawing group at nitrogen in combination with the two fluorine atoms on the β-carbon of the enamide functionality, enamides **xxv** and **xxvii** showed electrophilic reactivity. Indeed, upon treatment of enamides **xxv** and **xxvii** with nucleophiles, an S_NV reaction was observed: addition of the nucleophile across the double bond is followed by elimination of fluoride. This reaction led to the formation of two isomers **xxviii** and **xxix**, with isomer **xxviii** being the major reaction product in all cases. The selectivity toward isomers **xxviii** was explained by evaluating the preferred conformation of the intermediate carbanions after addition of the nucleophile.



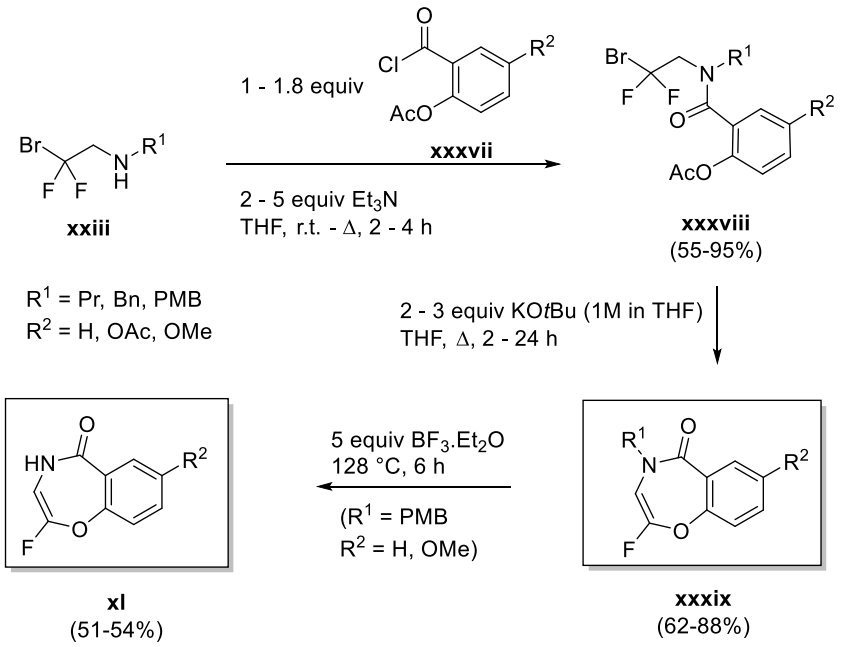
The electrophilic reactivity of enamides **xxv** and **xxvii** was exploited toward the synthesis of fluorinated heterocycles by incorporating the nucleophile and the electrophilic enamide moiety in the same precursor. Whereas the synthesis of 6-fluoro-1,4-oxazines gave poor results, the synthesis of 2-fluoro-1,4-benzoxazines **xxxvi** was optimized. Amides **xxx**, which were synthesized *via* condensation of the corresponding 2-aminophenols with ethyl bromodifluoroacetate, were protected as *tert*-butyldimethylsilyl ethers **xxxi**. Reduction with borane dimethylsulfide complex afforded amines **xxxii** which were converted into amides **xxxiv** by reaction with different benzoyl chlorides **xxxiii**. Next, amides **xxxiv** were evaluated as precursors for the synthesis of 2-fluoro-1,4-benzoxazines, by treatment with different bases. Treatment of amides **xxxiv** with 2.2 equivalents LiHMDS led to the formation of ynamides **xxxv** as sole end products, which were isolated in excellent yields. However, upon use of KO*t*Bu, amides **xxxiv** were converted into 2-fluorobenzoxazines **xxxvi**. After screening different other bases (NaHMDS,

KHMDS and LiO*t*Bu), it was concluded that the cation of the base plays an important role in the reaction outcome. The use of lithium bases led to the formation of end products in which the *tert*-butyldimethylsilyl ether was still present, while upon use of sodium or potassium bases deprotection was observed. It was also demonstrated that ynamides **xxxv**, a group of compounds which were synthesized in excellent yields for the first time, showed electrophilic reactivity since deprotection of the *tert*-butyldimethylsilyl ether of compounds **xxxv** also resulted in the formation of 2-fluoro-1,4-benzoxazines **xxxvi**, *via* addition of the phenolic oxygen atom across the triple bond.

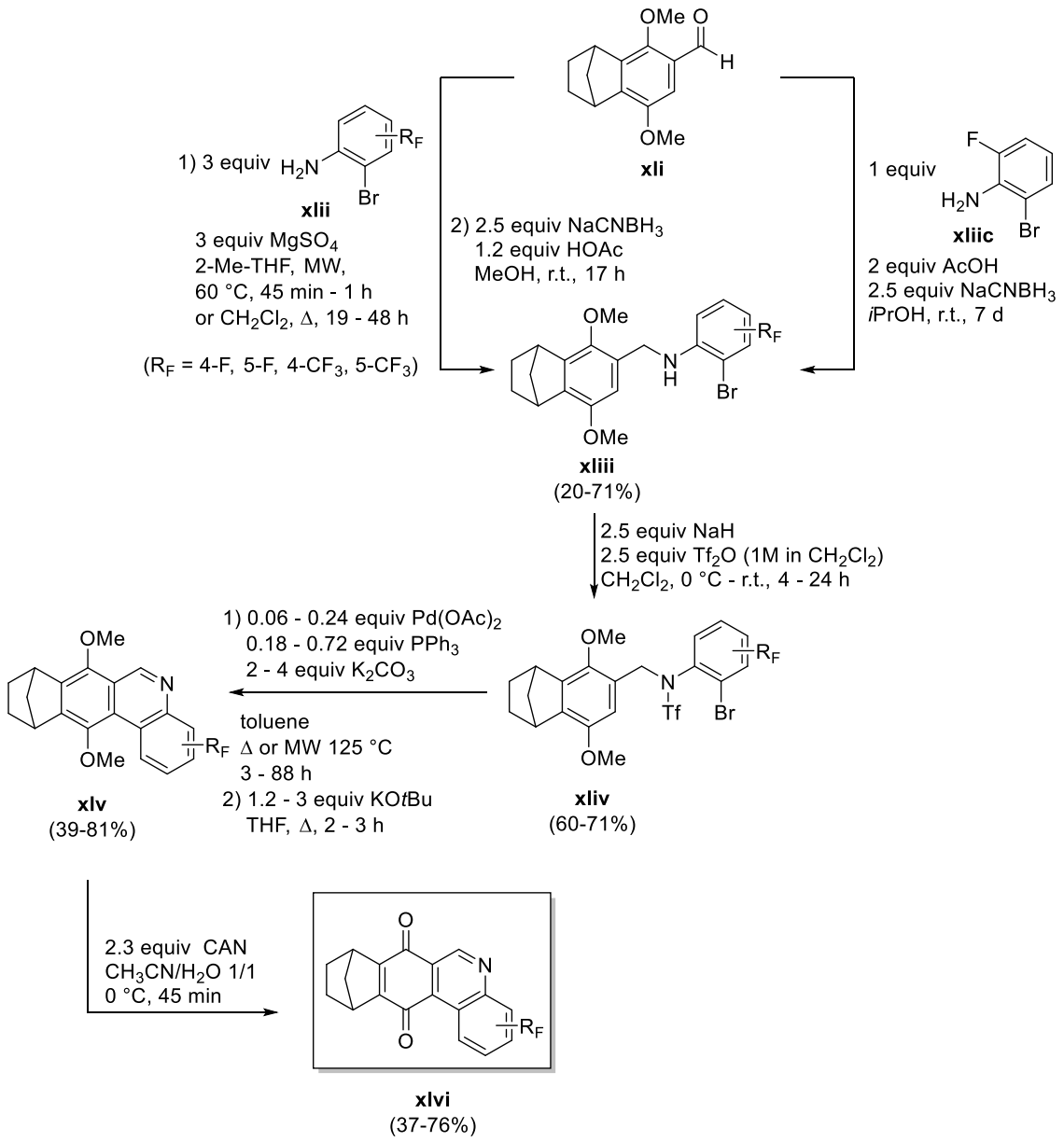


The synthesis of fluorinated benzo-fused seven-membered rings could also be achieved, by using amides **xxxviii** as precursors, which were synthesized *via* condensation of amines **xxiii** with acid chlorides **xxxvii**. Upon treatment of amides **xxxviii** with KO*t*Bu, an efficient conversion toward 2-fluoro-1,4-benzoxazepin-5-ones **xxxix** was achieved, which were isolated in good yields. Finally, removal of the *para*-methoxybenzyl

group was achieved by reaction of *N*-PMB substituted benzoxazepinones **xxxix** with $BF_3.Et_2O$, resulting in 4*H*-2-fluoro-1,4-benzoxazepin-5-ones **xl**.



In the last part of this PhD thesis, the synthesis of 8,9,10,11-tetrahydro-8,11-methanobenzo[*j*]-phenanthridine-7,12-diones **xlvi** was developed, as potential antimycobacterial compounds. The synthetic route started from aldehyde **xli** which was converted into different amines **xliii** *via* reductive amination with various fluorinated 2-bromoanilines **xlii**. In the next step, amines **xliii** were treated with triflic anhydride resulting in trifluoromethanesulfonamides **xliv**. Palladium-catalyzed ring closure followed by treatment with KO*t*Bu afforded phenanthridines **xlv**, which were subsequently oxidized toward 8,9,10,11-tetrahydro-8,11-methanobenzo[*j*]phenanthridine-7,12-diones **xlvi**.

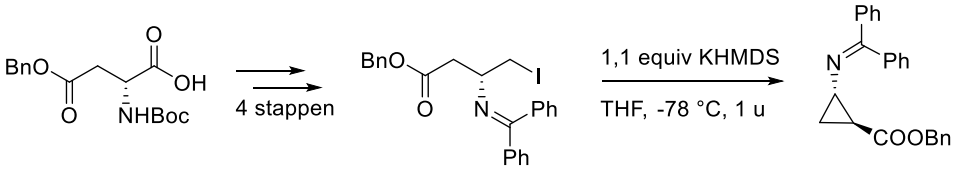


It can be concluded that this PhD thesis resulted in the optimized synthesis of derivatives of two classes of carbocyclic amino acids. However, the synthesis of the fluorinated small-membered ring containing amino acids proved to be difficult, resulting in the formation of unstable fluorinated β-ACC derivatives, while the ring closure toward fluorinated azetidine-2-carboxylates could not be effectuated. The synthesis of novel β,β-difluoroenamides as novel building blocks was successful and was exploited toward the synthesis of novel fluorinated heterocycles and elusive fluorinated ynamides. Finally, the synthesis of fluorinated 8,9,10,11-tetrahydro-8,11-methanobenzo[*j*]phenanthridine-7,12-diones was achieved, as potential antimycobacterial compounds.

7 Samenvatting

Cyclische aminozuren bestaande uit een drie- of vierring als basisstructuur zijn belangrijke bouwstenen voor de synthese van nieuwe peptidomimetica. Meer specifiek verhogen conformationeel beperkte β-aminozuren de conformationele stabiliteit en rigiditeit van peptiden en zijn er minder bouwstenen nodig om peptiden te bekomen met een goed gedefinieerde secundaire structuur. In het eerste deel van deze doctoraatsthesis werden nieuwe cyclische β-aminozuurderivaten, die een cyclopropaan- of een cyclobutaanring bevatten als hun basisstructuur, gesynthetiseerd.

Zo werd in het eerste deel de synthese van benzyl-2-(difenylmethylideenamino)cyclopropaancarboxylaat (1*S*,2*S*)-**iii** beschreven, waarbij (*R*)-β-benzyl-*N*-(*tert*-butoxycarbonyl)aspartaat (*R*)-**i** gebruikt werd als chirale bouwsteen. Aspartaat (*R*)-**i** werd hierbij eerst omgezet in γ-iood-β-amino ester (*R*)-**ii** in vier stappen, in een totaalrendement van 39%. De diastereoselective ringsluiting van deze precursor (*R*)-**i** werd bewerkstelligd door reactie met KHMDS in THF bij -78 °C gedurende één uur, waarbij een diastereomeer mengsel werd bekomen met een diastereomere ratio *trans*:*cis* = 97:3. Na opzuivering werd diastereomeer zuiver benzyl-2-(difenylmethylideenamino)cyclopropaancarboxylaat (1*S*,2*S*)-**iii** bekomen in een rendement van 75% (dr > 99:1).

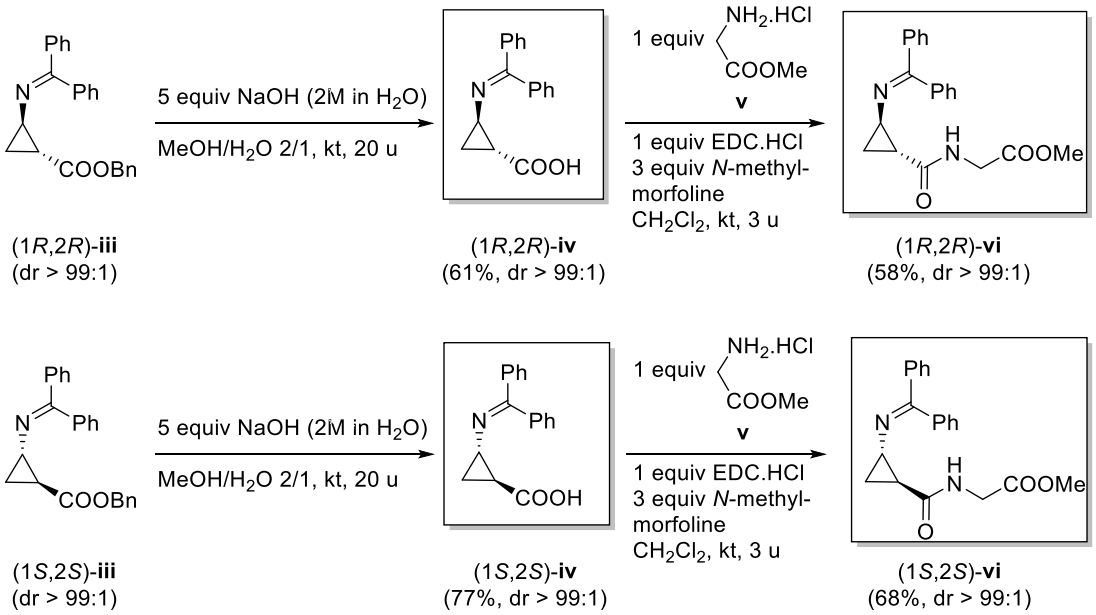


(*R*)-**i**

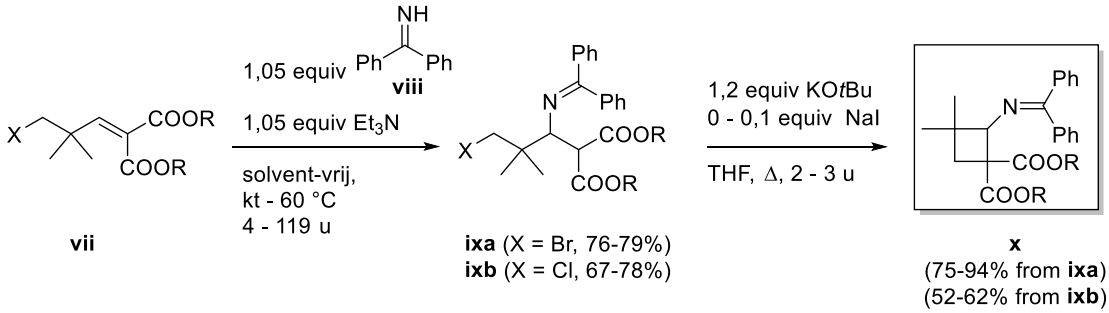
(*R*)-**ii**
(39%)

(1*S*,2*S*)-**iii**
dr 97:3 na reactie
(75%, dr > 99:1)

Vervolgens werd de verzeping van de beide enantiomeren van cyclopropaancarboxylaat **iii** bewerkstelligd door reactie met vijf equivalenten NaOH in een MeOH/H_2O mengsel gedurende 20 uur bij kamertemperatuur, waarna cyclopropaancarbonzuren (1*R*,2*R*)-**iv** en (1*S*,2*S*)-**iv** geïsoleerd werden in respectievelijk 61% en 77% rendement. De koppeling van aminozuren **iv** met het hydrochloride zout van methylglycinaat **v** werd bewerkstelligd onder standaard reactieomstandigheden voor peptidevorming, waarbij dipeptiden (1*R*,2*R*)-**vi** en (1*S*,2*S*)-**vi** bekomen werden in goede rendementen.

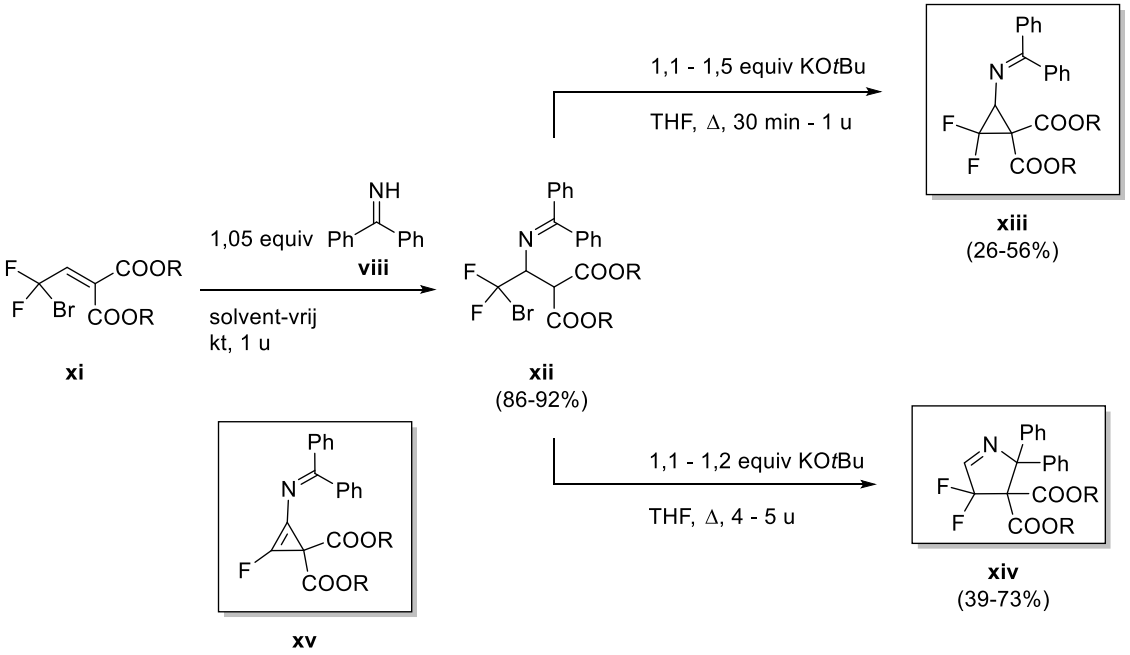


In het tweede deel van deze doctoraatsthesis werd de synthese van dialkylcyclobutaan-1,1-dicarboxylaten **x** geoptimaliseerd, waarbij vertrokken werd van 3-halogeenpropylideenmalonaten **vii**. Nadat verschillende reactieomstandigheden geëvalueerd werden, bleek dat de additie van difenylmethylideenamine **viii** aan alkylideenmalonaten **vii** gerealiseerd werd onder solvent-vrije reactieomstandigheden, waarbij adducten **ix** bekomen werden in goede rendementen na omkristallisatie. De ringsluiting van adducten **ix** naar de overeenkomstige cyclobutanen **x** werd tenslotte verwezenlijkt door behandeling met KO*t*Bu in het geval van de gebromeerde adducten **ixa**, terwijl de additie van een katalytische hoeveelheid NaI aan het reactiemengsel nodig was om ringsluiting van de gechloreerde derivaten **ixb** te bewerkstelligen.



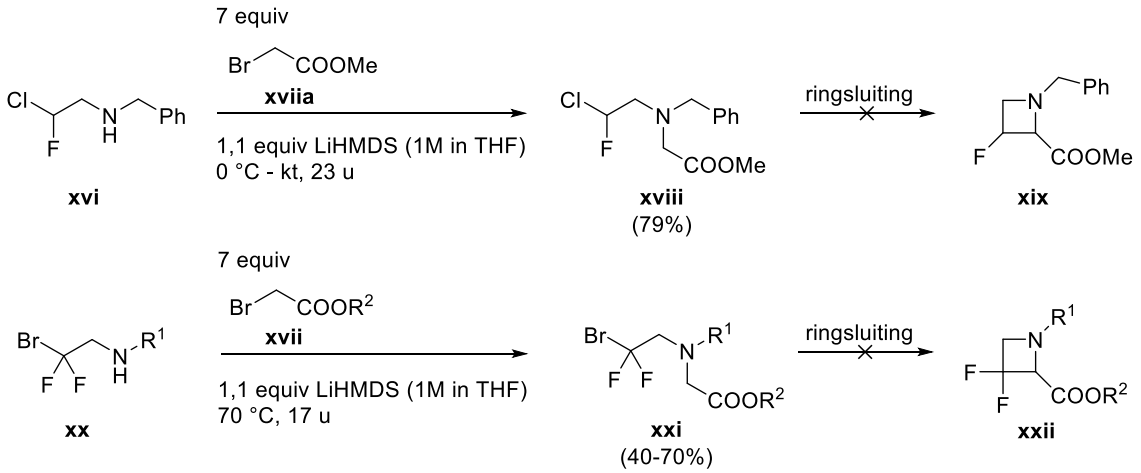
In de volgende hoofdstukken van deze doctoraatsthesis lag de focus op de synthese van gefluoreerde verbindingen. Door zijn unieke eigenschappen (hoge elektronegativiteit, kleine van der Waals straal) leidt de introductie van fluor in verbindingen tot een verandering in de chemische en farmacologische eigenschappen van deze verbindingen. Hierdoor bestaat er vanuit de farmaceutische industrie een grote interesse in de synthese van gefluoreerde verbindingen.

De synthese van gefluoreerde dialkyl-β-aminocyclopropaan-1,1-dicarboxylaten **xiii** werd beoogd via dezelfde methodologie als diegene die hierboven beschreven werd voor de synthese van dialkylcyclobutaan-1,1-dicarboxylaten **x**, waarbij gefluoreerde ethylideenmalonaten **xi** gebruikt werden als Michaël acceptoren. De Michaël-type additie van difenylmethylideenamine **viii** werd bewerkstelligd onder solvent-vrije reactieomstandigheden en leverde adducten **xii** in goede rendementen. Vervolgens werd de ringsluiting van deze Michaël adducten naar de beoogde β-aminocyclopropaan-1,1-dicarboxylaten **xiii** onderzocht. Wanneer adducten **xii** in reactie gebracht werden met een base, werden reactiemengsels bekomen waarin zowel beginproduct **xii**, cyclopropanen **xiii**, pyrrolinen **xiv** (gevormd door ring-transformatie van cyclopropanen **xiii**) en gefluoreerde cyclopropenen **xv** werden teruggevonden, in wisselende verhoudingen afhankelijk van de reactieomstandigheden. Deze ringsluitingsreactie bleek moeilijk te verlopen en weinig reproduceerbaar te zijn door de onstabiliteit van de reactieproducten. Wanneer adducten **xii** werden behandeld met 1,1 tot 1,5 equivalenten KO*t*Bu gedurende een korte reactietijd van 30 minuten tot één uur, werden cyclopropanen **xiii** bekomen als de hoofdproducten. Door een langere reactietijd (4 - 5 uur) toe te passen, werden pyrrolinen **xiv** bekomen als hoofdproduct door de ringtransformatie van cyclopropanen **xiii** naar pyrrolinen **xiv** onder deze omstandigheden. Onder alle reactieomstandigheden werden ook gefluoreerde cyclopropeendicarboxylaten **xv** gevormd als bijproducten, die konden geïsoleerd worden in lage rendementen.

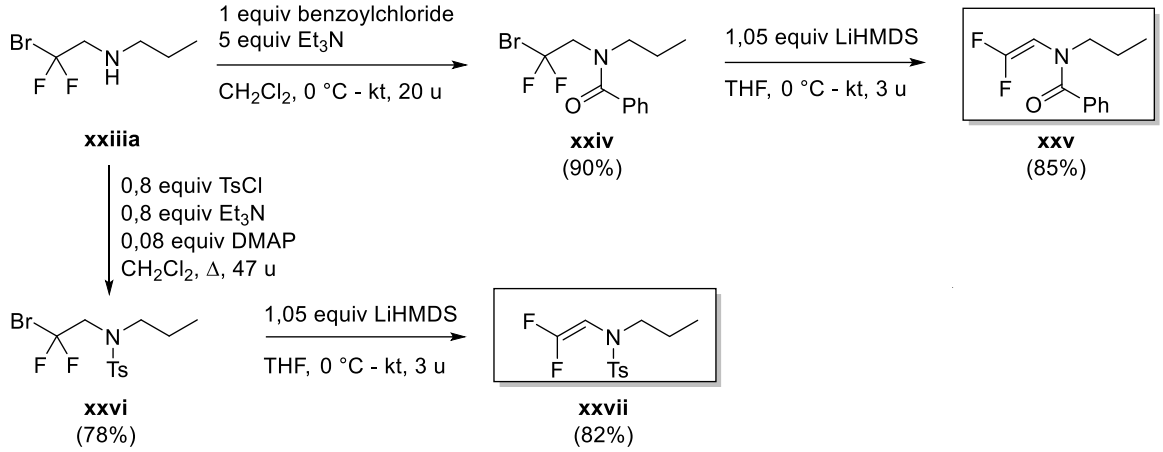


Vervolgens werd de reductie van pyrrolinen **xiv** geëvalueerd door reactie met $NaCNBH_3$, maar dit leidde tot de vorming van acyclische amino esters die onstabiel waren en dus niet volledig gekarakteriseerd konden worden.

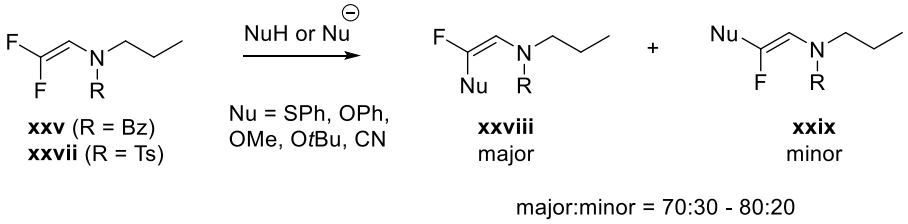
Verder werd ook de synthese van een andere klasse conformationeel beperkte gefluoreerde aminozuren beoogd, meer specifiek de gefluoreerde azetidine-2-carboxylaten **xix** en **xxii**. Hiervoor werden verschillende routes geëvalueerd naar precursoren **xviii** en **xxi** en uiteindelijk werden deze verbindingen gesynthetiseerd door reactie van aminen **xvi** en **xx** met een overmaat broomacetaten **xvii** in de aanwezigheid van LiHMDS (1M in THF) gedurende 17-23 uur bij kamertemperatuur of 70 °C. Jammer genoeg faalden alle pogingen om amino esters **xviii** en **xxi** om te zetten in de overeenkomstige azetidinen. Terwijl reactie met KO*t*Bu en BuLi aanleiding gaf tot een nucleofiele additie aan de ester functie, trad geen reactie op wanneer NaH en KHMDS gebruikt werden als base. Wanneer amino esters **xviii** en **xxi** behandeld werden met LiHMDS tenslotte, werd een eigenaardige reactie waargenomen, namelijk de afsplitsing van de alkoxycarbonylmethyl groep, waarbij aminen **xvi** en **xx** gevormd werden.



In het volgende deel van deze doctoraatsthesis werd de synthese van β,β-gedifluoreerde enamiden **xxv** en **xxviia** beschreven, als bouwstenen voor de synthese van azaheterocyclische verbindingen. Bescherming van het secundaire amine **xxiiia** door reactie met benzoylchloride, gevolgd door behandeling met LiHMDS leverde enamide **xxv**, terwijl bescherming van amine **xxiiia** als tosylamide **xxvi**, gevolgd door behandeling met base resulteerde in de vorming van enamide **xxxvii**.

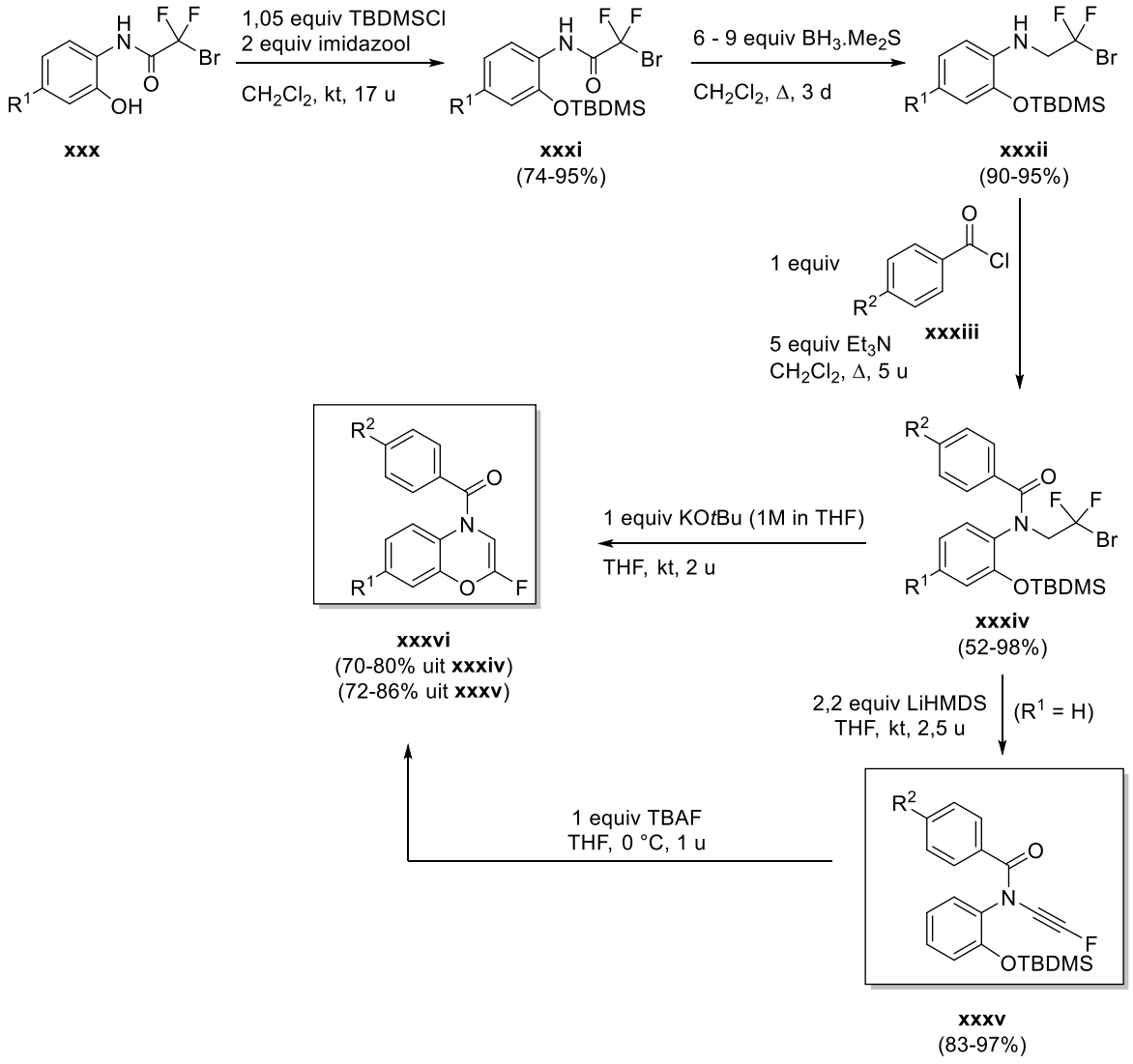


Door de aanwezigheid van de elektronenzuigende groep op het stikstofatoom, in combinatie met de twee fluoratomen op het β-koolstofatoom van de enamide eenheid, vertonen enamiden **xxv** en **xxvii** een elektrofiele reactiviteit. Inderdaad, wanneer enamiden **xxv** en **xxvii** behandeld werden met nucleofielen werd een S_NV reactie waargenomen: additie van het nucleofiel aan de dubbele binding werd gevolgd door eliminatie van fluor. Deze reactie resulteerde in de vorming van twee isomeren **xxviii** en **xxix**, waarbij isomeer **xxviii** in alle gevallen bekomen werd als het hoofdisomeer. Deze selectiviteit voor isomeer **xxviii** werd verklaard door evaluatie van de conformatie van de intermediaire carbanionen, bekomen na additie van het nucleofiel aan de dubbele binding.

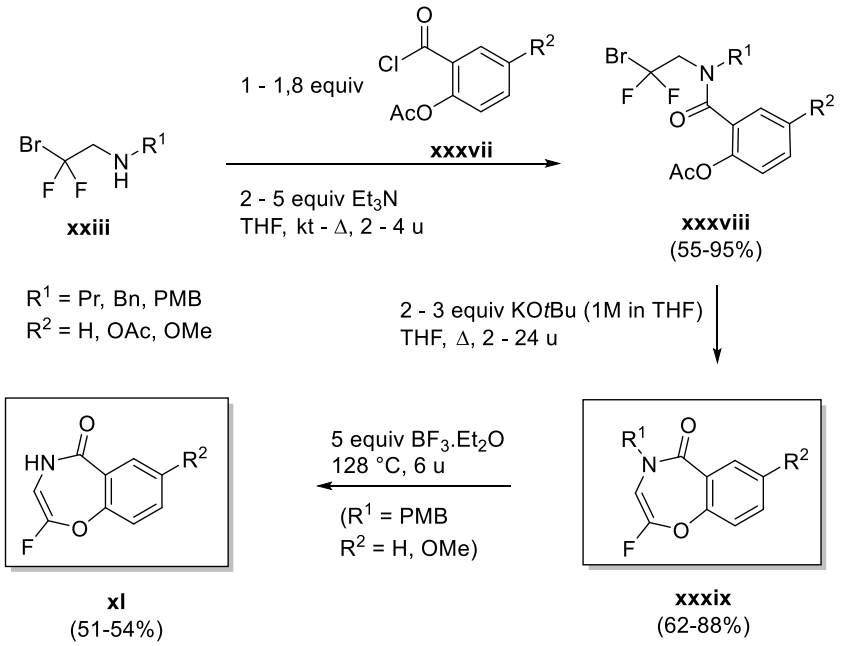


De elektrofiele reactiviteit van enamiden **xxv** en **xxvii** werd vervolgens uitgewerkt tot de synthese van gefluoreerde heterocyclische verbindingen, door het nucleofiel en de elektrofiele enamide-eenheid te incorporeren in één precursor. Terwijl de synthese van 6-fluor-1,4-oxazinen enkel slechte resultaten gaf, kon de synthese van 2-fluor-1,4-benzoxazinen **xxxvi** geoptimaliseerd worden. Amiden **xxx**, die gesynthetiseerd werden *via* de condensatie van de overeenkomstige 2-aminofenolen met ethylbroomdifluoracetaat, werden vervolgens beschermd als *tert*-butyldimethylsilyl ethers **xxxi**. Reductie van deze verbindingen door behandeling met boraan dimethylsulfide complex resulteerde in aminen **xxxii**, die vervolgens werden omgezet in amiden **xxxiv** door reactie met verschillende benzoylchloriden **xxxiii**. Vervolgens werden amiden **xxxiv** geëvalueerd als precursoren voor de synthese van 2-fluor-1,4-benzoxazinen door behandeling met verschillende basen. De reactie van amiden **xxxiv** met 2,2

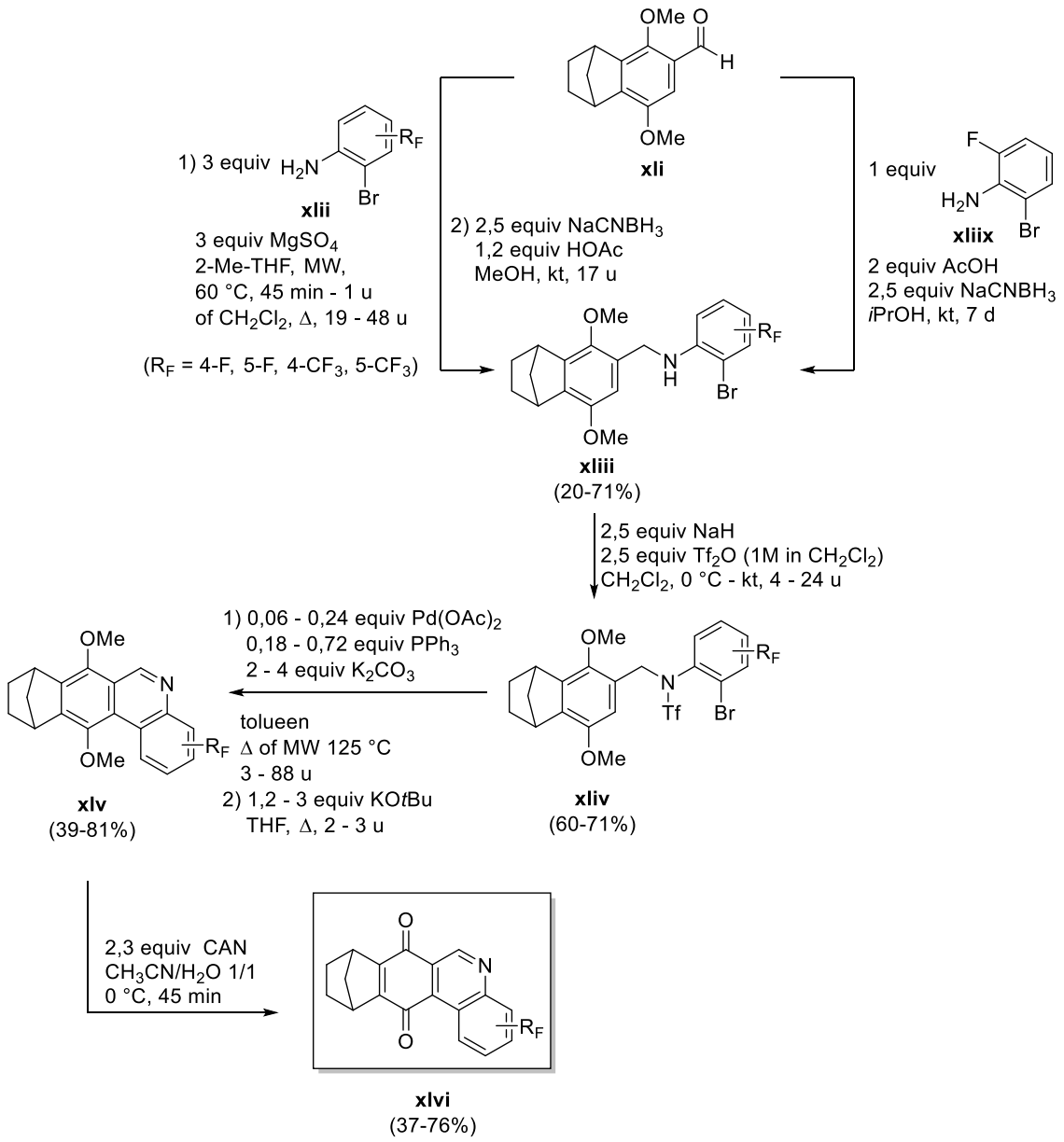
equivalenten LiHMDS resulteerde in de selectieve vorming van ynamiden **xxxv**, die geïsoleerd werden in excellente rendementen. Wanneer KO*t*Bu werd gebruikt als base werden amiden **xxxiv** omgezet in 2-fluorbenzoxazinen **xxxvi**. Nadat nog verschillende andere basen (NaHMDS, KHMDS en LiO*t*Bu) getest werden, werd geconcludeerd dat het kation van de base een zeer belangrijke rol speelde in het resultaat van de reactie. Met lithium basen werden eindproducten bekomen waarin het *tert*-butyldimethylsilylether nog aanwezig was, terwijl bij het gebruik van natrium of kalium basen de ontscherming van deze groep werd vastgesteld. Verder kon ook aangetoond worden dat ynamiden **xxxv**, die in dit onderzoek voor het eerst werden gesynthetiseerd in uitstekende rendementen, een elektrofiele reactiviteit vertonen aangezien ontscherming van de *tert*-butyldimethylsilyl groep van deze verbindingen aanleiding gaf tot de vorming van 2-fluor-1,4-benzoxazinen **xxxvi**, *via* additie van de fenolische zuurstof aan de drievoudige binding.



De synthese van gefluoreerde benzo-gefuseerde zevenringen kon gerealiseerd worden met het gebruik van amiden **xxxviii** als precursoren. Deze amiden werden bekomen *via* condensatie van aminen **xxiii** met zuurchloriden **xxxvii**. Wanneer amiden **xxxviii** behandeld werden met KO*t*Bu werd een efficiënte conversie naar 2-fluor-1,4-benzoxazepin-5-onen **xxxix** waargenomen, die geïsoleerd werden in goede rendementen. De verwijdering van de *para*-methoxybenzyl groep werd tenslotte bewerkstelligd door reactie van de *N*-PMB gesubstitueerde benzoxazepinonen met $BF_3.Et_2O$, waarbij 4*H*-2-fluor-1,4-benzoxazepin-5-onen **xl** gevormd werden.



In het laatste deel van deze doctoraatsthesis werd de synthese van 8,9,10,11-tetrahydro-8,11-methanobenzo[*j*]fenantridine-7,12-dionen **xlvi** ontwikkeld, als potentieel antimycobacteriële verbindingen. De synthetische route vertrok van aldehyde **xli**, dat omgezet werd in aminen **xliii** *via* een reductieve aminering met gefluoreerde 2-broomanilinen **xlii**. In de volgende stap werden aminen **xliii** behandeld met trifluormethaansulfonzuuranhydride, wat resulteerde in de vorming van trifluormethaansulfonamiden **xliv**. Na de palladium-gekatalyseerde ringsluiting, gevolgd door behandeling met KO*t*Bu, werden fenantridinen **xlv** bekomen, die vervolgens geoxideerd werden tot 8,9,10,11-tetrahydro-8,11-methanobenzo[*j*]fenantridine-7,12-dionen **xlvi**.



Als algemeen besluit kan gesteld worden dat deze doctoraatsthesis resulteerde in de geoptimaliseerde synthese van derivaten uit twee klassen van carbocyclische aminozuren. Echter, de synthese van gefluoreerde aminozuren met een drie- of een vierring als basisstructuur bleek moeilijker te verlopen. De synthese van gefluoreerde β-ACC derivaten leverde onstabiele eindproducten, terwijl de ringsluiting tot gefluoreerde azetidine-2-carboxylaten niet kon gerealiseerd worden. De synthese van nieuwe β,β-difluorenamiden was wel succesvol en werd uitgewerkt tot de synthese van nieuwe gefluoreerde heterocyclische verbindingen en tot nu toe onbekende gefluoreerde ynamiden. Tenslotte kon de synthese van gefluoreerde 8,9,10,11-tetrahydro-8,11-methanobenzo[*j*]fenantridine-7,12-dionen, als potentieel antimycobacteriële verbindingen, met succes verwezenlijkt worden.

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Meiresonne, T.; Mangelinckx, S.; De Kimpe, N. 'Synthesis of new β-aminocyclobutanecarboxylic acid derivatives via the MIRC reaction', (poster presentation) 14th Sigma-Aldrich Organic Synthesis Meeting. Spa, Belgium (December 2-3, 2010).

Meiresonne, T.; Mangelinckx, S.; De Kimpe, N. 'Synthesis of novel β-aminocyclobutanedicarboxylic acid derivatives by a solvent-free aza-Michael addition across homoallylic halides and subsequent ring closure', (oral presentation) COST Action CM803, Foldamers: From synthesis and folding, to function. Leeds, England (September 7-9, 2011).

Meiresonne, T.; Mangelinckx, S.; De Kimpe, N. 'Synthesis of novel β-aminocyclobutanedicarboxylic acid derivatives by a solvent-free aza-Michael addition and subsequent ring closure', (poster presentation) 15th Sigma-Aldrich Organic Synthesis Meeting. Spa, Belgium (December 1-2, 2011).

Meiresonne, T.; Mangelinckx, S.; De Kimpe, N. 'Stereoselective synthesis of both enantiomers of *trans*-2-(diphenylmethylideneamino)cyclopropanecarboxylic acid using a chiral pool approach and their

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Meiresonne, T.; Mangelinckx, S.; De Kimpe, N. 'Synthesis of both enantiomers of a novel unsubstituted *trans*-β-aminocyclopropanecarboxylic acid derivative using a chiral pool approach and their incorporation in dipeptides', (poster presentation) COST Action CM803, Foldamers: From synthesis and folding, to function. Paris, France (April 10-12, 2013).

Meiresonne, T.; Verniest, G.; De Kimpe, N. Mangelinckx, S. 'Synthesis of novel fluorinated 1,4-benzoxazines and 1,4-benzoxazepin-5-ones', (poster presentation) 14th Belgian Organic Synthesis Symposium. Louvain-La-Neuve, Belgium (July 13-18, 2014).

Meiresonne, T.; Verniest, G.; De Kimpe, N. Mangelinckx, S. 'Exploitation of the fluorine-induced umpolung of enamides and ynamides leading to the synthesis of 2-fluoro-1,4-benzoxazines and 2-fluoro-1,4-benzoxazepin-5-ones', (poster presentation) 18th Sigma-Aldrich Organic Synthesis Meeting. Blankenberge, Belgium (December 4-5, 2014).