



HAL
open science

Design and synthesis of new fluorinated hydrazines

Tingting Cao

► **To cite this version:**

Tingting Cao. Design and synthesis of new fluorinated hydrazines. Organic chemistry. Université Paris-Saclay, 2022. English. NNT : 2022UPASQ072 . tel-04058237

HAL Id: tel-04058237

<https://theses.hal.science/tel-04058237v1>

Submitted on 4 Apr 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Design and Synthesis of New Fluorinated Hydrazines

Conception et Synthèse de Nouvelles Hydrazines Fluorées

Thèse de doctorat de l'université Paris-Saclay

École doctorale n° 569, Innovation thérapeutique : du fondamental à l'appliqué (ITFA)
Spécialité de doctorat : Chimie thérapeutique

Graduate School : Santé et médicament
Référent : Faculté de Pharmacie

Thèse préparée dans l'unité de recherche **BioCIS** (Université Paris-Saclay, CNRS), sous
la direction de **Benoît Crousse**, Directeur de recherche CNRS

Thèse présentée et soutenue à Orsay, le 19 Décembre 2022, par

Tingting CAO

Composition du Jury

Thierry Lequeux Professeur, Université de Caen	Président
Fabienne Grellepois Maître de conférence, Université de Reims Champagne-Ardenne	Rapportrice et examinatrice
Eric Léonel Professeur, Université Paris-Est Créteil	Rapporteur et examinateur
Emmanuelle Drège Maître de conférence, Université Paris-Saclay	Examinatrice

Acknowledgement

Firstly, I would like to express my sincerest and special thanks to my supervisor, Dr. Benoît Crousse. Thanks for his patient guidance, valuable suggestions as well as precious time, which makes this thesis be completed smoothly. Most importantly, I want to be grateful for his constant and always patient guidance, significant advice and kindness that he showed to me during the period of my Ph.D research. Of course, it's more than that, he cares about not only my scientific work, but also helped a lot in my life when I first came to France. I really appreciate that he offered me chance to come to France for my Ph.D study. His rigorous academic, immense knowledge, serious attitude towards science and responsible attitude towards his work, but funny and humorous characters towards the life inspired and influenced me, and these qualities would continue to influence me.

Then I would like to show my gratitude to Dr. Fabienne Grellepois (Université de Reims Champagne-Ardenne), Professor Eric Léonel, (Université Paris-Est Créteil), Dr. Emmanuelle Drège, (Université Paris-Saclay), Professor Thierry Lequeux, (Université de Caen) for reviewing and ameliorating my thesis as well as evaluating my work.

I am also deeply grateful for all professors in our group, Prof. Sandrine Ongeri, Prof. Tâp Ha Duong, and Dr. Thierry Milcent, Dr. Julia Kaffy, Dr. Nicolo Tonali, Dr. Jean-Louis Soulier, Dr. Liuba Mazzanti for their advice or helps in my research work or in the daily life.

Additionally, I want to give my sincere thanks to three former Ph.D students, Dr. Monika-Lilianna Skibinska, Dr. Sondês Ghrairi and Dr. Jacopo Lesma for their help in research work and daily life when I first arrived in France. And also thanks to another two former Ph.D students, Dr. Renjing TANG and Dr. Jose Laxio-Arenas for their helps. I also owe my deep gratitude to all the other colleagues in my group, Nicolo Bisi, Davide Di Lorenzo, postdoc Dr. Léa Radal. And especial thanks to Maxence Delaunay for his help to go with me on dealing with chemical waste even if he is a molecular simulation Ph.D. This deep gratitude is similarly shown to the Chinese students in Faculty of Pharmacy, Anqi Li, Yunxin Yao, Yaowei Lu, Yingmin Jiang..... for those

happy hours we spent together and the beautiful memory during the three years.

I would like to thank M. Remi Franco and Dr. Jean-Christophe Jullian for their help on NMR experiment. I also would like to thank Dr. Karine Leblanc for the Mass/Chiral HPLC analysis.

I give my gratitude to the financial support of China Scholarship Council (CSC).

I also would like to express my gratitude to my parents and family, as well as my friends and professors in China for their support and encouragement. Special thanks to my roommate Xiaoqian Wang during my master research for the funny jokes which she brought to me even though she is in China and Xinyue Wang.

Last and most special appreciation should be shown to my funny, humorous and lovely friends Ping GAO and Chenghui Shi. We spent these years together, encouraged each other and had a lot of precious memories whether in the tough time or happy hours.

Abbreviations

CSD	Cambridge Structural Database (X-Ray structures)
IUPAC	International Union of Pure and Applied Chemistry
PgI ₂	Prostacyclin
CF ₃ TMS	Trimethyl(trifluoromethyl)silane
BTC	Bis(trichloromethyl)carbonate
DCM	Dichloromethane
SET	Single-electron transfer
DMAP	4-Dimethylaminopyridine
TBHP	<i>Tert</i> -butyl hydroperoxide
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
HAT	Hydrogen atom transfer
NBS	N-Bromosuccinimide
HPLC	High-performance liquid chromatography
HFIP	1,1,1,3,3,3- Hexafluoro-2-propanol
TFA	Trifluoroacetic acid
ISO	International Organization for Standardization
TfOH	Trifluoromethanesulfonic acid
USD	United States dollar
PPII	Polyproline type-II
RGD	Arginylglycylaspartic acid

APTS	<i>p</i> -Toluenesulfonic acid
Boc	<i>Tert</i> -butyloxycarbonyl
Cbz	Benzyloxycarbonyl
THF	Tetrahydrofuran
EDCI	3-[(Ethylimino)methylidene]amino-N,N-dimethylpropan-1-amine
HOBt	1-Hydroxybenzotriazole
DIPEA	N, N-Diisopropylethylamine
HATU	Hexafluorophosphate azabenzotriazole tetramethyluronium
Oxyma	Ethyl cyanohydroxyiminoacetate
DIC	Diisopropylcarbodiimide
EEDQ	<i>N</i> -Ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline

Contents

General Introduction

Chapter I General Introduction on Fluorine and Its Properties

1.1 Properties of fluorine	1
1.2 Effects of fluorine on physical-chemical properties of compounds	2
1.2.1 Acidity, basicity and hydrogen bond.....	2
1.2.1.1 Acidity and basicity.....	2
1.2.1.2 Hydrogen bond.....	3
1.2.2 Boiling point	4
1.2.3 Bond energies and reactivity.....	5
1.2.4 Lipophilicity.....	5
1.3 Effects of fluorine substitution on biological properties.....	6
1.3.1 Affinity.....	6
1.3.2 Absorption.....	7
1.3.3 Metabolism	8
1.3.3.1 oxidative/reductive metabolism.....	8
1.3.3.2 hydrolytic metabolism	9
1.4 Contribution of fluorine-containing compounds to pharmaceuticals	10
References	12

Chapter II Synthesis of *N*-CF₃ Hydrazines and *N*-CF₃ Compounds

2.1 New generation of fluorinated groups.....	14
2.2 Overview of the introduction of fluorinated groups on the nitrogen.....	17
2.2.1 Previous synthesis of <i>N</i> -CF ₃ group.....	18
2.2.2 Recent <i>N</i> -CF ₃ trifluoromethylation.....	20
2.3 <i>N</i> -CF ₃ hydrazines.....	32
2.3.1 Literature.....	32
2.3.2 Our approach to the synthesis of <i>N</i> -CF ₃ hydrazines	35
2.3.3 Access to new <i>N</i> -CF ₃ peptidomimetic scaffolds	43
2.3.4 Deprotection of <i>N</i> -CF ₃ hydrazine derivatives.....	44

2.4 Conclusion.....	51
Experimental part.....	52
References	72

Chapter III Synthesis of Trifluoromethanesulfonyl Hydrazides and Sulfenylation of Indoles

3.1 Deprotection of di- or trifluoromethanesulfonyl hydrazides	75
3.2 The trifluoromethyl sulfenyl group: SCF ₃	80
3.3 Conclusion.....	90
Experimental part.....	91
References	99

Chapter IV Fluorinated Azapeptides and Azapeptoids

4.1 Peptide-based drugs.....	101
4.2 Azapeptides and azapeptoids.....	102
4.3 Synthesis of <i>N</i> -Fluorinated peptides, azapeptides and azapeptoids	106
4.3.1 Preparation of <i>N</i> -Fluorinated hydrazones and hydrazines	106
4.3.2 Access to <i>N</i> -trifluoro and difluoroethyl azapeptoids	108
4.3.3 Access to <i>N</i> -trifluoro and difluoroethyl azapeptides.....	114
4.4 Conclusion.....	118
Experimental part.....	119
References	144

General Conclusion

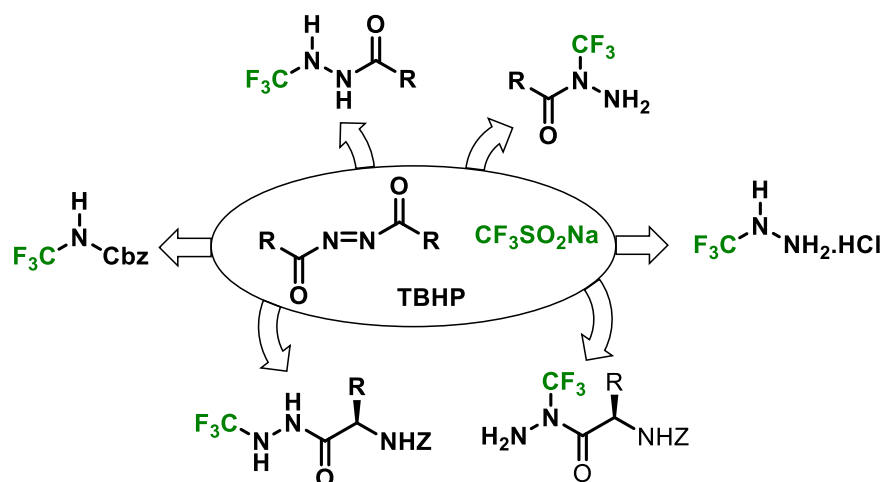
General Introduction

The very specific physicochemical properties of fluorine make it an increasingly important element in medicinal, agrochemical chemistry and materials. Whether by structural modifications induced by its size or by modulations of reactivity due to its strong electron-attracting effect, fluorine became in the 1960s an essential element in the development of drugs. Indeed, today nearly 25% of molecules on the market contain at least one fluorine atom. Among these fluorinated groups, the Rf-O and the Rf-S have attracted attention, because heteroatom-containing compounds are frequently found in biologically active products. However, the Rf-N scaffold in diverse fields is less developed and present in pharmaceutical compounds. Indeed, the synthesis of N-Rf-related structures is still limited.

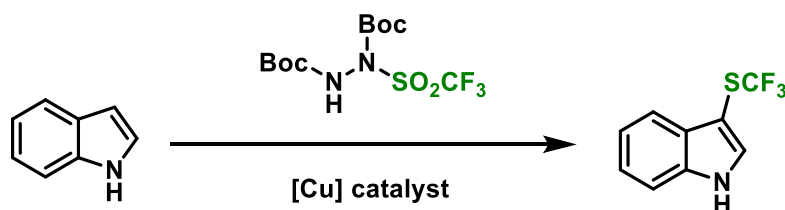
Hydrazines are essential for synthesising N-heterocyclic functionalised compounds and for their many applications in many areas of synthetic chemistry in materials, pharmaceuticals and agrochemicals, dyes, and directing groups important in catalysis. Surprisingly, the synthesis of fluorinated hydrazines is very little developed in the literature.

In this context, our laboratory's objective is to design and synthesize new fluorinated hydrazines. This thesis mainly focused on synthesizing fluorinated hydrazines, particularly *N-N*-CF₃, *N-N*-CH₂CF₃ and *N-N*-CH₂CF₂H.

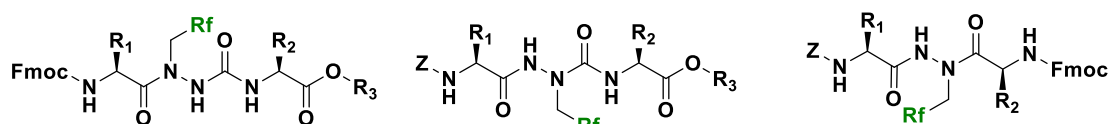
In the first Chapter, the interest of fluorine in medicinal chemistry will be presented. Then in the chapter two, after a bibliographical reminder on the main access routes to *N*-CF₃ derivatives, an innovative synthesis of new fluorinated hydrazines by adding the CF₃[•] radical, generated from the Langlois reagent (CF₃SO₂Na) on azodicarboxylate derivatives, will be exposed. Subsequently, reactivity studies were carried out on these new compounds. Thus we coupled them with amino acids to lead to *N*-CF₃ hydrazino peptidomimetics. Also, these new *N*-CF₃ hydrazines underwent different reactions to lead to new hitherto unknown compounds.



In parallel of this study, in chapter three, we exploited a side product of the previous reaction, the trifluoromethyl sulfonyl hydrazide (Boc-NH-N(Boc)SO₂CF₃), in the trifluoromethylthiolation reaction of indoles.



In chapter four, we report the synthesis of a new family of fluorinated hydrazines containing the trifluoromethyl and difluoromethyl groups prepared from hydrazones. Then the hydrazines *N-N*-CH₂CF₃ and *N-N*-CH₂CF₂H were coupled with aminoacids to afford unknown azapeptides and azapeptoids.



Chapter I

General Introduction on Fluorine and Its Properties

1.1 Properties of fluorine

Fluorine is the thirteenth element in order of abundance in the earth's crust (0.028%) and the first halogen. Fluorine is the most electronegative element in the periodic table. Because of its electronic structure $1s^2 2s^2 2p^5$, fluorine has very specific properties, as indicated by the extreme values of the atomic parameters (Table 1.1a).^{[1]-[2]}

The relatively small size of the fluorine atom, as indicated by the value (Van der waals radius = 1.47 Å), is more than the radius of hydrogen, but less than other halogens even oxygen atom. As a result, the fluorine atom mimics a hydroxyl group and engages in hydrogen-bonding interactions.^{[3]-[4]}

<i>Atom</i>	Van Der Waals radius (Å)	Pauling's Electronegativity X_p	Atom polarizability (Å ³)	Electron Affinity (kcal/mol)	Ionization Potential (kcal/mol)
H	1.20	2.20	0.667	17.7	313.6
F	1.47	3.98	0.557	79.5	401.8
C	1.70	2.55	1.76	29.0	240.5
N	1.55	3.04	1.10	-6.20	335.1
O	1.52	3.44	0.82	33.8	314.0
Cl	1.74	3.16	2.18	83.3	299.0
Br	1.85	2.96	3.05	72.6	272.4
I	1.98	2.66	4.70	70.6	241.2

Table 1.1a Atom parameters of fluorine atom

The very high electronegativity of fluorine and the excellent overlap of the 2s or 2p orbitals with corresponding orbitals of carbon mean that a fluorine atom carried by a carbon atom is always an electron-withdrawing substituent. C–F Bonds are always highly polarized.^{[1],[5]-[6]} These features are associated with the low polarizability of fluorine atoms, leading that the C–F bond has a relatively important ionic character and possesses one of the highest bond-dissociation energy (~485 kJ/mol) (Table 1.1b).

$D^{\circ}(\text{C-X})$	Bond Dissociation Energy (Kcal/mol)
CH ₃ -H	104.3
CH₃-F	108.3
CH ₃ -Cl	82.9
CH ₃ -Br	69.6

Table 1.1b Bond Dissociation Energy of CH₃-X

In briefly, special properties of fluorine atom mainly include relatively small size, high electronegativity, very low polarizability and very strong C-F bond.

1.2 Effects of fluorine on physical-chemical properties of compounds

1.2.1 Acidity, basicity and hydrogen bond

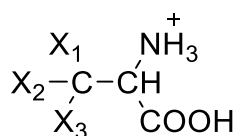
1.2.1.1 Acidity and basicity

Acidity/basicity is not only a fundamental physicochemical property, but it also controls many reactivity and bioactivity characteristics. The introduction of fluorine (mono-, di-, tri-) increases acidity such as carboxylic acids. Fluorine substituents exert powerful effects and decrease the basicity of proximal functional groups like amines, dramatically altering the pK values of compounds, as shown in Table 1.2.1.1a.^{[7]-[11]}

Acidity		Basicity	
<i>Compound</i>	<i>pK_a</i>	<i>Compound</i>	<i>pK_a</i>
CH ₃ COOH	4.76	CH ₃ CH ₂ NH ₂	10.7
CF₃COOH	0.5	CF₃CH₂NH₂	5.9
C ₆ H ₅ COOH	4.21	C ₆ H ₅ NH ₂	4.6
C₆F₅COOH	1.75	C₆F₅NH₂	-0.36

Table 1.2.1.1a Values of part of fluorinated compounds

The relative effects of fluorination on amino acid acidity and basicity seem unusual. The monofluorination has a negligible impact, but the trifluorination has a significant effect on basicity but only a moderate effect on acidity (Table 1.2.1.1b).^[7]



$$pK_a^{\text{COOH}}=2.3, pK_a^{\text{NH}_3^+}=9.9$$

X_1	X_2	X_3	$\Delta pK_a^{\text{COOH}}$	$\Delta pK_a^{\text{NH}_3^+}$
H	H	H	0.0	0.0
F	H	H	+0.1	-0.1
F	F	H	-0.8	-1.5
F	F	F	-1.1	-4.5

Table 1.2.1.1b ΔpK_a of β -fluoro-, β , β -difluoro-, β,β,β -trifluoroalanine^[8]

1.2.1.2 Hydrogen bond

It is known that hydrogen-bonding interactions play an essential role in many chemical structure systems and biological processes. Fluorine possesses lone pairs of electrons and high electronegativity. Based on Pauling's definition, it would behave as a nice acceptor, but in fact, it is not. Organofluorine as a hydrogen bond acceptor has been a controversial issue for a long time, and researchers have often reached opposite conclusions. Finally, according to investigations and analysis, experimental and computational evidence demonstrated that this interaction between hydrogen-bonding donor and fluorine atom exists.^{[12]-[15]}

The theoretical calculation described that the strength of $\text{C}(\text{sp}^3)\text{-F}\cdots\text{H-O}$ bond (2.38 kcal/mol) is less than half of $\text{C-O}\cdots\text{H-O}$.^[16] Experimental small-molecules extracted from the Cambridge Structural Database (CSD) X-ray structures also show hydrogen bonds involving fluorine atoms^[17] (Example as shown Figure 1.2.1.2). In this example, the distances of $\text{F}\cdots\text{H}$ and $\text{F}\cdots\text{O}$ are shorter than the sum of two atoms' Van Der Waals radius. The $\text{F}\cdots\text{H-O}$ angle is 162.1° and meets the criteria for an IUPAC (International

Union of Pure and Applied Chemistry) 2011 H-bond which is generally between 110 and 180°.^[15]

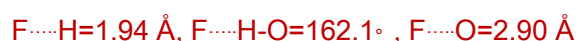
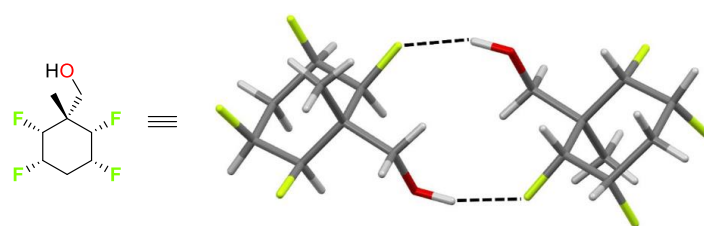


Figure 1.2.1.2. X-ray structure of secondary alkyl fluoride involved in an intermolecular hydrogen bond

It is worth emphasizing that the hydrogen bond related to organofluorine is a type of weak interaction, even possibly not stabilizing interaction. However, in systems designed such that a hydrogen bond with fluorine would also affect measurable chemical equilibrium (acidity/basicity, preferential conformation, reactivity, etc.), which finally leads to impacts on biological activity, even if it is indirect.^{[15],[16],[18]}

1.2.2 Boiling point

The boiling points of perfluorinated compounds, functionalized or not, are always lower than their hydrogenated analogues, excluding some rare cases, for instance, examples in Table 1.2.2.^[1]

Compounds (bp/ °C)	$H_3C-COOH$ (118)	H_3C-CCl_3 (75)	 (112)
	$F_3C-COOH$ (78)	F_3C-CCl_3 (43)	 (105)

Table 1.2.2 Effect of fluorination on boiling points

1.2.3 Bond energies and reactivity

Fluorine is the most electronegative element in the periodic table. When bound to carbon, it forms the strongest bonds.^[5] The strength of the C-F bond increases with the number of fluorine atoms borne by carbon, while it's the opposite for other halogens (Table 1.2.3).

<i>Compound</i>	<i>D</i> ^o (C-X) (kcal/mol)			
	H	F	Cl	Br
CH ₃ -X	-	108.3	82.9	69.6
CH ₂ X ₂	-	119.5	81.0	64
CHX ₃	-	127.5	77.7	62
CX ₄	104.3	130.5	72.9	56.2

Table 1.2.3 Bond dissociation energy of methanes

Moreover, the effects of α -fluorination cannot be generalized to β -fluorination. α -Fluorination does not have much influence on the C-H bond. It increases the strength of C-C, C-O and C-F bonds, for example the C-O bond in CF₃-O-CF₃ (105.2 kcal/mol) is 22 kcal/mol stronger than dimethyl ether (83.2 kcal/mol), the C-C bond of ethane (88.8 kcal/mol) is 10 kcal/mol lower than trifluoroethane (101.2 kcal/mol). In contrast, β -fluorination influences have little effect on C-F bonds but strongly increase C-H bond strengths. An obvious case is that the C-H bond in (CF₃)₂C-H is 15 kcal/mol stronger than (CH₃)₂C-H. ^{[1],[19]}

1.2.4 Lipophilicity

In the design and application of drugs, lipophilicity is of extraordinary importance. It controls many parameters such as absorption, distribution and pathway of transportation into organs or cells, as well as interaction with the macromolecular target. It is generally recognized that fluorination induces an increase in lipophilicity. However,

there are still some opposite examples. For instance, the presence of fluorine atoms in an aliphatic molecule provokes a decrease in lipophilicity as described in Table 1.2.4. Lipophilicity is often evaluated by using its $\log P_{\text{octanol}}$ value, which is the logarithm of its octanol/water partition coefficient.^[1] It is obvious that whether lipophilicity increases or decreases, these effects of fluorine atoms are not to be ignored.

Compound	$\log P$	Compound	$\log P$
CH_3CH_3	1.81	CH_3CHF_2	0.75
$\text{CH}_3(\text{CH}_2)_3\text{CH}_3$	3.11	$\text{CH}_3(\text{CH}_2)_3\text{CH}_2\text{F}$	2.33

Table 1.2.4 Octanol-water partition ($\log P$) of aliphatic compounds ^[1]

1.3 Effects of fluorine substitution on biological properties

As mentioned in much literature, when fluorine is inserted into molecules, it can cause changes in physicochemical properties, which finally leads to the possibility of modifying and modulating the pharmaceutical profile of a molecule. Meanwhile, the distribution, recognition, interaction with biological target, absorption, as well as metabolism and elimination of this molecule, are affected.

1.3.1 Affinity

The affinity of a substrate with its biological target is first connected to its complementarity with this macromolecule target. The molecule recognition and affinity depend on all the favorable interactions that exist in the supramolecular assembly formed between the substrate and the macromolecule. The main parameters involved are the steric and conformational effects, the hydrogen bonds, and the dipolar or hydrophobic interactions.^[1]

The steric hindrance induced by the presence of fluorine atoms may destabilize the supramolecular structure formed between the macromolecule and the fluoro analogue of the substrate or even prevent its formation.^[20] In addition, the influence of

conformational changes, induced by the presence of fluorine atoms, on the affinity of a substrate for its target is well-known. Furthermore, the strong electronegativity of the fluorine atom, and thus the strong dipole of the C–F bond, favors dipole-dipole interactions in the binding site.^[1]

1.3.2 Absorption

Almost all cellular organisms, including many viruses, are constituted of phospholipid bilayers which cause significant obstacles to the distribution and transportation of the drugs to their target. For instance, in the case of oral administration, drugs must be first absorbed by the intestine, then enter the blood, and reach organs from blood, which would go through the intestine barrier and other barriers (e.g. brain-blood barrier) even if the drugs have reached organs. Finally, these molecules must go into the cells of the diseased organs by passing through several cell barriers. These procedures of transportation and absorption have relied on lipophilicity, pKa, solubility and molecular weight of drug molecules.^[1] The presence of fluorine atoms may have an effect on these parameters.^[21]

An example of 5-HT_{1D} agonists^[22] shows the influence of fluorine atoms on the pKa and absorption. Quite often, a change in the pKa has a strong effect on both the pharmacokinetic properties of the molecule and its binding affinity. In the case of 5-HT_{1D} agonists, the incorporation of fluorine was found to significantly reduce the pKa of compounds. This reduction of basicity, with the concomitant weakening of the affinity to the receptor, was shown to have a strong beneficial influence on oral absorption.^[23]

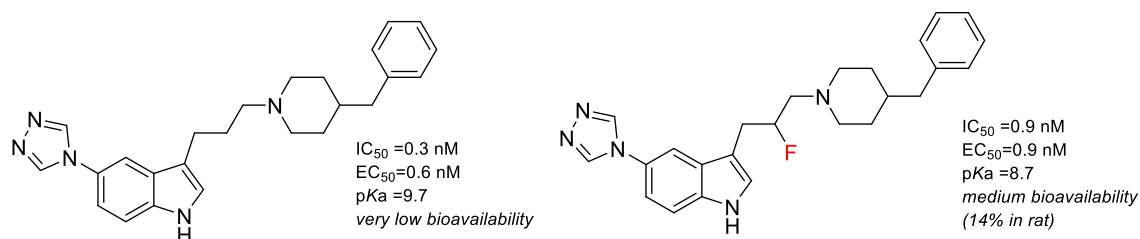


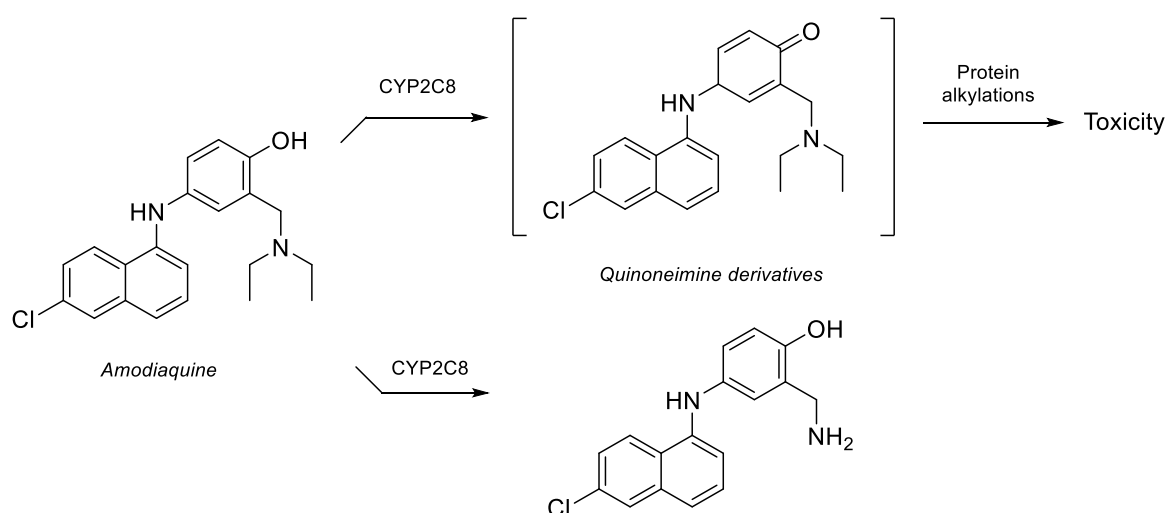
Figure 1.3.2 Effect of fluorine atom on the absorption

1.3.3 Metabolism

Due to the properties of the fluorine atom, in particular its electronic effects, it may interact differently during the biotransformation steps, including oxidative/reductive, hydrolytic pathways for example.

1.3.3.1 oxidative/reductive metabolism

Slowing down the oxidative metabolism process is one of the most frequent reasons for introducing fluorine atoms into a lead compound to transform it into a drug candidate. The stability of oxidative processes is generally attributed to the strength of the C-F bond. Aside from modification for the drug's metabolism rates, the presence of fluorine atoms could also change metabolic pathways and metabolites. In oxidative metabolism, the formation of reactive species can be a source of toxicity. An example is that the metabolism of the antimalarial amodiaquine produces quinone-imine, which is an electrophilic metabolite responsible for hepatotoxicity and agranulocytosis. Replacement of the phenolic hydroxyl by fluorine prevents the oxidation process, and then *N*-dealkylation becomes a major process, which successfully avoids the toxic side effect (Figure 1.3.3.1).^[24]



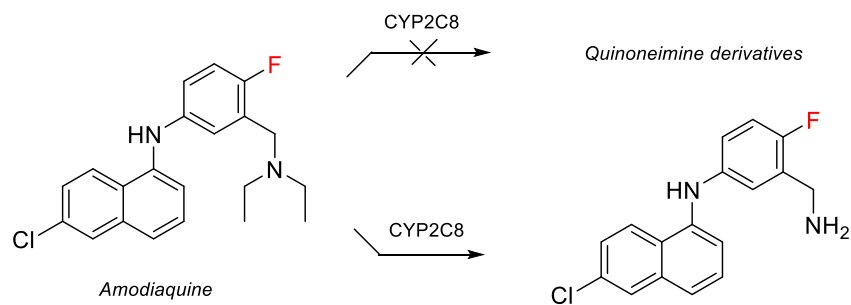


Figure 1.3.3.1 Metabolism of amodiaquine and fluoroamodiaquine

1.3.3.2 hydrolytic metabolism

Hydrolytic processes are common in human metabolism. The presence of fluorine atoms protects a molecule not only from oxidative metabolism but also from proteolysis by disfavoring the formation of cationic intermediates involved in the proteolysis process. An example concerns the instability of prostacyclin (Pgl₂) in a physiological medium, which is connected to the presence of the enol ether function ($t_{1/2}$ =5-10 min at PH=7.4 and 37 °C). Since hydrolysis is very fast, its function as a vasodilator and inhibitor of platelet adhesion cannot be clinically exploited. Fluorine atoms have been introduced on the position β to the enolic double of *Iloprost*, a more stable derivative of Pgl₂. The proteolysis is dramatically slowed since protonation of the enol ether to give an oxonium ion is inhibited by the presence of fluorine atoms. Thus, the drug candidate AFP-07 possesses good metabolic stability, meanwhile, retains an intense activity as an inhibitor of platelet adhesion.^{[25]-[26]}

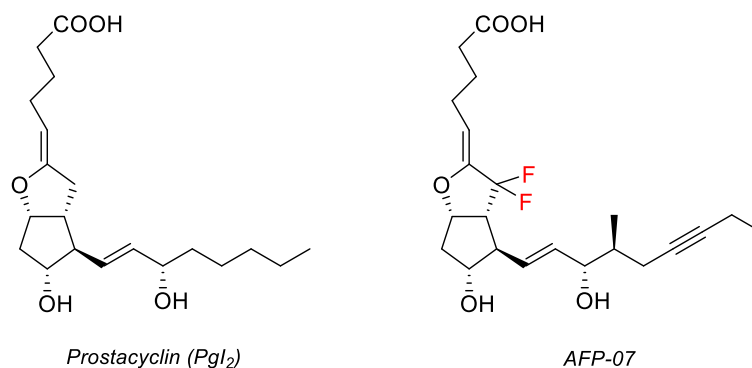


Figure 1.3.3.2 Enhancement of the hydrolytic stability of Prostaglandin derivatives

1.4 Contribution of fluorine-containing compounds to pharmaceuticals

Since the groundbreaking discovery and introduction to the market of fluorocortisone and 5-fluorouracil in the mid-1950s, biological applications of fluorine have become a mature field of mainstream multidisciplinary research advancing the healthcare industry. Fluorine-containing molecules constitute more than 50% of so-called blockbuster drugs with Lipitor being possibly the most profitable medicine ever introduced to the market.^[27]

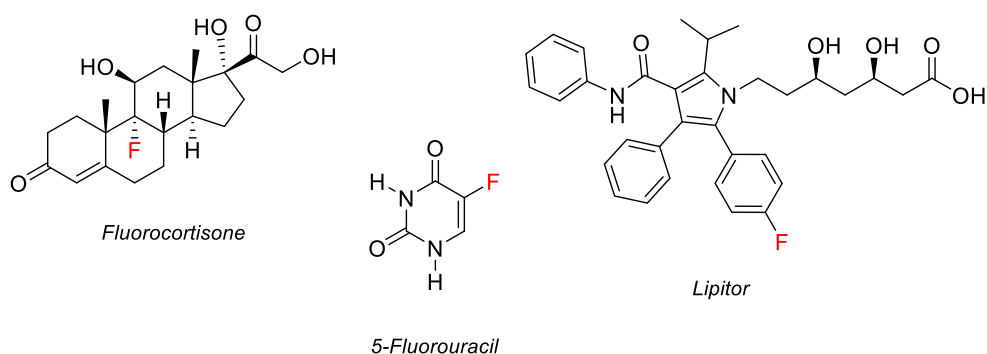


Figure 1.4a Structures of fluorocortisone, 5-fluorouracil and lipitor

In the recent database of fluoro-pharmaceuticals, according to the category of chemotypes, the largest family of fluoro-pharmaceuticals is Ar-F-containing drugs ($C_{sp^2}\text{-F}$, 167 compounds, 45.3%), followed by molecules with alkyl-CRF (with monofluorinated moieties) ($C_{sp^3}\text{-F}$, 55 compounds, 14.9%), aryl- CF_3 ($C_{sp^2}\text{-CF}_3$, 54 compounds, 14.6%), F-heterocycles ($C_{sp^2}\text{-F}$, 20 compounds, 5.4%), and CF_3 -heterocycles ($C_{sp^2}\text{-CF}_3$, 10 compounds, 2.7%). It is clear that to date pharmaceutical products containing monofluorinated fragments (Ar-F, alkyl-CRF, Het-F, alkyl- CH_2F , 67.2%) are the most common.^[28]

Nowadays, it is already not surprising that fluorine-substituted compounds can impact on properties of organic compounds. One of the major effects of fluorination is a modulation of the acidity and the basicity of a parent compound. This can strongly

influence binding affinity, pharmacokinetic properties, and bioavailability of a given drug candidate.^[29] Therefore, the presence of fluoride in pharmaceuticals is of lasting importance.

Here are some recent examples of drugs involved in different pathologies (Figure 1.4b).

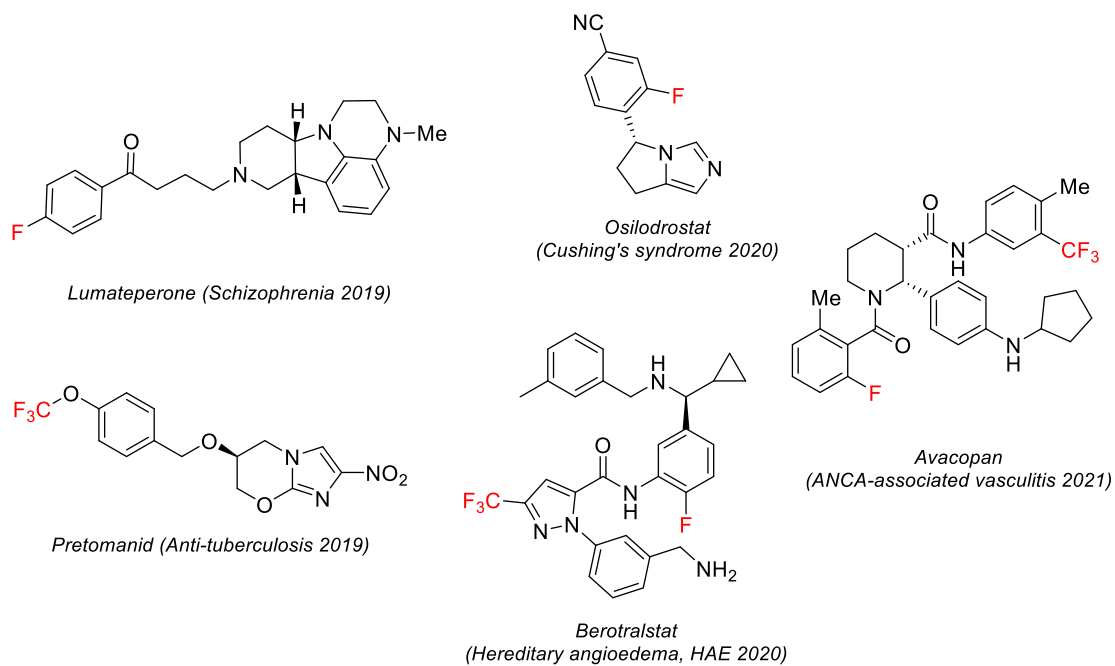


Figure 1.4b Selected fluoro-pharmaceuticals approved by FDA from 2019-2021

References

- [1] J.-P. Bégué, D. Bonnet-Delpon, *Bioorganic and Medicinal Chemistry of Fluorine*, John Wiley & Sons, **2008**.
- [2] B. E. Smart, *J. Fluor. Chem.* **2001**, 109, 3–11.
- [3] S. Fioravanti, *Tetrahedron*. **2016**, 72, 4449–4489.
- [4] G. Haufe, F. Leroux, *Fluorine in Life Sciences: Pharmaceuticals, Medicinal Diagnostics, and Agrochemicals*, **2018**.
- [5] D. O'Hagan, *Chem. Soc. Rev.* **2008**, 37, 308-319.
- [6] D. Chopra, T. N. Guru Row, *CrystEng. Comm.* **2011**, 13, 2175-2186.
- [7] M. H. Abraham, P. L. Grellier, D. V. Prior, P. P. Duce, J. J. Morris, P. J. Taylor, *J. Chem. Soc. Perkin Trans.***1989**, 2, 699-771.
- [8] M. H. Abraham, P. L. Grellier, D. V. Prior, J. J. Morris, P. J. Taylor, *J. Chem. Soc. Perkin Trans.***1990**, 2, 521-529.
- [9] I. Ojima, *Fluorine in Medicinal Chemistry and Chemical Biology*, John Wiley & Sons, **2009**.
- [10] R. D. Chambers, *Fluorine in Organic Chemistry*, Blackwell Publishing, Oxford, **2000**.
- [11] M. Morgenthaler, E. Schweizer, A. Hoffmann-Röder, F. Benini, R. E. Martin, G. Jaeschke, B. Wagner, H. Fischer, S. Bendels, D. Zimmerli, J. Schneider, F. Diederich, M. Kansy and K. Müller, *ChemMedChem*. **2007**, 2, 1100-1115.
- [12] C. Dalvit, C. Invernizzi, A. Vulpetti, *Chem. Eur. J.* **2014**, 20, 11058-11068.
- [13] H. J. Schneider, *Chem. Sci.* **2012**, 3, 1381-1394.
- [14] P. A. Champagne, J. Desroches, J. F. Paquim, *Synthesis*. **2015**, 47, 306-322.
- [15] C. Dalvit, A. Vulpetti, *Chem. Eur. J.* **2016**, 22, 7592-7601.
- [16] J. A. K. Howard, V. J. Hoy, D. O'Hagan G. T. Smith, *Tetrahedron*. **1996**, 52, 12613-12622.
- [17] A. Vulpetti, C. Dalvit, *Chem. Eur.J.* **2021**, 27,1–11.
- [18] W. Pietrusz , R. Kafel, A. J. Bojarski, R. Kurczab, *Molecules*. **2022**, 27, 1005.
- [19] B. E. Smart, ACS Monograph 187, ACS, Washington DC, **1995**, Vol. 1, p. 979.
- [20] T. Nagai, G. Nishioka, M. Koyama, A. Ando, T. Miki, I. Kumadaki, *Chem. Pharm. Bull.* **1991**, 39, 233.
- [21] G. Gerebtzoff, X. Li-Blatter, H. Fischer, A. Frentzel, A. Seeling, *ChemBioChem*.

2004, 5, 676.

[22] B. V. N. Monique et al. *J. Med. Chem.* **1999**, 42, 2087-2104.

[23] H. J. Bohm, D. Banner, S. Bendels, M. Kansy, B. Kuhn, K. Muller, U. Obst-Sander, M. Stahl, *ChemBioChem.* **2004**, 5, 637-643.

[24] P. M. O'Neill, S. A. Ward, N. Berry, E. Asadollady, P. G. Bary, *Curr. Top. Med. Chem.* **2006**, 6, 479.

[25] C. S. Chang, M. Negishi, T. Nakano, Y. Morizawa, Y. Matasumura, *Prostaglandins.* **1997**, 53, 83.

[26] J. P. Begue, D. Bonnet-Delpon, F. Benayoud, T. T. Tidwell, R. A. Cox, A. Allen, *Gazz. Chim. Ital.* **1995**, 125, 399.

[27] H. B. Mei, A. M. Remete, Y. P. Zou, H. Moriwaki, S. Fustero, L. Kiss, V. A. Soloshonok, J. L. Han, *Chinese Chemical Letters.* **2020**, 31, 2401-2413.

[28] M. Inoue, Y. Sumii, N. Shibata, *ACS Omega.* **2020**, 5, 10633–10640.

[29] J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. D. Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev.* **2014**, 114, 4, 2432–2506

Chapter II

Synthesis of *N*-CF₃ Hydrazines and *N*-CF₃ Compounds

2.1 New generation of fluorinated groups

New fluorinated groups have emerged, in recent years, directly incorporating a fluorinated function on heteroatoms, especially on oxygen and sulfur. These *O*-Rf and *S*-Rf groups (OCF₃ and SCF₃) have become more and more present. Today, several bioactive molecules contain this kind of derivative, whether in agrochemistry^[1] or pharmaceutical chemistry^[1].

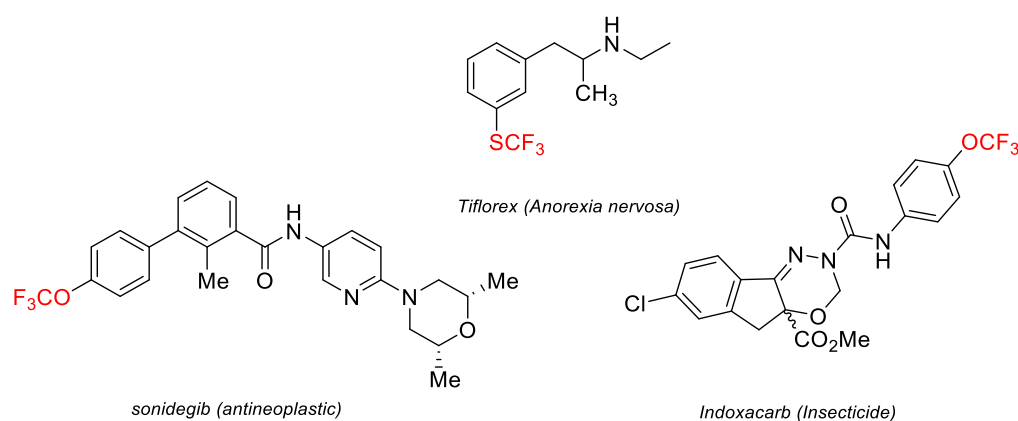


Figure 2.1a Some examples of active molecules with *O*-Rf or *S*-Rf

The physicochemical properties of these groups are very studied, and they are mainly used for their very strong lipophilicity (Table 2.1).^{[2]-[3]}

	OCH ₃	OCF ₃	SCH ₃	SCF ₃
Hansch-leo Coefficient π (log P _x – log P _H)	-0.02	1.04	0.61	1.44

Table 2.1 Coefficient of Hansch-Leo for different X-Rf

There are increasingly effective methods in the literature for functionalizing molecules with this type of function. *O*-CF₃ derivatives can be obtained by following three distinct routes. The first routes reported in the literature involve the fluorination of *O*-CCl₃, *O*-

COF and the oxidative desulfurization fluorination of O-CS₂R groups under very harsh conditions in the presence of HF or SF₄ and at high temperatures. The second consists in carrying out the trifluoromethylation of hydroxyl groups by the trifluoromethyl group electrophile “CF₃⁺” (Umemoto **6** or Togni **7** reagents), and finally, the last use the nucleophilic attack of “F₃C-O⁻” (Figure 2.1b).^{[4]-[5]} It's important to note that in most cases, only the hydroxyl group of aromatics are functionalized.

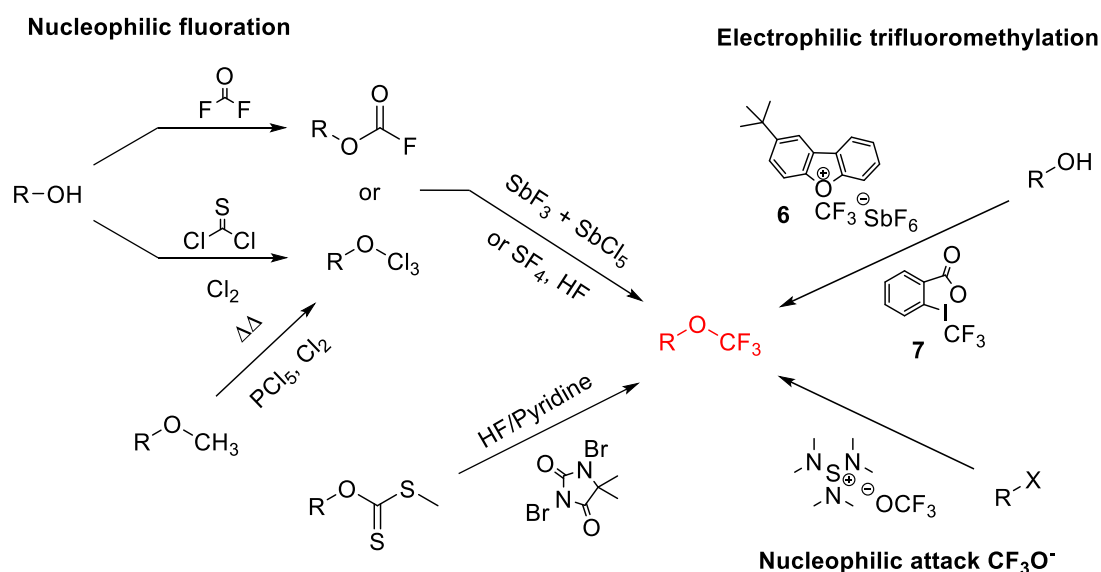
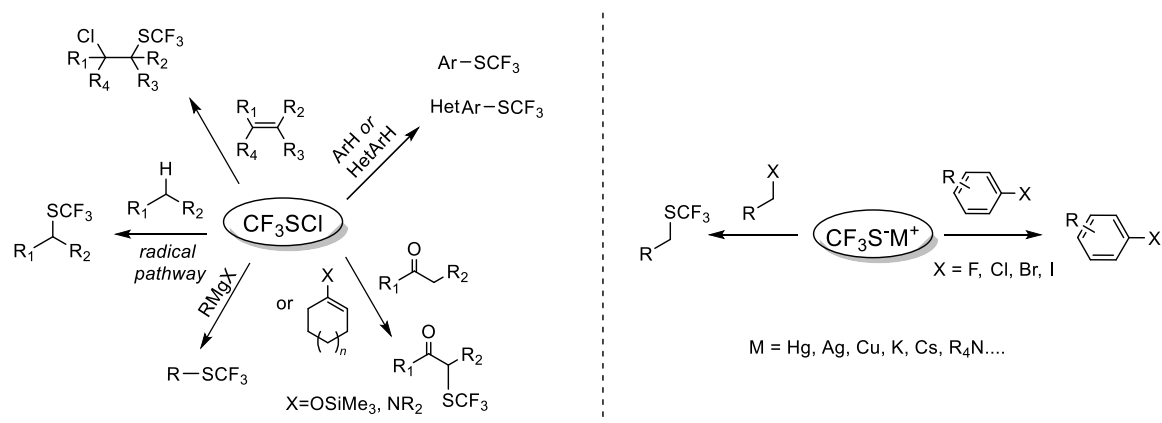


Figure 2.1b Different ways to obtain the O-CF₃ group

The S-CF₃ group was historically introduced into molecules using two reagents, F₃C-S-Cl or metal salts of trifluoromethyl thiolate F₃CS⁻; ⁺M. In the first case, the reagent could react with fluorinated alkanes or alkenes by radical route or be used as an electrophile and react with various nucleophiles. One finds in the literature examples of attacks by Grignards reagents, β-ketoesters or 1,3-diketones, enamine or even Friedel-Craft reaction. Metallic salts can be used to carry out the nucleophilic trifluoromethylthiolation of halogenated alkyl or aryl compounds (Figure 2.1c).

Figure 2.1c Overview of CF_3SCL and $\text{CF}_3\text{S}^+\text{M}^+$

More recently, new electrophilic trifluoromethylthiolation reagents have been developed, particularly derivatives with hypervalent iodine **8** or trifluoromethanesulfenamide **9** (Figure 2.1d). These reagents make it possible to functionalize a wide variety of substrates with yields that can be excellent.^[6]

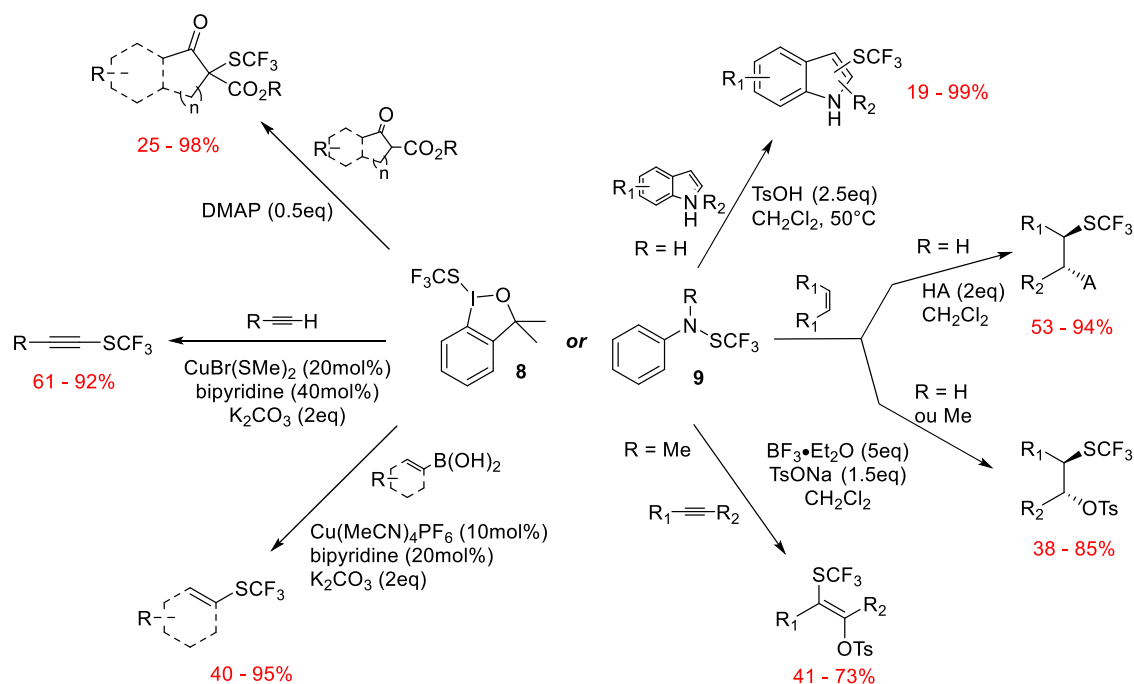


Figure 2.1d New methods of electrophilic trifluoromethylthiolation

In comparison to the OCF_3 and SCF_3 groups, nitrogen analogues are much less described. Even if their physicochemical properties can be interesting, there are very

few examples of fluorinated groups on nitrogen in the literature. Only a few active molecules containing *N*-CF₃ or *N*-CF₂H groups are described (Figure 2.1e).^[7]

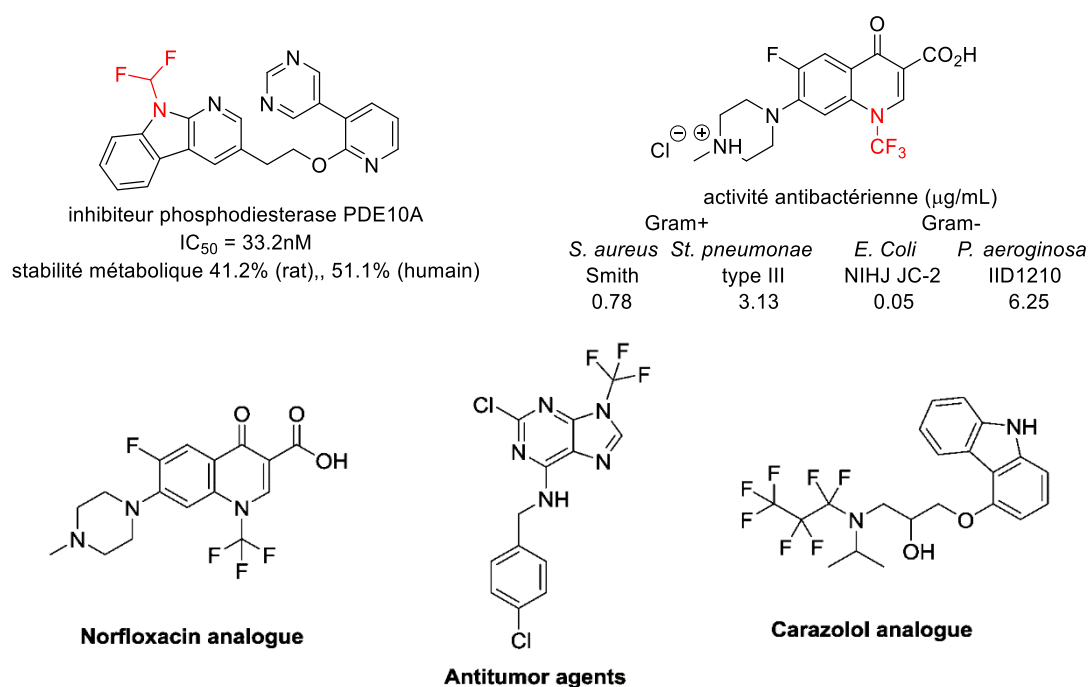


Figure 2.1e Example of bioactive molecules incorporating *N*-CF₂H and *N*-CF₃ groups

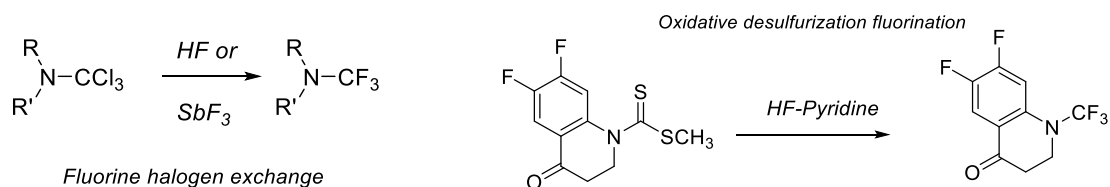
The methods of access to these *N*-Rf groups are quite limited. There are only very few examples of effective synthesis of *N*-CF₃ derivatives, even fewer for *N*-CF₂H and almost none for *N*-CF₂R. Faced with this lack, we were interested in developing new ways of accessing this type of function.

2.2 Overview of the introduction of fluorinated groups on the nitrogen

Traditionally, *N*-CF₃ compounds were prepared by fluorination of functionalized amine derivatives, but methods of fluorination usually suffer from the use of hazardous reagents and multistep procedures.^[25] Interestingly, mild and commercially available fluorinating reagents are emerging and more efficient approaches are developing, especially since 2017.

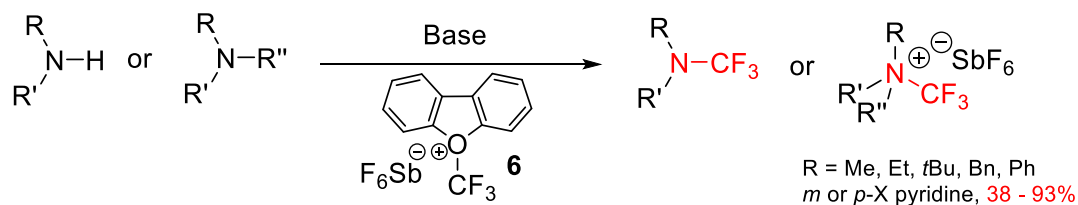
2.2.1 Previous synthesis of *N*-CF₃ group

The first methods to synthesize the *N*-CF₃ compounds are the fluorine halogen exchange^[8] and the oxidative desulfurization fluorination.^[9]



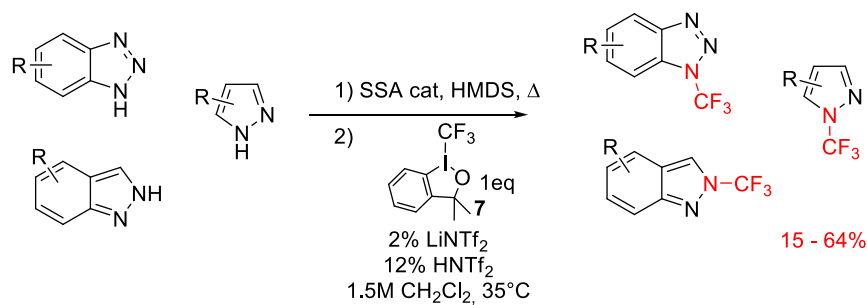
Scheme 2.2.1a Fluorine halogen exchange & oxidative desulfurization fluorination

More recently, new reagents have been developed to generate trifluoromethylated carbocations. In 2007, the Umemoto team developed the *O*-(trifluoromethyl)dibenzofuranylium tetrafluoroborate **6** which proved to be excellent agents for trifluoromethylation amines, whether primary, secondary or aromatic (Scheme 2.2.1b).^[10]



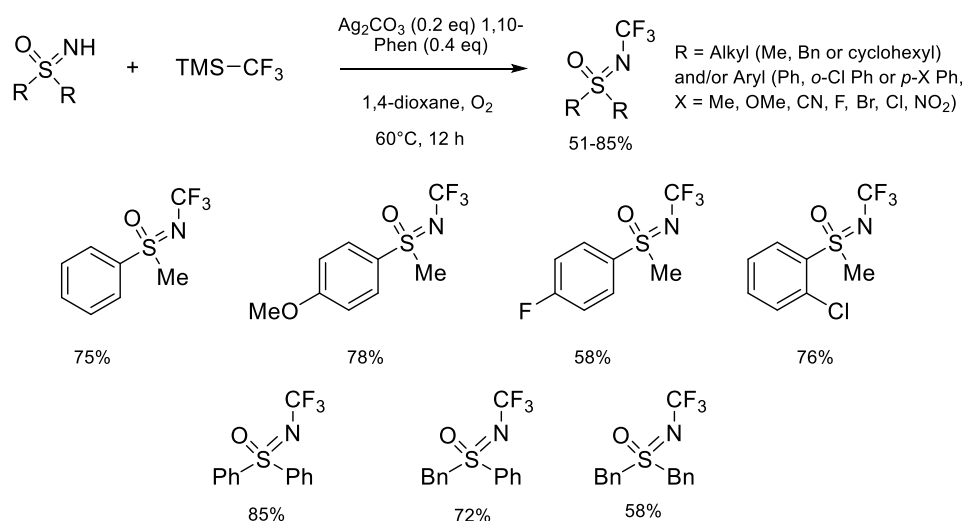
Scheme 2.2.1b Trifluoromethylation by trifluoromethyl-oxonium derivative

In 2006, Togni's group developed a trifluoromethylated hypervalent iodine derivative **7** as a trifluoromethylated carbocation precursor, which is used on a wide range of nucleophiles.^[11] It was not until 2012 that they successfully carried out the trifluoromethylation of amines but only with aromatic nitrogens.^[12]



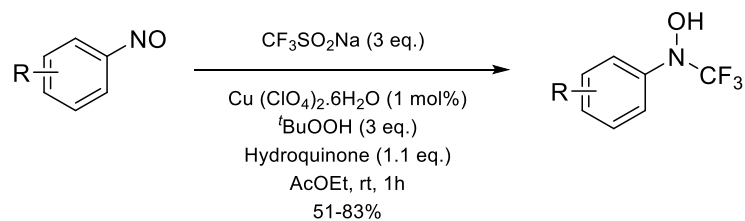
Scheme 2.2.1c Trifluoromethylation of *N*-heterocycles with the Togni's reagent

In 2015, Bolm et al.^[13] released the first radical trifluoromethylation on sulfoximines with the Ruppert-Prakash reagent (CF₃TMS) catalyzed by silver carbonate in the presence of 1,10-phenanthroline. After 12 h at 60°C, symmetrical or unsymmetrical sulfoximines substituted by various aliphatic and/or aromatic series were isolated in moderate to good yields.

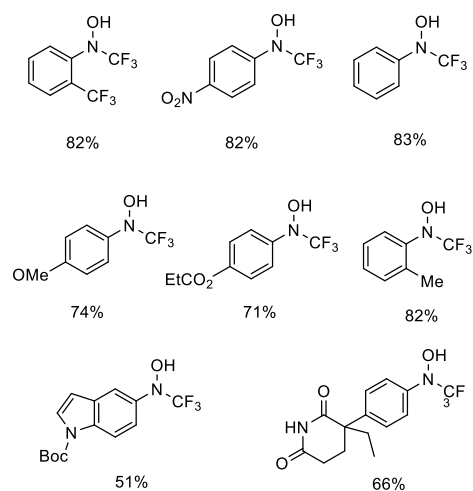
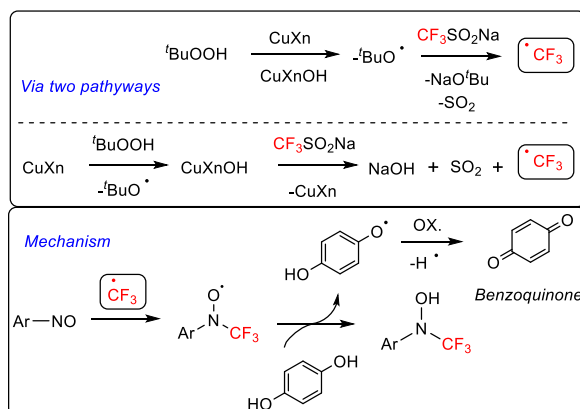


Scheme 2.2.1d Synthesis of *N*-trifluoromethyl sulfoxamines

In 2017, Selander et al.^[14] reported the radical addition of the trifluoromethyl group from the reagent of Langlois (CF₃SO₂Na) on aryl nitroso derivatives. The CF₃ radical was generated in the combination of copper (II) (Cu(ClO₄)₂) and *t*-butyl hydroperoxide. Once the radical was added to the nitrosoarenes, the hydroquinone transferred a proton and released the *N*-CF₃ hydroxylamines and radical trifluoromethylation.



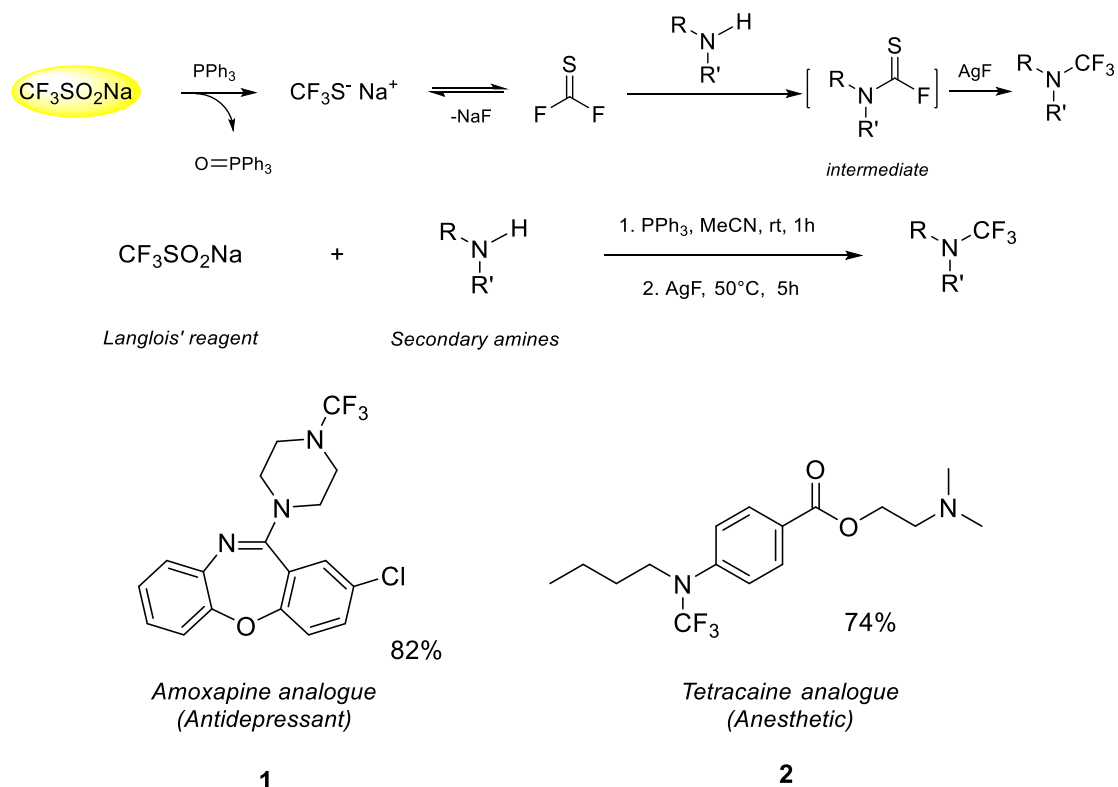
R = Alkyl, Ar, Cl, Br, CF₃, NO₂, MeO, CHO, CO₂Me



Scheme 2.2.1e *N*-CF₃ hydroxylamine synthesis

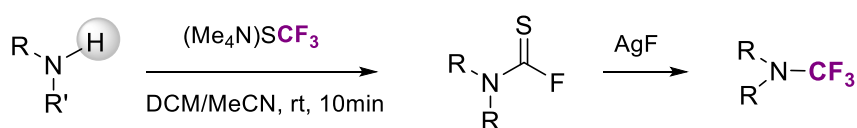
2.2.2 Recent *N*-CF₃ trifluoromethylation

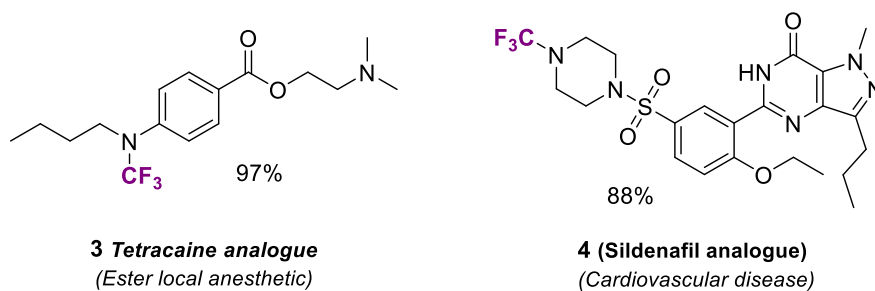
Currently, the *N*-trifluoromethylation of secondary amines with the sodium triflate (CF₃SO₂Na, Langlois' reagent) by one-pot synthesis was reported by Yi's group.^[15] In this research, CF₃SO₂Na can produce CF₃S⁻ (unstable) under reductive conditions, which then undergoes a reversible decomposition to form thiocarbonyl fluoride and fluoride. The generated thiocarbonyl fluoride then reacts with amine to afford thiocarbamoyl fluorides intermediate, and finally convert to trifluoromethyl amines by employing AgF. A wide range of secondary amines bearing electron-donating or -withdrawing groups proceeded well, as well as heterocyclic (furan, thiophene, pyridine etc.) amines, particularly some drug-like molecules (**1-2**) (Scheme 2.2.2a).



Scheme 2.2.2a One-pot synthesis of trifluoromethyl amines with CF₃SO₂Na

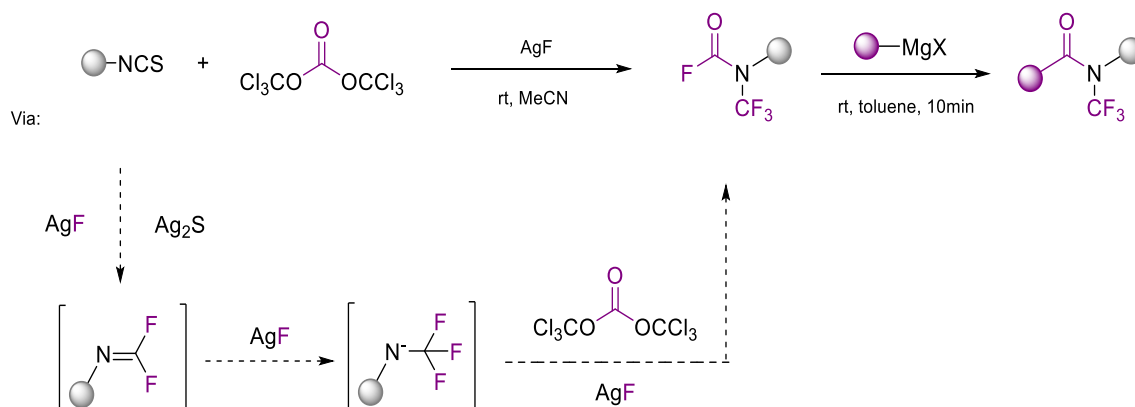
Then, the Schoeneberg's group was involved in synthesizing the *N*-CF₃ group by reporting different access routes. Firstly, *N*-CF₃ compounds were prepared by a two-step sequence but in a one-pot synthesis. Schoenebeck and co-workers investigated this strategy, which proceeds via a formal initial reaction between the SCF₃-anion offered by readily accessible (Me₄N)SCF₃ salt and the amine, giving quantitative formation of thiocarbamoyl fluoride intermediates within minutes that can easily be transformed to corresponding *N*-CF₃ compounds upon reaction with AgF. This protocol is only compatible with simple secondary amines and allowed to the incorporation of the CF₃ group on the nitrogen-containing drug molecules of greater complexity, for example, the *N*-trifluoromethylated tetracaine **3**, the *N*-CF₃ analogue of Sildenafil **4**.^[16]

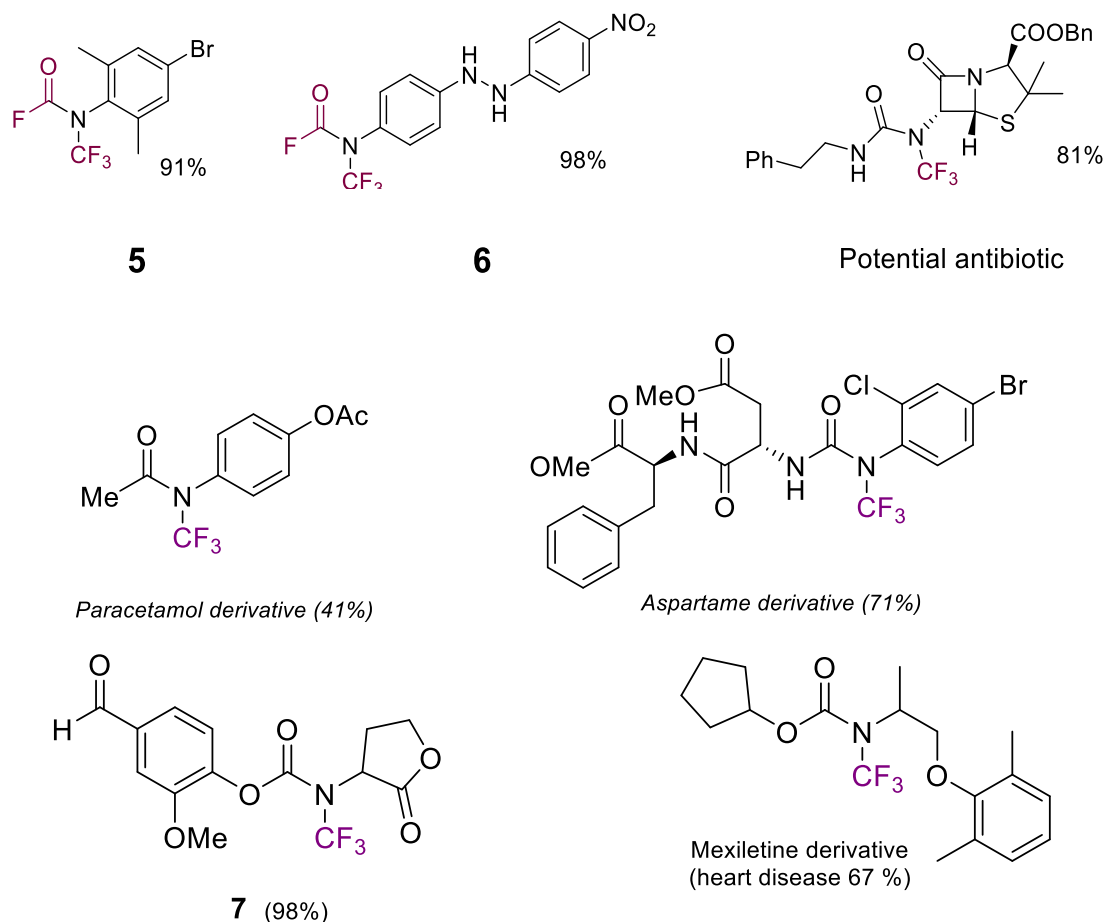




Scheme 2.2.2b Synthesis of Trifluoromethyl amines by two step strategy and *N*-trifluoromethylated complex drug molecules **3** and **4**

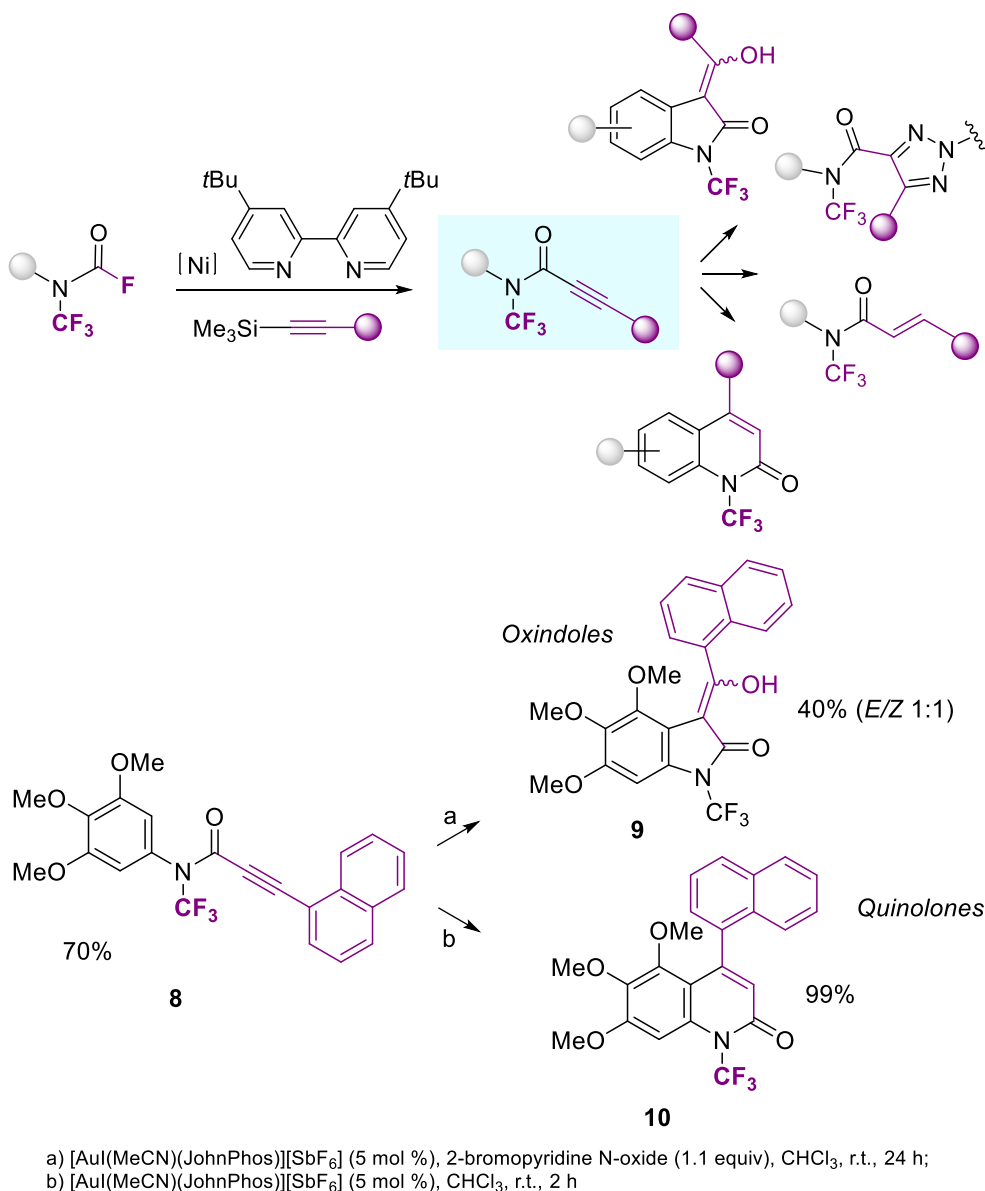
In 2019, the same group developed another way involving isothiocyanates from primary amines to access *N*-trifluoromethyl analogues of amides and related carbonyl compounds. In this process, the isothiocyanates treated with silver fluoride lead to the $\text{RN}=\text{CF}_2$ *in situ*. This compound reacts with AgF to give the amide $[\text{RNCF}_3]^-$ which adds on $\text{O}=\text{CF}_2$ (generated *in situ* from bis(trichloromethyl)carbonate (BTC) and AgF) to form the *N*-trifluoromethylcarbamoyl fluorides. These bench-table precursors could be readily applied to directly access *N*-trifluoromethyl amides through the addition of Grignard reagents, phenolates, alcohols, amines. Diverse and general transformations from broader carbonyl families were developed. Meanwhile, numerous functional groups were tolerated, simple precursors such as halogen (**5**), hydrazine groups (**6**), and drug analogues (**7**).^[17]





Scheme 2.2.2c Synthesis of *N*-trifluoromethylcarbamoyl fluorides and *N*-trifluoromethyl amides

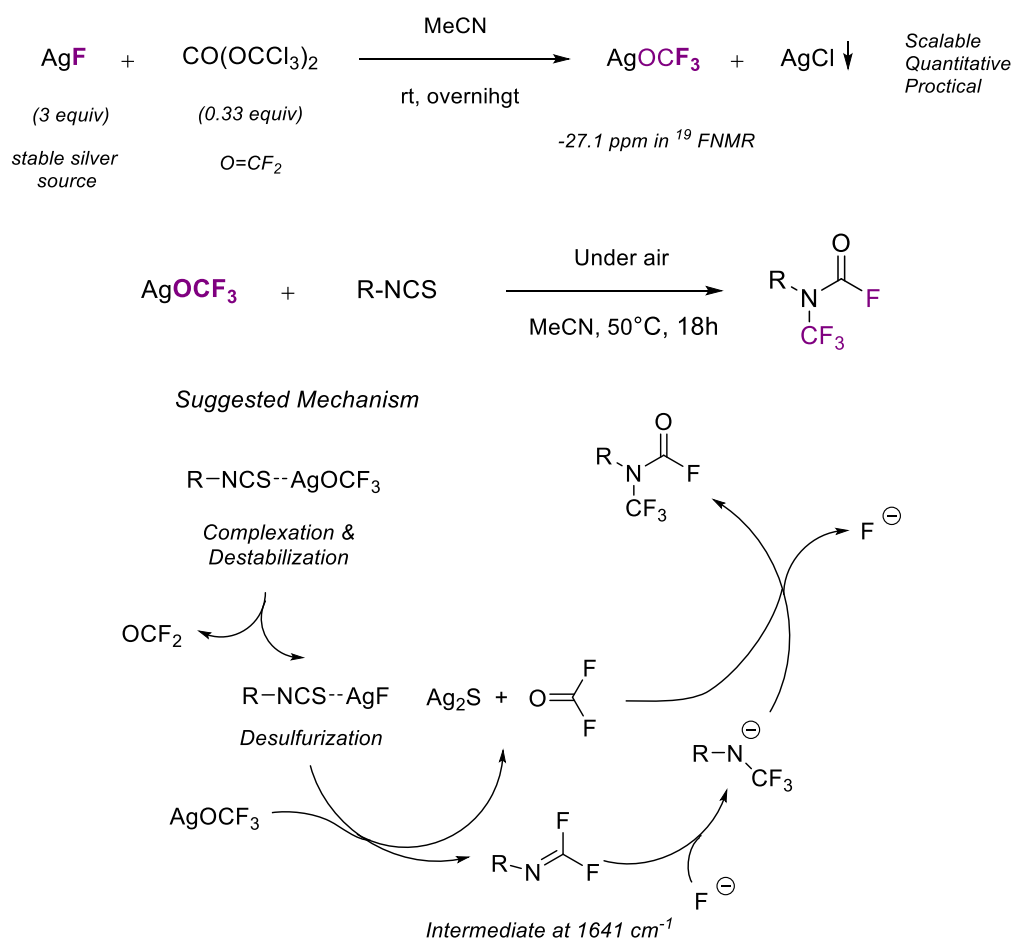
Based on synthesis of this class of *N*-trifluoromethylcarbamoyl fluorides, the group of Schoenebeck also constructed *N*-CF₃ alkynamide derivatives by Ni-catalyzed.^[18] Furthermore, these alkynamides are important and valuable precursors to numerous alternative structural motifs in medicinal chemistry, such as quinolones and oxindoles, which appear in anticancer drugs such as sunitinib and tipifarnib.^{[19]-[20]} Actually, alkynamides are also important and valuable precursors to numerous alternative structural motif in medicinal chemistry. Alkenyl amides are featured in >70% of covalent kinase inhibitors (Scheme 2.2.2d).^[21]



Scheme 2.2.2d Synthesis of *N*-CF₃ alkyne amides (**8**) and derivatization (oxindoles, quinolones)

In the previous description, it is known that the addition of AgF to the solid reagent BTC leads to the release of O=CF₂ *in situ*, along with AgCl formation. In this context, Schoenebeck's group reported a simple, environmentally benign and quantitative approach to the synthesis of AgOCF₃ and tested its robust performance in the direct trifluoromethoxylation, as an O=CF₂ precursor.^[22] AgOCF₃ solution was first prepared from stable silver source AgF and BTC in MeCN quantitatively. In the *N*-trifluoromethylation, the authors showed that AgOCF₃ could not spontaneously release O=CF₂ even under heating in the medium but got “activated” by coordinating with

isothiocyanates to liberate O=CF₂ and AgF. Finally, the isothiocyanates are converted to *N*-CF₃ carbamoyl fluorides by the suggested mechanism as shown in Scheme 2.2.2e.

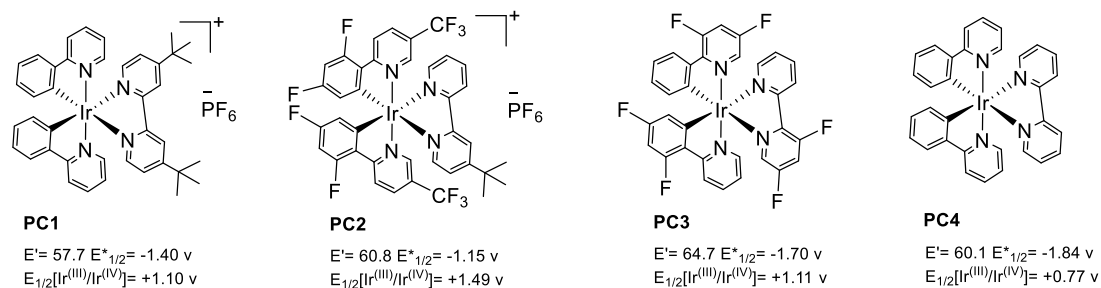
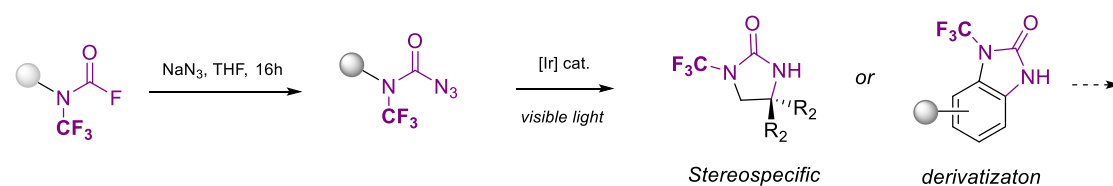


Scheme 2.2.2e Preparation of AgOCF₃ and synthesis of *N*-CF₃ carbamoyl fluorides

Recently, considering more potentially significant applications of *N*-CF₃ carbamoyl fluorides, this group published the realization of a photosensitized conversion of aromatic and aliphatic *N*-CF₃ carbamoyl azides to the corresponding cyclic *N*-CF₃ ureas and showcased the robustness of the new motif in numerous follow-up derivatizations.^[23] Schoenebeck and co-workers exposed *N*-CF₃ carbamoyl azides, prepared from *N*-CF₃ carbamoyl fluorides and sodium azide, to the Ir photocatalyst, [Ir(dtbbpy)(ppy)₂]-PF₆, under blue light irradiation in DCM to afford cyclic *N*-CF₃ ureas. The scope of this transformation applies to electron-donating (trimethoxy **11**) and electron-withdrawing groups, such as CF₃ (**12**), additionally, for the nonsymmetric case

(12), a mixture of two possible isomers was obtained.

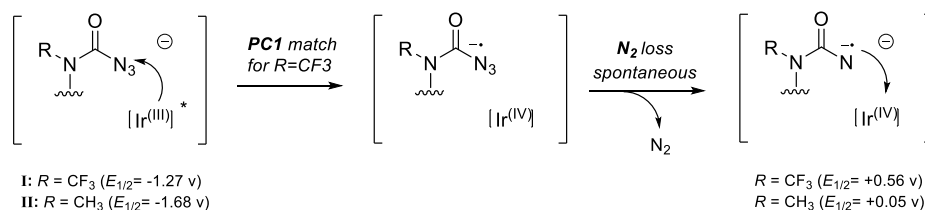
Authors indicated that the mechanism of this process is likely undergoing a reductive rebound between the photocatalyst and carbamoyl azides, in which SET triggers N₂ loss and subsequent re-oxidation generates a nitrene intermediate which undergoes C-H insertion. The ring formation and formal nitrene C-H insertion are fully stereospecific (example 13) in high yield.



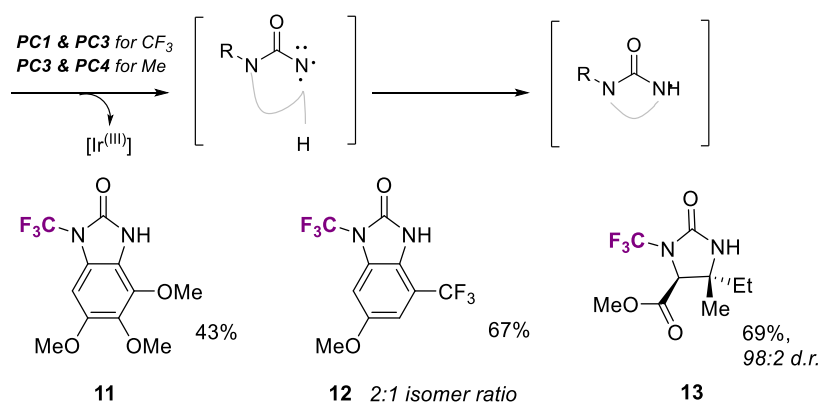
Likely mechanism: *Electron rebound triggered nitrene formation*

excited [Ir] reduces azides

electron rebound

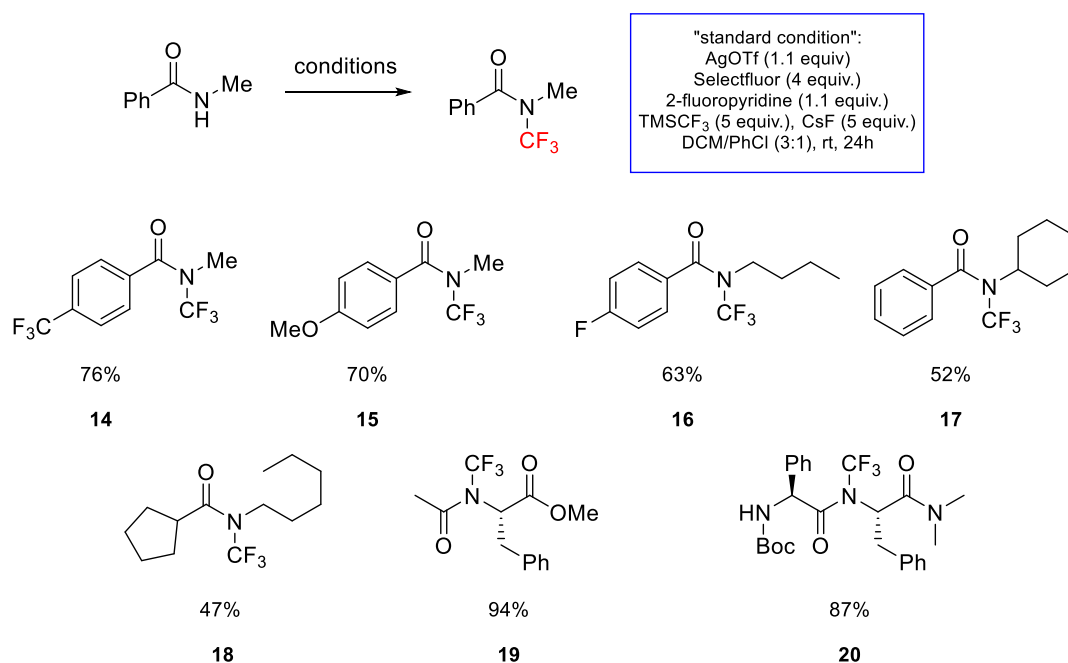


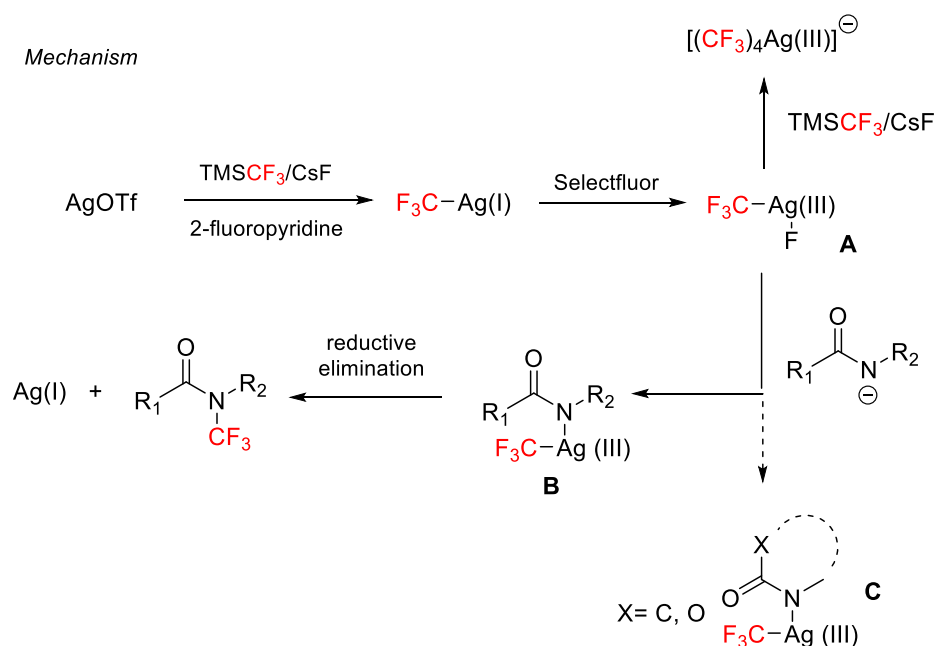
nitrene C-H insertion



Scheme 2.2.2f Synthesis of cyclic *N*-CF₃ ureas under photochemistry and corresponding examples

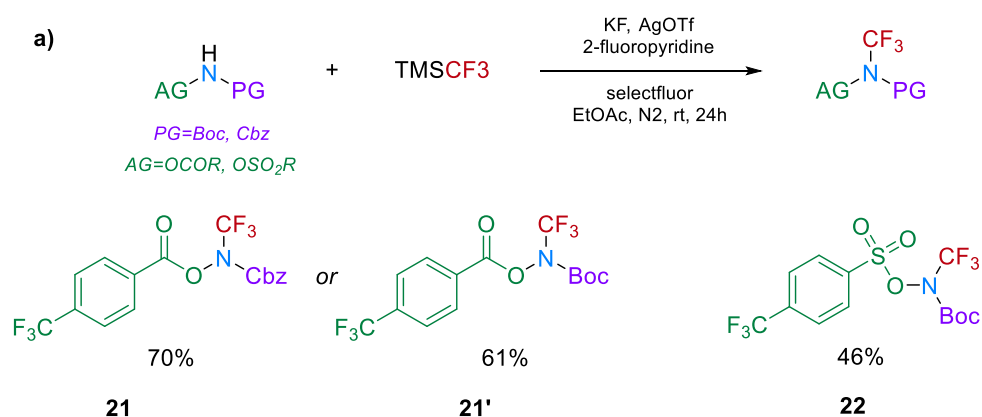
Then, in 2020, Li's group reported the directed *N*-trifluoromethylation of *N*-H amides.^[24] Promoted by AgOTf, 2-fluoropyridine, Selectfluor, TMSCF₃ and CsF, a variety of amides reacts smoothly at room temperature leading to the corresponding *N*-trifluoromethylated products in satisfactory yields. The reaction is compatible with a number of *N*-methylbenzamides with either electron-withdrawing or electron-donating substituents on the aromatic ring (**14**, **15**), of benzamides with different *N*-alkyl-substitutions (**16**, **17**), a variety of *N*-alkylalkanamides (**18**), as well as α -amino acids derivatives and peptides (**19**, **20**). Additionally, the presence of a range of functional group was tolerated, such as ether, ketones, esters, nitriles and aryl halides (F, Cl, Br). Proposed mechanism shows that interaction of AgOTf with 2-fluoropyridine and CF₃⁻ anion derived from TMSCF₃/CsF generates Ag(I)-CF₃ intermediate that is then oxidized by Selectfluor to give the Ag(III)-CF₃ species **A**. Meanwhile, deprotection of an amide by CF₃⁻ anion gives the corresponding amidyl anion. Ligand exchange of **A** with the amidyl anion produces the Ag(III)-complex **B**, which undergoes reductive elimination to provide the *N*-trifluoromethylated amide.

Scheme 2.2.2g Silver-mediated *N*-trifluoromethylation of amides and peptides



Scheme 2.2.2h Plausible mechanism

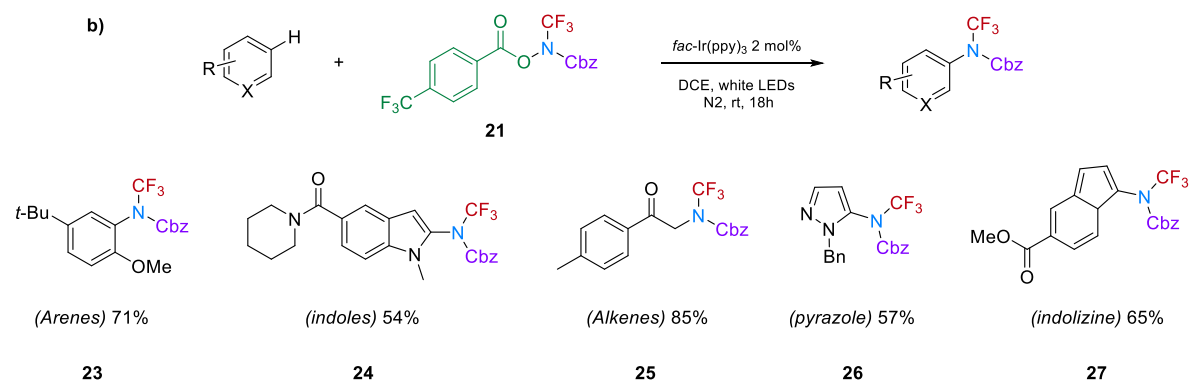
In 2022, Xu's group reported the direct incorporation of the *N*-CF₃ motif on different substrates under photoredox catalysis with *Tert*-butyl and benzyl (trifluoromethyl)((4-(trifluoromethyl)benzoyl)oxy)carbamates. These reagents are prepared by the previous approach involving silver-mediated oxidative trifluoromethylation (Scheme 2.2.2i).^[25]



Scheme 2.2.2i

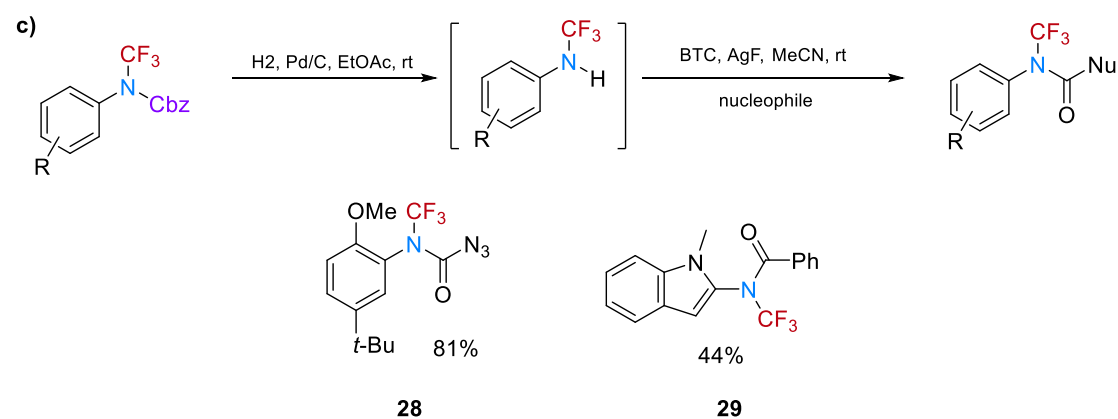
Thus, under photochemistry by a radical pathway with Iridium catalyst, the *N*-CF₃ moiety can be incorporated in arenes (**23**), indoles (**24**), alkenes (**25**), and functional

groups (pyrazole **26**, indolizine **27** etc.).



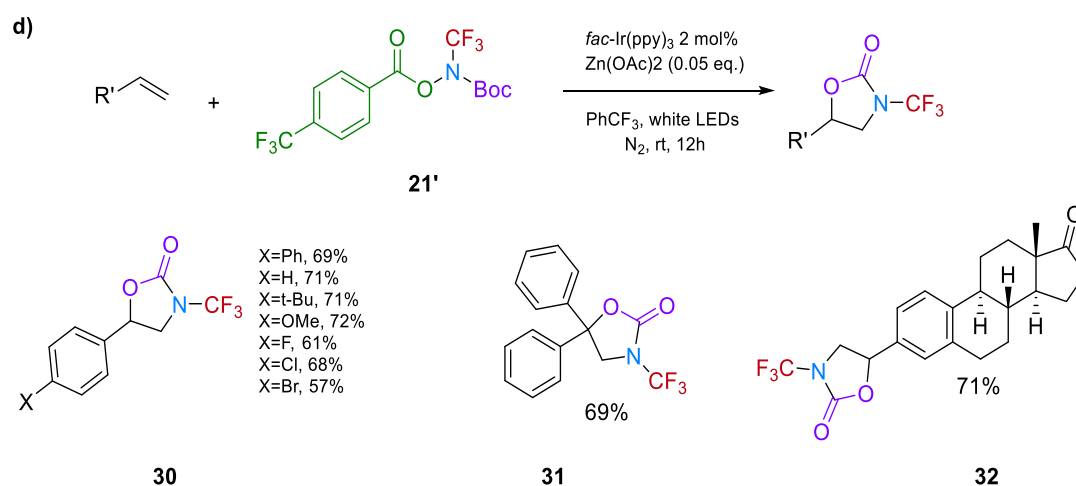
Scheme 2.2.2j

The *N*-Cbz-protected trifluoromethylaminated (hetero)-aromatic and aliphatic products are easily deprotected by hydrogenolysis and then functionalized by the method of Schoenebeck involving BTC and AgF to give diverse acyclic *N*-CF₃ amide compounds (**28**, **29**).



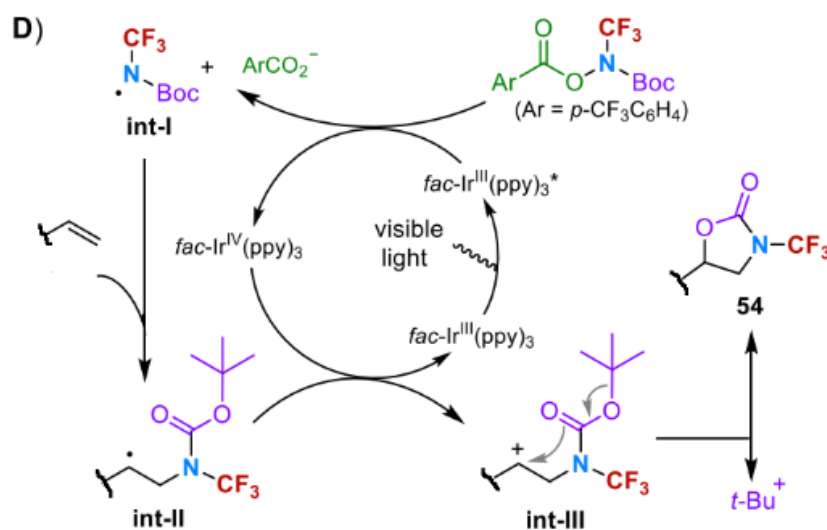
Scheme 2.2.2k

Interestingly, from the *Tert*-butyl (trifluoromethyl)((4-(trifluoromethyl)benzoyl)oxy)carbamate and alkenes, diversified oxazolidin-2-ones could be obtained in good yields. The Boc group intervenes in the reaction to lead to the cyclic compounds.



Scheme 2.2.2l

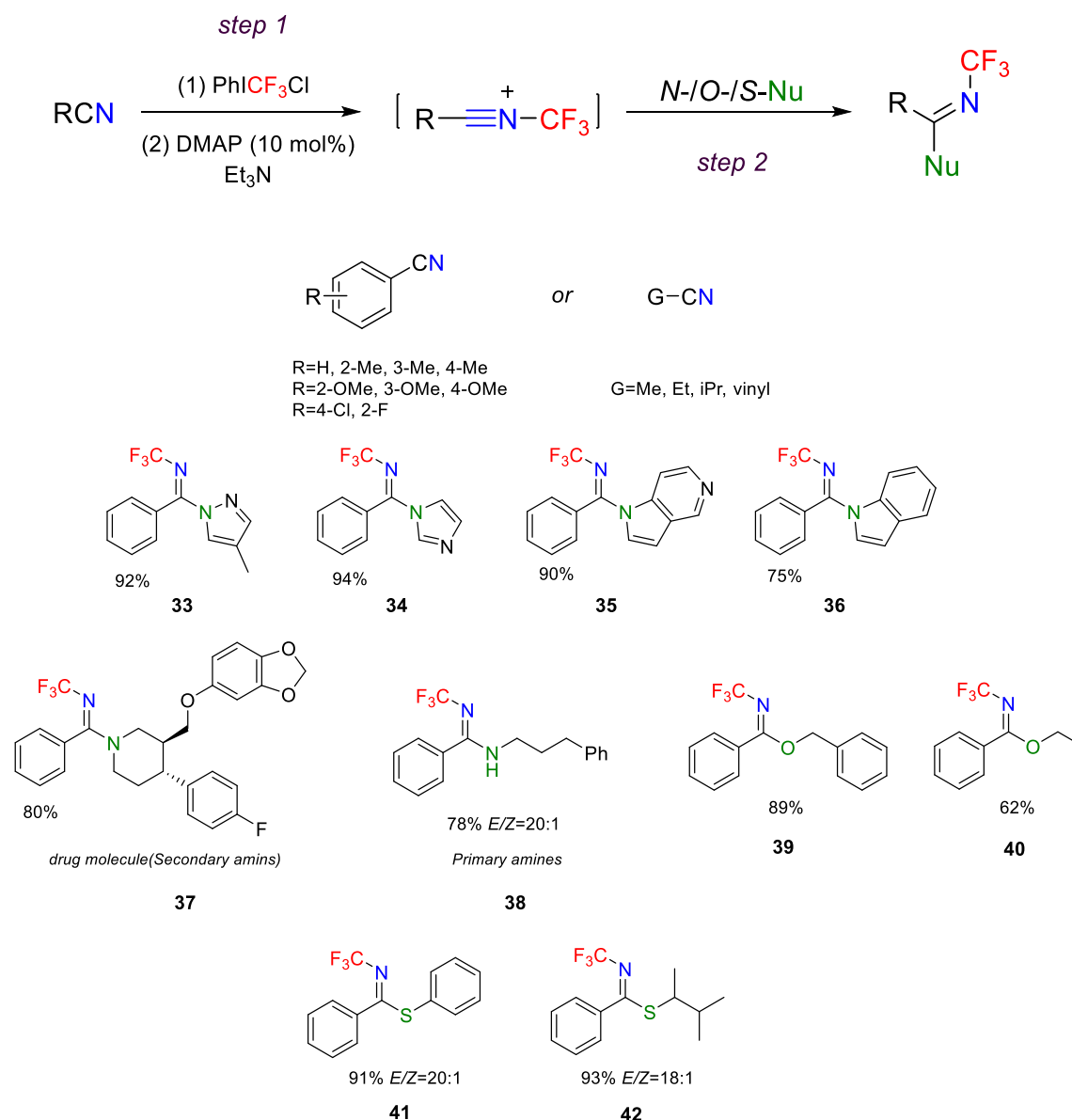
Xu's group proposed that initially, the photoexcitation of *fac*-IrIII(ppy)₃, generates *fac*-IrIII(ppy)₃^{*}, and then, single-electron transfer (SET) reduction of reagent **21'** with *fac*-IrIII(ppy)₃^{*} affords N-centered radical int-I and *fac*-IrIV(ppy)₃. Immediately, the addition of radical int-I to for example styrenes delivers radical intermediate int-II, which is oxidized by *fac*-IrIV(ppy)₃ to cation intermediates int-III and regenerate *fac*-IrIII(ppy)₃. Int-III finally undergoes intramolecular nucleophilic attack, delivering *N*-CF₃ oxazolidinones (**30-32**).



Scheme 2.2.2m Proposed Mechanism by Xu's group

In the same year, Wang's group developed a methodology for synthesizing *N*-

trifluoromethyl amidines, thioimidates, and imidates via *N*-CF₃ nitrilium ions. The *N*-CF₃ nitrilium ions were generated via *N*-trifluoromethylation of nitriles using PhICF₃Cl under catalysis with DMAP, followed by the capture of *N*-, *O*-, or *S*-centered nucleophiles.^[26]

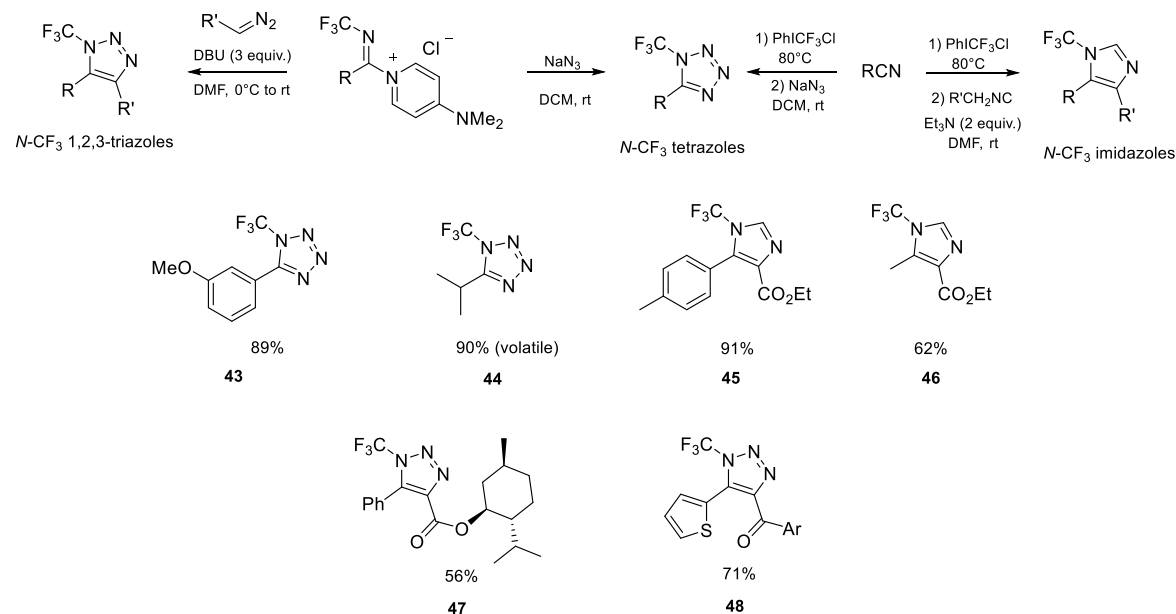


Scheme 2.2.2n Synthesis of *N*-CF₃ amidines/imidates/thioimidates via *N*-CF₃ nitrilium ions

In this line, the same group exploited *N*-CF₃ nitrilium intermediates in cycloaddition reactions to obtain a wide range of azoles. This approach involves the [3+2] cycloaddition between nitrilium derivatives *N*-CF₃ and 1,3-dipoles.^[27]

As a result, a generic platform was established to synthesis *N*-trifluoromethylated

azoles. In particular, *N*-CF₃ tetrazoles (**43**, **44**), *N*-CF₃ imidazoles (**45**, **46**), and *N*-CF₃ 1,2,3-triazoles (**47**, **48**) have been prepared conveniently from azide, isocyanates and diazo compounds (Scheme 2.2.2o).



Scheme 2.2.2o Synthesis of *N*-CF₃ tetrazoles, imidazoles and 1,2,3-triazoles

2.3 *N*-CF₃ hydrazines

2.3.1 Literature

We have seen that access to the *N*-CF₃ motif has generated a lot of excitement over the past few years and is now well developed. However, it turns out that on closer inspection, the synthesis of *N*-CF₃ hydrazines is currently very limited. Hydrazines are important for synthesizing *N*-heterocyclic functionalized compounds and for their many applications in many areas of synthetic chemistry in materials^[28], pharmaceuticals^[29] and agrochemicals^[29d], dyes^[30], and as valuable precursors to heterocycles (pyrazoles, indoles....) and popular directing groups in catalysis^[31].

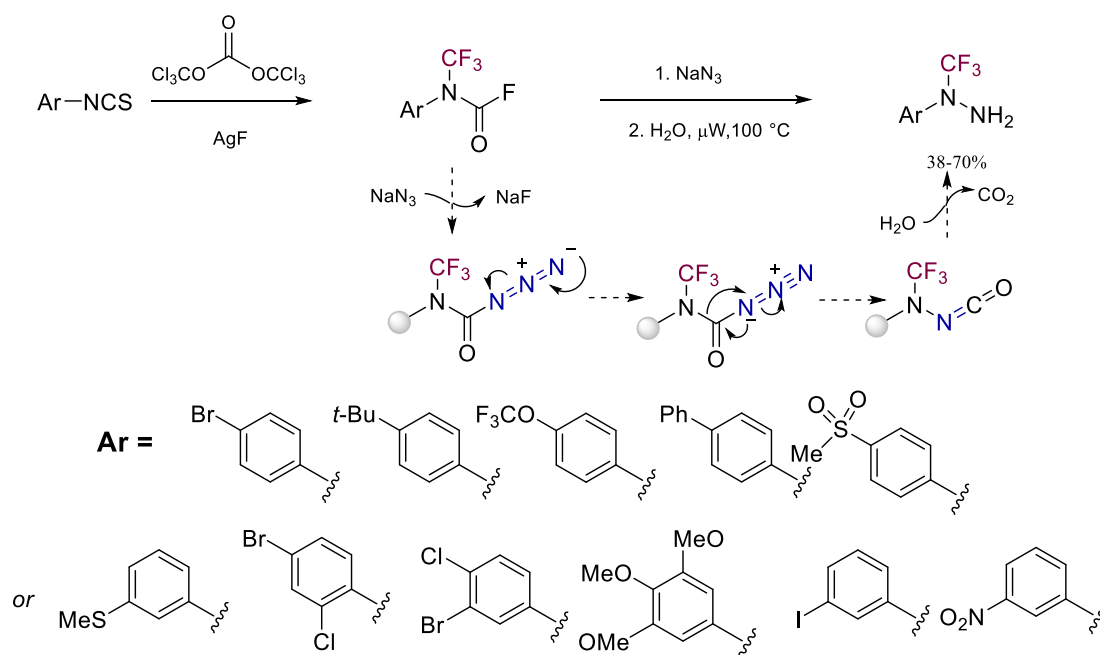
Currently, we can list only two pathways that lead to hydrazines possessing a single CF₃ group on a nitrogen. The first is that reported by our group involving the

nucleophilic addition of CF₃⁻ to *t*-Butyl azodicarboxylate. The corresponding hydrazine is obtained with a low yield of 30%. Nucleophilic addition of CF₃⁻ generated by TMSCF₃ and AcONa on other azodicarboxylates led to mixture of compounds. [32]

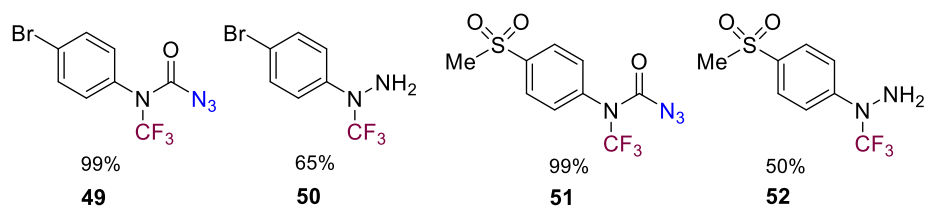


Scheme 2.3.1a Preparation of di-*tert*-butyl 1-(trifluoromethyl) hydrazine-1,2-dicarboxylate

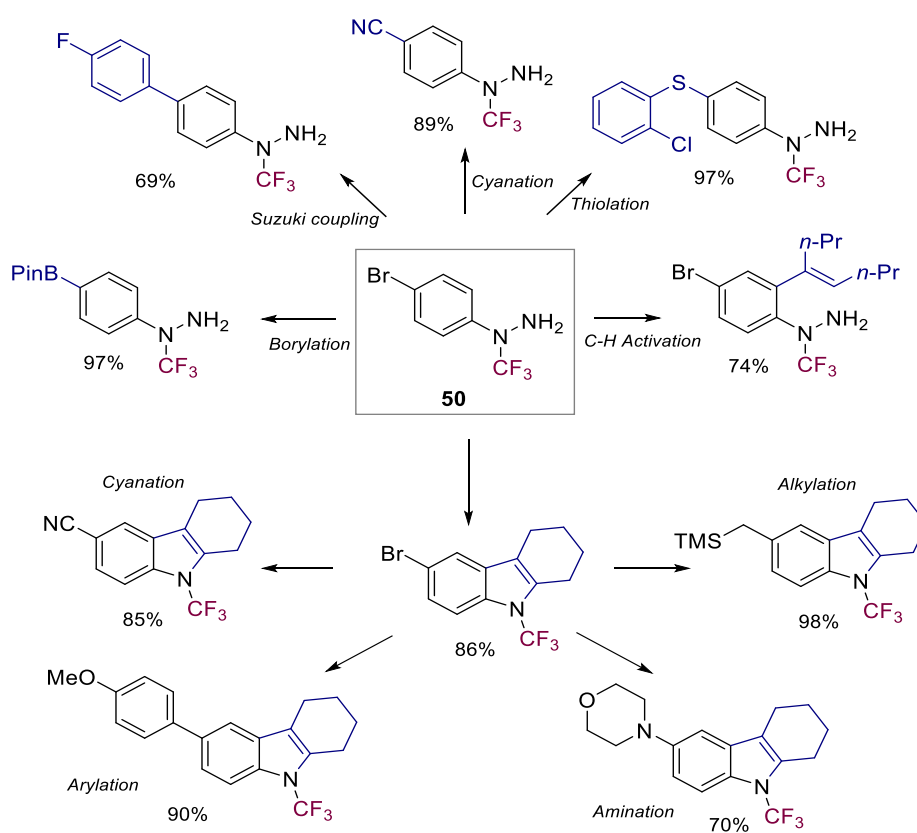
Another strategy was proposed by Schoenebeck et.al in 2020. [33] It was starting from their previous development of a direct synthetic route to *N*-CF₃ carbamoyl fluorides, which is described in 2.2.2(Scheme 2.2.c). Subsequently, these carbamoyl fluorides could be converted to the corresponding acyl azides which through Curtius-type rearrangement under microwave-based heating, led to Aryl *N*-CF₃ hydrazines (**49-52**).



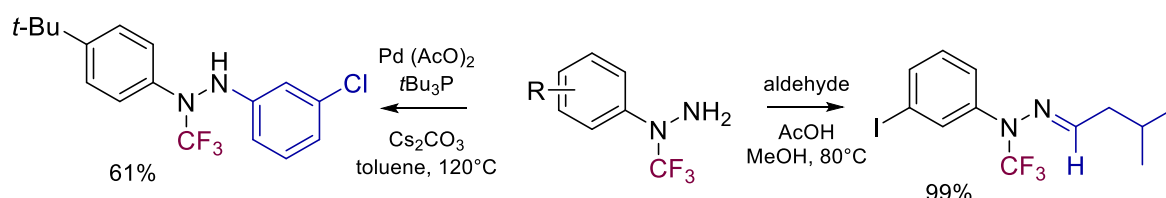
Some examples:

Scheme 2.3.1b Azidation of carbamoyl fluorides and access to *N*-CF₃ hydrazines

For more in-depth exploration, their group developed derivatizations of *N*-CF₃ hydrazines. The first one is **50**-based derivatization such as C-H activation, thiolation, cyanation, borylation and formation of *N*-CF₃ indoles as shown in the following scheme (Scheme 2.3.1c). Also, the *N*-CF₃ hydrazine **50** could be converted in a Fischer indole synthesis using ketone, H₂SO₄ as catalyst, MeOH and heating at 80°C. The corresponding indole was functionalized according different reactions (cyanation, alkylation, arylation and amination).

Scheme 2.3.1c Products of **50**-based derivatization

The derivatization of *N*-CF₃ on the free NH₂ fragment has been also investigated by the group. The NH₂ could be selectively coupled with 3-chlorobromobenzene via Pd catalysis in a Buchwald–Hartwig amination to give the diaryl hydrazine. Equally, hydrazone could be obtained in quantitative yield after heating at 80°C for 3 h in acetic acid. (Scheme 2.3.1d).

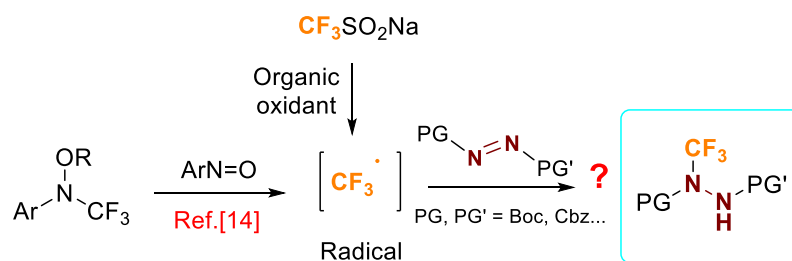


Scheme 2.3.1d Derivatization of *N*-CF₃ on the free NH₂ moiety

In the interest of our group to study the access of fluorinated amines and fluorinated peptidomimetics, we were interested in the synthesis of new fluorinated hydrazines. To date, the synthesis and incorporation of *N*-fluorinated peptidomimetics is not yet well exploited. First of all, we focused on the synthesis of *N*-CF₃ hydrazines.

2.3.2 Our approach to the synthesis of *N*-CF₃ hydrazines

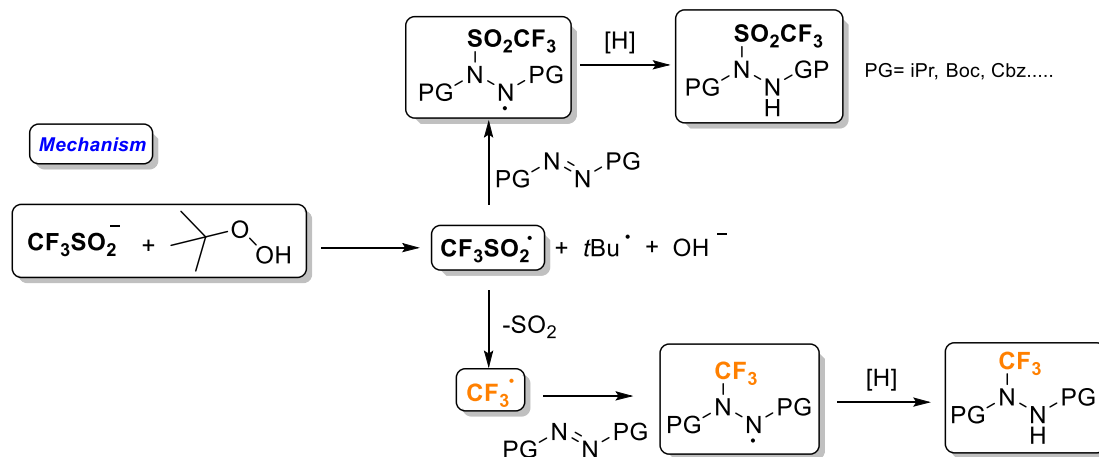
Inspired by previous work of Selander^[14] realizing the addition of the radical CF₃[•] on nitroso aryls, it is expected that the CF₃-radical generated from CF₃SO₂Na and TBHP (*tert*-butyl hydroperoxide) adds onto commercially available azodicarboxylates to give corresponding *N*-CF₃ hydrazides. (Scheme 2.3.2a).



Scheme 2.3.2a Access to *N*-CF₃ hydrazides from CF₃SO₂Na

First, we tested Selander's conditions involving triflate **2-1**, Cu(ClO₄)₂·6H₂O, TBHP (70% in water, 1.5 equiv.), hydroquinone, and the diisopropyl azodicarboxylate **2-2a** in ethyl acetate. At the end of the reaction, we obtain, after only a few minutes, a single product in fluorine NMR corresponding to the *N*-trifluoromethyl-sulfonylated compound **2-4a** (-72 ppm). Other metals such as CuI, Cu(OAc)₂, Fe(NO₂)₃...for example, have been tested, but none gives the expected product, but always the compound **2-4a**, and the azodicarboxylate reagent decomposes in the media.

We then undertook the addition of the oxidant TBHP (70% in water, 1.5 equiv.) in the solution of sodium triflate **2-1** (CF₃SO₂Na, 1.5 equiv.) and diisopropyl azodicarboxylate **2-2a** (1 equiv.) in acetonitrile at 0°C without metal catalyst. After the addition of the oxidant, and the complete disappearance of the yellow color characteristic of the presence of **2-2a**, ¹⁹F NMR of the crude revealed two compounds (Figure 2.3.2a). The first corresponds to the *N*-trifluoromethyl-sulfonylated compound **2-4a** (-72 ppm) [34], and the second one is *N*-CF₃ hydrazide **2-3a** (-60 ppm) in a ratio 90/10, respectively.



Mechanism of radical reaction

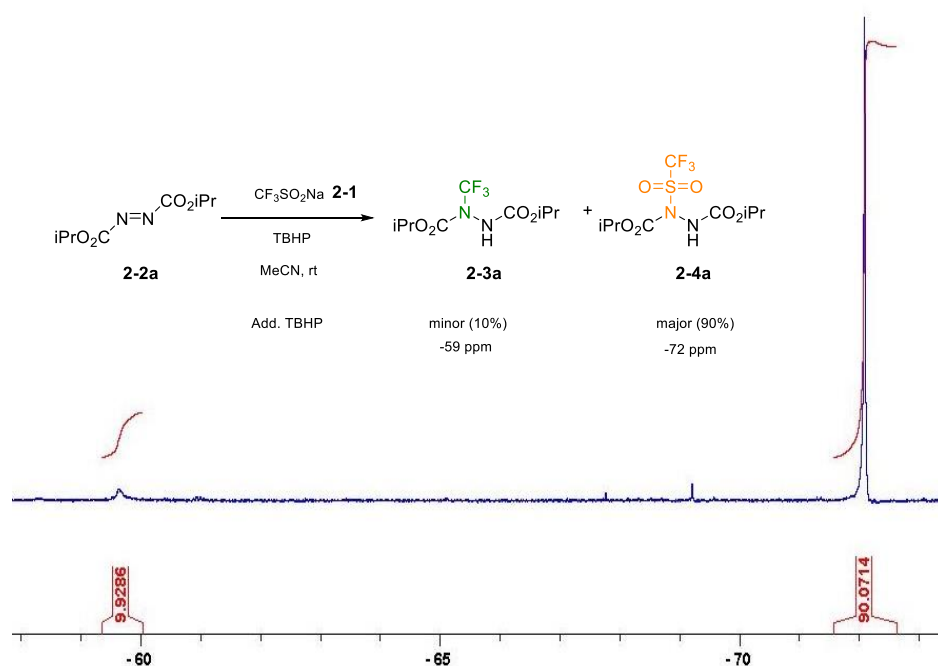
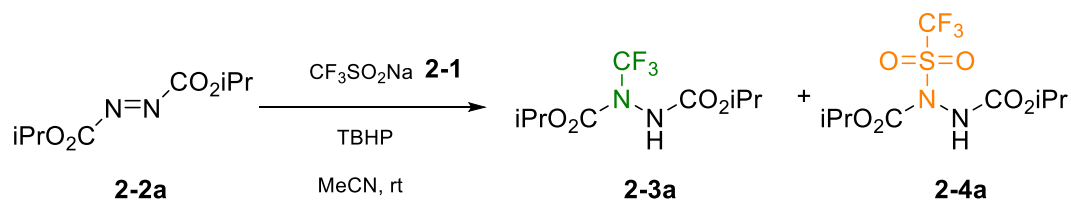


Figure 2.3.2a

This primary result seems very interesting because, for the first time, the expected compound *N*-CF₃ is detected. Considering the high electrophilicity of azodicarboxylate **2-2a**, the nucleophilic addition of the triflate takes precedence over the trifluoromethyl radical less nucleophile. To promote radical trifluoromethylation, we thought to perform the reverse addition of the reagents. The sodium triflate **2-1** was added to the mixture of diazene **2-2a** and TBHP in acetonitrile. Under these conditions, the decomposition of triflate **2-1** into the CF₃ radical is excessive and preferred. As a result, the majority product detected is the expected product (Figure 2.3.2b), i.e. the compound *N*-CF₃ **2-3a** isolated in 34% yield (Scheme 2.3.2b).



Scheme 2.3.2b Preliminary conditions

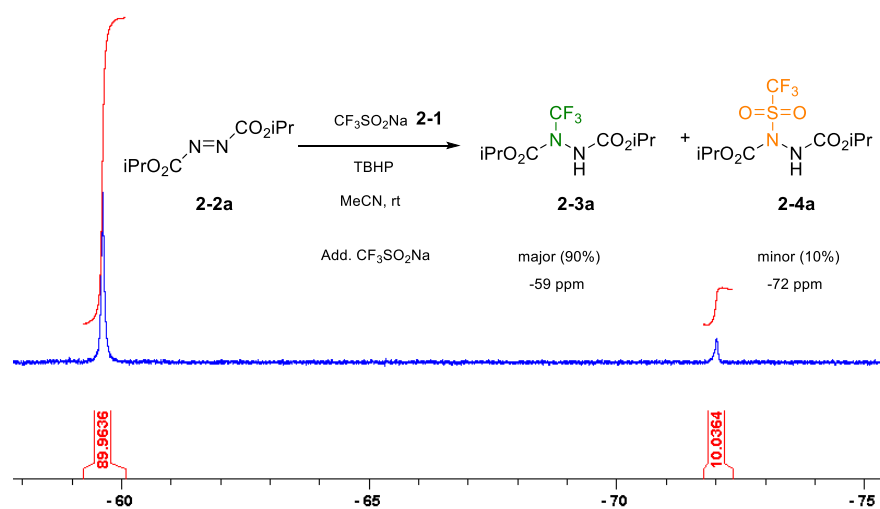


Figure 2.3.2b

Subsequently, in order to improve ratio of *N*-CF₃ hydrazine, the reaction was optimized with different solvents and oxidants (Table 2.3.2a and Table 2.3.2b).

$ \begin{array}{c} \text{iPrO}_2\text{C}-\text{N}=\text{N}-\text{CO}_2\text{iPr} \xrightarrow[\text{solvent, T}^\circ\text{C}]{\text{CF}_3\text{SO}_2\text{Na } \mathbf{2-1}, \text{oxidant}} \\ \mathbf{2-2a} \qquad\qquad\qquad \mathbf{2-3a} \qquad\qquad\qquad \mathbf{2-4a} \qquad\qquad\qquad \mathbf{2-C} \end{array} $							
Entry	CF ₃ SO ₂ Na	Oxidant (eq.)	solvent		T ^o C	2-3a/ 2-4a	Yield of 2-3a (%)
1	1.5 eq.	TBHP (1.5)	MeCN	\	rt	90/10	34
2	2.5 eq.	TBHP (2.5)	DMF	\	rt	10/90	-
3	2.5 eq.	TBHP (2.5)	AcOEt	\	rt	40/60	-
4	2.5 eq.	TBHP (2.5)	DCM/H ₂ O	\	rt	80/20	-
5	1.5 eq.	TBHP (1.5)	DMSO	\	rt	93/7	45
6	1.5 eq.	TBHP (1.5)	DMSO	MeOH 1.5 eq.	rt	88/12	37

Table 2.3.2a Optimization of solvents with TBHP as Oxidant

As shown in the table 2.3.2a, in this process, DCM/H₂O, AcOEt, DMF, MeCN, DMSO were screened by employing TBHP as oxidant. According to the different conditions,

the DMSO was the best solvent. The main compounds **2-3a** was obtained in 45% after purification. The addition of MeOH or the excess of sodium triflinate and TBHP (3 or 5 equiv.) did not enhance the yield.

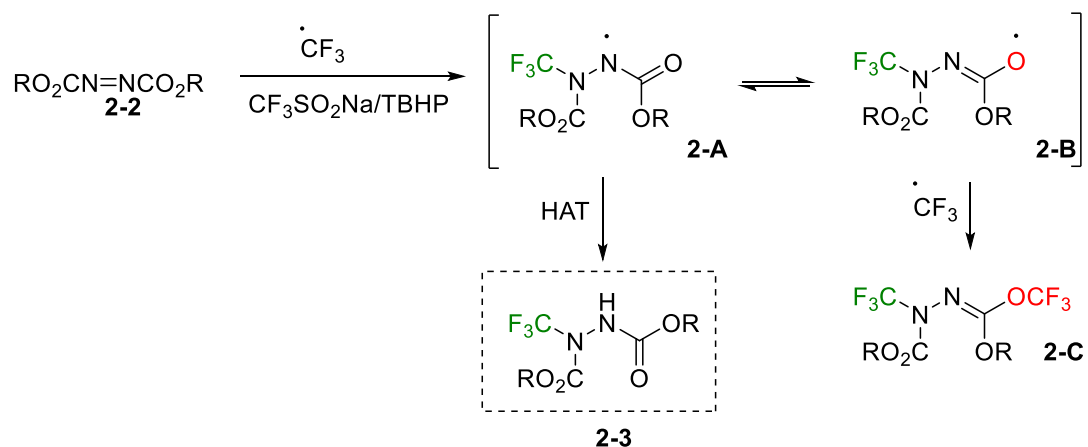
Additionally, no improvement was observed with K₂S₂O₈ as oxidant which required 90°C with slow addition of sodium triflinate.

Reaction scheme: **2-2a** (iPrO₂C-N=N-CO₂iPr) reacts with **2-1** (CF₃SO₂Na) as oxidant in a solvent at T°C to produce **2-3a** (iPrO₂C-NH-CF₃-CO₂iPr), **2-4a** (iPrO₂C-NH-SO₂-CO₂iPr), and **2-C** (iPrO₂C-N(CF₃)-N(OCF₃)-CO₂iPr).

Entry	CF ₃ SO ₂ Na	Oxidant (eq.)	solvent	T°C	2-3a/ 2-4a	Yield of 2-3a (%)	
1	1.5 eq.	K ₂ S ₂ O ₈ (1.5)	DMSO	\	rt	14/86	-
2	1.5 eq.	K ₂ S ₂ O ₈ (1.5)	DMSO	\	50°C	26/74	-
3	1.5 eq.	K ₂ S ₂ O ₈ (1.5)	DMSO	\	90°C	2/96	-
4	1.5 eq.	K ₂ S ₂ O ₈ (1.5)	DMSO(H ₂ O)	\	50°C	53/47	-
5	1.5 eq.	K ₂ S ₂ O ₈ (1.5)	DMSO(H ₂ O)	\	90°C	90/10	38
6	1.5 eq.	K ₂ S ₂ O ₈ (1.5)	MeCN(H ₂ O)	\	70°C	49/51	-

Table 2.3.2b Optimization of oxidant with DMSO as solvent

During our study, we observed that when reactions were carried out in acetonitrile or dichloromethane, the presence of side products was detected. One of these compounds **2-C** was isolated (14%) and characterized, and corresponded to bis *N*- and *O*-trifluoromethylation of the azodicarboxylate. The formation of this compound could be explained by the following mechanism (Scheme 2.3.2c). On the one hand, the CF₃ radical was added to the diazene to give the *N*-CF₃ hydrazide radical **2-A**. The latter led to the expected product **2-3** after hydrogen atom transfer (HAT). On the other hand, the intermediate **2-A** could isomerize into the intermediate **2-B** to react with the CF₃ radical to afford the compound **2-C**.

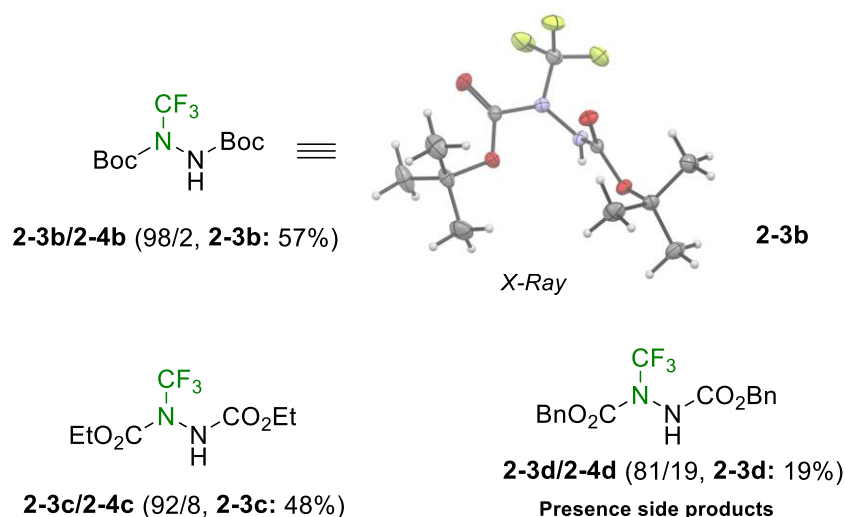
Scheme 2.3.2c Proposed mechanism for formation of side product **2-C**

The presence of the hydrazine (*i*PrO₂CNH-NHCO₂*i*Pr) which can be recovered (15-20%), was also observed at the end of the reaction and possibly due to radical chain and H-bond abstraction pathways. Attempts to trap the nitrogen radical of **2-A** have been undertaken. Unfortunately, whatever the scavenger used (hydroquinone, alkanes, alcohols), no improvement was observed.

Optimized conditions have been applied to other commercially available azodicarboxylate derivatives such as *t*Bu **2-2b**, Et **2-2c**, Bn **2-2d** (Scheme 2.3.2d). The *N*-CF₃ hydrazides **2-3b** and **2-3c** were obtained with yield of 57% and 48%, respectively. The structure of **2-3b** was determined by X-Ray crystallographic analysis. It is interesting to note that the *N*-CF₃ hydrazines are very stable on column chromatography, in air and several months in fridge. For **2-4d**, yield was low and led to a mixture of side products.

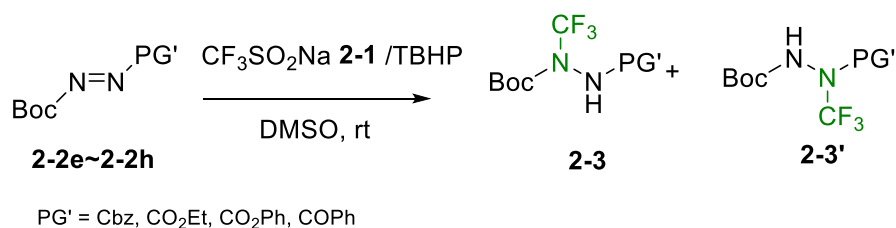


Symmetric diazenes

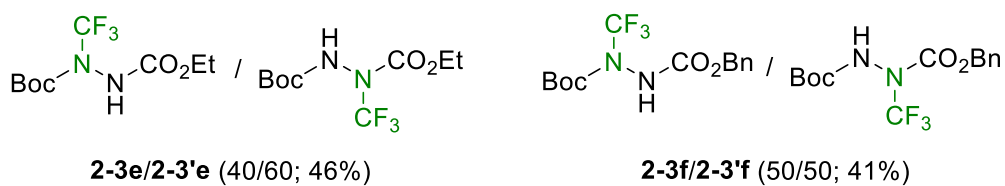


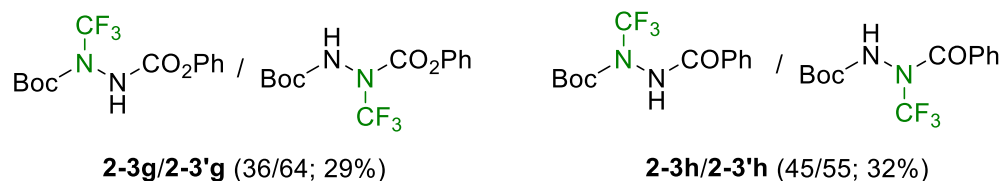
Scheme 2.3.2d Trifluoromethylation of azodicarboxylates

The reaction was then extended to unsymmetrical azodicarboxylates to get access to dissymmetric and free *N*-CF₃ hydrazides. The addition of the triflate **2-1** was performed with a series of Boc-protected azodicarboxylates **2-2e~2-2h** with esters, ketones and phenyl groups. Reactions led to a mixture of inseparable regioisomers **2-3e/2-3'e** and **2-3f/2-3'f** isolated in moderate yield, 46% (60/40) and 41% (50/50), respectively. Hydrazides **2-3g/2-3'g** and **2-3h/2-3'h** were obtained in 29% and 32%.



From unsymmetric diazenes



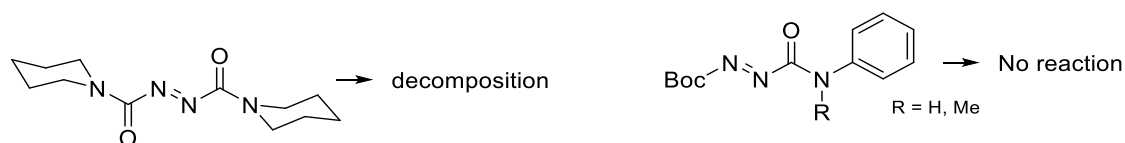


*In these cases, regioisomers are indistinguishable respectively, the ratio in brackets only represent two isomers

Scheme 2.3.2e Trifluoromethylation of azodicarboxylates

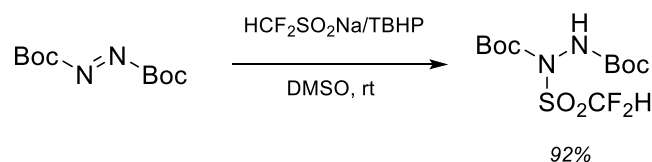
In addition, in the exploration of applicable scope for this condition, for diazenes with carboxamides, the complete decomposition was observed from 1,1'-(azodicarbonyl)-dipiperidine and no reaction occurred from the *tert*-butyl-2-(methyl(phenyl)carbamoyl) diazene-1-carboxylate and the *tert*-butyl-2-(phenylcarbamoyl) diazene-1-carboxylate.

From carboxamide diazenes



Scheme 2.3.2f Trifluoromethylation of other azodicarboxylates

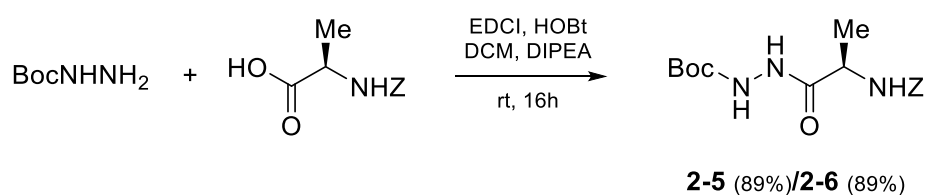
It seemed interesting to us to incorporate other fluorinated groups and in particular the CF₂H group. We, therefore, carried out the addition of sodium difluoromethylsulfinate on the azodicarboxylate and the TBHP. Unfortunately, under these conditions, only the compound possessing the CF₂HSO₂ group is detected (Scheme 2.3.2g). The use of metals such as iron, and copper catalysts led to the same product without a trace of the expected compounds. At this stage, we have not continued this study.



Scheme 2.3.2g Reaction of azodicarboxylate and HCF₂SO₂Na

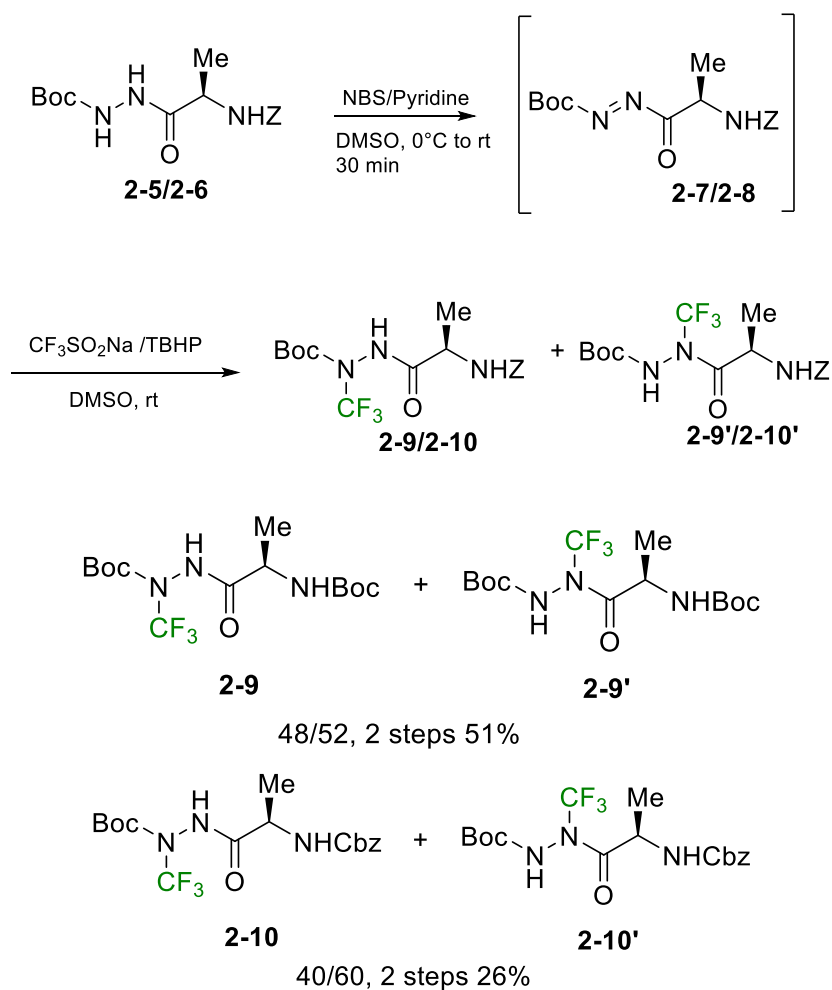
2.3.3 Access to new *N*-CF₃ peptidomimetic scaffolds

Hydrazine motifs are well-known and showcased abundant applications. In such many cases, hydrazines are often used to build peptidomimetics and induce conformations in peptides.^[35] We therefore set out to combine the *N*-CF₃ hydrazine with an amino acid. To access the diazenes **2-7~2-8**, which has never been reported, we first prepared the hydrazine Boc amino-acids **2-5~2-6** by classical peptide coupling between the *tert*-butyl carbazate and the alanine.



Scheme 2.3.3a Synthesis of Boc amino-acids

Then the hydrazides **2-5~2-6** were treated with NBS and pyridine in dichloromethane at 0°C or -78°C.^[36] Unfortunately, while the diazene was formed in the medium, it could not be isolated due to its instability. In order to avoid the isolation of the diazene, a one pot sequential reaction was then undertaken in dichloromethane. After total consumption of the hydrazides **2-5~2-6** into diazene with NBS and pyridine (30 min. at room temperature), DMSO and the TBHP were added and then the aqueous solution of the triflate **2-1**. Unfortunately, the mixture dichloromethane and DMSO as solvents led to a complex mixture of compounds. So, in order to avoid the presence of dichloromethane, we performed the one pot reaction only in DMSO. Thanks to these new conditions, the *N*-CF₃ hydrazines **2-9~2-9'** and **2-10~2-10'** could be obtained in 51 and 26% yield after two steps with a ratio of 48/52 and 40/60 respectively (Scheme 2.3.3b). Interestingly each regioisomers could be easily separated on silica gel. It should be noted that at the end of the reaction the starting hydrazines **2-5~2-6** are present and could be recovered after purification (15-27%).



Scheme 2.3.3b Trifluoromethylation of aminoacid-diazenes

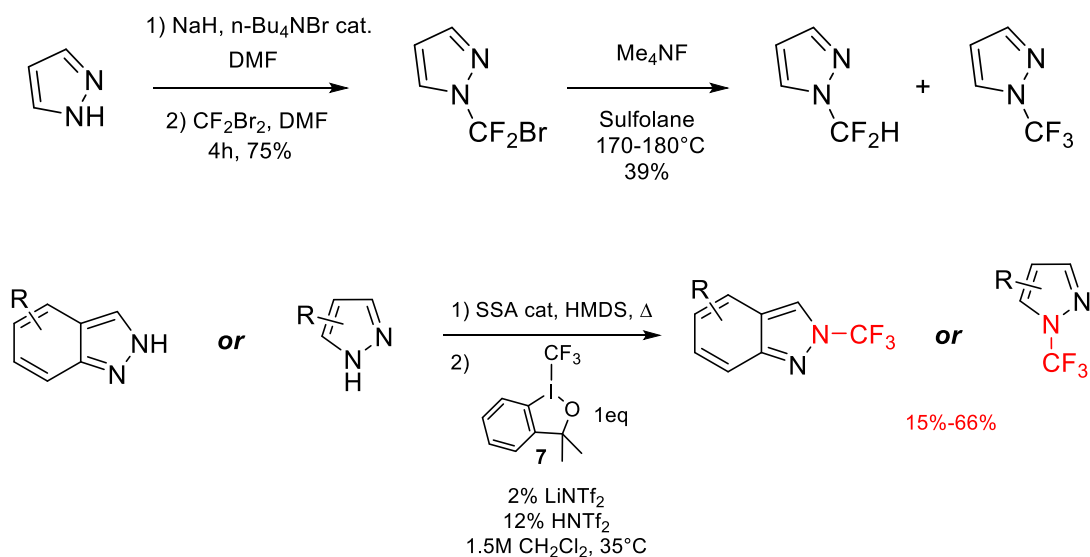
2.3.4 Deprotection of *N*-CF₃ hydrazine derivatives

We prepared different families of *N*-CF₃ compounds with protective groups such as Boc and Cbz. The other challenge is, therefore, obtaining deprotected *N*-CF₃ hydrazine building blocks to exploit them in the construction of new molecules.

- Deprotection of the hydrazine 2-3b

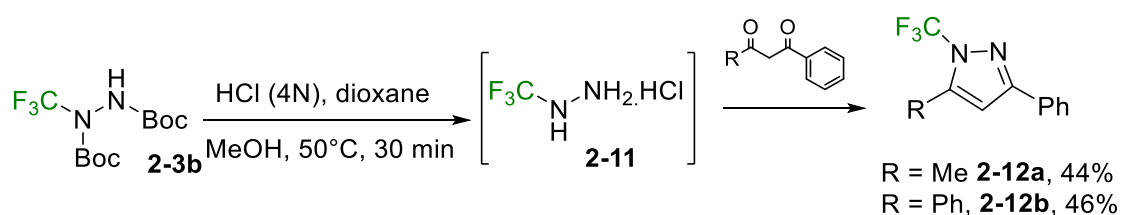
Accordingly, we attempted the deprotection of compound **2-3b** with HCl (4N in dioxane). Thankfully CF₃NHNH₂.HCl **2-11** was obtained and could be characterized but is too unstable to be stored for several days even at low temperatures. Thus, we attempted to synthesize *N*-CF₃ pyrazole in a one-pot approach. Pyrazoles are potent

medicinal scaffolds and exhibit a full spectrum of biological activities.^[37] To date, there are very few methods for accessing *N*-CF₃ pyrazoles. The first involves the use of CF₂Br₂, a known ozone-depleting reagent, followed by fluorination.^{[38]-[39]} The second involves the electrophilic *N*-trifluoromethylation of pyrazoles with Togni's reagent.^[11]



Scheme 2.3.4a Methods for accessing *N*-CF₃ pyrazoles

Thus **2-11** was trapped directly in the medium with 1,3-diones to give the corresponding *N*-CF₃ pyrazoles **2-12** in reasonable yields (Scheme 2.3.4b).^[40] Our new approach is an excellent alternative to the synthesis of *N*-CF₃ pyrazoles.

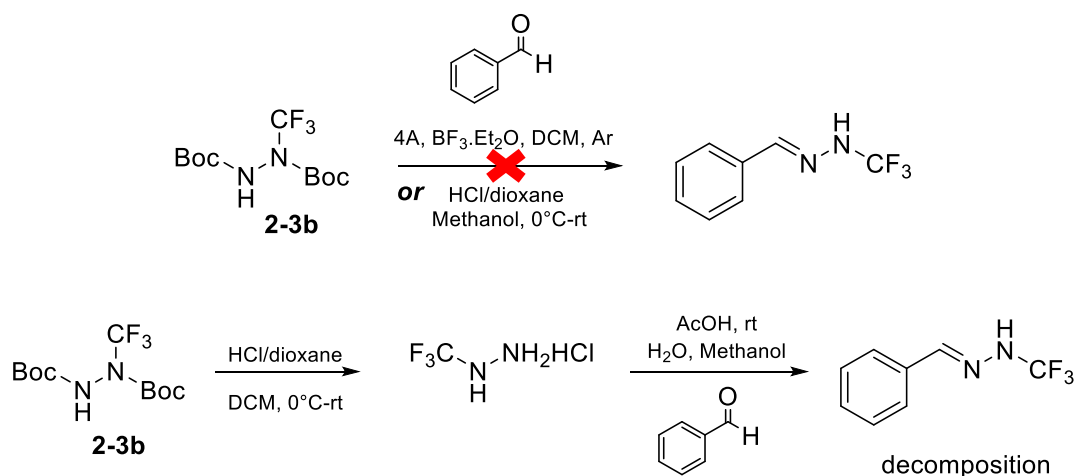


Scheme 2.3.4b Synthesis of *N*-CF₃ pyrazoles

In addition, recent studies have shown that the *N*-CF₃ pyrazoles have excellent stability in aqueous media, improved metabolic stability, and higher lipophilicity.^[41]

Alternatively, some attempts were also carried out with **2-3b** and benzaldehyde to

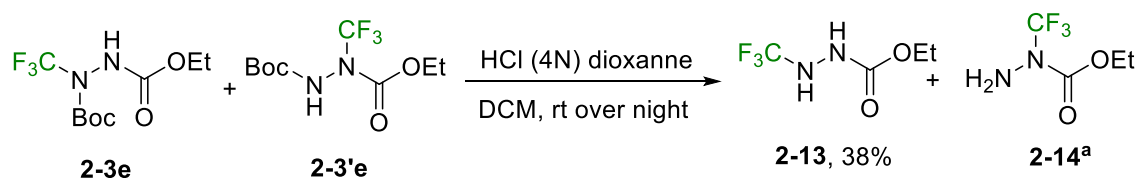
prepare fluorinated hydrazone as shown in Scheme 2.3.4c. However, in this process, decomposition always was detected (along with elimination of fluorine anion F⁻).



Scheme 2.3.4c Reaction of **2-3b** and benzaldehyde

- Deprotection of the unsymmetrical hydrazines

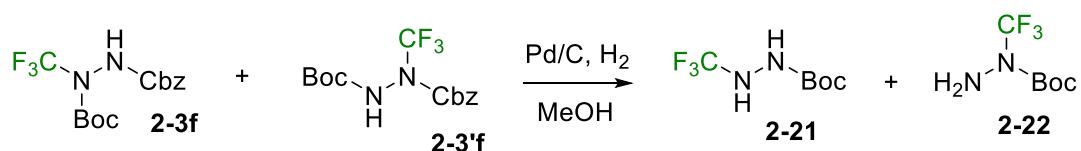
Then deprotection of the unsymmetrical *N*-CF₃ hydrazides (as a mixture of regioisomers) was carried out with HCl (4 N in dioxane) overnight (Scheme 2.3.4d). The Boc group could be removed to afford the clean and stable corresponding *N*-CF₃ hydrazides **2-13**~**2-20**. From the hydrazides **2-3e**/**2-3'e**, only the hydrazide **2-13**, which sublimes slowly at room temperature, could be recovered at the end of the reaction with a not optimized yield of 38%. Unfortunately, compound **2-14** is too volatile to be isolated, although detected in fluorine NMR at -60 ppm.



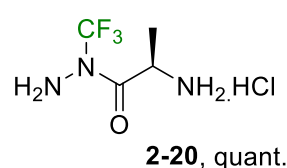
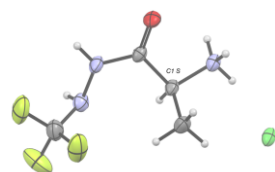
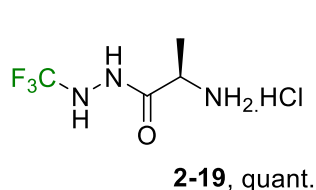
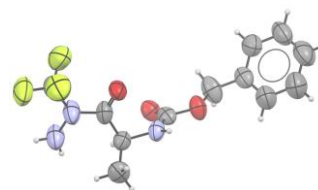
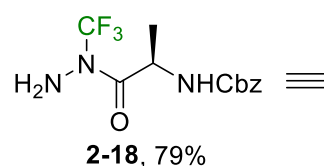
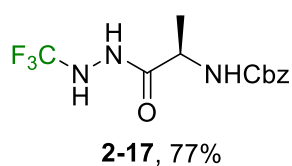
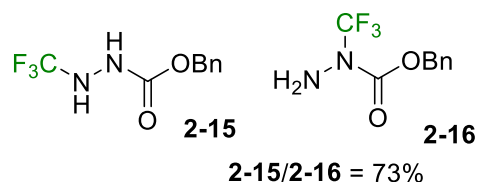
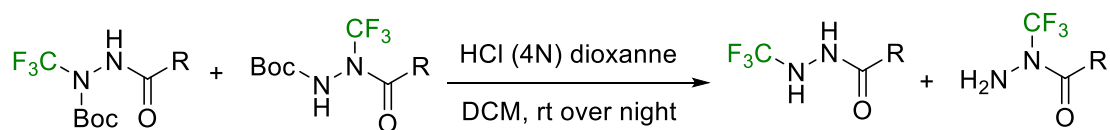
Scheme 2.3.4d Deprotection of the unsymmetrical hydrazines. [a] The hydrazine **2-14** was too volatile to be isolated

The *N*-debenzylation of the hydrazides **2-3f**/**2-3'f** was also carried out in the presence

of Pd/C under the atmosphere of H₂. The *N*-CF₃ hydrazide **2-21** was isolated in a moderate yield of 38% due to its sublimation. Product **2-22** was detected in the ¹⁹F NMR of the crude but is too volatile to obtain pure (Scheme 2.3.4e).

Scheme 2.3.4e Hydrogenolysis of **2-3f/2-3'f**

The products **2-3f/2-3'f** afforded the hydrazides **2-15** and **2-16** in good yield (73%), easily separated on silica gel. In the case of the amino acid-hydrazides **2-9/2-9'** and **2-10/2-10'**, each molecule has been treated independently to lead pure hydrazides **2-17**, **2-18**, and as chlorhydrate salts **2-19**, **2-20**, respectively.



Scheme 2.3.4f Deprotection under acid conditions

Chiral HPLC analysis of the hydrazines **2-17**, **2-18** showed no racemisation of the stereocenter of the amino acid following three reactions from **6**. We unambiguously determined the structure of molecules **2-18**, **2-19** thanks to the achievement of their X-ray analyses. By comparing the different X-ray analyses of compounds **2-3b**, **2-18** and **2-19**, the N–N–CF₃ length bond was observed in a range of 1.381–1.413 Å showing an interesting influence of the CF₃ group, while in the nonfluorinated derivatives, the length is around 1.454 Å.^[42]

We also investigated the potential interactions between N–H---F and C–H---F in *N*-CF₃ peptidomimetics **2-18**, **2-19**. For the molecule **2-19**, one fluorine atom strongly interacts with the NH proton close to the CF₃ showing a distance of 2.29 Å and an angle of 72.4° (Figure 2.3.4a). We can suppose an intramolecular H-Bond while the angle is below IUPAC standards ($\theta=110\text{--}180^\circ$). The other both fluorines also interact with hydrogen: one with both NH and one with the C–H of the methyl group. The distances are 2.56 Å and 2.61 Å for the NH---F and 2.43 Å for the C–H---F, respectively. Here also, a second intramolecular H-bond is observed with an angle of 152.06° (Figure 2.3.4a).

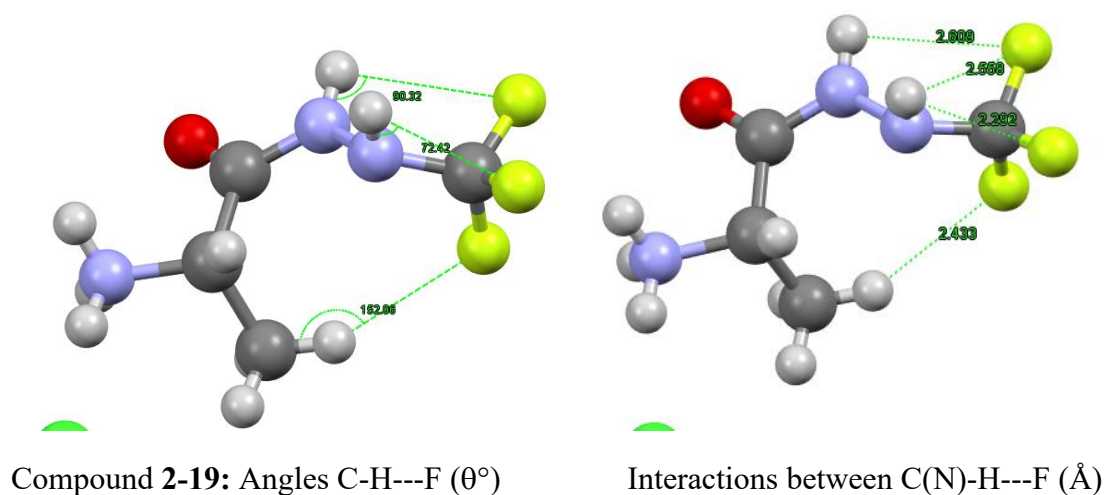
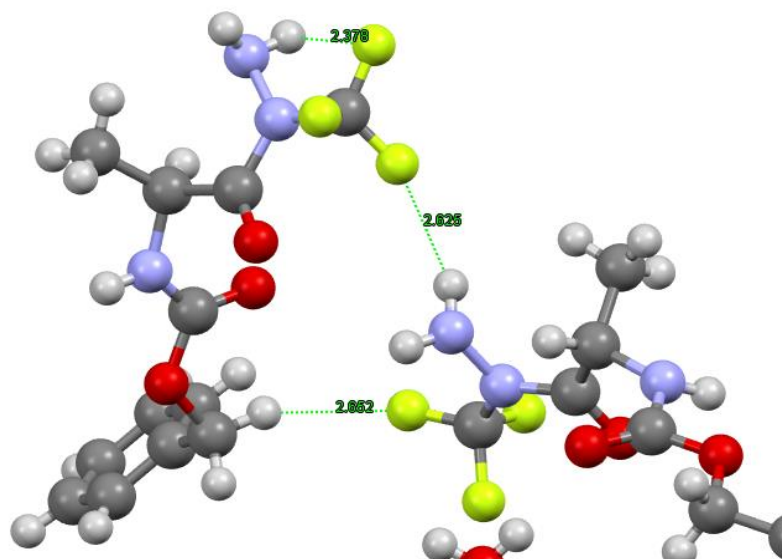


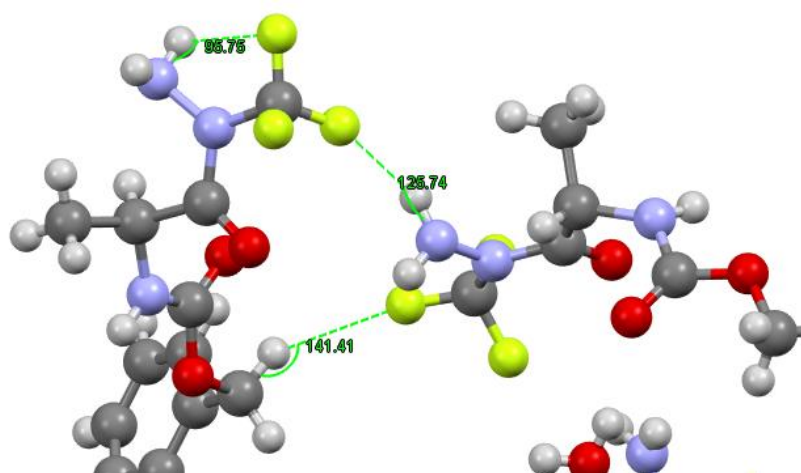
Figure 2.3.4a Intramolecular interaction of F---H-C(N)

Concerning compound **2-18**, one fluorine and one H of the NH₂ group interact to form an intramolecular hydrogen bond with a distance of 2.38 Å and an angle of 95.75° (Figure 2.3.4b). Otherwise, two main intermolecular interactions are observed between

one fluorine and the NH of NH₂ group (2.62 Å and $\theta = 125.7^\circ$) and one fluorine with the H of the CH₂ group of the benzyl (2.65 Å and $\theta = 141.4^\circ$) (Figure 2.3.4b).



Interactions C(N)-H...F (Å)



Angles C-H...F (θ°)

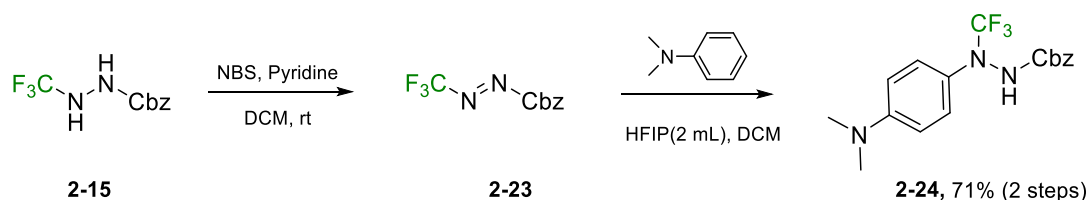
Figure 2.3.4b Intermolecular interaction of C(N)...F

These NH...F and C-H...F interactions have gained more and more interest, in particular, in medicinal chemistry either for protein-ligand interactions or for stabilizing particular conformations.^{[43]-[45]}

- Exploitation of *N*-CF₃ hydrazines to elaborate new compounds

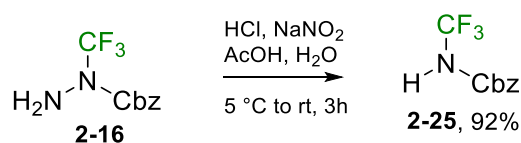
The potential of certain *N*-CF₃ hydrazides has been studied in some reactions to elaborate on the first-time inaccessible compounds. To illustrate their reactivity, we performed some reactions on the *N*-CF₃ hydrazides **2-15** and **2-16**.

First, the hydrazide **2-15** could be oxidized into diazene **2-23** after treatment with NBS and pyridine in DCM in quantitative yield. In our laboratory, we studied the potential of fluorinated solvent, particularly the 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) in this line, we realized the C-H amination of azodicarboxylate with electron rich arenes.^[46] Then, C-H amination was carried out between the *N*-CF₃- azodicarboxylate **2-23** and the *N*-dimethylaniline in HFIP to afford the corresponding hydrazine **2-24** with excellent regioselectivity and good yield (71% in 2 steps).



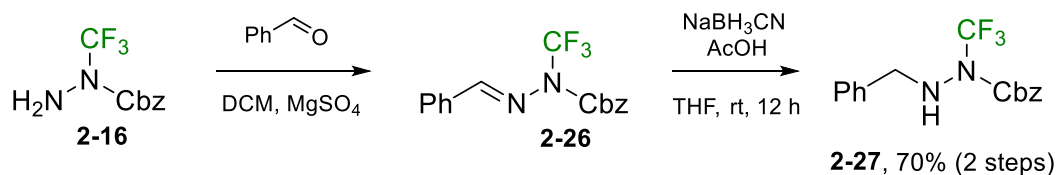
Scheme 2.3.4g Access to regioselective *N*-CF₃ hydrazine

Interestingly, from the hydrazide **2-16**, the benzyl (*N*-trifluoromethyl) carbamate **2-25** was obtained after treatment with sodium nitrite and HCl in dichloromethane, which is a stable form of the trifluoromethylamine (Scheme 2.3.4h).



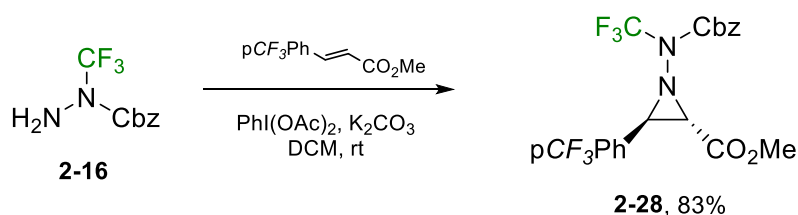
Scheme 2.3.4h Preparation of trifluoromethylamine

The benzyl hydrazide **2-27** was isolated after reduction of the corresponding hydrazone **2-26** formed from the benzaldehyde and **2-16** (Scheme 2.3.4i).



Scheme 2.3.4i Synthesis of new fluorinated hydrazine

The aziridination reaction^[47] could be realized easily in the presence of (diacetoxyiodo)benzene and the methyl *trans*-4-(trifluoromethyl) cinnamate to afford the *N*-CF₃ aminoaziridine **2-28** in excellent yield (83%).

Scheme 2.3.4j Reactivity of the 1-*N*-CF₃ hydrazide **2-16**

2.4 Conclusion

A new and efficient pathway to *N*-CF₃ hydrazides was prepared by adding of the CF₃ radical generated *in situ* from sodium triflinate on symmetric and unsymmetric azodicarboxylates. This reaction could also be carried out on diazenes comprising amino acids to afford regioisomers of *N*-CF₃ hydrazide peptidomimetics.

The *N*-CF₃ products with removable protecting groups could generate RCO-*N*(CF₃)-NH₂ and H-*N*(CF₃)-NHCOR hydrazines. These hydrazines could find applications in synthesising of new compounds, such as access to *N*-CF₃ pyrazoles, formation of *N*-CF₃ hydrazones, preparation of trifluoromethylamine as well as *N*-CF₃ aminoaziridine, alternatively, synthesis of excellent regioselective product in good yield.

Therefore, new *N*-CF₃ scaffolds have been developed, and these *N*-CF₃ hydrazine units have contributed to a new interesting family of *N*-CF₃.

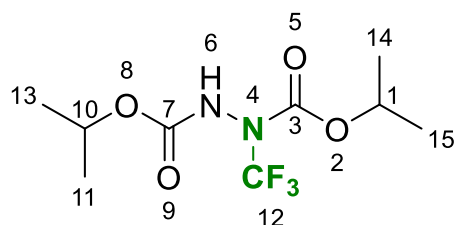
Experimental part

General Procedure (I)

1. Radical trifluoromethylation from symmetrical azodicarboxylates

To a stirred solution of azodicarboxylates (di-ethyl, isopropyl, tert-butyl, benzyl) (1.0 mmol) in DMSO (8 mL) and 70 % TBHP in water (1.5 mmol) was added at room temperature drop by drop the sodium triflinate (1.5 mmol) dissolved in water (2 mL). At the end of the addition, the yellow disappeared to give a colorless media. After that, 15 mL water was added, and the reaction mixture was extracted with ether (3×15 mL). The organic layers dried with Na₂SO₄ anhydrous and was evaporated under reduce pressure. The crude product was purified by column chromatography on silica gel using cyclohexane: ethyl acetate (100/0-70/30) as eluent to give corresponding *N*-CF₃ hydrazides.

Diisopropyl 1-(trifluoromethyl)hydrazine-1,2-dicarboxylate [2-3a]

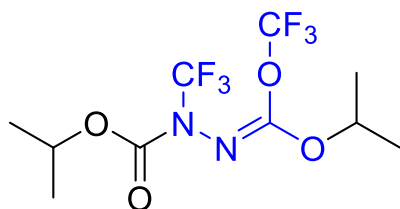


2-3a

2-3a was afforded from diisopropyl azodicarboxylate **2-2a** (202 mg, 1 mmol) which was treated with TBHP (192 mg, 1.5mmol) and sodium triflinate **2-1** (2mL, 1.5 mmol) in DMSO (8 mL) at rt following general procedure (I) as off-white solid (123 mg, 45% yield). ¹H NMR (300 MHz, CDCl₃) δ (ppm) 6.95 (s, 1H, H₆), 5.02-4.88 (m, 2H, H₁, H₁₀), 1.24 (d, *J* = 6.18 Hz, 6H, H_{methyl}), 1.20 (d, *J* = 6.60 Hz, 6H, H_{methyl}); ¹³C NMR (75 MHz, CDCl₃) δ (ppm) 154.9 (C₃), 151.2 (C₇), 120.1 (q, *J* = 261.9 Hz, C₁₂), 72.7 (C₁), 70.9 (C₁₀), 21.6 (C_{methyl}), 21.5 (C_{methyl}), 21.4 (C_{methyl}); ¹⁹F NMR (188 MHz, CDCl₃) δ (ppm) -59.63 (s, CF₃). HRMS *m/z* C₉H₁₅F₃N₂O₄ [M+Na]⁺ cal. 295.0882, found. 295.0875.

m.p. = 67-68°C.

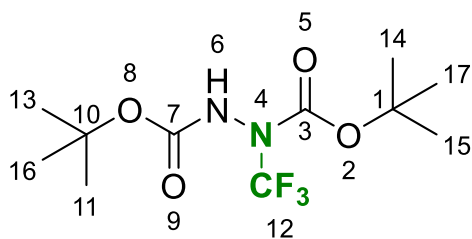
Isopropyl (Z)-2-(isopropoxy (trifluoromethoxy) methylene)-1-(trifluoromethyl) hydrazine-1-carboxylate [2-C]



2-C

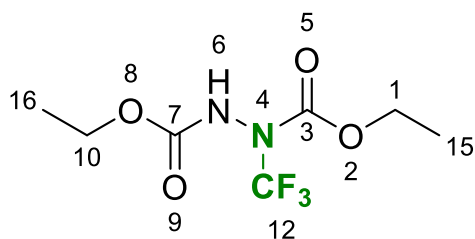
¹H NMR (200 MHz, CDCl₃) δ (ppm) 5.08 (m, 2H, H_{9,14}), 7.25-7.11 (m, 2H), 1.38-1.28 (m, 12H, H_{methyl}); ¹³C NMR (75 MHz, CDCl₃) δ (ppm) 153.2 (C₃), 148.7 (C₇), 122.8 (q, *J* = 264.6 Hz, C₁₀), 119.3 (q, *J* = 266.7 Hz, C₁₈), 75.0 (C₁₄), 74.5 (C₉), 21.4 (C_{methyl}), 21.3 (C_{methyl}); ¹⁹F NMR (188 MHz, CDCl₃) δ (ppm) -59.4 (brs, 1×CF₃), and -65.1 (q, *J* = 4.3 Hz, 1×CF₃).

Di-tert-butyl 1-(trifluoromethyl)hydrazine-1,2-dicarboxylate [2-3b]



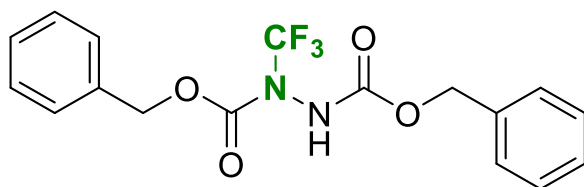
2-3b

2-3b was prepared from di-tert-butyl azodicarboxylate **2-2b** (690 mg, 3 mmol) which was treated with TBHP (405 mg, 4.5mmol) and sodium triflinate **2-1** (6mL, 4.5 mmol) in DMSO (24 mL) at rt following general procedure (I) as off-white solid (514 mg, 57% yield). ¹H NMR (300 MHz, CDCl₃) δ (ppm) 6.59 (br s, 1H, H₆), 1.52 (s, 9H, H_{methyl}), 1.49 (s, 9H, H_{methyl}). ¹³C NMR (75 MHz, CDCl₃) δ (ppm) 154.2 (C₃), 150.3 (C₇), 120.3 (q, *J* = 261.0 Hz, C₁₂), 84.9 (C₁), 82.5 (C₁₀), 27.9 (C_{methyl}), 27.8 (C_{methyl}). ¹⁹F NMR (188 MHz, CDCl₃) δ (ppm) -59.37 (s, CF₃). HRMS *m/z* C₁₁H₁₉F₃N₂O₄ [M+Na]⁺ cal. 323.1195, found. 323.1195. m.p. = 69-70°C.

Diethyl 1-(trifluoromethyl)hydrazine-1,2-dicarboxylate [2-3c]**2-3c**

(CF₃SO₂-N(CO₂Et)-NHCO₂Et was contained in it)

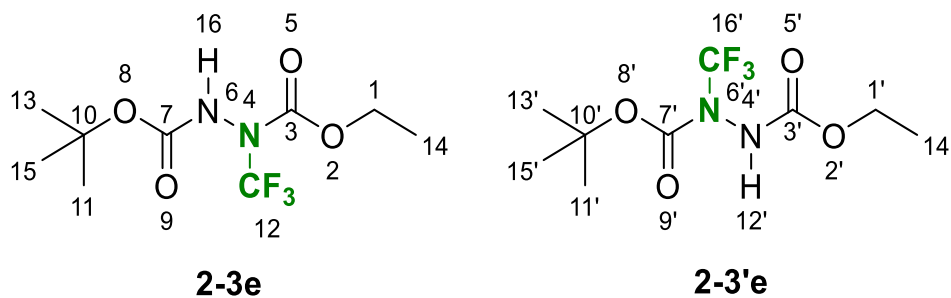
2-3c was prepared from diethyl azodicarboxylate **2-2c** (174 mg, 1 mmol) which was treated with TBHP (192 mg, 1.5 mmol) and sodium triflate **2-1** (2 mL, 1.5 mmol) in DMSO (8 mL) at rt following general procedure (I) (117 mg, 48% yield). ¹H NMR (300 MHz, CDCl₃) δ (ppm) 7.23 (s, 1H, H₆), 4.24 (q, *J* = 7.13 Hz, 2H, H₁), 4.16 (q, *J* = 7.05 Hz, 2H, H₁₀), 1.24 (t, *J* = 5.31 Hz, 3H, H₁₅), 1.21 (t, *J* = 5.21 Hz, 3H, H₁₆); ¹³C NMR (75 MHz, CDCl₃) δ (ppm) 155.4 (C₃), 151.7 (C₇), 120.0 (q, *J* = 262.2 Hz, C₁₂), 64.2 (C₁), 62.8 (C₁₀), 14.1 (C_{methyl}), 13.8 (C_{methyl}); ¹⁹F NMR (188 MHz, CDCl₃) δ (ppm) -59.71 (s, CF₃). HRMS *m/z* C₇H₁₁F₃N₂O₄ [M+Na]⁺ cal. 267.0569, found. 267.0564.

Dibenzyl 1-(trifluoromethyl) hydrazine-1,2-dicarboxylate [2-3d]**2-3d**

The title compound was prepared between diazene **3-2d** (298 mg, 1 mmol), TBHP (192 mg, 1.5 mmol) and triflate **3-1** (2 mL, 1.5 mmol) in DMSO (8 mL) at rt, and purified on silica gel (cyclohexane/EtOAc: 70/30) to afford **2-3d/2-4d** (69 mg, 19%).

2. Radical trifluoromethylation from asymmetrical azodicarboxylates

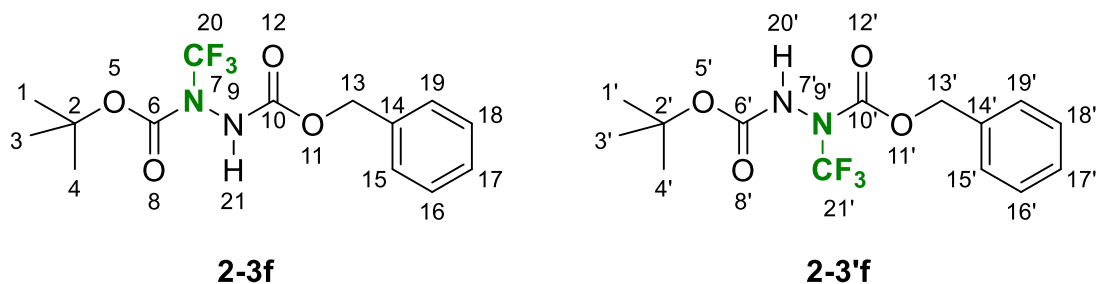
2-(Tert-butyl) 1-ethyl 1-(trifluoromethyl)hydrazine-1,2-dicarboxylate and 1-(tert-butyl) 2-ethyl 1-(trifluoromethyl)hydrazine-1,2-dicarboxylate [2-3e/2-3'e]



Firstly, *tert*-butyl carbazate (5.28 g, 40mmol) in Et₂O (200 mL) was added pyridine (3.48 g, 44mmol), followed by ethyl chloroformate (3.8 mL, 40 mmol) at 0°C. The mixture was stirred at 0°C for 50 minutes and warmed to room temperature for additional 50 minutes. Reaction was monitored by TLC. Subsequently, the mixture was treated with H₂O (20 mL), 5% HCl (20 mL) and 5% NaHCO₃ (20 mL) successively, organic phase was dried by NaSO₄ anhydrous. BocNH-NHCO₂Et (7.27 g, 89% yield) was afforded by purification of silica gel as white solid.

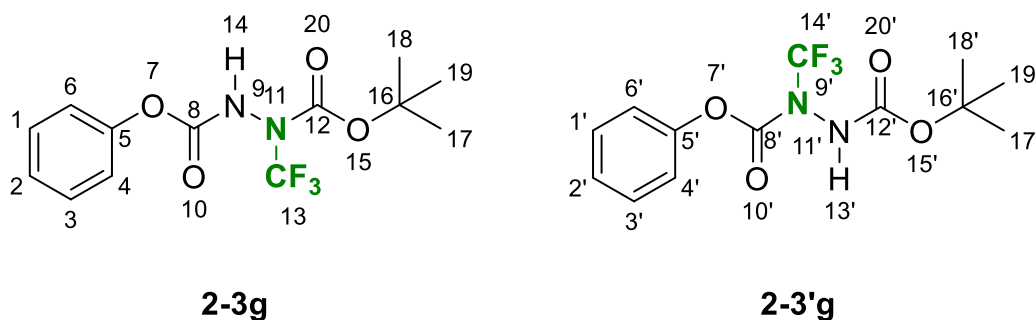
The title compound **2-3e/2-3'e** was prepared by BocNH-NHCO₂Et (202 mg, 1 mmol), NBS (196 mg, 1.1 mmol) and pyridine (87 mg, 1,1 mmol) in DCM, followed by TBHP (192 mg, 1.5 mmol) and sodium triflinate **2-1** (2 mL, 1.5 mmol) in DMSO (8 mL) at rt, and purified on silica gel (cyclohexane/EtOAc:100/0-70/30) to afford **2-3e/2-3'e** (141 mg, 49% yield) as liquid. ¹H NMR (300 MHz, CDCl₃) δ (ppm) 6.82 and 6.70 (s, 1H, H₁₆ and 12'), 4.25 and 4.16 (q, *J*_{4.25} = 7.01 Hz, *J*_{4.16} = 7.11 Hz, 2H, H₁ and 1'), 1.44 and 1.41 (s, 9H, H_{11,13,15} and 11', 13', 15'), 1.25 and 1.22 (t, *J*_{1.25} = 5.2 Hz, *J*_{1.22} = 5.1 Hz, 3H, H₁₄ and 14'). ¹³C NMR (75 MHz, CDCl₃) δ (ppm) 155.5 (C₃ and 7'), 154.1 (C_{3'} and 7), 120.3 and 120.1 (q, *J*_{120.3} = 262.0 Hz, *J*_{120.1} = 261.9 Hz, C₁₂ and 16'), 85.3 and 82.8 (C₁₀ and 10'), 64.1 and 62.7 (C₁ and 1'), 27.9 and 27.8 (C_{11,13,15} and 11', 13', 15'), 14.2 and 14.0 (C₁₄ and 14'). ¹⁹F NMR (188 MHz, CDCl₃) δ (ppm) -59.26 and -59.76 (s, CF₃). HRMS *m/z* C₉H₁₅F₃N₂O₄ [M+Na]⁺ cal. 295.0882, found. 295.0883.

2-Benzyl 1-(tert-butyl) 1-(trifluoromethyl)hydrazine-1,2-dicarboxylate and 1-benzyl 2-(tert-butyl) 1-(trifluoromethyl)hydrazine-1,2-dicarboxylate [2-3f/2-3'f]



CbzNH-NHBoc was first prepared by adding benzyl chloroformate (1.28 g, 7.57 mmol) into mixture of *tert* butyl carbazate (1.0 g, 7.57 mmol) and *N*-methyl morpholine (765 mg, 7.57 mg) in THF (50 mL) at 0°C as white solid (2.0 g, 99% yield). **2-3f/2-3'f** was afforded through BocNH-NHCbz (264 mg, 1 mmol), NBS (196 mg, 1.1 mmol) and pyridine (87 mg, 1.1 mmol) in DCM, followed by TBHP (192 mg, 1.5 mmol) and sodium triflate (2 mL, 1.5 mmol) in DMSO (8 mL) at rt, and purified on silica gel (cyclohexane/EtOAc:100/0-70/30), (138 mg liquid, 41% yield). **¹H NMR (300 MHz, CDCl₃)** δ (ppm) 7.39-7.10 (m, 5H, H_{arom}), 6.83 and 6.61 (s, 1H, H₂₁ and 20'), 5.25-5.11 (m, 2H, H₁₃ and 13'), 1.37 (s, 9H, H_{methyl}). **¹³C NMR (75 MHz, CDCl₃)** δ (ppm) 155.3 and 153.9 (C₆ and 10'), 151.7 and 150.1 (C_{6'} and 10), 135.2 and 134.4 (C₁₄ and 14'), 128.7 (C_{arom}), 128.6 (C_{arom}), 128.3 (C_{arom}), 120.3 and 120.1 (q, $J_{120,3}=261.8$ Hz, $J_{120,1}=262.7$ Hz, C₂₀ and 21'), 85.4 and 82.9 (C₂ and 2'), 69.5 and 68.3 (C₁₃ and 13'), 27.9 (C_{methyl}), 27.5 (C_{methyl}). **¹⁹F NMR (188 MHz, CDCl₃)** δ (ppm) -59.25 and -59.72 (s, CF₃). **HRMS m/z C₁₄H₁₇F₃N₂O₄ [M+Na]⁺ cal. 357.1038, found. 357.1034.**

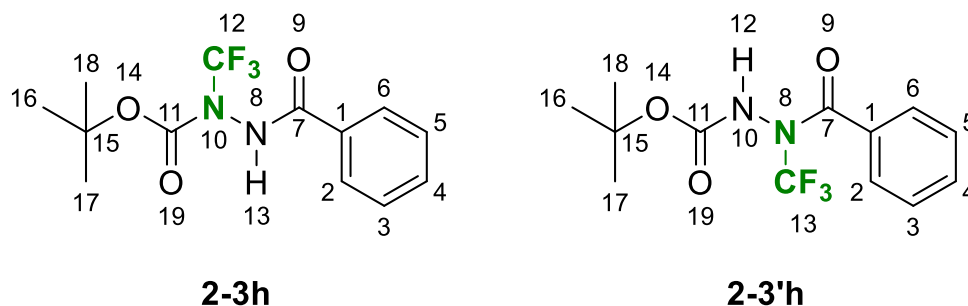
1-(*Tert*-butyl) 2-phenyl 1-(trifluoromethyl)hydrazine-1,2-dicarboxylate and 2-(*tert*-butyl) 1-phenyl 1-(trifluoromethyl)hydrazine-1,2-dicarboxylate [2-3g/2-3'g]



The title compound was prepared between diazene (BocNH=NHCO₂Ph, 250 mg, 1 mmol), TBHP (192 mg, 1.5 mmol) and sodium triflate (2 mL, 1.5 mmol) in DMSO

(8 mL) at rt, and purified on silica gel (cyclohexane/EtOAc: 100/0-70/30) to afford **2-3g/2-3'g** (94 mg, 29% yield). ¹H NMR (200 MHz, CDCl₃) δ (ppm) 7.54-7.32 (m, 3H, H_{arom}), 7.25-7.11 (m, 2H, H_{arom}), 6.99 and 6.69 (s, 1H, H₁₄ and 13'), 1.55 and 1.51 (s, 9H, H_{methyl}). ¹³C NMR (75 MHz, CDCl₃) δ (ppm) 153.1 (C_{8'} and 12), 152.9 (C₈ and 12'), 149.4 and 149.1 (C₅ and 5'), 128.6 (C_{arom}), 128.4 (C_{arom}), 125.6 (C_{arom}), 125.0 (C_{arom}), 120.1 (C_{arom}), 119.3 and 119.1 (q, *J*_{119,3} = 263.7 Hz, *J*_{119,1} = 265.6 Hz, C₁₃ and 14'), 84.7 (C₁₆ and 16'), 26.9 and 26.8 (C_{methyl}). ¹⁹F NMR (188 MHz, CDCl₃) δ (ppm) -59.09 and -59.88 (s, CF₃). HRMS *m/z* C₁₃H₁₅F₃N₂O₄ [M+Na]⁺ cal. 343.0882, found. 343.0873.

***Tert*-butyl 2-benzoyl-1-(trifluoromethyl)hydrazine-1-carboxylate and *tert*-butyl 2-benzoyl-2-(trifluoromethyl)hydrazine-1-carboxylate [2-3h/2-3'h]**

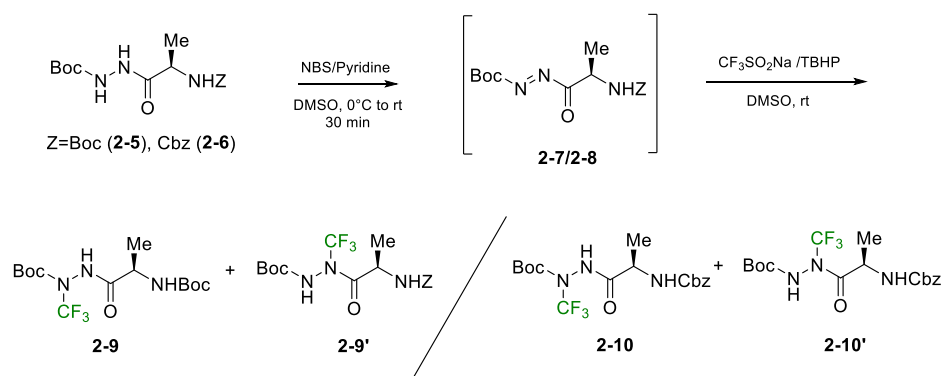


PhCONHNHBoc was obtained through stirring the mixture of benzohydrazide (1.36 g, 10 mmol) and di-*tert*-butyl dicarbonate ((Boc)₂O) (2.7 mL, 12mmol) in dichloromethane (50 mL) at room temperature (2.0 g, 85% yield, white solid). **2-3h/2-3'h** was prepared by PhCONHNHBoc (236 mg, 1mmol), NBS (196 mg, 1.1 mmol) and pyridine (87 mg, 1.1 mmol) in DCM, followed by TBHP (192 mg, 1.5 mmol) and sodium triflate (2 mL, 1.5 mmol) in DMSO (8 mL) at rt, and purified on silica gel (cyclohexane/EtOAc:100/0-70/30), (98 mg, 32% yield).

(-SO₂CF₃ inside, ¹H NMR and ¹³C NMR complex determination)

¹⁹F NMR (188 MHz, CDCl₃) δ (ppm) -58.88 and -61.02 (s, CF₃). HRMS *m/z* C₁₃H₁₅F₃N₂O₃ [M+NH₄]⁺ cal. 322.1379, found. 322.1382.

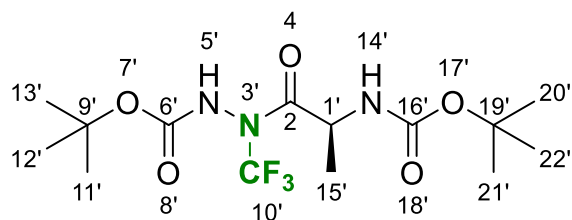
3. Preparation of *N*-CF₃ hydrazides 2-9/2-9' and 2-10/2-10' from hydrazines 2-5/2-6 via diazenes 2-7/2-8:



A stirred solution of hydrazides (**2-5/2-6**) and pyridine (1.1 eq.), in DMSO at 0 °C was treated with NBS (1.1 eq.) in a single portion. The reaction mixture was allowed to room temperature and stirred 5 min, and had changed to a pale yellow to give the diazene **2-7, 2-8**. Then at room temperature, TBHP (1.5 eq.) and drop by drop the triflate **2-1** (1.5 eq.) dissolved in water were added. At the end of the addition the yellow disappeared to give a colorless media. After, 15 mL of water was added, and the reaction mixture was extracted with ether (3×15mL). The organic phases dried on Na₂SO₄ was evaporated under reduce pressure. The crude product was purified by column chromatography on silica gel using cyclohexane: ethyl acetate (80/20) as the eluent to give *N*-CF₃ hydrazide **2-9, 2-9'** (51%), **2-10, 2-10'** (26%).

***Tert*-butyl 2-((*tert*-butoxycarbonyl)-*L*-alanyl)-2-(trifluoromethyl)hydrazine-1-carboxylate [**2-9'**] and *Tert*-butyl 2-((*tert*-butoxycarbonyl)-*L*-alanyl)-1-(trifluoromethyl)hydrazine-1-carboxylate [**2-9**]**

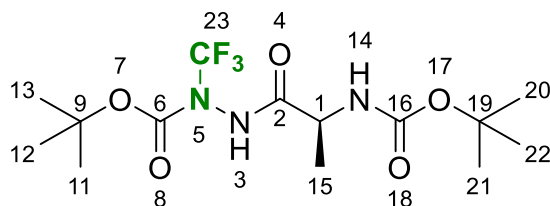
The title compounds **2-9, 2-9'** were prepared between hydrazine **2-5** (303 mg, 1 mmol), NBS (196 mg, 1.1mmol), pyridine (87 mg, 1.1mmol) in DMSO (10 mL), then TBHP (192 mg, 1.5 mmol) and triflate **2-1** (234 mg, 1.5 mmol) dissolved in water (2 mL), and purified on silica gel (cyclohexane/EtOAc: 80/20).



2-9'

¹H NMR (300 MHz, CDCl₃) δ (ppm) 8.18 (s, 1H, H_{5'}), 5.35 (s, 1H, H_{14'}), 4.66 (q,

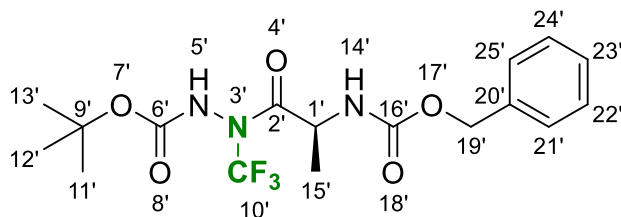
$J=7.19$ Hz, 1H, H_{1'}), 1.42 and 1.41 (s, 9H, H_{methyl}), 1.35 and 1.33 (s, 9H, H_{methyl}), 1.26 (d, $J=6.9$ Hz, 3H, H_{15'}). ¹³C NMR (75 MHz, CDCl₃) δ (ppm) 174.6 (C_{2'}), 155.6 (C_{6'}), 154.2 (C_{16'}), 119.6 (q, $J=267.1$ Hz, C_{10'}), 82.9 (C_{19'}), 80.4 (C_{9'}), 47.2 (C_{1'}), 28.1 (C_{methyl}), 27.9 (C_{methyl}), 17.3 (C_{15'}). ¹⁹F NMR (188 MHz, CDCl₃) δ (ppm) (mixture of rotational isomers) -60.62 (s, CF₃), -60.59 (s, CF₃). HRMS m/z C₁₄H₂₄F₃N₃O₅ [M+Na]⁺ cal. 394.1566, found. 394.1569. $[\alpha]_D^{20} = +15.0^\circ$ (c 0.0373, CH₃OH).

**2-9**

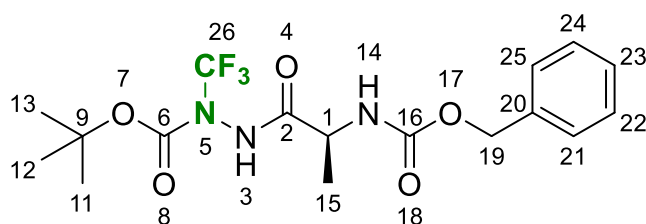
¹H NMR (300 MHz, CDCl₃) δ (ppm) 9.11 (s, 1H, H₃), 5.31-5.25 (brs, 1H, H₁₄), 4.32 (m, 1H, H₁), 1.41 (s, 9H, H_{methyl}), 1.36 (s, 9H, H_{methyl}), 1.31 (d, $J=4.8$ Hz, 3H, H₁₅). ¹³C NMR (75 MHz, CDCl₃) δ (ppm) 172.2 (C₂), 155.9 (C₆), 149.7 (C₁₆), 120.2 (q, $J=265.4$ Hz, C₂₃), 84.8 (C₉), 80.7 (C₁₉), 48.1 (C₁), 28.2 (C_{methyl}), 27.8 (C_{methyl}), 17.7 (C₁₅). ¹⁹F NMR (188 MHz, CDCl₃) δ (ppm) -59.17 (s, CF₃). HRMS m/z C₁₄H₂₄F₃N₃O₅ [M+Na]⁺ cal. 394.1566, found. 394.1573. $[\alpha]_D^{20} = -27.3^\circ$ (c 0.0386, CH₃OH).

***Tert*-butyl 2-(((benzyloxy)carbonyl)-L-alanyl)-2-(trifluoromethyl)hydrazine-1-carboxylate [2-10'] and *Tert*-butyl 2-(((benzyloxy)carbonyl)-L-alanyl)-1-(trifluoromethyl)hydrazine-1-carboxylate [2-10]**

The title compounds **2-10**, **2-10'** were prepared between hydrazine **2-6** (337 mg, 1 mmol), NBS (196 mg, 1.1mmol), pyridine (87mg, 1.1mmol) in DMSO (10 mL), then TBHP (192 mg, 1.5 mmol) and triflinate **2-1** (234 mg, 1.5 mmol) dissolved in water (2 mL), and purified on silica gel (cyclohexane/EtOAc: 80/20).

**2-10'**

¹H NMR (300 MHz, CD₃OD) δ (ppm) 7.36-7.28 (m, 5H, H_{arom}), 5.09 (m, 2H, H_{19'}), 4.68 (q, *J* = 7.15 Hz, 1H, H_{1'}), 1.52 (s, 9H, H_{methyl}), 1.37 and 1.32 (d, *J*₁ = 7.14 Hz, *J*₂ = 7.05 Hz, 3H, H_{15'}). **¹³C NMR (75 MHz, CD₃OD)** δ (ppm) 175.9 (C_{2'}), 175.5 (C_{2'}), 158.2 (C_{6'} and 16'), 138.1 (C_{20'}), 129.5 (C_{arom}), 129.0 (C_{arom}), 128.8 (C_{arom}), 121.4 (q, *J* = 265.4 Hz, C_{10'}), 83.6 (C_{9'}), 67.8 (C_{19'}), 49.5 (C_{1'}), 28.4 (C_{methyl}), 16.9 (C_{15'}). **¹⁹F NMR (188 MHz, CDCl₃)** δ (ppm) (mixture of rotational isomers) -59.45 (brs, CF₃), -60.30 (s, CF₃), -60.56 (s, CF₃). **HRMS** *m/z* C₁₇H₂₂F₃N₃O₅ [M+Na]⁺ cal. 428.1409, found. 428.1416. [α]_D²⁰ = +23.6° (*c* 0.0233, CH₃OH).



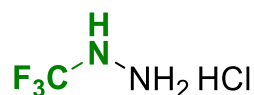
2-10

¹H NMR (300 MHz, CD₃OD) δ (ppm) 7.25-7.16 (m, 5H, H_{arom}), 4.98 (m, 2H, H₁₉), 4.14 (q, *J* = 9.24 Hz, 1H, H₁), 1.39 and 1.36 (s, 9H, H_{methyl}), 1.29 and 1.26 (d, *J* = 4.41 Hz, *J* = 4.35 Hz, 3H, H₁₅). **¹³C NMR (75 MHz, CD₃OD)** δ (ppm) 174.8 (C₂), 158.2 (C₆), 151.2 (C₁₆), 138.1 (C₂₀), 129.5 (C_{arom}), 129.0 (C_{arom}), 128.9 (C_{arom}), 121.7 (q, *J* = 260.5 Hz, C₂₆), 85.9 (C₉), 67.7 (C₁₉), 50.5 (C₁), 28.1 (C_{methyl}), 18.1 (C₁₅). **¹⁹F NMR (188 MHz, CDCl₃)** δ (ppm) (mixture of rotational isomers) -59.08 (s, CF₃). **HRMS** *m/z* C₁₇H₂₂F₃N₃O₅ [M+Na]⁺ cal. 428.1409, found. 428.1401. [α]_D²⁰ = -37.6° (*c* 0.0086, CH₃OH).

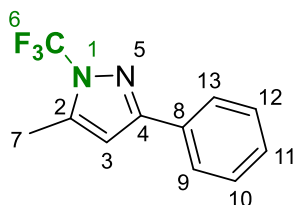
General Procedure (II)

1. Deprotection of Hydrazide [2-3b] and Synthesis of pyrazole [2-12]

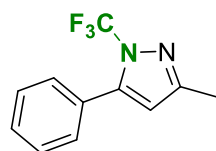
(Trifluoromethyl)hydrazine hydrochloride [2-11]

**2-11**

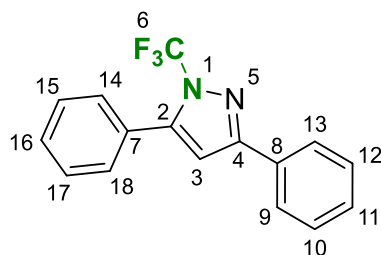
At a solution of *N*-CF₃ hydrazide **2-3b** (300 mg, 1 mmol) in dichloromethane (10 mL) was added HCl 4N in dioxane (10 eq.) at 0°C. After stirring overnight, the solvents are evaporated to afford crude solid (quantitative yield). ¹H NMR (300 MHz, CDCl₃) δ (ppm) 5.36 (brs, 4H). ¹³C NMR (75 MHz, CD₃OD) δ (ppm) 124.0 (q, *J* = 259.9 Hz). ¹⁹F NMR (188 MHz, CD₃OD) δ (ppm) -66.63 (s, CF₃). HRMS compound instable.

5-Methyl-3-phenyl-1-(trifluoromethyl)-1H-pyrazole [2-12a]**2-12a**

At a solution of *N*-CF₃ hydrazide **2-3b** (326 mg, 1.1 mmol) and 1-phenyl-1,3-butanedione (162 mg, 1 mmol) in MeOH (8 ml) was added HCl 4N in dioxane (4 mL) at 0°C. The mixture was stirred for 10 minutes at room temperature, then placed in a 60°C oil-bath for 30 minutes, the solution of reaction was concentrated and crude product partitioned between CH₂Cl₂ and NaHCO₃(aq), and the organic phase was separated and washed with NaCl (aq). The organic extract was dried (Na₂SO₄), filtered and concentrated. The compound was purified on silica gel to give pyrazole **2-12a** as a pale-yellow liquid (101 mg, 44% yield). ¹H NMR (300 MHz, CDCl₃) δ (ppm) 7.35-7.24 (m, 5H, H_{arom}), 6.09 (s, 1H, H₃), 2.23 (s, 3H, H₇). ¹³C NMR (75 MHz, CDCl₃) δ (ppm) 151.8 (C₄), 145.6 (C₂), 129.3 (C₈), 128.9 (C_{arom}), 128.3 (C_{arom}), 126.1 (C_{arom}), 118.7 (q, *J* = 262.1 Hz, C₆), 111.1 (C₃), 13.4 (C₇). ¹⁹F NMR (188 MHz, CDCl₃) δ (ppm) -54.90 (s, CF₃) and -57.61 (s, CF₃, *isomer). HRMS *m/z* C₁₁H₉F₃N₂ [M+H]⁺ cal. 227.0796, found. 227.0804.



* isomer

3,5-Diphenyl-1-(trifluoromethyl)-1H-pyrazole [2-12b]**2-12b**

At a solution of *N*-CF₃ hydrazide **2-3b** (122 mg, 0.41 mmol) and 1,3-diphenyl-1,3-propanedione (82 mg, 0.37 mmol) in MeOH (3 mL) was added HCl 4N in dioxane (1.5 mL) at 0°C. The mixture was stirred for 10 minutes at room temperature, then placed in a 60°C oil-bath for 30 minutes, the solution of reaction was concentrated and crude product partitioned between CH₂Cl₂ and NaHCO₃ (aq), and the organic phase was separated and washed with NaCl (aq). The organic layer was dried (Na₂SO₄), filtered and concentrated. The compound was purified on silica gel to give pyrazole **2-12b** as a colorless liquid (49 mg, 46% yield).

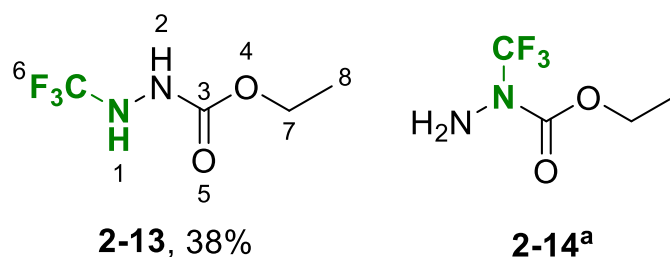
¹H NMR (300 MHz, CDCl₃) δ (ppm) 7.78 (m, 2H, H_{arom}), 7.37-7.29 (m, 8H, H_{arom}), 6.60 (s, 1H, H₃). ¹³C NMR (75 MHz, CDCl₃) δ (ppm) 153.7 (C₄), 146.0 (C₂), 131.0 (C₈ and 7), 129.6 (C_{arom}), 129.1 (C_{arom}), 129.04 (C_{arom}), 128.8 (C_{arom}), 128.4 (C_{arom}), 128.39 (C_{arom}), 126.3 (C_{arom}), 118.9 (q, *J* = 262.9 Hz, C₆), 108.2 (C₃). ¹⁹F NMR (188 MHz, CDCl₃) δ (ppm) -54.88 (s, CF₃). HRMS *m/z* C₁₆H₁₁F₃N₂ [M+H]⁺ cal. 289.0953, found. 289.0952.

2. Boc group deprotection

At a solution of *N*-CF₃ hydrazide in dichloromethane was added HCl 4N in dioxane (10 eq.) at 0°C. After stirring at room temperature overnight, the solvents are evaporated to afford crude as chlorhydrate salt or neutral compound which are or not purified on silica

gel.

Ethyl 2-(trifluoromethyl)hydrazine-1-carboxylate [2-13] and Ethyl 1-(trifluoromethyl)hydrazine-1-carboxylate [2-14]



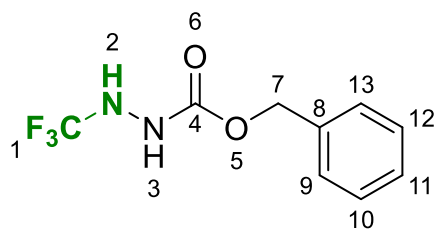
The title compounds **2-13** and **2-14** were prepared between hydrazine **2-3e/2-3'e** (544 mg, 2 mmol), in DCM (20 mL), then HCl 4N (5 ml, 20 mmol), and purified on silica gel (cyclohexane/EtOAc: 80/20).

[2-13]: ¹H NMR (200 MHz, CDCl₃) δ (ppm) 6.20 (brs, 1H, H₂), 5.32 (s, 1H, H₁), 4.23 (q, *J*= 7.1 Hz, 2H, H₇), 1.29 (t, *J*= 7.1 Hz, 3H, H₈). ¹³C NMR (75 MHz, CD₃OD) δ (ppm) 159.3 (C₃), 124.7 (q, *J*= 255.1 Hz, C₆), 62.7 (C₇), 14.8 (C₈). ¹⁹F NMR (188 MHz, CDCl₃) δ (ppm) -67.20 (d, *J*= 6.2 Hz, CF₃). ¹⁹F NMR (188 MHz, CD₃OD) δ (ppm) -67.70 (s, CF₃). HRMS *m/z* C₄H₇F₃N₂O₂ [M+H]⁺ cal. 173.0521, found. 173.0565. m.p. = 92-93°C.

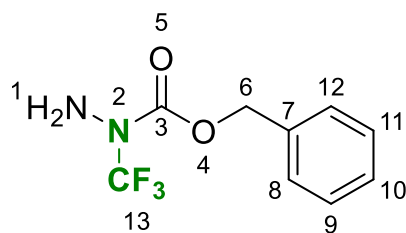
[2-14]: ¹⁹F NMR (188 MHz, CDCl₃) δ (ppm) -60.20 (s, CF₃). The product is volatile, spectra of crude in mixture with **[2-13]**

Benzyl 2-(trifluoromethyl)hydrazine-1-carboxylate [2-15] and benzyl 1-(trifluoromethyl)hydrazine-1-carboxylate [2-16]

The compounds **[2-15]** and **[2-16]** were prepared between hydrazine **2-3f/2-3'f** (334 mg, 1 mmol), in DCM (10 mL), then HCl 4N (2.5 mL, 10 mmol), purified and separated on silica gel (cyclohexane/EtOAc: 70/30) to afford **[2-15]** (81 mg, 35 %, white solid) and **[2-16]** (88 mg, 38 %, colorless oil) in global 73% yield.

**2-15**

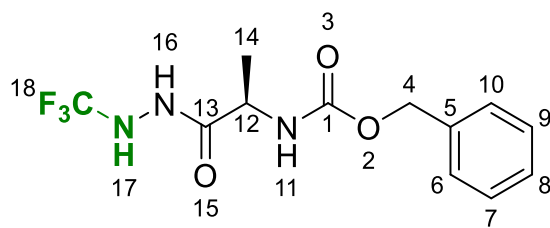
¹H NMR (200 MHz, CDCl₃) δ (ppm) 7.45-7.32 (m, 5H, H_{arom}), 6.35 (s, 1H, H₃), 5.40 (s, 1H, H₂), 5.21 (s, 2H, H₇). ¹H NMR (300 MHz, CD₃OD) δ (ppm) 7.38-7.2 (m, 5H, H_{arom}), 5.15 (s, 2H, H₇). ¹³C NMR (75 MHz, CD₃OD) δ (ppm) 159.2 (C₄), 137.7 (C₈), 129.5 (C_{arom}), 129.2 (C_{arom}), 128.9 (C_{arom}), 124.8 (q, *J* = 255.0 Hz, C₁), 68.3 (C₇). ¹⁹F NMR (188 MHz, CDCl₃) δ (ppm) -67.10 (d, *J* = 6.19 Hz, CF₃). HRMS *m/z* C₉H₉F₃N₂O₂ [M-H]⁻ cal. 233.0538, found. 233.0536. m.p. = 114-115°C.

**2-16**

¹H NMR (300 MHz, CDCl₃) δ (ppm) 7.45-7.35 (m, 5H, H_{arom}), 5.30 (s, 2H, H₆), 4.17 (brs, 2H, H₁). ¹³C NMR (75 MHz, CDCl₃) δ (ppm) 154.2 (C₃), 134.7 (C₇), 128.7 (C_{arom}), 128.4 (C_{arom}), 128.1 (C_{arom}), 120.7 (q, *J* = 259.4 Hz, C₁₃), 69.3 (C₆). ¹⁹F NMR (188 MHz, CDCl₃) δ (ppm) -59.99 (s, CF₃). HRMS *m/z* C₉H₉F₃N₂O₂ [M+Na]⁺ cal. 257.0514, found. 257.0489.

Benzyl (R)-(1-oxo-1-(2-(trifluoromethyl)hydrazineyl)propan-2-yl)carbamate [2-17] and benzyl (R)-(1-oxo-1-(1-(trifluoromethyl)hydrazineyl)propan-2-yl)carbamate [2-18]

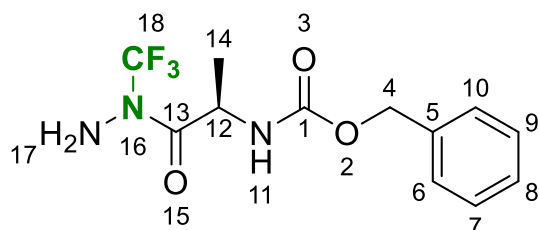
The title compounds **2-17** was prepared between hydrazine **2-10** (138 mg, 0.34 mmol), in DCM (5 mL), then HCl 4N (0.9 ml, 3.4 mmol), and obtained in 77% (80 mg) yield and in excellent purity without purification (presence of conformers and some traces of side products could not be removed).

**2-17**

¹H NMR (300 MHz, CD₃OD) δ (ppm) 7.36-7.29 (m, 5H, H_{arom}), 5.1 (s, 2H, H₄), 4.19 (q, *J* = 6.9 Hz, 1H, H₁₂), 1.36 (d, *J* = 6.96 Hz, 3H, H₁₄). **¹³C NMR (75 MHz, CD₃OD)** δ (ppm) 175.5/174.2 (C₁₃), 158.2 (C₁), 138.1 (C₅), 129.4 (C_{arom}), 129.0 (C_{arom}), 128.8 (C_{arom}), 124.5 (q, *J* = 256.0 Hz, C₁₈), 67.8/67.7 (C₄), 50.5/50.6 (C₁₂), 18.3 (C₁₄). **¹⁹F NMR (188 MHz, CD₃OD)** δ (ppm) -67.2 (s, CF₃). **HRMS** *m/z* C₁₂H₁₄F₃N₃O₃ [M+Na]⁺ cal. 328.0885, found. 328.0880. [α]_D²⁰ = -10.6° (*c* 0.036, CH₃OH).

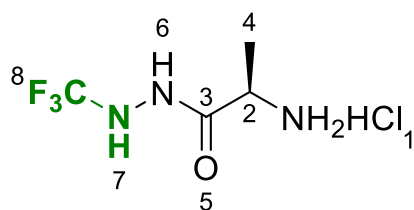
Benzyl (*R*)-1-oxo-1-(1-(trifluoromethyl)hydrazineyl)propan-2-yl carbamate [2-18]

2-18 was prepared between hydrazine **2-10'** (200 mg, 0.49 mmol), in DCM (5 mL), then HCl 4N (1.3 ml, 4.9 mmol), and obtained in 79% (118 mg) yield and in excellent purity without purification.

**2-18**

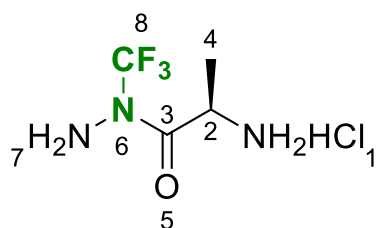
¹H NMR (300 MHz, CDCl₃) δ (ppm) 7.50-7.18 (m, 5H, H_{arom}), 5.60 (brs, 1H, H₁₁), 5.10 (m, 3H, H₄ and 12), 4.25 (brs, 2H, H₁₇), 1.39 (d, *J* = 6.84 Hz, 3H, H₁₄). **¹³C NMR (75 MHz, CDCl₃)** δ (ppm) 175.0 (C₁₃), 155.7 (C₁), 136.3 (C₅), 128.5 (C_{arom}), 128.2 (C_{arom}), 128.0 (C_{arom}), 120.5 (q, *J* = 264.2 Hz, C₁₈), 66.9 (C₄), 48.6 (C₁₂), 18.4 (C₁₄). **¹⁹F NMR (188 MHz, CDCl₃)** δ (ppm) -61.28 (s, CF₃). **HRMS** *m/z* C₁₂H₁₄F₃N₃O₃ [M+H]⁺ cal. 306.1066, found. 306.1065. m.p. = 89-90°C. [α]_D²⁰ = -5.6° (*c* 0.078, CH₃OH).

(*R*)-2-amino-*N'*-(trifluoromethyl)propanehydrazide hydrochloride [2-19]

**2-19**

2-19 was prepared between hydrazine **2-9** (295 mg, 0.79 mmol), in DCM (8 mL), then HCl 4N (2 ml, 7.9 mmol), and obtained in quantitative yield as salt (some side products could not be removed). ¹H NMR (300 MHz, CD₃OD) δ (ppm) 4.0 (q, *J*=7.0 Hz, 1H, H₂), 1.54 (d, *J*=7.08 Hz, 3H, H₄). ¹³C NMR (75 MHz, CD₃OD) δ (ppm) 171.3 (C₃), 124.4 (q, *J*=256.5 Hz, C₈), 49.2 (C₂), 17.5 (C₄). ¹⁹F NMR (188 MHz, CD₃OD) δ (ppm) -67.08 (s, CF₃). HRMS *m/z* C₄H₈F₃N₃O [M+H]⁺ cal. 172.0698, found. 172.0690.

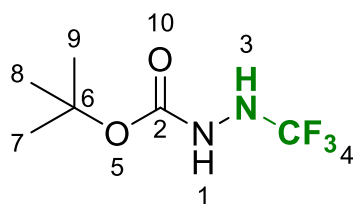
(*R*)-2-amino-N-(trifluoromethyl)propanehydrazide hydrochloride [2-20]

**2-20**

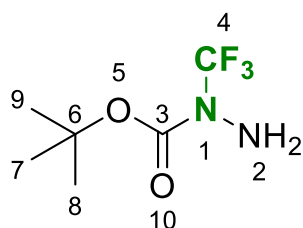
Compounds **2-20** was prepared between hydrazine **2-9'** (392 mg, 1.06 mmol), in DCM (10 mL), then HCl 4N (2.6 ml, 10.6 mmol), and obtained in quantitative yield as salt. ¹H NMR (300 MHz, CD₃OD) δ (ppm) 4.8 (m, 1H, H₂), 1.64 (d, *J*= 6.9 Hz, 3H, H₄). ¹³C NMR (75 MHz, CD₃OD) δ (ppm) 173.7 (C₃), 121.8 (q, *J*= 264.4 Hz, C₈), 50.1 (C₂), 16.3 (C₄). ¹⁹F NMR (188 MHz, CD₃OD) δ (ppm) -63.11 (s, CF₃). HRMS *m/z* C₄H₈F₃N₃O [M+H]⁺ cal. 172.0698, found. 172.0691.

3. Deprotection of the Cbz group with hydrogen of hydrazides 2-3g/2-3'g

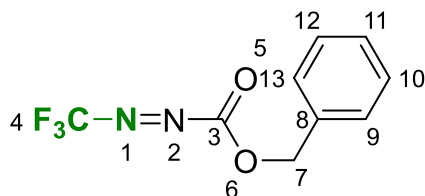
At a solution of hydrazides **2-3g/2-3'g** (334 mg, 1 mmol) in 10 mL methanol under hydrogen (1 atm) was added Pd/C 10%-15% (33 mg). After 3 h at room temperature, the mixture was filtered on celite and washed with ether. The solvents were evaporated under low pressure. The crude was purified on silica gel (eluent Cyclohexane/ether: 90/10) to afford **2-21** in 38% (76 mg). Compound **2-22** is too volatile to give a yield.

***Tert*-butyl 2-(trifluoromethyl)hydrazine-1-carboxylate [2-21]****2-21**

¹H NMR (300 MHz, CDCl₃) δ (ppm) 6.14 (s, 1H, H₁), 5.39 (s, 1H, H₃), 1.50 (s, 9H, H_{methyl}). ¹³C NMR (75 MHz, CD₃OD) δ (ppm) 158.3 (C₂), 124.8 (q, *J* = 254.8 Hz, C₄), 81.8 (C₆), 28.54 (C_{methyl}). ¹⁹F NMR (188 MHz, CDCl₃) δ (ppm) -67.2 (s, CF₃). m.p. = 99-100°C.

***Tert*-butyl 1-(trifluoromethyl)hydrazine-1-carboxylate [2-22]****2-22**

Presence of compound 2-21. ¹H NMR (300 MHz, CDCl₃) δ (ppm) 4.0 (s, 2H, H₂), 1.52 (s, 9H, H_{methyl}). ¹³C NMR (75 MHz, CDCl₃) δ (ppm) 153.1 (C₃), 120.9 (q, *J* = 258.8 Hz, C₄), 84.8 (C₆), 27.9 (C_{methyl}). ¹⁹F NMR (188 MHz, CDCl₃) δ (ppm) -59.57 (s, CF₃).

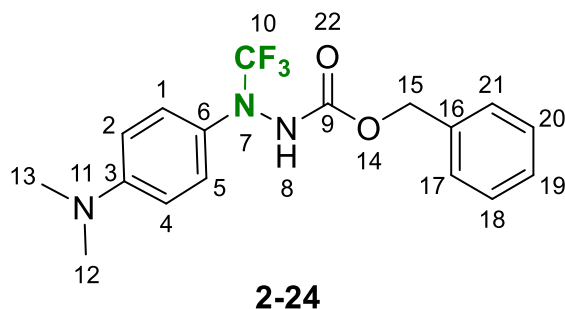
4. Reaction with the compound 2-15**Benzyl 2-(trifluoromethyl)diazene-1-carboxylate [2-23]****2-23**

In CH₂Cl₂ solvent. ¹⁹F NMR (188 MHz, CDCl₃) δ (ppm) -75.34 (s, CF₃).

In a solution of *N*-CF₃ hydrazide 2-15 (140 mg, 0.66mmol) in dichloromethane (6 mL)

were added successively at 0°C, pyridine (52 mg, 0.66mmol) and NBS (117 mg, 0.66 mmol). After 10 minutes, the solution of **2-23** in dichloromethane was directly used for the next step.

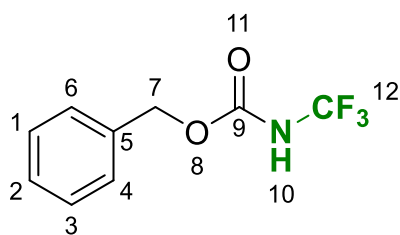
Benzyl 2-(4-(dimethylamino)phenyl)-2-(trifluoromethyl)hydrazine-1-carboxylate [2-24]



At the previous solution of *N*-CF₃ azodicarboxylate **2-23** in CH₂Cl₂ was added 2 mL of hexafluoroisopropanol (HFIP) then the dimethylaniline (66 mg, 0.55 mmol) at 25°C. The mixture was stirred at this temperature for 5 h. Upon completion of the reaction, the mixture was concentrated under reduce pressure to give a crude product. Then, the crude product was purified by column chromatography (silica gel; cyclohexane/Ethyl acetate, 70/30) to afford **2-24** in two steps as white solid (150 mg, 71% yield). ¹H NMR (300 MHz, CDCl₃) δ (ppm) 7.23-7.14 (m, 7H, H_{arom}), 6.80 (s, 1H, H₈), 6.54 (m, 2H, H_{arom}), 5.05 (s, 2H, H₁₅), 2.84 (s, 6H, H_{methyl}). ¹³C NMR (75 MHz, CDCl₃) δ (ppm) 155.6 (C₉), 150.4 (C₃), 135.6 (C₁₆), 129.7 (C_{arom}), 128.6 (C_{arom}), 128.3 (C_{arom}), 128.11 (C_{arom}), 126.9 (C_{arom}), 122.7 (q, *J* = 256.9 Hz, C₁₀), 112.4 (C_{arom}), 67.8 (C₁₅), 40.4 (C_{methyl}). ¹⁹F NMR (188 MHz, CDCl₃) δ (ppm) -64.77 (s, CF₃). HRMS *m/z* C₁₇H₁₈F₃N₃O₂ [M+H]⁺ cal. 354.1429, found. 354.1429. m.p. = 139-140°C.

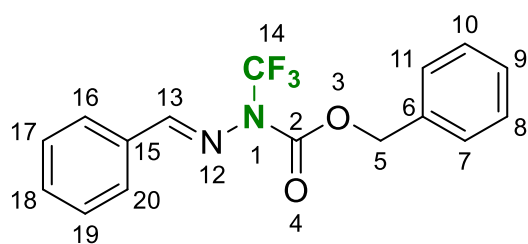
5. Reaction with the compound 2-16

Benzyl (trifluoromethyl)carbamate [2-25]

**2-25**

To a stirred mixture of **2-16** (100 mg, 0.43 mmol) in 1.5 mL of acetic acid and 0.5 mL of 1N hydrochloric acid, a solution of sodium nitrite (30 mg, 0.43 mmol) in 0.5 mL of water was added dropwise at 5°C. The reaction mixture was stirred at 5°C for 20 minutes, then warmed to rt for 3 h, solution of reaction was concentrated, the resulting residue was diluted with ether, solid was filtered. After removal of the solvents to give **2-25** as a pale-yellow solid (86 mg, 92% yield). ¹H NMR (300 MHz, CDCl₃) δ (ppm) 7.41-7.34 (m, 5H, H_{arom}), 6.66 (brs, 1H, H₁₀), 5.22 (s, 2H, H₇). ¹³C NMR (75 MHz, CDCl₃) δ (ppm) 151.2 (C₉), 134.7 (C₅), 128.7 (C_{arom}), 128.6 (C_{arom}), 128.3 (C_{arom}), 118.8 (q, *J* = 256.9 Hz, C₁₂), 68.3 (C₇). ¹⁹F NMR (188 MHz, CDCl₃) δ (ppm) -56.89 (s, CF₃). HRMS *m/z* C₉H₈F₃NO₂ [M-H]⁻ cal. 218.0429, found. 218.0431. m.p. = 66-67°C.

Benzyl (E)-2-benzylidene-1-(trifluoromethyl)hydrazine-1-carboxylate [2-26]

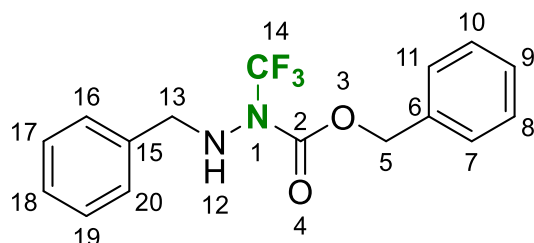
**2-26**

Compound **2-16** (78 mg, 0.15 mmol) was mixed with benzaldehyde (29 mg, 0.12 mmol) in dichloromethane, followed by MgSO₄ at rt. After stirring overnight, MgSO₄ was filtered and the solvent was evaporated to give 118 mg of hydrazone **2-26**.

¹H NMR (300 MHz, CDCl₃) δ (ppm) 8.48 (s, 1H, H₁₃), 7.65-7.62 (m, 2H, H_{arom}), 7.38-7.30 (m, 3H, H_{arom}), 7.25-7.22 (m, 5H, H_{arom}), 5.20 (s, 2H, H₅). ¹³C NMR (75 MHz, CDCl₃) δ (ppm) 164.3 (C₂), 151.7 (C₁₃), 134.7 (C₆), 132.7 (C₁₅), 131.9 (C_{arom}), 128.8 (C_{arom}), 128.7 (C_{arom}), 128.67 (C_{arom}), 128.5 (C_{arom}), 128.0 (C_{arom}), 120.7 (q, *J* = 262.2

Hz, C₁₄), 69.3 (C₅). ¹⁹F NMR (188 MHz, CDCl₃) δ (ppm) -59.17 (s, CF₃). HRMS *m/z* C₁₆H₁₃F₃N₂O₂ [M+Na]⁺ cal. 345.0827, found. 345.0781.

Benzyl 2-benzyl-1-(trifluoromethyl)hydrazine-1-carboxylate [2-27]

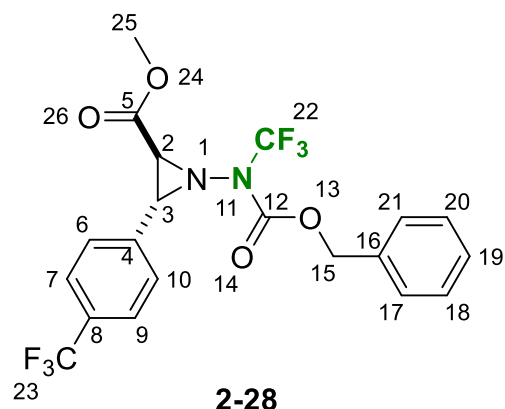


2-27

The crude compound **2-26** was directly used and dissolved in THF (4 mL) and acetic acid (0.74 mmol) then NaBH₃CN (35 mg, 0.56 mmol) was added at rt. After 12 hours of stirring, the reaction medium was quenched with NaHCO₃ aqueous, the mixture was stirred for 30 minutes. The crude was then extracted with ether and purified by chromatography on silica gel (eluent AcOEt/Cyclohexane; 70/30) to give the compound **2-27** as colorless oil (62 mg, 70% yield).

¹H NMR (300 MHz, CDCl₃) δ (ppm) 7.33-7.25 (m, 5H, H_{arom}), 7.23-7.18 (m, 5H, H_{arom}), 5.19 (s, 2H, H₅), 4.32 (brs, 1H, H₁₂), 3.93 (d, *J* = 6.03 Hz, 2H, H₁₃). ¹³C NMR (75 MHz, CDCl₃) δ (ppm) 153.5 (C₂), 136.0 (C₆), 134.7 (C₁₅), 129.3 (C_{arom}), 128.7 (C_{arom}), 128.5 (C_{arom}), 128.1 (C_{arom}), 128.0 (C_{arom}), 125.5 (C_{arom}), 120.9 (q, *J* = 260.9 Hz, C₁₄), 69.3 (C₅), 56.1 (C₁₃). ¹⁹F NMR (188 MHz, CDCl₃) δ (ppm) -59.50 (s, CF₃). HRMS *m/z* C₁₆H₁₅F₃N₂O₂ [M+Na]⁺ cal. 347.0983, found. 347.0979.

Methyl (2*S*,3*R*)-1-(((benzyloxy) carbonyl) (trifluoromethyl)amino)-3-(4-(trifluoromethyl) phenyl) aziridine-2-carboxylate [2-28]



N-CF₃ hydrazine **2-16** (62 mg, 0.26 mmol) was added to a solution of methyl 4-(trifluoromethyl)cinnamate (43 mg, 0.26 mmol), iodobenzene diacetate (126 mg, 0.39 mmol) and K₂CO₃ (101 mg, 0.73 mmol) in dichloromethane. The resulting solution was stirred at room temperature until 12 hours. The reaction medium was washed with brine, dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude was then purified by chromatography on silica gel (eluent AcOEt/Cyclohexane; 80/20) to afford the compound **2-28** (87 mg, 83% yield).

¹H NMR (300 MHz, CDCl₃) δ (ppm) 7.46 (d, *J* = 8.25 Hz, 2H, H₇ and 9), 7.25-7.15 (m, 7H, H_{arom}), 5.16 (d, H_a, *J* = 12.15 Hz, 1H, H₁₅), 5.10 (d, H_b, *J* = 12.12 Hz, 1H, H₁₅), 4.01 (d, *J* = 5.07 Hz, 1H, H₃), 3.63 (s, 3H, H₂₅), 3.16 (d, *J* = 5.22 Hz, 1H, H₂). ¹³C NMR (75 MHz, CDCl₃) δ (ppm) 165.6 (C₅), 152.5 (C₁₂), 138.6 (C₄), 134.2 (C₁₆), 130.7 (q, *J* = 32.6 Hz, C₈), 128.7 (C_{arom}), 128.6 (C_{arom}), 128.2 (C_{arom}), 127.1 (C_{arom}), 125.5 (q, *J* = 3.4 Hz, C_{arom}), 123.9 (q, *J* = 272.2 Hz, C₂₃), 121.1 (q, *J* = 266.8 Hz, C₂₂), 69.5 (C₁₅), 52.8 (C₃), 51.5 (C₂₅), 49.0 (C₂). ¹⁹F NMR (188 MHz, CDCl₃) δ (ppm) -58.77 (s, CF₃), -62.76 (s, CF₃). HRMS *m/z* C₂₀H₁₆F₆N₂O₄ [M+Na]⁺ cal. 485.0912, found. 485.0915.

References

- [1] J. Wang, M. Sanchez-Rosello, J. L. Acena, C. Del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev.* **2014**, 114, 2432.
- [2] J.-P. Bégué, D. Bonnet-Delpon, *Bioorganic and Medicinal Chemistry of Fluorine*, John Wiley & Sons, **2008**.
- [3] C. Hansch, A. Leo, R. W. Taft, *Chem. Rev.* **1991**, 91, 165-195.
- [4] F. Leroux, P. Jeschke, M. Schlosser, *Chem. Rev.* **2005**, 105, 827-856.
- [5] F. R. Leroux, B. Manteau, J. -P. Vors, S. Pazenok, *Beilstein J. Org. Chem.* **2008**, 4, 13.
- [6] F. Toulgoat, S. Alazet, T. Billard, *Eur. J. Org. Chem.* **2014**, 2014, 2415-2428.
- [7] S. Das, R. L. Harde, D. E. Shelke, N. Khairatkar-Joshi, M. Bajpai, R. S. Sapalya, H. V. Surve, G. S. Gudi, R. Pattem, D. B. Behera, S. B. Jadhav, A. Thomas, *Bioorg. Med. Chem. Lett.* **2014**, 24, 2073–2078
- [8] L. M. Yagupolskii, D. V. Fedyuk, K. I. Petko, V. I. Troitskaya, V. I. Rudyk, V. V. Rudyuk, *J. Fluor. Chem.* **2000**, 106, 181-187.
- [9] Y. Asahina, I. Araya, K. Iwase, F. Inuma, M. Hosaka, T. Ishizaki, *J. Med. Chem.* **2005**, 48, 3443-3446.
- [10] T. Umemoto, K. Adachi, S. Ishihara, *J. Org. Chem.* **2007**, 72, 6905-6917 6905.
- [11] P. Eisenberger, S. Gischig, A. Togni, *Chem. Eur. J.* **2006**, 12, 2579 – 2586.
- [12] K. Niedermann, N. Früh, R. Senn, B. Czarniecki, R. Verel, A. Togni, *Angew. Chem. Int. Ed.* **2012**, 51, 6511 –6515.
- [13] F. Teng, J. Cheng, C. Bolm, *Org. Lett.* **2015**, 17, 12, 3166–3169.
- [14] A. van Der Werf, M. Hribersek, N. Selander, *Org. Lett.* **2017**, 19, 9, 2374–2377.
- [15] S. Liang, J. Wei, L. Jiang, J. Liu, Y. Mumtaz, W. Yi, *Chem. Commun.* **2019**, 55, 8536--8539.
- [16] T. Scattolin, K. Deackers, F. Schoenebeck, *Angew. Chem. Int. Ed.* **2017**, 56, 221.
- [17] T. Scattolin, S. Bouayad-Gervais, F. Schoenebeck, *Nature*, **2019**, 573, 7772, 102-107.
- [18] C. D.-T. Nielsen, F. G. Zivkovic, and F. Schoenebeck, *J. Am. Chem. Soc.* **2021**, 143, 13029–13033.
- [19] G. S. Papaetis, K. N. Syrigos, *Bio. Drugs.* **2009**, 23 (6), 377–389.
- [20] J. M. Kraus, H. B. Tatipaka, S. A. McGuffin, N. K. Chennamaneni, M. Karimi, J.

- Arif, C. L. M. J. Verlinde, F. S. Buckner, M. H. Gelb, *J. Med. Chem.* **2010**, 53 (10), 3887–3898.
- [21] Z. Zhao, P. E. Bourne, *Drug Discovery Today*. **2018**, 23 (3), 727–735.
- [22] A. Tursoy, T. Scattolin, S. Bouayad-Gervais, F. Schoenebeck, *Chem. Eur. J.* **2020**, 26, 2183–2186.
- [23] S. Bouayad-Gervais, C. D.-T. Nielsen, A. Tursoy, T. Sperger, K. Deckers, F. Schoenebeck, *J. Am. Chem. Soc.* **2022**, 144, 6100–6106.
- [24] Z. Z. Zhang, J. Y. He, L. Zhu, H. W. Xiao, Y. W. Fang, C. Z. Li, *Chin. J. Chem.* **2019**, 38, 924–928.
- [25] S. Liu, Y. G. Huang, J. Wang, F. L. Qing, X. H. Xu, *J. Am. Chem. Soc.* **2022**, 144, 1962–1970.
- [26] R. Z. Zhang, W. Q. Huang, R. X. Zhang, C. Xu, M. Wang, *Org. Lett.* **2022**, 24, 2393–2398.
- [27] R. Z. Zhang, R. X. Zhang, S. Wang, C. Xu, W. Guan, M. Wang, *Angew. Chem. Int. Ed.* **2022**, 61, E202110749.
- [28] a) X. Su, I. Aprahamian, *Chem. Soc. Rev.* **2014**, 43, 1963; b) G. Men, J.-M. Lehn, *J. Am. Chem. Soc.* **2017**, 139, 2474; c) R. Lygaitis, V. Getautis, J. V. Grazulevicius, *Chem. Soc. Rev.* **2008**, 37, 770; d) A. Mahmoodi, M. Ebrahimi, *Prog. Org. Coat.* **2018**, 114, 223.
- [29] a) R. Narang, B. Narasimhan, S. Sharma, *Curr. Med. Chem.* **2012**, 19, 569; b) D. K. Kçlmeç, E. T. Kool, *Chem. Rev.* **2017**, 117, 10358; c) C. S. Meira, J. M. Dos Santos Filho, C. C. Sousa, P. S. Anjos, J. V. Cerqueira, H. A. Dias Neto, R. G. Da Silveira, H. M. Russo, J.-L. Wolfender, E. F. Queiroz, D. R. M. Moreira, M. B. P. Soares, *Bioorg. Med. Chem.* **2018**, 26, 1971; d) G. Verma, A. Marella, M. Shaquiquzzaman, M. Akhtar, M. Ali, M. Alam, *J. Pharm. Bioall. Sci.* **2014**, 6, 69; e) E. Nieddu, B. Pollarolo, M. T. Mazzei, M. Anzaldi, S. Schenone, N. Pedemonte, L. J. V. Galiotta, M. Mazzei, *Arch. Pharm. Chem. Life Sci.* **2016**, 349, 112; f) F. López-Muñoz, C. Iamo, G. Juckel, H.-J. Assion, *J. Clin. Psychopharmacol.* **2007**, 27, 555.
- [30] a) M. P. Elizalde-González, S. A. Lozano-Morales, *Mater. Chem. Phys.* **2019**, 228, 15; b) A. Matoliukstyte, R. Lygaitis, J. V. Grazulevicius, V. Gaidelis, V. Jankauskas, E. Montrimas, Z. Tokarski, N. Jubran, *Mol. Cryst. Liq. Cryst.* **2005**, 427, 107.
- [31] a) C. Sambriago, D. Schçnbauer, R. Blicke, T. Dao-Huy, G. Pototschnig, P. Schaaf, T. Wiesinger, M. F. Zia, J. Wencel-Delord, T. Besset, B. U. W. Maes, M.

- Schnürch, *Chem. Soc. Rev.* **2018**, 47, 6603; b) Y. Xue, Z. Fan, X. Jiang, K. Wu, M. Wang, C. Ding, Q. Yao, A. Zhang, *Eur. J. Org. Chem.* **2014**, 7481.
- [32] M. Mamone, E. Morvan, T. Milcent, S. Ongerì, B. Crousse. *J. Org. Chem.* **2015**, 80, 1964.
- [33] S. Bouayad-Gervais, T. Scattolin, F. Schoenebeck, *Angew. Chem. Int. Ed.* **2020**, 59, 11908 – 11912.
- [34] P. Wang, S. S. Zhu, D. F. Lu, Y. F. Gong, *Org. Lett.* **2020**, 22, 5, 1924–1928.
- [35] A. Y. Dang-i, T. Huang, N. Mehwish, X. Dou, L. Yang, V. Mukwaya, C. Xing, S. Lin, C. -L. Feng, *ACS Applied Bio Materials*, **2020**, 3, 2295.
- [36] R. Chingle, W. D. Lubell, *Org. Lett.* **2015**, 17, 5400–5403.
- [37] M. J. Naim, O. Alam, F. Nawaz, M. J. Alam, P. Alam, *J. Pharm. Bioallied. Sci.* **2016**, 8, 2-17.
- [38] J. Wang, M. Sanchez-Rosello, J. L. Acena, C. Del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev.* **2014**, 114, 2432.
- [39] T. Milcent, B. Crousse, *C. R. Chim.* **2018**, 21, 771.
- [40] W. H. Li, J. G. Gan, D. W. Ma, *Org. Lett.* **2009**, 11, 24.
- [41] S. Schiesser, H. Chepliaka, J. Kollback, T. Quennesson, W. Czechtizky, R. J. Cox, *J. Med. Chem.* **2020**, 63, 13076-13089.
- [42] F. H. Allen, O. Kennard, D. G. Watson, L. Brammer, A. G. Orpen and R. J. Taylor, *J. Chem. Soc. Perkin Trans.* **1987**, 2, S1–S19.
- [43] B. Kuhn, E. Gilberg, R. Taylor, J. Cole, O. Korb, *J. Med. Chem.* **2019**, 62, 10441.
- [44] K. Müller, C. Faeh, F. Diederich, *Science.* **2007**, 317, 1881.
- [45] S. A. Harry, M. Kazim, P. Minh Nguyen, A. Zhu, M. R. Xiang, J. Catazaro, M. Siegler, T. Lectka, *Angew. Chem. Int. Ed.* **2022**, E202207966.
- [46] R. J. Tang, T. Milcent, B. Crousse, *Eur. J. Org. Chem.* **2017**, 4753–4757.
- [47] B. Schweitzer-Chaput, M. Keita, T. Milcent, S. Ongerì, B. Crousse, *Tetrahedron.* **2012**, 68, 7028-7034.

Chapter III

Synthesis of Trifluoromethanesulfonyl Hydrazides and Sulfonylation of Indoles

3.1 Deprotection of di- or trifluoromethanesulfonyl hydrazides

In the previous chapter, an efficient and economical method of accessing *N*-CF₃ hydrazides has been described, and the presence of side products has caught our attention, particularly the trifluoromethanesulfonyl hydrazide. Heteroatom attached trifluoromethyl units, such as trifluoromethanesulfonyl (SO₂CF₃) groups, are of considerable interest. They are considered to be a strong electron-withdrawing groups, with high lipophilicity.^{[1]-[2]} Besides, it is noticed that the unit of CF₃SO₂-N-N plays an important role in pharmaceuticals and metabolism. Furthermore, the incorporation of this group is generally incorporated with (CF₃SO₂)₂O, CF₃SO₂Cl(F) from the functionalized drugs. However, only one example reported the synthesis of biological molecules from the CF₃SO₂-NH-NH₂ hydrazine. The over-expression of the α -amylase enzyme causes hyperglycemia which leads to many physiological complications, including oxidative stress, one of the most commonly associated problems with diabetes mellitus. A compound (Figure 3.1a) with the trifluoromethylsulfonyl group was prepared by multi-step reactions (Scheme 3.1a). The corresponding hydrazone was found to be significantly potent in α -amylase enzyme inhibitory activities.^[3]

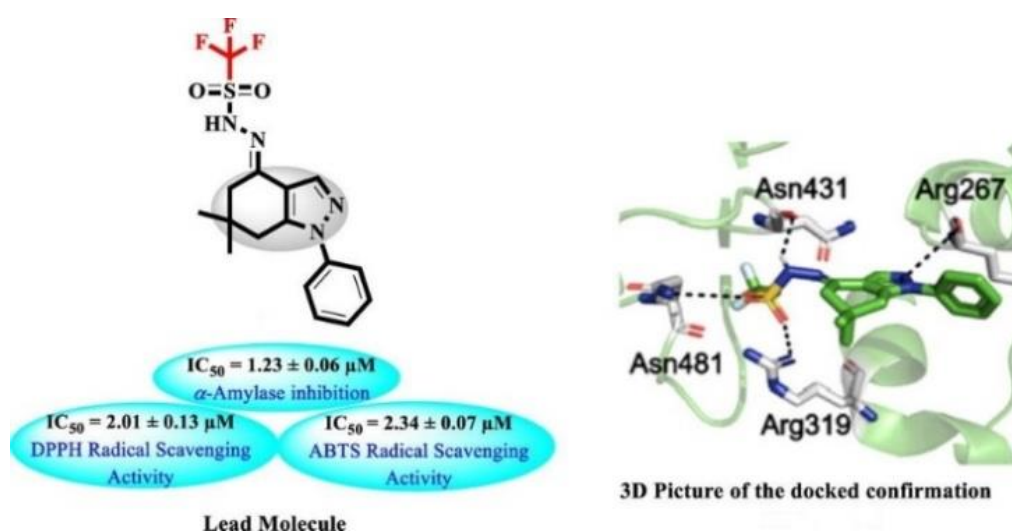
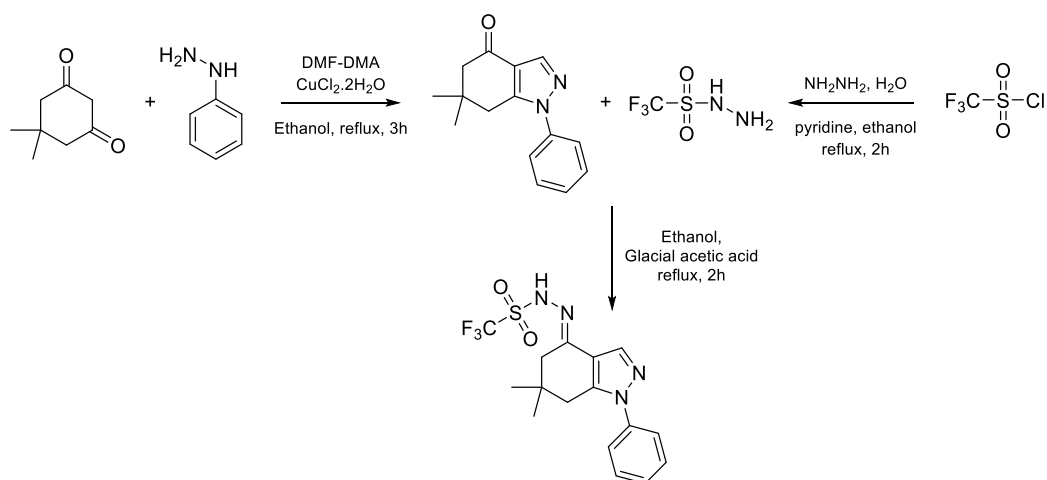


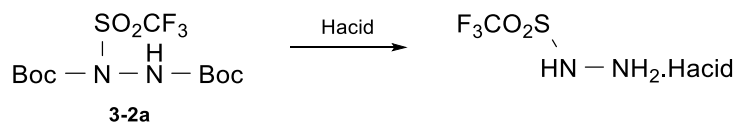
Figure 3.1a Compound with unit of trifluoromethanesulfonyl hydrazides and its inhibitory activity, molecular docking study

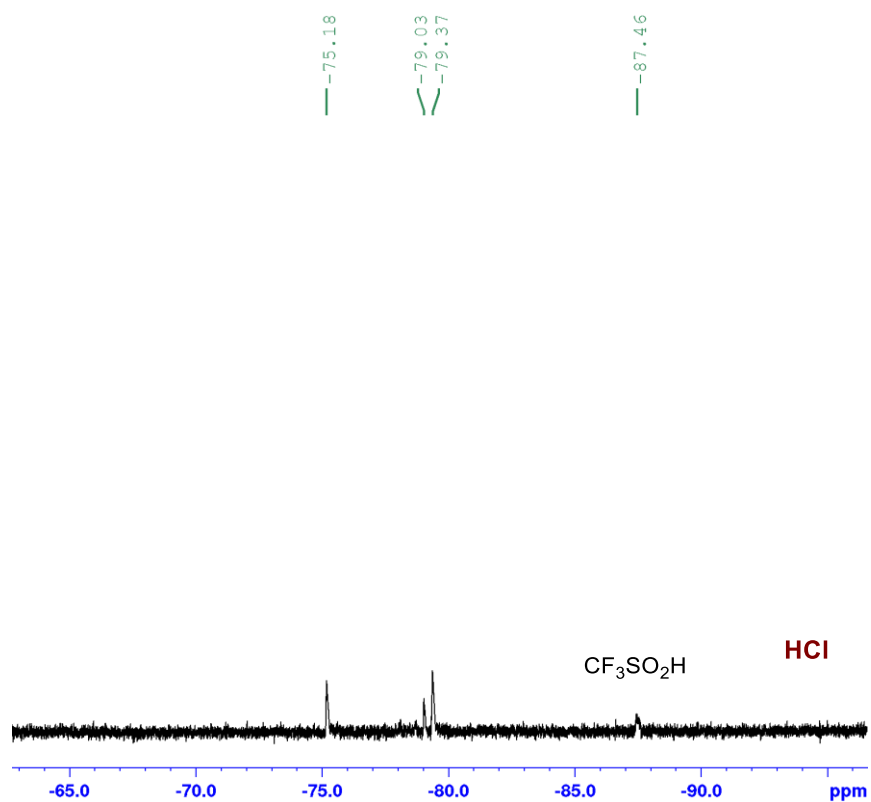


Scheme 3.1a Preparation of lead molecule

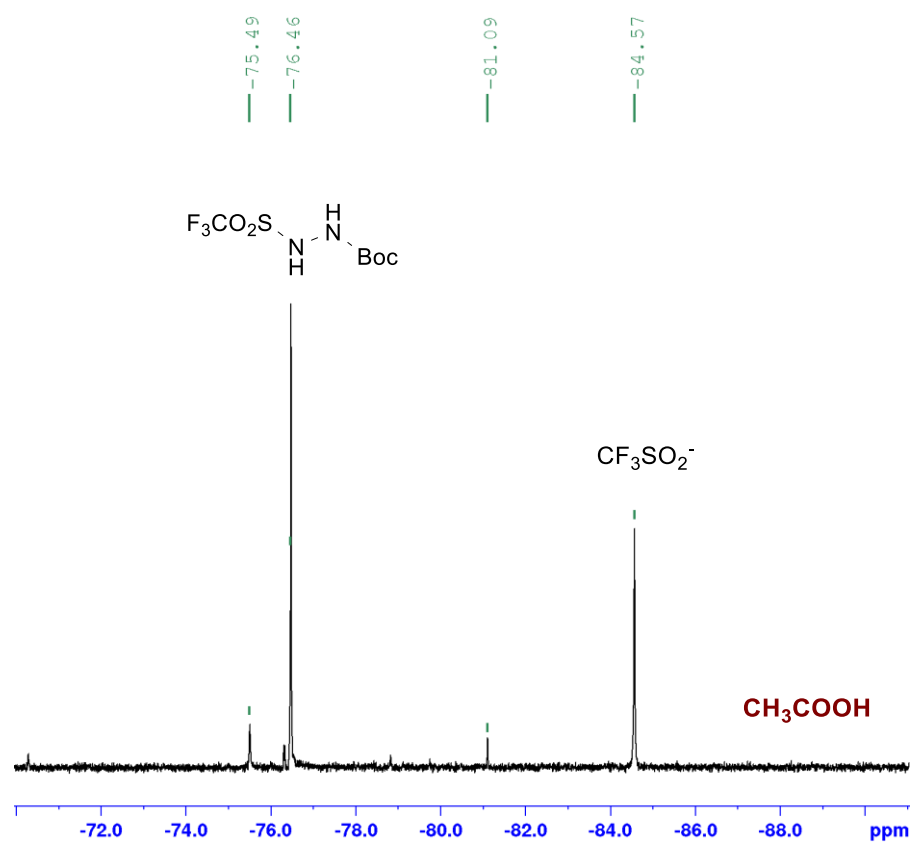
As described above, the unit of trifluoromethanesulfonyl hydrazine is significant potential, which exists in the bioactive structures. Having in hand key intermediates, we undertook to prepare this fluorinated hydrazine ($\text{CF}_3\text{SO}_2\text{-NH-NH}_2$) and study its reactivity for constructing motifs of interest to incorporate them or access bioactive molecules.

In this process, we investigated the deprotection of the Boc and Cbz trifluoromethanesulfonyl hydrazides **3-2a/3-2c**. For di-*tert*-butyl 1-((trifluoromethyl)sulfonyl) hydrazine-1,2-dicarboxylate **3-2a**, the deprotection was firstly performed with a solution of HCl/dioxane (10 equiv.) in DCM. The signal in the ^{19}F NMR spectrum is shifted from -75 to -87 ppm. These peaks probably belong to trifluoromethanesulfonic acid derivatives $\text{CF}_3\text{SO}_2\text{X}$ ($\text{X} = \text{OH}, \text{NH}_2, \text{N}_3, \dots$)^[4], (Figure 3.1b(1)). We obtained the same result with the trifluoroacetic acid (TFA; 10 equiv.) in DCM. In addition, acetic acid was also employed for the deprotection, but it was not efficient at room temperature and 50°C , while at higher temperatures (75°C), decomposition was detected (Figure 3.1b (2)). Unfortunately, under acidic conditions, these fluoromethanesulfonyl hydrazines are too unstable to be isolated.





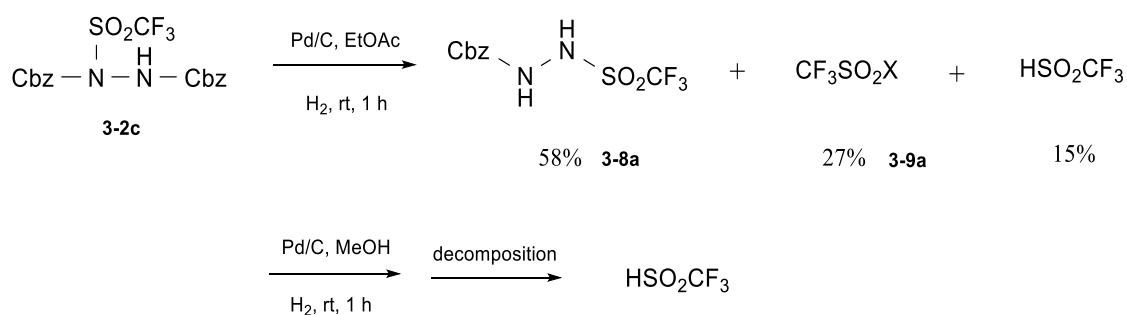
(1)



(2)

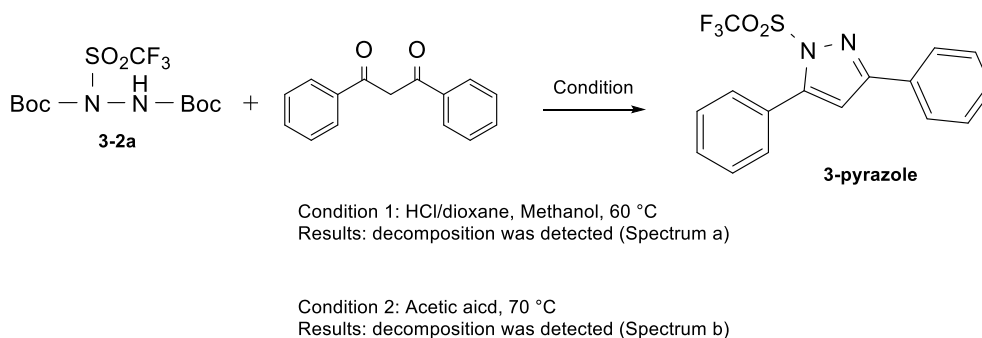
Figure 3.1b Spectrum of deprotection with HCl and acetic acid respectively

We set out to deprotect the di-benzyl-1-((trifluoromethyl)sulfonyl) hydrazine-1,2-dicarboxylate **3-2c** with the Pd/C, H₂ in EtOAc. The signal of ¹⁹F NMR showed a mixture of **3-8a** (-76.13 ppm), **3-9a** (-77.09 ppm) and triflic acid (-88.80 ppm) with ratio of 58%, 27% and 15%, respectively. While in methanol, triflic acid was directly observed and was the only product after 1 hour at room temperature. (Scheme 3.1b). Here also in these conditions, the CF₃SO₂NH-NH₂ is not stable in free form.



Scheme 3.1b Deprotection of di-benzyl 1-((trifluoromethyl)sulfonyl) hydrazine-1,2-dicarboxylate

Moreover, following the success of the preparation of pyrazoles with **2-3b** and diones in one pot, we carried out the same method from **3-2a**. Unfortunately, during the reaction, a decomposition is also observed, whether with HCl or acetic acid. (Scheme 3.1c and Figure 3.1c).



Scheme 3.1c Reactions of **3-2a** and 1,3-diphenyl-1,3-propanedione

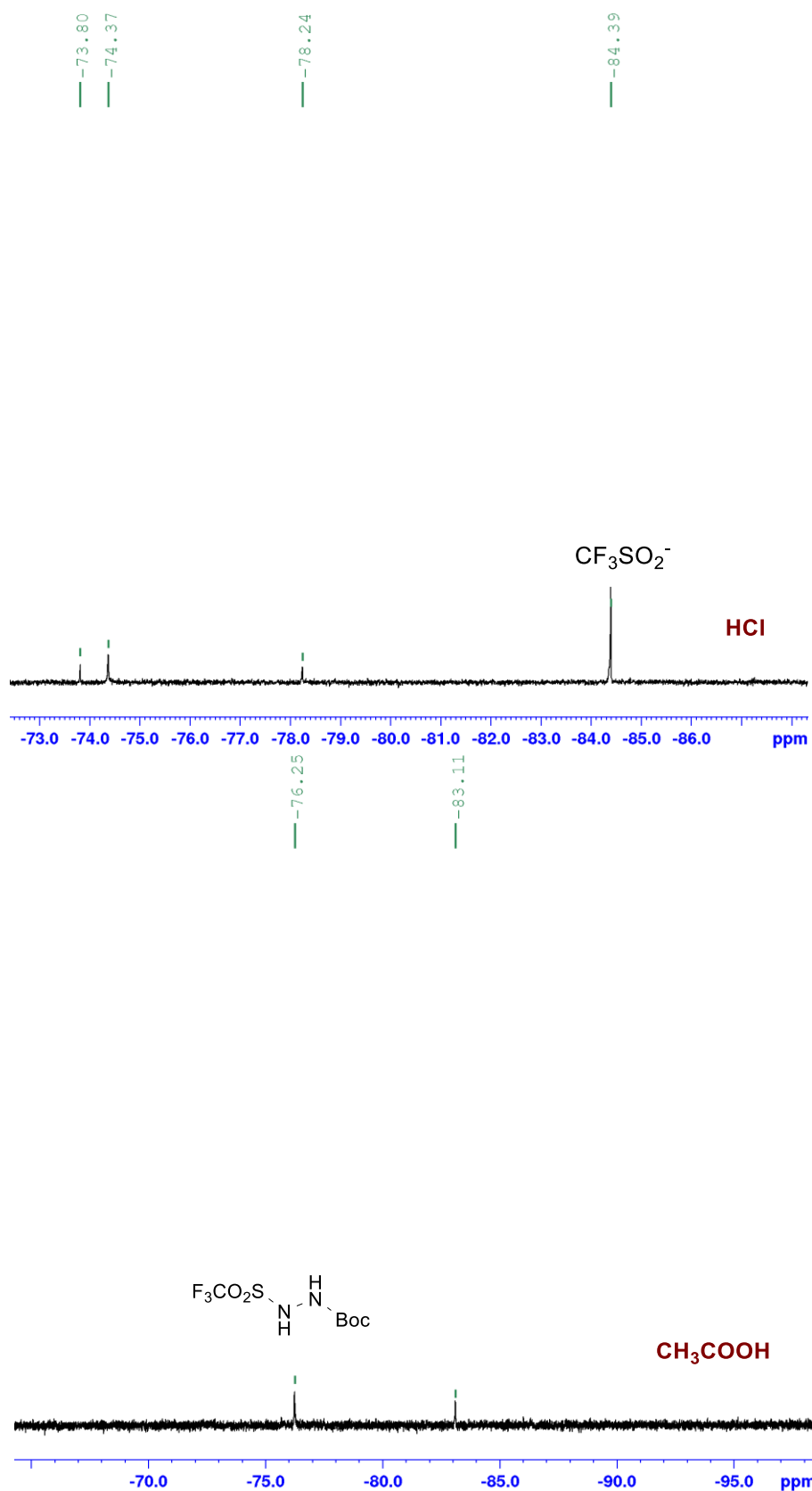


Figure 3.1c ^{19}F NMR spectra of cyclisation

Faced with the instability of these compounds, we turned our research to another approach concerning the reactivity of fluoro-sulfonyl hydrazines. These compounds are excellent precursors for the incorporation, for example, of the SCF₃ group from the trifluoromethylsulfonyl hydrazines. The next chapter will study their reactivity in incorporating the SCF₃ group.

3.2 The trifluoromethyl sulfenyl group: SCF₃

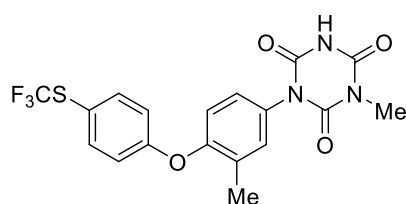
SCF₃ shows extremely high lipophilicity ($\pi = 1.44$) and strong electron-withdrawing power ($\sigma_m = 0.40$, $\sigma_p = 0.50$) in comparison to CF₃, OCF₃ and SO₂CF₃ groups, Table 3.2.

"Aromatic" substituent constants of selected fluorine-containing groups				
Fluorine-containing group	CF ₃	OCF ₃	SCF ₃	SO ₂ CF ₃
π	0.88	1.04	1.44	0.55
σ_m	0.43	0.38	0.40	0.79
σ_p	0.54	0.35	0.50	0.93

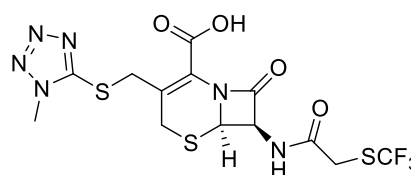
σ is electronic parameters. σ_m emphasizes non-resonance capability of substituents. σ_p emphasizes resonance capability of substituents, σ_p^- is for the nitro substituent.

Table 3.2 "Aromatic" substituent constants of selected fluorine-containing groups

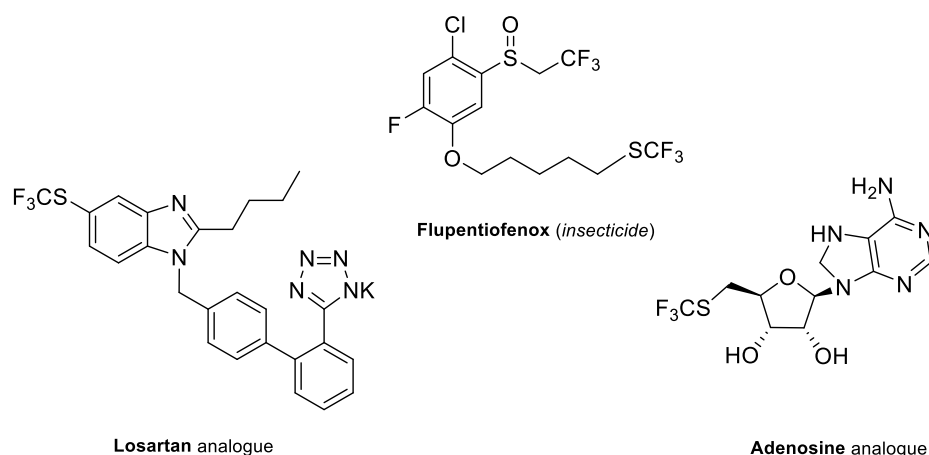
Compounds containing SCF₃, as well as analogous, are frequently found in many pharmaceutical and agrochemical products. Representative examples are shown in Figure 3.2a: Toltrazuril is a coccidiostat drug, Cefazaflur is a first-generation cephalosporin antibiotic, flupentiofenox is a new acaricide. The analogue of losartan has been developed as a potential hypotensive agent, while the analogue of adenosine shows good inhibitory activity against *P. falciparum*.^{[5]-[6]}



Toltrazuril (Antiprotozoal agent)



Cefazaflur (cephalosporin antibiotic)

Figure 3.2a Selected SCF₃-containing examples

This specific group has fascinated researchers for a long time. In the past, numerous methods for forming trifluoromethylthio compounds have been developed. These methods were described in detail by reviews.^{[7]-[8]} For example, different synthetic methods of alkyl trifluoromethyl sulfides are summarized in Figure 3.2b. Trifluoromethanesulfonylation reactions have been developed.

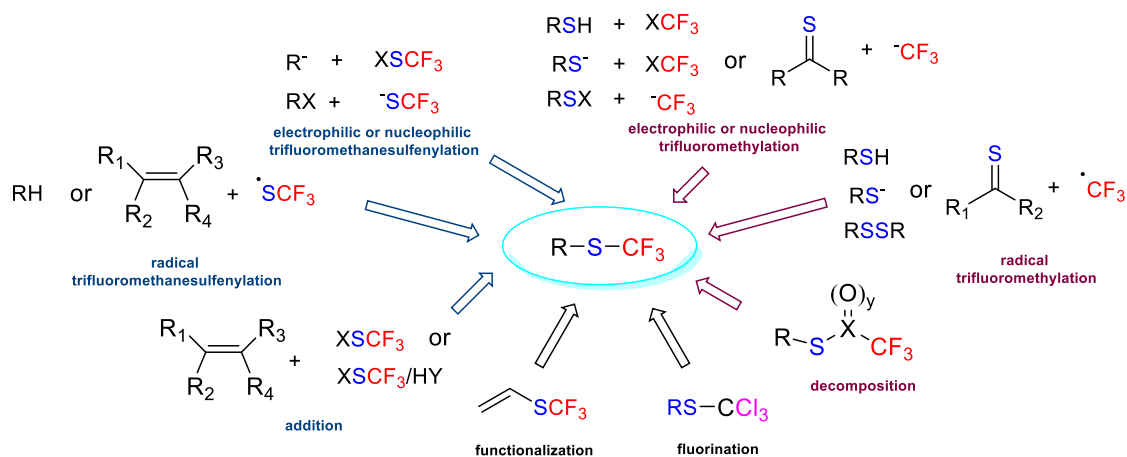
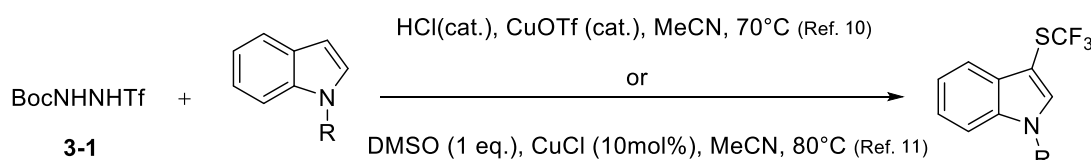


Figure 3.2b Different methods for the incorporation of trifluoromethyl sulfenyl group

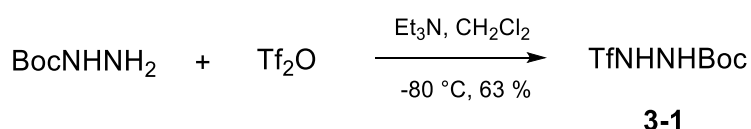
Aside from synthetic methods, CF₃S-reagents play a quite crucial role. In previous research, the CF₃S-reagents are usually toxic gas such as ClSCF₃ or F₃CSSCF₃, and unstable trifluoromethylthiolate salts.

Among the reagents, trifluoromethanesulfonyl hydrazide (TfNHNHBoc **3-1**)^{[9]-[11]} is a useful synthetic precursor for a variety of organic transformations, in particular, the well-known trifluoromethylthiolation reaction.^{[12]-[18]} The trifluoromethylsulfonyl hydrazide could achieve trifluoromethylthiolation of indoles in the presence of a copper catalyst in acetonitrile (Scheme 3.2a).



Scheme 3.2a Trifluoromethanesulfonyl hydrazide **3-1** as source of -SCF₃ group

Hydrazide **3-1** was usually prepared in the literature from (CF₃SO₂)₂O (triflic anhydride) and Boc-NHNH₂ at a very low temperature (-80 °C) and was often obtained in moderate yield (Scheme. 3.2b)^[19]. Alternatively, trifluoromethylsulfonyl group could also be introduced onto nitrogen by treating hydrazine with trifluoromethanesulfonyl chloride (CF₃SO₂Cl)^[20]. However, both of (CF₃SO₂)₂O and CF₃SO₂Cl are corrosive and moisture sensitive.



Scheme 3.2b Preparation of *tert*-butyl trifluoromethylsulfonyl hydrazide

We thus thought di-*tert* butyl trifluoromethylsulfonyl hydrazide **3-2a** having a structure close to **3-1** could be of great interest as a potential reagent for the trifluoromethylthiolation reaction (Figure 3.2c).

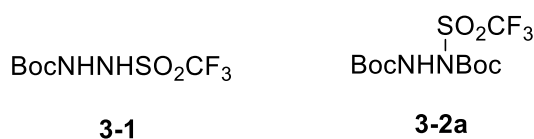
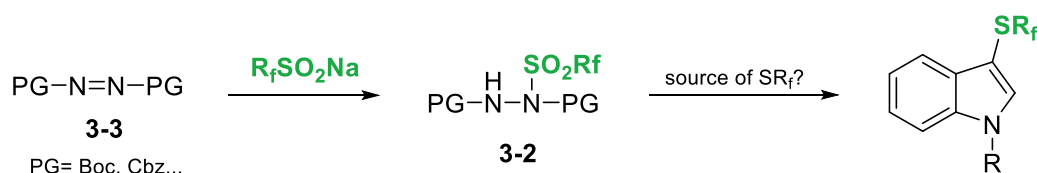


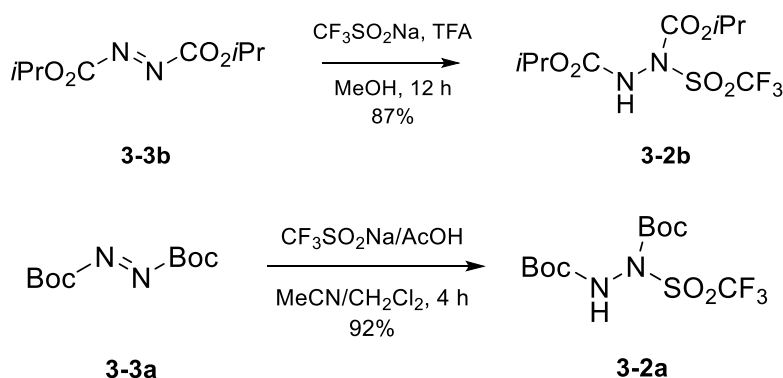
Figure 3.2c Structure of **3-1** and **3-2a**

Furthermore, the synthesis of this type of hydrazides from diazene is very little described in the literature, and no example with other fluorinated groups has been reported. Given the poor scope and the unknown reactivity of fluorinated sulfonyl hydrazides in the sulfenylation of indoles, we set out to prepare a wide range of hydrazides and test them as a source of SR_f on indoles.



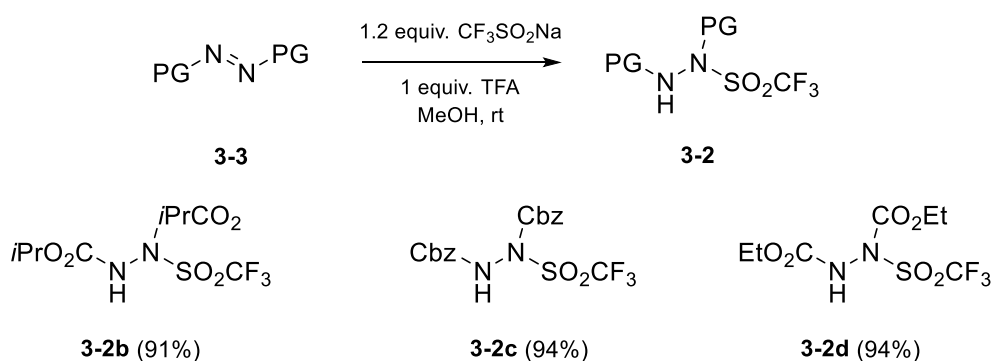
Scheme 3.2c Potential reagent (3-2) for the trifluoromethylthiolation reaction

We were first interested in the synthesis of fluorinated sulfonyl hydrazides. In 2015, Wang *et.al.* reported one example of the preparation of trifluoromethylsulfonyl hydrazides **3-2b** from trifluoromethyl sulfinic acid and di (propan-2-yl) diazene-1,2-dicarboxylate (**3-3b**) in methanol. They showed that the reaction could also be carried out from sodium sulfonates in the presence of trifluoroacetic acid (TFA) in methanol (Scheme 3.2d).^[21] While our work was in progress, Gong and Lu published the study of intermolecular trifluoromethyl hydrazination of alkenes by photoredox catalysis and also observed compound **3-2a** as a side product. To explain the mechanism, the group optimized conditions (acetic acid, triflate in dichloromethane and acetonitrile) to obtain only the compound **3-2a** (Scheme 3.2d).^[22]



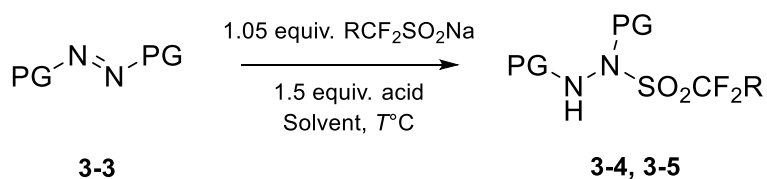
Scheme 3.2d Preparation of fluoroalkylsulfonyl hydrazides

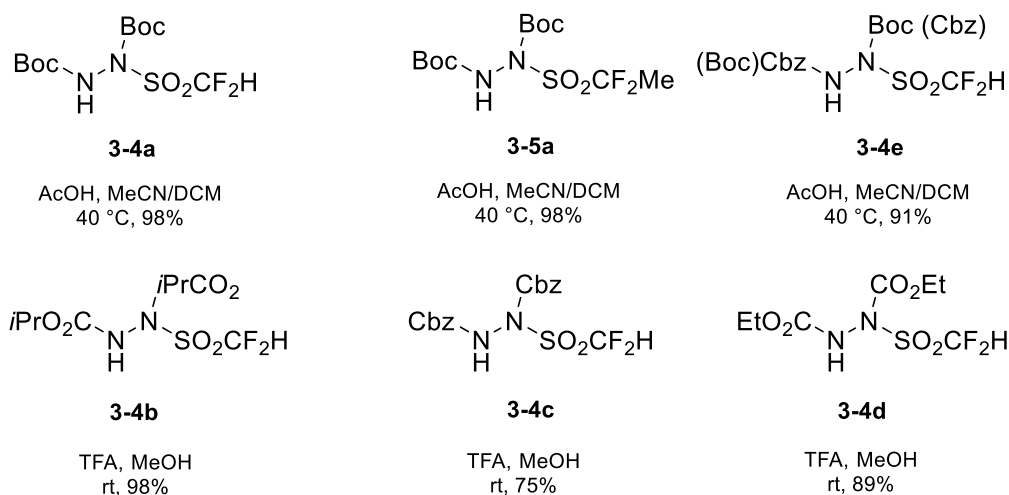
These conditions are very interesting because sodium sulfinates are easily accessible in the form of salts and easier to handle. So, we investigated the previous conditions with the sodium triflinate. First, the preparation of CF_3SO_2 hydrazides was carried out between various azodicarboxylates, sodium triflinate and one equivalent of trifluoroacetic acid (TFA). The results are reported in Scheme 3.2e. The corresponding hydrazides **3-2** were obtained with excellent yield, and these products are solids, air-stable, and can be stored in the fridge for several months.



Scheme 3.2e. Synthesis of trifluoromethylsulfonyl hydrazides

CF_2 and MeCF_2 sulfinates commercially available reacted smoothly to give the corresponding difluoromethyl- and difluoroethylsulfonyl hydrazides (**3-4**, **3-5**) in good to excellent yields (Scheme 3.2f). From di-*tert*-butyl azodicarboxylate (**3-3a**), reactions were carried out with acetic acid to avoid deprotection and decomposition of the starting material having the Boc group. For the other diazenes possessing the Cbz or the CO_2Et or the CO_2iPr functions, trifluoroacetic acid is preferred because the reactions are faster and can be carried out at room temperature.





Scheme 3.2f. Preparation of difluoromethyl- and difluoroethylsulfonyl hydrazides

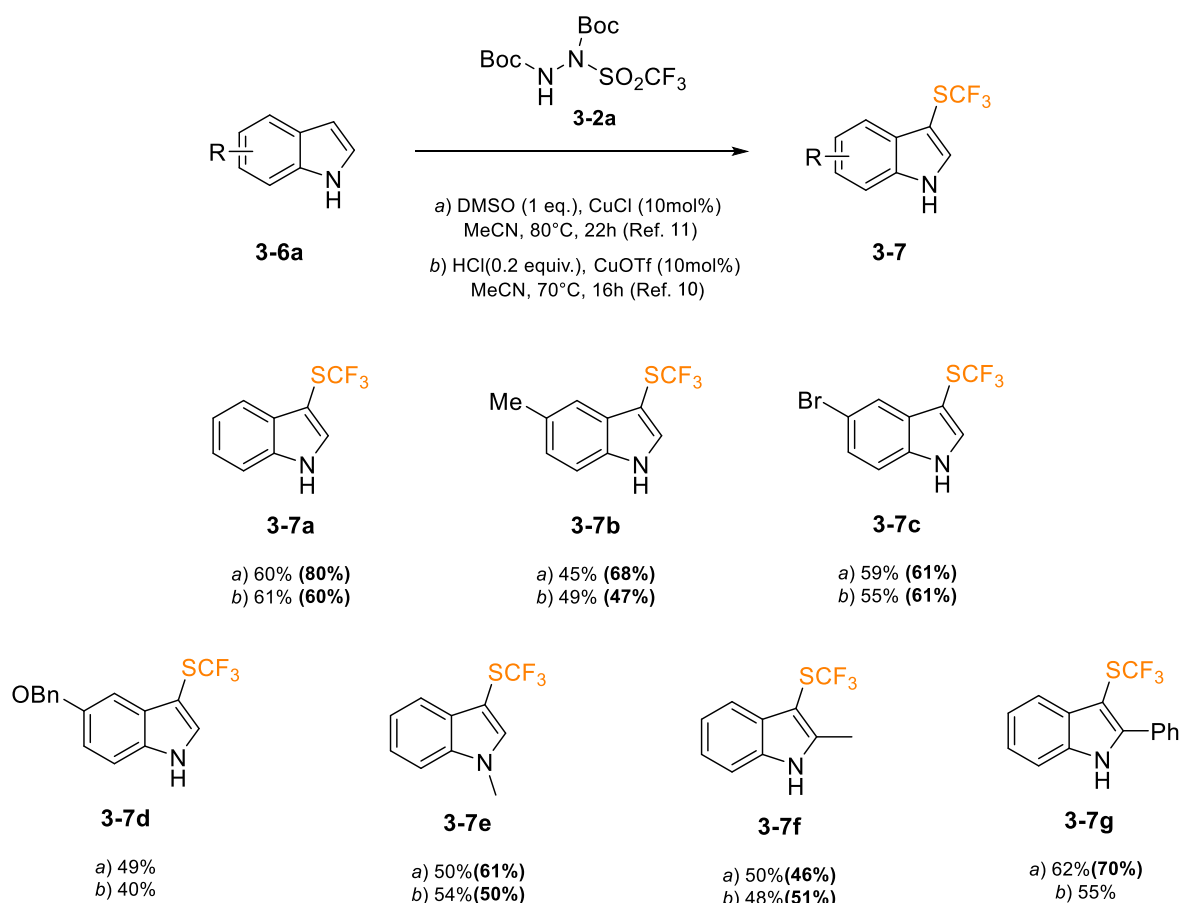
To highlight the synthetic utility of this protocol, we performed the reaction on a gram scale. Under the optimized conditions, the gram scale (1.15 g of **3-3a**) proceeded smoothly to give the corresponding trifluoromethylsulfonyl hydrazide **3-2a** in 84% yield (1.53 g).

With various fluorinated sulfonylhydrazides in our hands, we studied and compared their reactivity in the sulfenylation reaction with indoles under two conditions from the literature involving hydrazide **3-1**. The first one is carried out in the presence of CuCl/DMSO^[10], and the second in the presence of CuOTf/HCl,^[11] each in acetonitrile. First, indole **3-6a** was treated under the two previous conditions with hydrazide **3-2a**. Thankfully, the trifluoromethylthiolation reaction succeeded in yielding indole **3-7a** at 60% (condition a) and 61% (condition b), respectively (Scheme 3.2g). Hydrazide **3-2a** is very effective under these conditions and appears to be an excellent alternative to TfNHNHBoc **3-1**.

However, reactions with other CF₃SO₂N-hydrazides (**3-2b-d**) failed under these conditions. Complete decomposition of hydrazides was observed.

Thus, these conditions allowed the incorporation of the SCF₃ group on a wide range of indoles with reasonable yields (Scheme 3.2g). The reaction was successful with groups such as methyl, bromide and benzyl ether on the aromatics. The corresponding

substituted 3-SCF₃-indoles were isolated in reasonable yields. Protected *N*-methyl indole reacted with **3-2a** to afford the SCF₃-indole **3-7e** in 50 and 54% yields. From indoles substituted in position 2 with a methyl and phenyl group, the fluorinated indoles **3-7f** and **3-7g** are isolated in reasonable to good yields.



Scheme 3.2g Trifluoromethylthiolation from **3-2a**

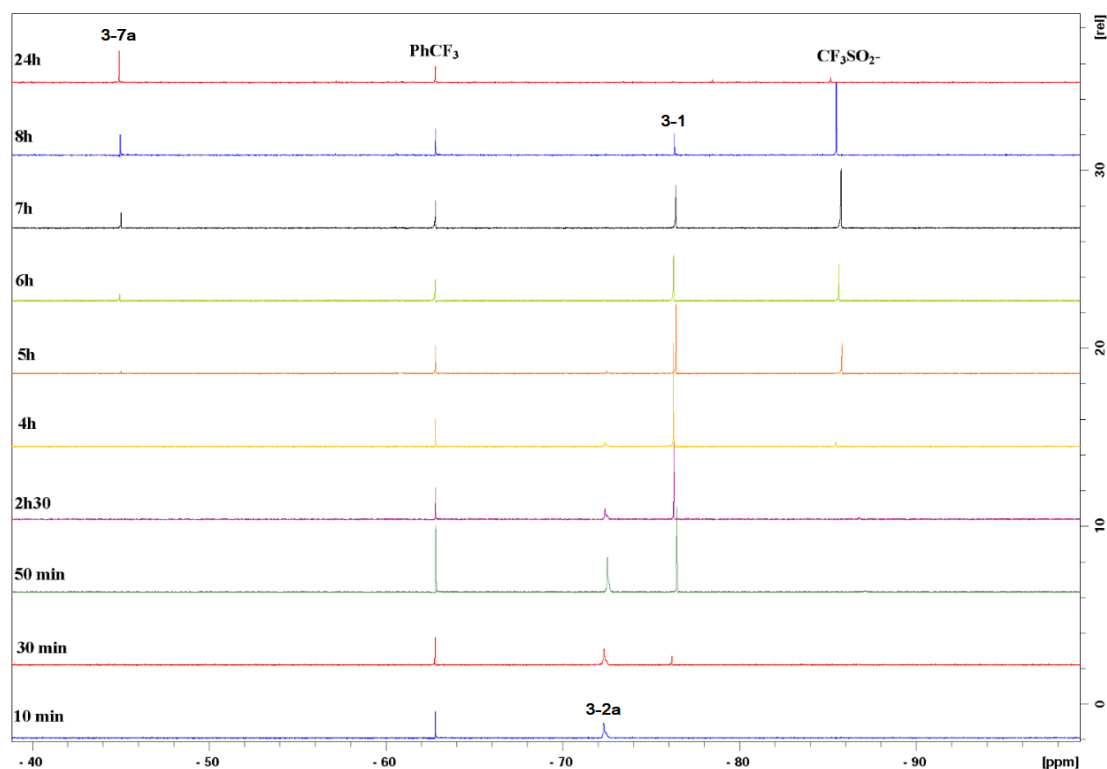
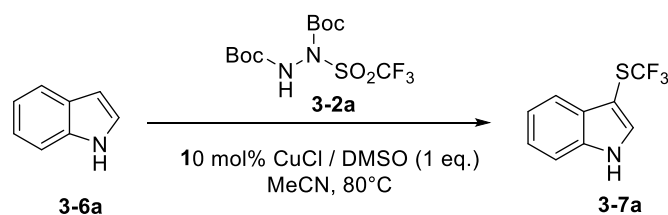
It could be noted that hydrazide **3-2a** reacted very well as a source of SCF₃ in the trifluoromethylthiolation of indoles. In the majority of cases, the yields are close to those reported in the literature (**in bold** in the Scheme 3.2g).

In this line, we attempted the reactivity of other fluorinated hydrazides having the CF₂H and the CF₂Me group. Unfortunately, only traces of compounds are detected from the hydrazides **3-4a** and **3-5a**, and total decomposition was observed for other sulfonyl hydrazides **3-4b-d**.

Subsequently, to understand the transformation of CF₃-sulfonyl hydrazide **3-2a**, we

monitored trifluoromethylthiolation under both conditions using ^{19}F NMR. In the case of condition **A** involving CuCl/DMSO , we first observed a deprotection of the Boc group of **3-2a** in **3-1**. After about five hours, when the compound **3-1** is majority in the medium, SCF_3 -indole **3-7a** begins to form. Then the reaction is left overnight to lead to **3-7a**.

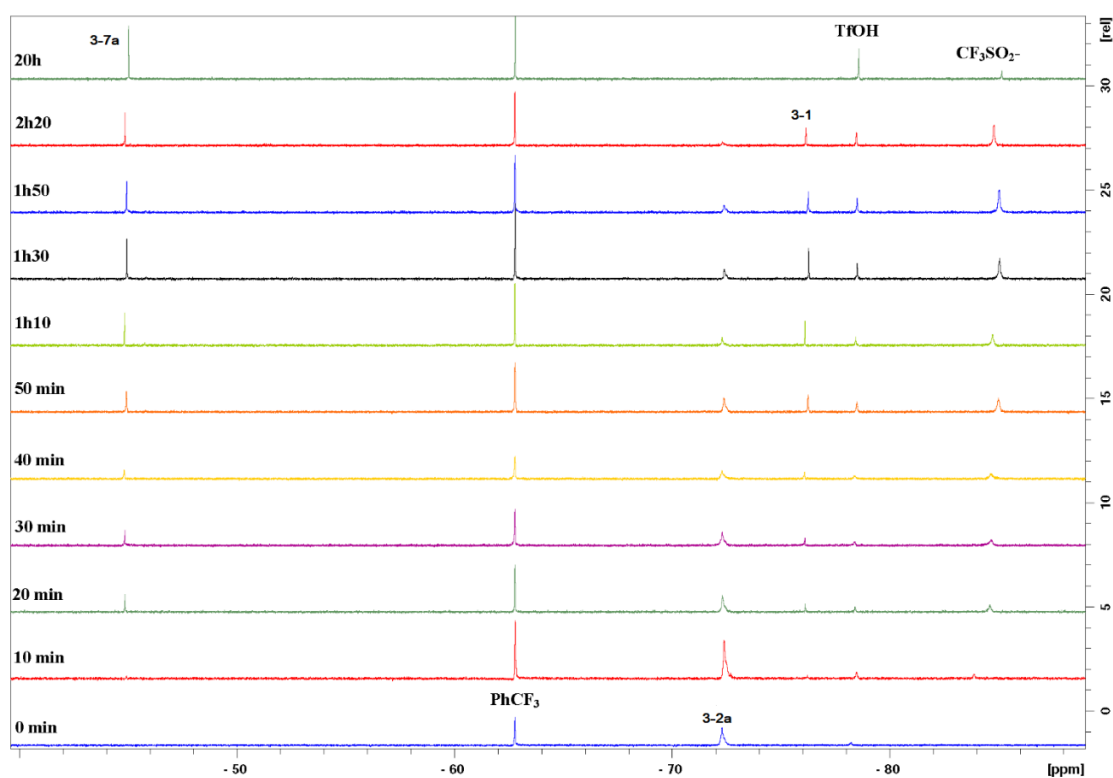
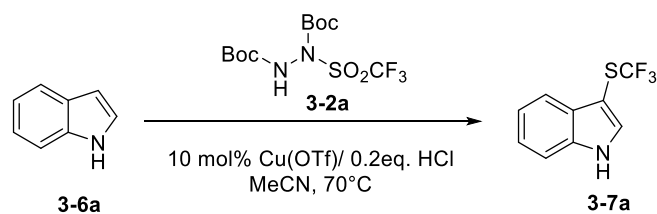
Conditions A: involving CuCl/DMSO in acetonitrile with PhCF_3 as internal standard



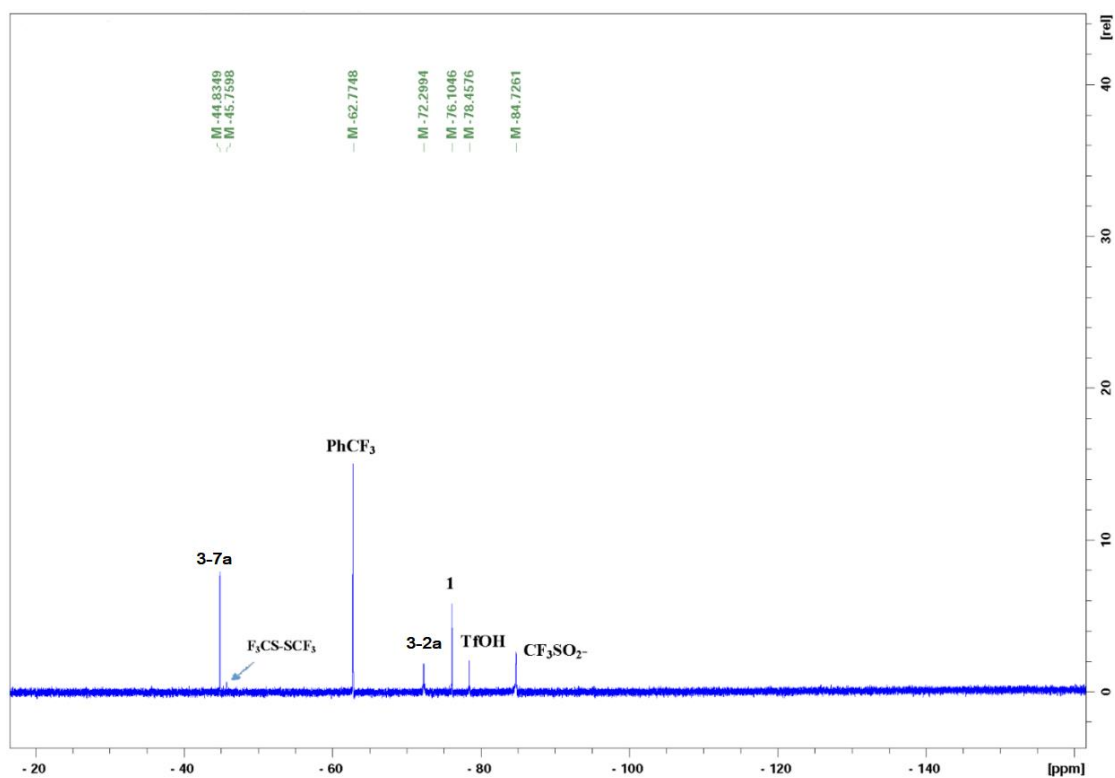
In contrast, in the case of conditions **B** involving CuOTf/HCl , a completely different reactivity is observed. The ^{19}F NMR monitoring shows four peaks after only 10 minutes. The majority peak is attributed to product **3-2a** ($\delta = -72.40$ ppm). The minority peak corresponds to **3-1** ($\delta = -76.20$ ppm), the other peaks are traces of TfOH ($\delta = -78.48$ ppm), and probably of trifluoromethanesulfonate ($\delta = -85.30$ ppm). After only 20 minutes, 3-

SCF₃-indole **3-7a** appeared. The reaction was complete after 20h without the compounds **3-2a** and **3-1**. Only the side products TfOH and CF₃SO₂Na were present.

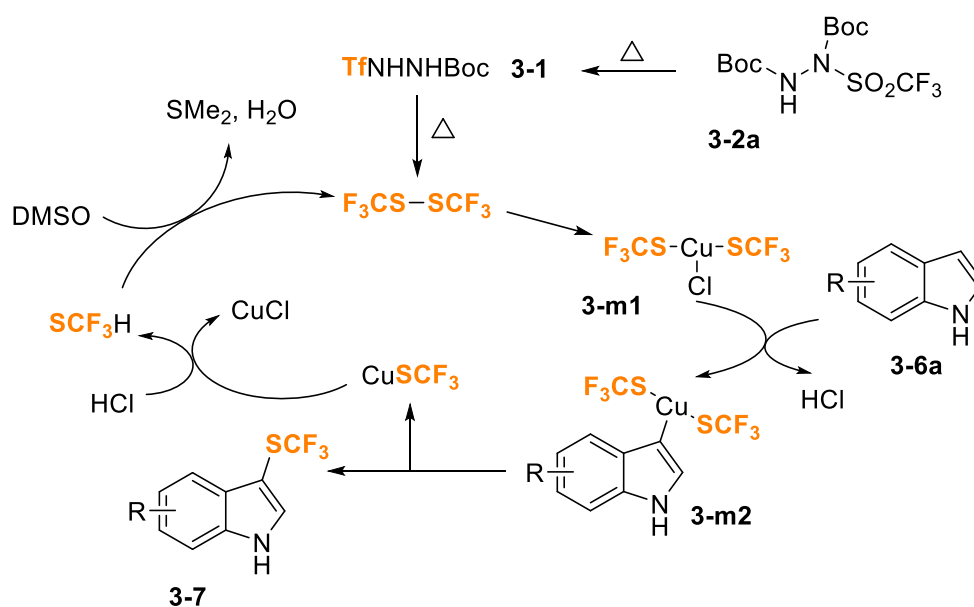
Conditions B: involving CuOTf/HCl in acetonitrile with PhCF₃ as internal standard

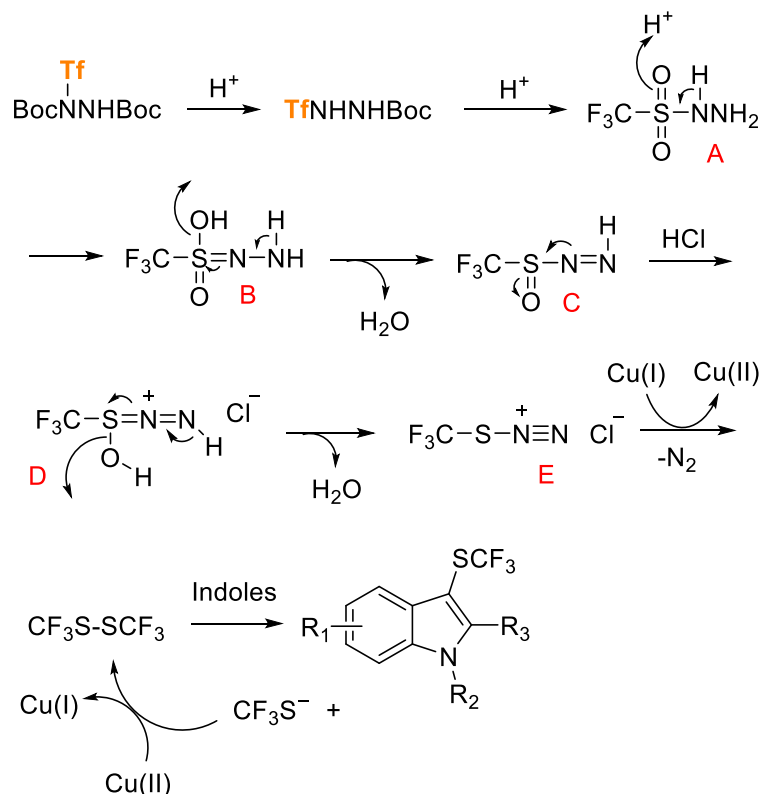


In addition, 1,2-bis(trifluoromethyl)disulfane (-45.76 ppm, Figure 3.2d), a key reaction intermediate, was detected in the medium.

Figure 3.2d Spectrum of ^{19}F NMR ($\text{F}_3\text{CS-SCF}_3$)

Based on the above experimental results and previous studies, the mechanism seems to be same with literature reported ^[11] (Scheme 3.2h and Scheme 3.2i).

Scheme 3.2h. Proposed reaction pathways with CuCl [Ref. 11]



Scheme 3.2i. Proposed reaction pathways with CuOTf [Ref. 10]

3.3 Conclusion

We have readily prepared a wide range of families of new fluorinated sulfonyl hydrazides from accessible and inexpensive sulfinates and azodicarboxylates. These hydrazides have been obtained under mild conditions and in excellent yields. In addition, these hydrazides are air-stable and can be stored for a long time.

Meanwhile, trifluoromethylsulfonyl hydrazide (Tf(Boc)N-NHBoc) is an efficient source of SCF₃ in the sulfenylation of indoles and is an alternative to the TfNHNHBoc reagent. Because in the case of sulfenylation of indoles with trifluoromethylsulfonyl hydrazide, it first undergoes Boc-group deprotection to give TfNHNHBoc, followed by the same mechanism to offer SCF₃-indoles.

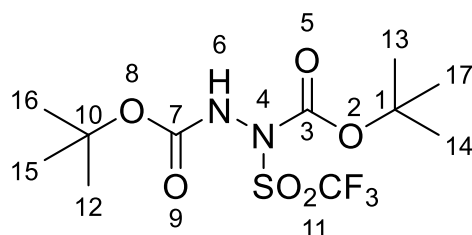
Experimental part

General Procedure (III) For the nucleophilic addition of sodium sulfinates on azodicarboxylates

1. With AcOH

To a solution of di-*tert*-butyl azodicarboxylate **3-3a** (1 equiv.) and R_fSO_2Na (1.2 equiv.) were added CH_3CN (8 mL), CH_2Cl_2 (2 mL) and AcOH (1.2 equiv.) successively. The mixture was stirred at 40 °C for 1~4 h. The crude product was diluted with CH_2Cl_2 , organic phase was washed by H_2O , $NaHCO_3$ (sat.) and brine successively, dried by Na_2SO_4 anhydrous. White solid was obtained after removing solvent, the hydrazide **3-2a/3-4a/3-5a** were afforded.

Di-*tert*-butyl 1-((trifluoromethyl) sulfonyl) hydrazine-1, 2-dicarboxylate [**3-2a**]



3-2a

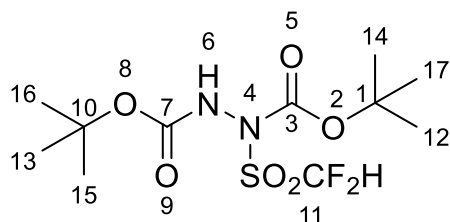
3-2a was prepared with di-*tert*-butyl azodicarboxylate (230 mg, 1 mmol), CF_3SO_2Na (187 mg, 1.2 mmol) and AcOH (72 mg, 1.2 mmol) in CH_3CN/CH_2Cl_2 (8mL/2mL) following general procedure. After evaporation of solvents, the hydrazide **3-2a** was isolated through a silica gel flash column (Cyclohexane/EtOAc: 9/1) as a white solid (307 mg, 84% yield).

On a large scale, the reaction was carried out with 1.15 g of **3-3a** and resulted in 1.53 g of **3-2a** with a yield of 84%.

1H NMR (300 MHz, $CDCl_3$) δ (ppm) 6.86 (brs, 1H, H_6), 1.48 (s, 9H, H_{methyl}), 1.42 (s, 9H, H_{methyl}). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 153.2 (C_3), 148.3 (C_7), 119.4 (q, $J = 324.4$ Hz, C_{11}), 88.1 (C_1), 83.6 (C_{10}), 27.9 (C_{methyl}), 27.6 (C_{methyl}). ^{19}F NMR (188 MHz,

CDCl_3) δ (ppm) -72.19 (s, $-\text{SO}_2\text{CF}_3$). **HRMS** m/z $\text{C}_{11}\text{H}_{19}\text{F}_3\text{N}_2\text{O}_6\text{S}$ $[\text{M}+\text{NH}_4]^+$ cal. 382.1260, found. 382.1268. m.p: 104°C - 106°C .

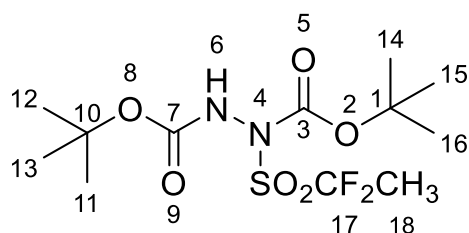
Di-*tert*-butyl 1-((difluoromethyl) sulfonyl) hydrazine-1, 2-dicarboxylate [3-4a]



3-4a

To a solution of di-*tert*-butyl azodicarboxylate (230 mg, 1 mmol) and $\text{HCF}_2\text{SO}_2\text{Na}$ (166 mg, 1.2 mmol) in $\text{CH}_3\text{CN}/\text{CH}_2\text{Cl}_2$ (8mL/2mL) was added AcOH (72 mg, 1.2 mmol) following general procedure to afford **3-4a** (339 mg, 98% yield). **^1H NMR (300 MHz, CDCl_3)** δ (ppm) 6.87 (s, 1H, H₆), 6.64 (t, $J = 54.16$ Hz, 1H, H₁₁), 1.47 (s, 9H, H_{methyl}), 1.42 (s, 9H, H_{methyl}). **^{13}C NMR (75 MHz, CDCl_3)** δ (ppm) 153.9 (C₃), 149.6 (C₇), 114.4 (t, $J = 286.1$ Hz, C₁₁), 87.6 (C₁), 83.6 (C₁₀), 27.9 (C_{methyl}), 27.7 (C_{methyl}). **^{19}F NMR (188 MHz, CDCl_3)** δ (ppm) -115.79 (dd, $J = 262.4$ Hz, $J = 54.6$ Hz, 1F), -118.22 (dd, $J = 261.9$ Hz, $J = 56.1$ Hz, 1F). **HRMS** m/z $\text{C}_{17}\text{H}_{15}\text{F}_3\text{N}_2\text{O}_6\text{S}$ $[\text{M}+\text{Na}]^+$ cal. 455.0501, found. 455.0507. m.p : 118°C - 119°C .

Di-*tert*-butyl 1-((1,1-difluoroethyl) sulfonyl) hydrazine-1, 2-dicarboxylate [3-5a]



3-5a

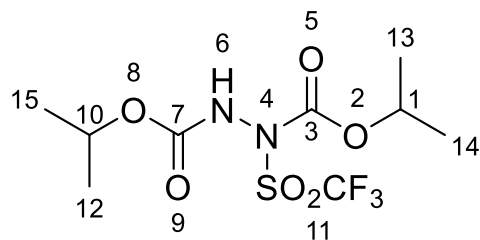
3-5a was prepared through di-*tert*-butyl azodicarboxylate (230 mg, 1 mmol), $\text{CH}_3\text{CF}_2\text{SO}_2\text{Na}$ (183 mg, 1.2 mmol) in $\text{CH}_3\text{CN}/\text{CH}_2\text{Cl}_2$ (8mL/2mL) and AcOH (72 mg, 1.2 mmol) following general procedure to obtain **3-5a** (353 mg, 98% yield). **^1H NMR (200 MHz, CDCl_3)** δ (ppm) 7.16 (s, 1H, H₆), 2.04 (t, $J = 18.93$ Hz, 3H, H₁₈), 1.47 (s,

9H, H_{methyl}), 1.43 (s, 9H, H_{methyl}). ¹³C NMR (75 MHz, CDCl₃) δ (ppm) 153.6 (C₃), 149.2 (C₇), 124.5 (t, *J* = 286.9 Hz, C₁₇), 86.6 (C₁), 82.8 (C₁₀), 27.8 (C_{methyl}), 27.6 (C_{methyl}), 19.3 (t, *J* = 22.2 Hz, C₁₈). ¹⁹F NMR (188 MHz, CDCl₃) δ (ppm) δ -91.56 (q, *J* = 17.65 Hz, 2F), -91.56 (brs, 2F). HRMS *m/z* C₁₂H₂₂F₂N₂O₆S [M+Na]⁺ cal. 383.1064, found. 383.1061. m.p :84°C-86°C.

2. With TFA (Trifluoroacetic acid)

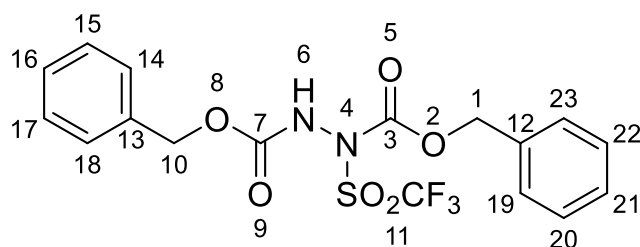
R_fSO₂Na (1.05 equiv.) firstly mixed with TFA (1.05 equiv.) in methanol for 15 minutes. The mixture was cooled down to 0 °C, azodicarboxylates (1 equiv.) was added slowly. After that, the solution was stirred at room temperature for 30 minutes to 1h and concentrated in vacuo. The crude product was diluted with CH₂Cl₂, organic phase was washed by H₂O, NaHCO₃ (sat.) and brine successively, dried by Na₂SO₄ anhydrous. After removal of solvent, corresponding products were afforded.

Di-isopropyl 1-((trifluoromethyl) sulfonyl) hydrazine-1, 2-dicarboxylate [3-2b]

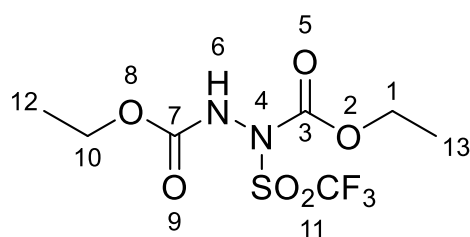


3-2b

The title compound was prepared with di-isopropyl azodicarboxylate (202 mg, 1 mmol), CF₃SO₂Na (164 mg, 1.05 mmol), TFA (120 mg, 1.05 mmol) in 10 mL methanol following general procedure as yellow solid (306 mg, 91% yield). ¹H NMR (300 MHz, CDCl₃) δ (ppm) 7.59 (brs, 1H, H₆), 5.08-4.89 (m, 2H, H₁ and 10), 1.24 (d, *J* = 19.56 Hz, 12H, H_{methyl}). ¹³C NMR (75 MHz, CDCl₃) δ (ppm) 154.3 (C₃), 149.6 (C₇), 119.3 (q, *J* = 324.5 Hz, C₁₁), 75.4 (C₁), 71.7 (C₁₀), 21.5 (C_{methyl}), 21.2 (C_{methyl}). ¹⁹F NMR (188 MHz, CDCl₃) δ (ppm) -72.22 (s, SO₂CF₃). HRMS *m/z* C₉H₁₅F₃N₂O₆S [M+Na]⁺ cal. 359.0501, found. 359.0506. m.p : 62°C-63°C.

Di-benzyl 1-((trifluoromethyl) sulfonyl) hydrazine-1, 2-dicarboxylate [3-2c]**3-2c**

The title compound was prepared with di-benzyl azodicarboxylate (298 mg, 1 mmol), $\text{CF}_3\text{SO}_2\text{Na}$ (164 mg, 1.05 mmol) and TFA (120 mg, 1.05 mmol) in 10 mL methanol following general procedure as white solid (406 mg, 94% yield). $^1\text{H NMR}$ (300 MHz, CDCl_3) δ (ppm) 7.51 (s, 1H, H_6), 7.39-7.36 (m, 10H, H_{arom}), 5.32 (s, 2H, H_1), 5.19 (s, 2H, H_{10}). $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ (ppm) 154.5 (C_3), 150.2 (C_7), 134.7 (C_{12}), 133.4 (C_{13}), 129.1 (C_{arom}), 128.8 (C_{arom}), 128.7 (C_{arom}), 128.6 (C_{arom}), 128.4 (C_{arom}), 128.3 (C_{arom}), 119.3 (q, $J = 324.8$ Hz, SO_2CF_3), 71.5 (C_1), 69.0 (C_{10}). $^{19}\text{F NMR}$ (188 MHz, CDCl_3) δ (ppm) -72.13 (s, SO_2CF_3). HRMS m/z $\text{C}_{17}\text{H}_{15}\text{F}_3\text{N}_2\text{O}_6\text{S}$ [$\text{M}+\text{Na}$] $^+$ cal. 455.0501, found. 455.0507. m.p : 92°C-95°C.

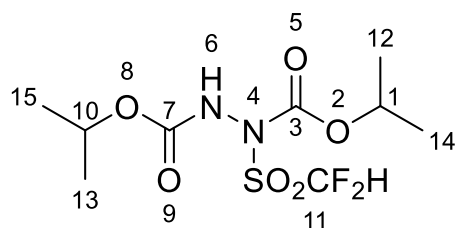
Di-ethyl 1-((trifluoromethyl) sulfonyl) hydrazine-1, 2-dicarboxylate [3-2d]**3-2d**

The title compound was prepared with di-ethyl azodicarboxylate (174 mg, 1 mmol), $\text{CF}_3\text{SO}_2\text{Na}$ (164 mg, 1.05 mmol), TFA (120 mg, 1.05 mmol) in 10 mL methanol following general procedure as yellow solid (289 mg, 94% yield). $^1\text{H NMR}$ (300 MHz, CDCl_3) δ (ppm) 7.55 (brs, 1H, H_6), 4.40 (q, $J = 7.11$ Hz, 2H, H_1), 4.26 (q, $J = 7.09$ Hz, 2H, H_{10}), 1.35 (t, $J = 7.14$ Hz, 3H, H_{methyl}), 1.29 (t, $J = 7.16$ Hz, 3H, H_{methyl}). $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ (ppm) 154.6 (C_3), 150.2 (C_7), 119.3 (q, $J = 324.6$ Hz, C_{11}), 66.2 (C_1), 63.5 (C_{10}), 14.0 (C_{methyl}), 13.7 (C_{methyl}). $^{19}\text{F NMR}$ (188 MHz, CDCl_3) δ (ppm) -

72.06 (s, SO₂CF₃). **HRMS** m/z C₇H₁₁F₃N₂O₆S [M+Na]⁺ cal. 331.0188, found. 331.0186.

m.p : 61°C-64°C.

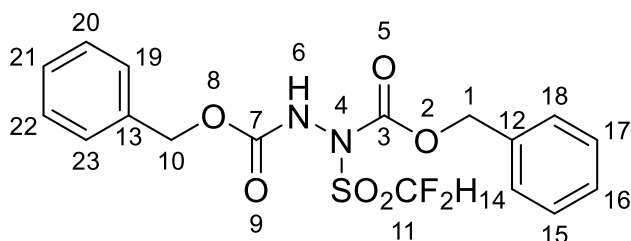
Di-isopropyl 1-((difluoromethyl) sulfonyl) hydrazine-1, 2-dicardoxylate [3-4b]



3-4b

Di-isopropyl azodicarboxylate (202 mg, 1 mmol), HCF₂SO₂Na (145 mg, 1.05 mmol), TFA (120 mg, 1.05 mmol) in 10 mL methanol following general procedure to afford **3-4b** white solid (311 mg, 98% yield). **¹H NMR (300 MHz, CDCl₃)** δ (ppm) 7.28 (s, 1H, H₆), 6.66 (t, $J = 53.78$ Hz, 1H, H₁₁), 5.08-4.88 (m, 2H, H₁ and 10), 1.29 and 1.27 (d, $J_{1.29} = 6.30$ Hz, $J_{1.27} = 6.36$ Hz, 6H, H_{methyl}), 1.23 (d, $J = 6.24$ Hz, 6H, H_{methyl}). **¹³C NMR (75 MHz, CDCl₃)** δ (ppm) 154.8 (C₃), 150.8 (C₇), 114.4 (t, $J = 288.6$ Hz, C₁₁), 74.9 (C₁), 71.9 (C₁₀), 21.7 (C_{methyl}), 21.5 and 21.4 (C_{methyl}). **¹⁹F NMR (188 MHz, CDCl₃)** δ (ppm) -116.28 (dd, $J = 261.9$ Hz, $J = 54.2$ Hz, 1F), -118.37 (dd, $J = 260.9$ Hz, $J = 56.5$ Hz, 1F). **HRMS** m/z C₉H₁₆F₂N₂O₆S [M+Na]⁺ cal. 341.0595, found. 341.0597. m.p : 81°C.

Di-benzyl 1-((difluoromethyl) sulfonyl) hydrazine-1, 2-dicardoxylate [3-4c]

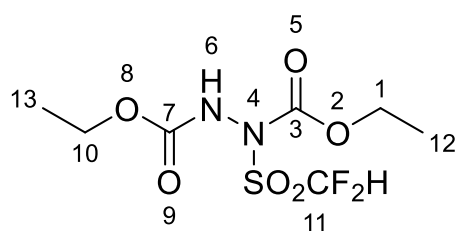


3-4c

The title compound was obtained from di-benzyl azodicarboxylate (298 mg, 1 mmol), HCF₂SO₂Na (145 mg, 1.05 mmol), TFA (120 mg, 1.05 mmol) in 10 mL methanol following general procedure as a white solid. (309 mg, 75% yield). **¹H NMR (300 MHz, CDCl₃)** δ (ppm) 7.56 (s, 1H, H₆), 7.38-7.36 (m, 10H, H_{arom}), 6.72 (t, $J = 53.88$ Hz, 1H,

H₁₁), 5.29 (s, 2H, H₁), 5.17 (s, 2H, H₁₀). ¹³C NMR (75 MHz, CDCl₃) δ (ppm) 155.0 (C₃), 151.3 (C₇), 134.7 (C₁₂), 133.5 (C₁₃), 129.1 (C_{arom}), 128.9 (C_{arom}), 128.8 (C_{arom}), 128.7 (C_{arom}), 128.4 (C_{arom}), 128.3 (C_{arom}), 114.3 (t, *J* = 287.3 Hz, C₁₁), 71.1 (C₁), 69.0 (C₁₀). ¹⁹F NMR (188 MHz, CDCl₃) δ (ppm) -116.39 (dd, *J* = 260.05 Hz, *J* = 54.5 Hz, 1F), -118.41 (dd, *J* = 262.1 Hz, *J* = 56.6 Hz, 1F). HRMS *m/z* C₁₇H₁₆F₂N₂O₆S [M+Na]⁺ cal. 437.0595, found. 437.0591. m.p : 86 °C.

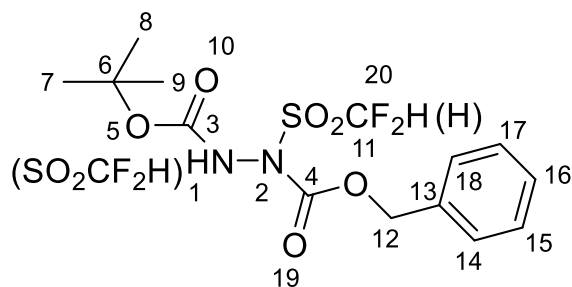
Di-ethyl 1-((difluoromethyl) sulfonyl) hydrazine-1, 2-dicarboxylate [3-4d]



3-4d

3-4d was prepared from di-ethyl azodicarboxylate (174 mg, 1 mmol), HCF₂SO₂Na (145 mg, 1.05 mmol), TFA (120 mg, 1.05 mmol) in 10 mL methanol following general procedure as a white solid. (259 mg, 89% yield). ¹H NMR (300 MHz, CDCl₃) δ (ppm) 7.49 (s, 1H, H₆), 6.66 (t, *J* = 53.72 Hz, 1H, H₁₁), 4.31 (q, *J* = 7.12 Hz, 2H, H₁), 4.19 (q, *J* = 7.23 Hz, 2H, H₁₀), 1.29 and 1.23 (t, *J*_{1.29} = 7.31 Hz, *J*_{1.23} = 7.74 Hz, 6H, H_{methyl}). ¹³C NMR (75 MHz, CDCl₃) δ (ppm) 155.2 (C₃), 151.4 (C₇), 114.4 (t, *J* = 288.0 Hz, C₁₁), 65.9 (C₁), 63.5 (C₁₀), 14.2 (C_{methyl}), 13.9 (C_{methyl}). ¹⁹F NMR (188 MHz, CDCl₃) δ (ppm) -116.28 (dd, *J* = 262.2 Hz, *J* = 52.8 Hz, 1F), -118.53 (dd, *J* = 260.2 Hz, *J* = 52.8 Hz, 1F). HRMS *m/z* C₇H₁₂F₂N₂O₆S [M+Na]⁺ cal. 313.0282, found. 313.0292. m.p : 66 °C.

2-Benzyl 1-(*tert*-butyl) 1-((difluoromethyl) sulfonyl) hydrazine-1,2-dicarboxylate and 1-benzyl 2-(*tert*-butyl) 1-((difluoromethyl) sulfonyl) hydrazine-1,2-dicarboxylate [3-4e]

**3-4e**

The title compounds were prepared from 1-benzyl 2-(*tert*-butyl) hydrazine-1,2-dicarboxylate (266 mg, 1 mmol), which was treated with NBS (196 mg, 1.1 mmol) and pyridine (87 mg, 1.1 mmol) in CH₂Cl₂ at 0 °C to afford corresponding diazene. After removal of solvent, the diazene was dissolved in CH₃CN/CH₂Cl₂ (8 mL/2mL), subsequently, mixture of acetic acid (120 mg, 2 mmol) and (207 mg, 1.5 mmol) in CH₃CN/CH₂Cl₂ (1 mL) was added into reaction solution drop by drop at room temperature. The mixture was stirred at rt for 1h and concentrated in vacuo. Crude product was diluted by CH₂Cl₂, organic phase was washed by H₂O, HCl (1N), NaHCO₃ (sat.) and brine successively, as well as dried by Na₂SO₄ anhydrous. Final product was obtained as colorless oil after evaporating solvent. (345 mg, 91% yield). **¹H NMR (300 MHz, CDCl₃)** δ (ppm) 7.51 (s, 1H, H₁), 7.26-7.22 (m, 5H, H_{arom}), 6.61 (t, *J* = 53.97 Hz, 1H, H₂₀), 5.21-5.06 (dd, *J*₁ = 15.88 Hz, *J*₂ = 15.40 Hz, 4H, H₁₂), 1.39 and 1.34 (s, 9 H, H_{methyl}). **¹³C NMR (75 MHz, CDCl₃)** δ (ppm) 155.3 and 153.9 (C₃ and 4), 151.6 and 149.5 (C₄ and 3), 134.9 and 133.7 (C₁₃), 129.0 (C_{arom}), 128.7 and 128.6 (C_{arom}), 128.4 and 128.3 (C_{arom}), 114.4 (t, *J* = 288.0 Hz, C₂₀), 88.0 and 83.9 (C₆), 70.8 and 68.8 (C₁₂), 27.9 and 27.6 (C_{methyl}). **¹⁹F NMR (188 MHz, CDCl₃)** δ (ppm) δ -115.30 to -120.05 (m, -CF₂H). **HRMS** *m/z* C₁₄H₁₈F₂N₂O₆S [M+Na]⁺ cal. 403.0751, found. 403.0749.

General Procedure (IV) Sulfenylation of indoles with TfHBocNHBoc

Conditions A: To a reaction a tube was charged with TfNBocNHBoc (**3-2a**) (211 mg, 0.80 mmol), indole **3-6a** (0.40 mmol), and CuCl (4.0 mg, 10 mol%). The tube was sealed with a septum, evacuated, and backfilled with nitrogen three times. DMSO (31.2

mg, 28 μ L, 0.40 mmol) and MeCN (2.0 mL) were added via syringe. After stirring at 80 °C for 22 h, the mixture was cooled to room temperature and purified directly by silica gel chromatography, eluting with ethyl acetate/cyclohexane (1:10), to give indole thioether **3-7a~3-7g**.

Conditions B: A 15 mL sealing tube with a magnetic stirring bar was charged with indole **3-6a** (0.5 mmol), TfNBocNHBoc (158 mg, 0.6 mmol) and CuOTf (11 mg, 0.05 mmol), and dry acetonitrile (2 mL) was added via a syringe with gentle stirring. Then 12 M HCl (aq.) (8 μ L, 0.1 mmol) was added to the reaction mixture. After stirring at 70 °C for 16h, the reaction mixture was concentrated and purified directly by silica gel chromatography, eluting with petroleum ether/ethyl acetate (9/1), to give compound **3-7a~3-7g**.

References

- [1] X. H. Xu, K. Matsuzaki, N. Shibata, *Chem. Rev.* **2015**, 115, 731.
- [2] H. Guyon, H. Chachignon, D. Cahard, *Beilstein J. Org. Chem.* **2017**, 13, 2764.
- [3] R. Rafique, K. M. Khan, Arshia, S. Chigurupati, A. Wadood, A. Ur Rehman, U. Salar, V. Venugopal, S. Shamim, M. Taha, S. Perveen, *Bioorg. Chem.* **2020**, 94, 103410.
- [4] B. A. Shainyan, L. L. Tolstikova, V. I. Meshcheryakov, Yu. S. Danilevich, *Russ. J. Org. Chem.* **2004**, 40, 1071-1075.
- [5] L. M. Yagupolskii, I. I. Maletina, K. I. Petko, D. V. Fedjuk, R. Handrock, S. S. Shavaran, B. M. Klebanov, S. Herzig, *J. Fluorine Chem.* **2001**, 109, 87.
- [6] M. E. Jr. Houston, D. L. V. Jagt, J. F. Honek, *Bioorg. Med. Chem. Lett.* **1991**, 1, 623.
- [7] F. Toulgoat, S. Alazet, T. Billard, *Eur. J. Org. Chem.* **2014**, 12, 2415-2428.
- [8] X. H. Xu, K. Matsuzaki, N. Shibata, *Chem. Rev.* **2015**, 115, 731–764.
- [9] J. Y. Guo, R. X. Wu, J. K. Jin, S. K. Tian, *Org. Lett.* **2016**, 18, 15, 3850–3853.
- [10] J. Y. Guo, R. H. Dai, W. C. Xu, R. X. Wu, S. K. Tian, *Chem. Commun.* **2018**, 54, 8980-8982.
- [11] K. Lu, Q. Li, X. L. Xi, Y. N. Huang, Z. Gong, P. Yu, X. Zhao, *Org. Chem. Front.* **2018**, 5, 3088–3092.
- [12] K. Lu, Z. Deng, M. Li, T. Li, X. Zhao, *Org. Biomol. Chem.* **2017**, 15, 1254-1260.
- [13] H. Chachignon, M. Maeno, H. Kondo, N. Shibata, D. Cahard, *Org. Lett.* **2016**, 18, 2467-2470.
- [14] L. Jiang, J. Qian, W. Yi, G. Lu, C. Cai, W. Zhang, *Angew. Chem. Int. Ed.* **2015**, 54, 14965-14969.
- [15] Q. Yan, L. Jiang, W. Yi, Q. Liu, W. Zhang, *Adv. Synth. Catal.* **2017**, 359, 2471-2480.
- [16] M. J. Bu, G. P. Lu, C. Cai, *Org. Chem. Front.* **2017**, 4, 266-270.
- [17] X. Zhao, A. Wei, B. Yang, T. Li, Q. Li, D. Qiu, K. Lu, *J. Org. Chem.* **2017**, 82, 9175-9181.
- [18] F. Wang, G. P. Lu, Y. Lin, *Tetrahedron Lett.* **2021**, 70, 153015.
- [19] A. Bredikhin, O. Tšubrik, R. Sillard, U. Mäeorg, *Synlett.* **2005**, No. 12, 1939–1941.
- [20] V. I. Meshcheryakov, B. A. Shainyan, L. L. Tolstikova, A. I. Albanov, *Russ. J.*

Org. Chem. **2003**, 39, 1517-1521.

[21] J. W. Wen, W. Wei, D. S. Yang, Y. F. Fan, L. L. Fu, H. Wang, *Synth. Commun.* **2015**, 45, 1574-1584.

[22] P. Wang, S. S. Zhu, D. F. Lu, Y. F. Gong, *Org. Lett.* **2020**, 22, 5, 1924–1928.

Chapter IV

Fluorinated Azapeptides and Azapeptoids

4.1 Peptide-based drugs

Peptide-based drugs generally offer greater efficacy, high potency and selectivity than non-peptide molecules, and thus their interest is growing regularly.^[1] In recent years, the peptide-based drug market has expanded expeditiously. It is estimated that the global peptide drugs market will be worth around USD 48.04 billion by 2025, with a compound annual growth rate of 9.4%.^[2] However, peptides as drugs usually suffer from rapid proteolysis, poor membrane permeability and sometimes poor solubility (Table 4.1).^[3]

Advantages	Disadvantages
High potency	Poor metabolic stability
High selectivity	Poor membrane permeability
Broad range of targets	Poor oral bioavailability
Potentially lower toxicity than small molecules	High production costs
Low accumulation in tissues	Rapid clearance
High chemical and biological diversity	Sometimes poor solubility
Discoverable at peptide and/or nucleic acid levels	

Table 4.1 Advantages and disadvantages of peptides as drugs

To overcome these problems, the development of peptidomimetics, which are more stable analogues of peptides, has experienced significant growth in recent years.^{[4]-[7]}

Indeed, in addition to increasing the selectivity and efficiency of natural peptides, these compounds can reduce side effects, improve bioavailability and prolong the pharmacological activity of related natural peptides.^[8]

The first peptidomimetics were obtained by modifying the N and C-terminal ends, the methylation of the nitrogen of the amide function or the replacement of *L* amino acids with *D* amino acids (Figure 4.1a).^{[9]-[10]} The introduction of isostere of amide function

makes it possible to avoid enzymatic degradation and modifies the peptide's biochemical properties, in particular, its conformation and hydrophobicity.^[11]

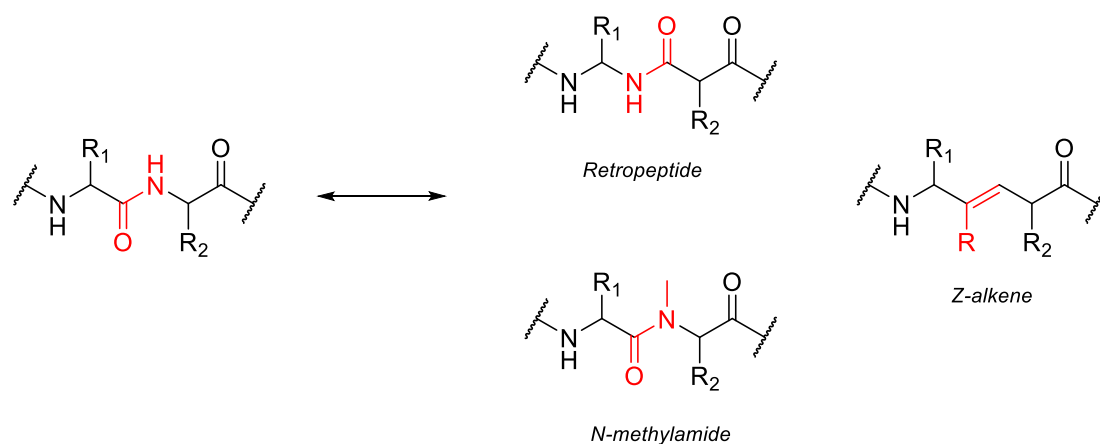


Figure 4.1a. Examples of isosteres of amide group

A very large number of peptidomimetics are described in the literature. In particular, azapeptides and azapeptoids which belong to the family of peptidomimetics, have attracted attention (Figure 4.1b).

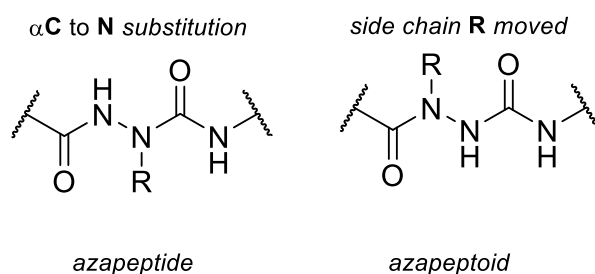


Figure 4.1b Azapeptides and azapeptoids

4.2 Azapeptides and azapeptoids

Aza-amino acids, where the α -carbon is replaced by a nitrogen atom, have found great utility in fine-tuning the structural and conformational properties of peptides for biomedical^{[12]-[13]} and biomaterials^{[14]-[17]} applications. Furthermore, the azapeptides bring specific advantages such as greater protease stability,^[18] higher hydrogen bonds

(Figure 4.2a (1)). For example, the replacement of the Glycine (Gly) by aza-Glycine (azGly) in collagen increased the number of interfacial cross-strand H-bonds, leading to hyperstability in the triple-helical form (PPII (polyproline type-II) helical secondary structures).^{[14],[16],[19]} In the case of azapeptides with different R groups, their incorporation in peptides favors β -turn^[20] (Figure 4.2a (2)).

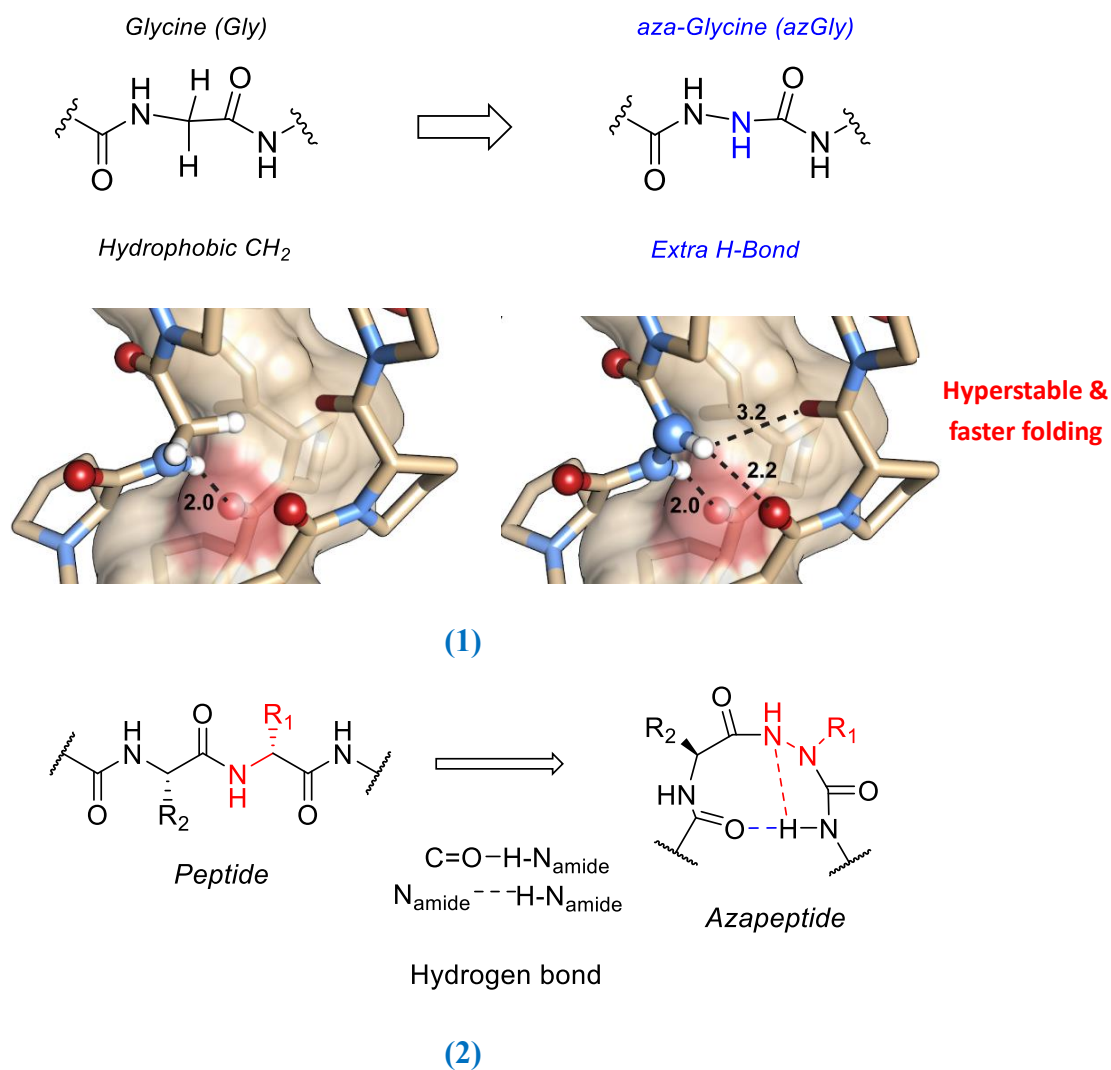


Figure 4.2a. (1) Additional H-bonds due to azGly substitution. (2) $\text{N}_{\text{amide}} \cdots \text{H}-\text{N}_{\text{amide}}$ HBs contribute to form β -turns

Unlike azapeptides, azapeptoids where the NH of the amide group is alkylated (Figure 4.2b), are poorly reported in the literature and no specific data reported. We can find, in one example, comparative analyses of RGD mimics that revealed profound differences in the binding affinities of azaGlycine (zaGly), azaSarcosine (azaSar) and

azaAlanine (azaAla) analogues (Figure 4.2b). The azaGly-containing RGD-mimetics showed weak inhibitory activity on receptors. Only the azapeptide derivative, azaSar, was found to bind selectively to the α Ib β 3 receptor.^[21] (Figure 4.2b)

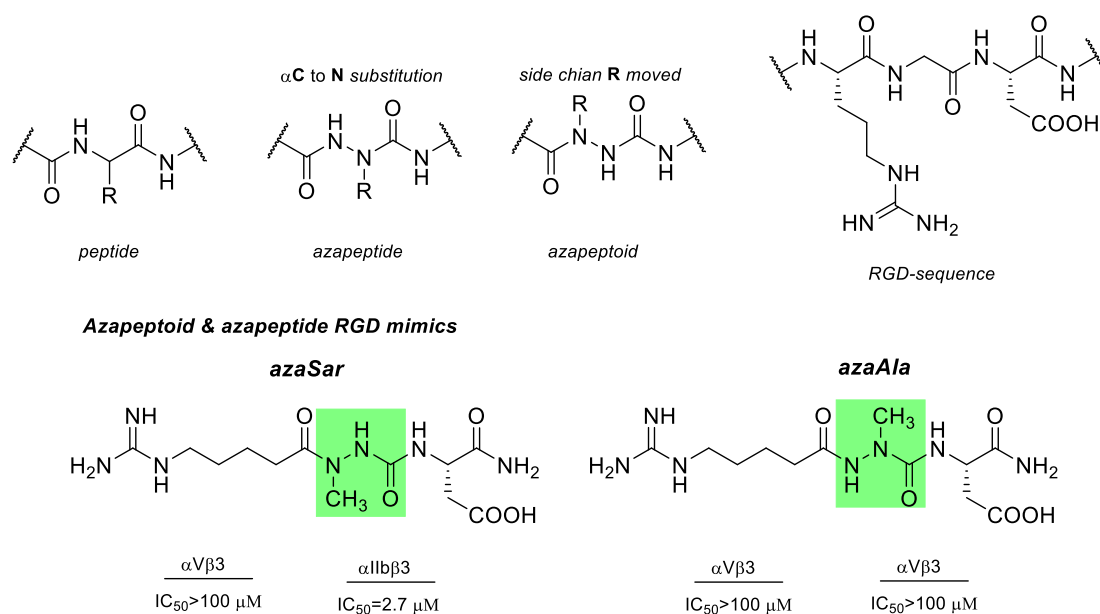
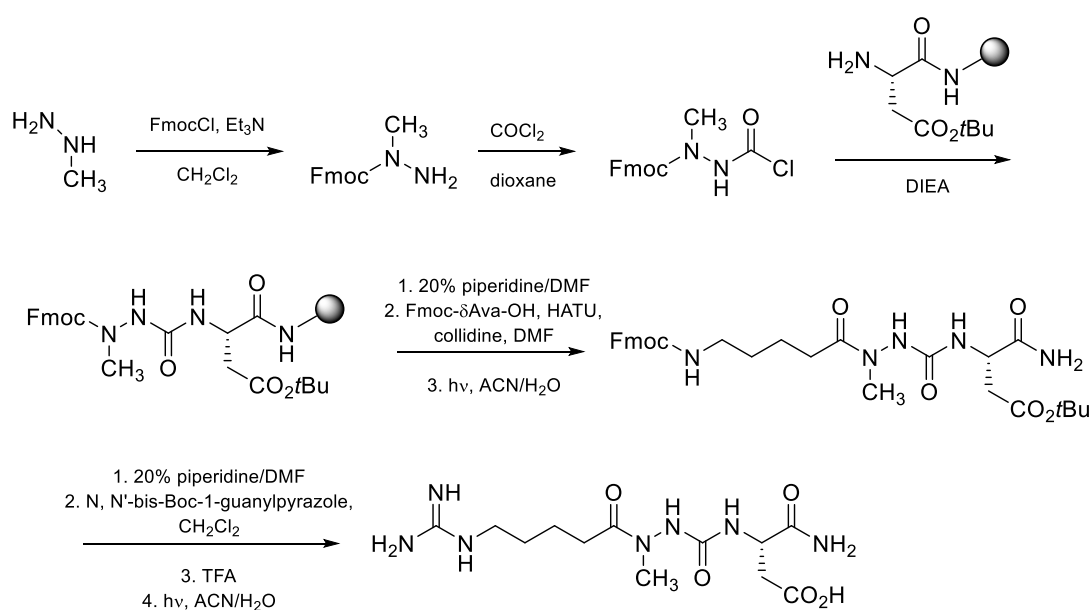


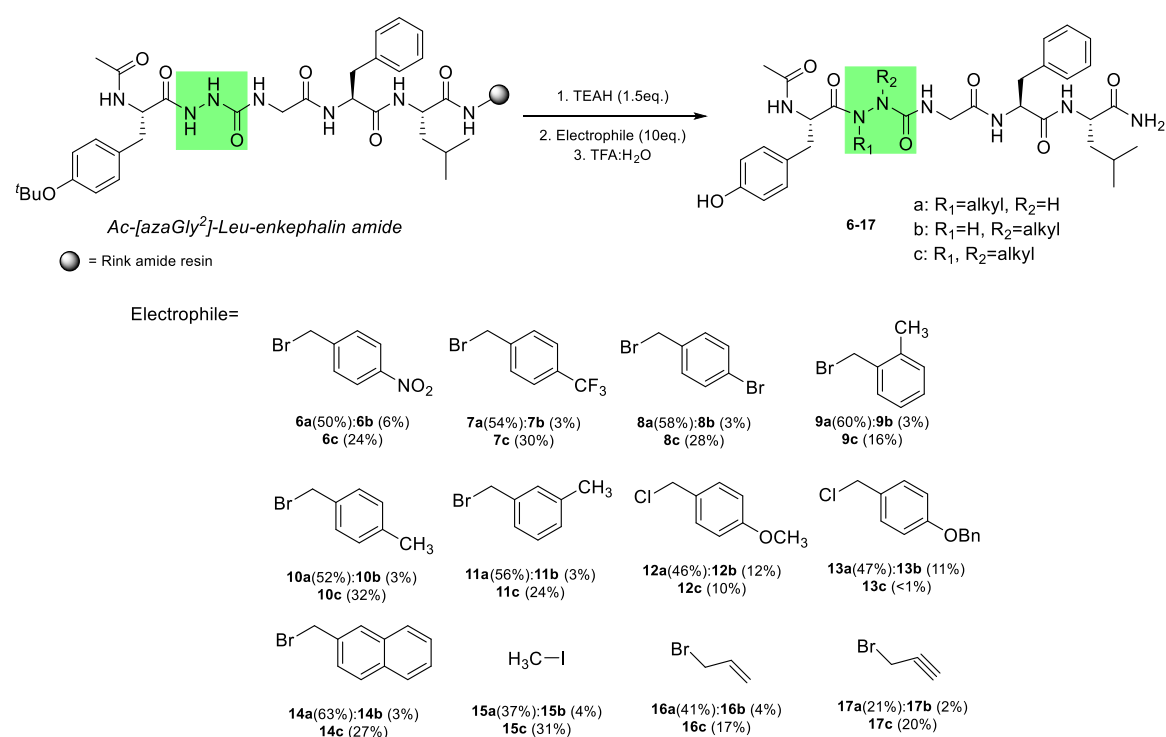
Figure 4.2b. Azapeptide/Azapeptoid, RGD-sequence and receptor binding and selectivity of azapeptoid and azapeptide RGD mimics

The azapeptoid is prepared according to peptide coupling from alkylated hydrazines. And it undergoes multi-step to afford the final product (Scheme 4.2a).



Scheme 4.2a Synthesis of azapeptoid

In this line, the Proulx's group^[22] recently reported the direct late-stage *N*-alkylation of aza-glycine on resin to afford azapeptoids selectively. The best conditions to obtain predominantly monoalkylated azapeptoids are the use of tetraethylammonium hydroxide (TEAH) and 10 equivalents of electrophile which are benzyl bromide derivatives, methyl iodide, allyl bromide and propargyl bromide (Scheme 4.2b). Interestingly, during this study, the authors noticed that when they changed the counterion of the hydroxide (tetramethylammonium hydroxide (TMAH) and 12 equivalents of electrophile), the dialkylated compounds were in the majority.



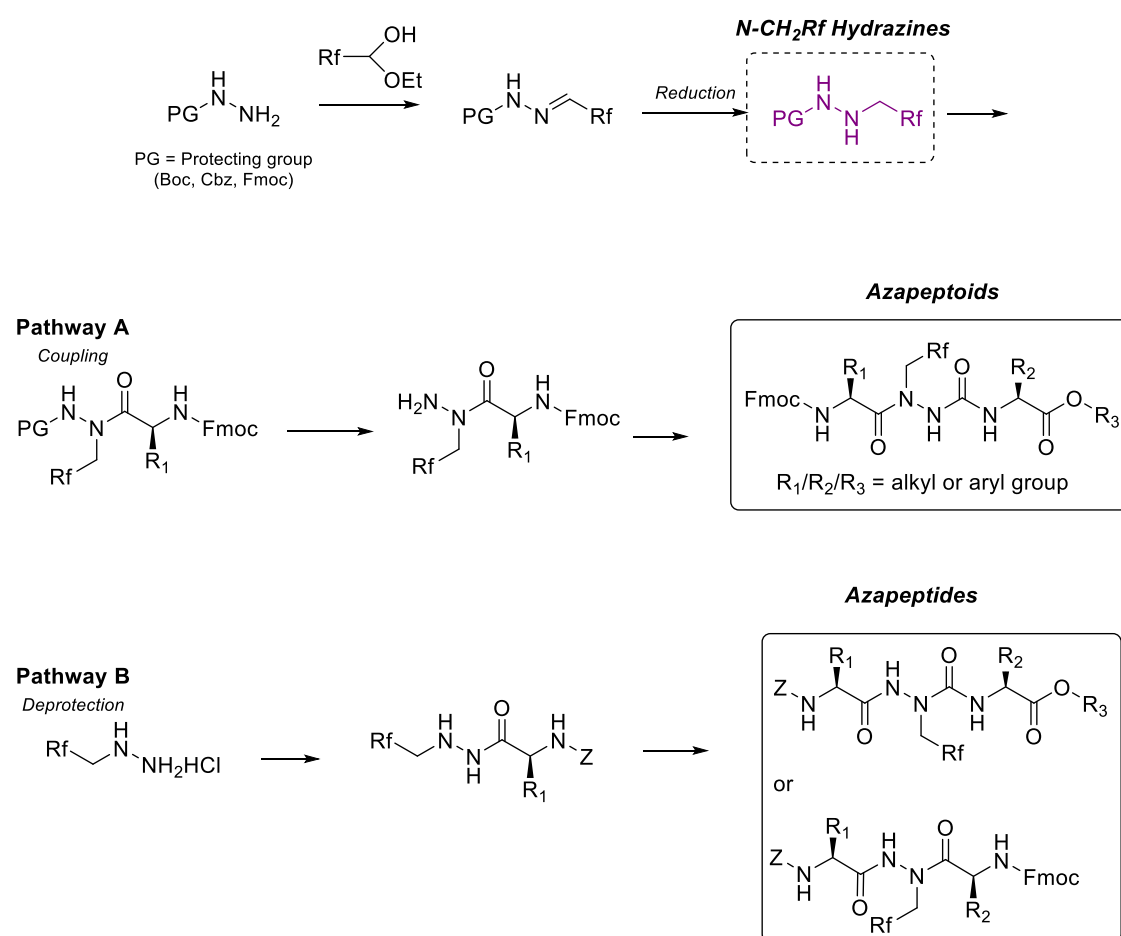
Scheme 4.2b Direct *N*-alkylation of aza-glycine to access selectively azapeptoids

Meanwhile, due to our interest in the synthesis of fluorinated amino-acids and peptidomimetics, we were particularly intrigued by the fact that the synthesis of RfCH₂N azapeptides and azapeptoids has not been reported in the literature to date. Only one example was reported in synthesising azapeptide inhibitors of Hepatitis C Virus Serine protease.^[23] However, the experimental conditions are not detailed. Faced with this lack of data, we were interested in the synthesis of fluorinated (CF₃ and CF₂H ethyl group) azapeptides and azapeptoids better to know their contribution in the

conformation of peptides.

4.3 Synthesis of *N*-Fluorinated peptides, azapeptides and azapeptoids

In order to access aza-derivatives, this procedure starts with fluorinated hydrazones which undergoes a reduction to afford hydrazines. These are coupled with amino acids to produce azapeptides. The different approaches are present in the following Scheme 4.3.

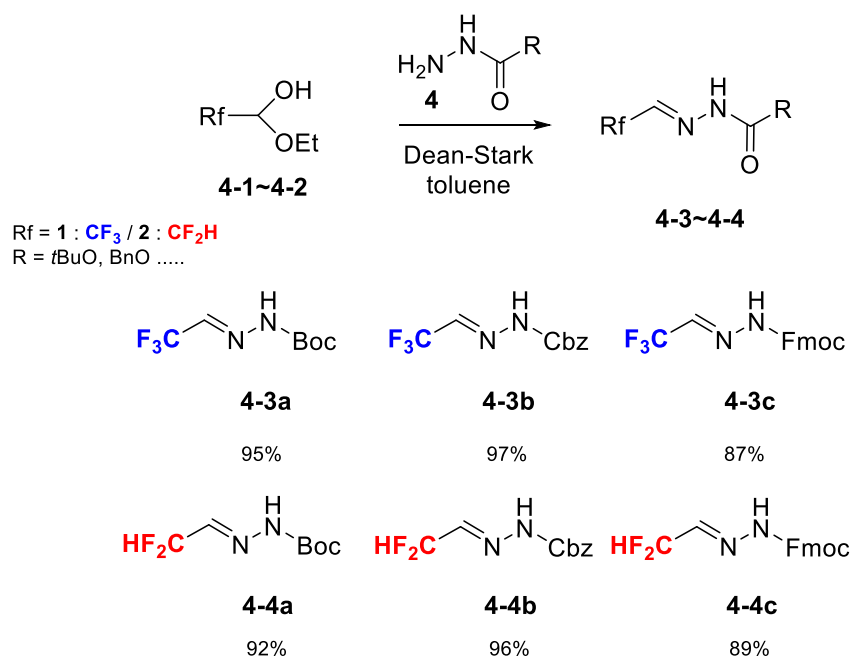


Scheme 4.3 General procedures of accessing to fluorinated aza-derivatives

4.3.1 Preparation of *N*-Fluorinated hydrazones and hydrazines

The trifluoromethyl and difluoromethyl hydrazones are first prepared in toluene with

catalytic amount of *p*-toluenesulfonic acid (APTS) from hydrazides having different protective groups such as Boc, Cbz, Fmoc and trifluoro or difluoro acetaldehyde ethyl hemiacetal (**4-1/4-2**).^[24] The formation of water is eliminated using a Dean-Stark apparatus. The corresponding fluorinated hydrazones (**4-3** and **4-4**) were successfully obtained with good to excellent yields. (Scheme 4.3.1a, 87%-97%).



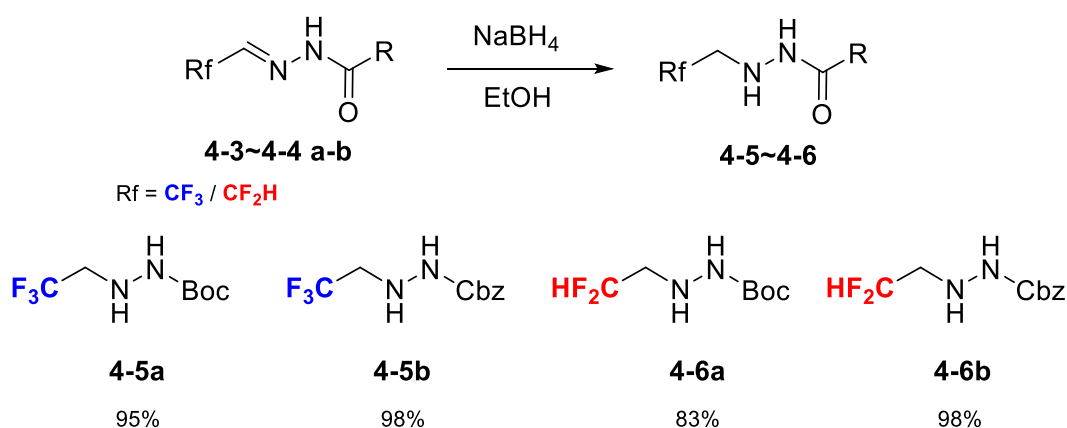
Scheme 4.3.1a Preparation of fluorinated hydrazones

Subsequently, we attempted the reduction of these hydrazones into fluorinated hydrazines. Thus, different conditions of reduction NaBH₃CN/AcOH/THF, NaBH₄/THF, NaBH₄/MeOH were employed. Under the conditions of NaBH₄ (2.5 equiv.)/MeOH, ¹⁹F NMR revealed a mixture of 85% of hydrazine **4-5b** (-72 ppm) and 15% of hydrazone **4-3b** (-67 ppm) at room temperature for overnight. We continued to add 1 equivalent NaBH₄ and raised the temperature to 50°C for 21h, there was no obvious improvement. Finally, using ethanol as a solvent with NaBH₄ (3 equiv.) was efficient at room temperature for 3 hours to afford pure hydrazines **4-5b/4-6b**.

Conditions of reduction	Results (Ratio of compounds in solution)
NaBH ₃ CN/AcOH/THF	No reaction
NaBH ₄ /THF	4-3b (-67 ppm): 19%, 4-5b (-72 ppm): 81%
NaBH ₄ /MeOH	4-3b (-67 ppm): 15%, 4-5b (-72 ppm): 85%
NaBH ₄ /EtOH	4-5b (-72 ppm): 100%

Table 4.3.1 Conditions and results of reduction

Meanwhile, **4-3a/4-4a** underwent the same condition to afford **4-6a/4-6b** in 83% and 98%, respectively (Scheme 4.3.1b).

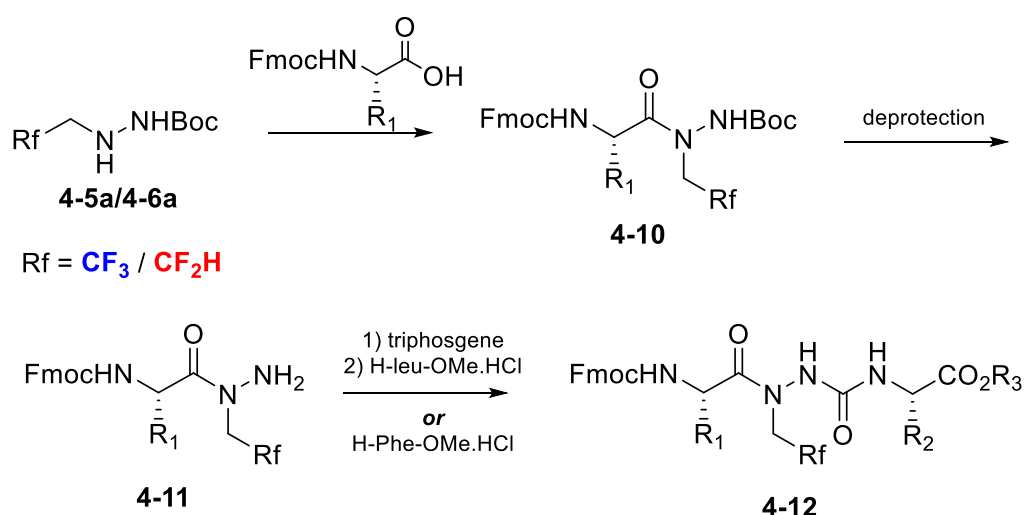


Scheme 4.3.1b Reduction of fluorinated hydrazones

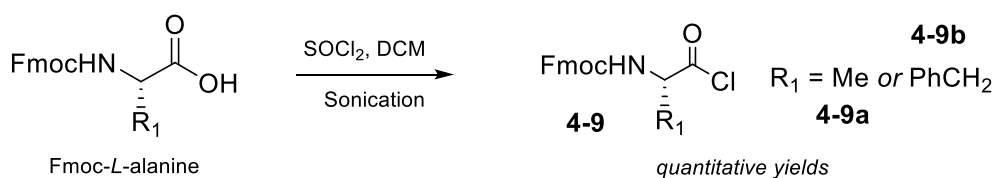
With these hydrazines in hand, two ways are possible in order to prepare azapeptides and azapeptoids.

4.3.2 Access to *N*-trifluoro and difluoroethyl azapeptoids

For the synthesis of fluorinated azapeptoids, we proposed the following reactions (Scheme 4.3.2a). First, we will investigate the coupling of amino acids with the hydrazine Boc. Then after deprotection of the Boc group, the amine will be treated with the trisphogene following of the addition of an amino acid.

Scheme 4.3.2a The general procedure for accessing to *N*-fluoroethyl azapeptoids

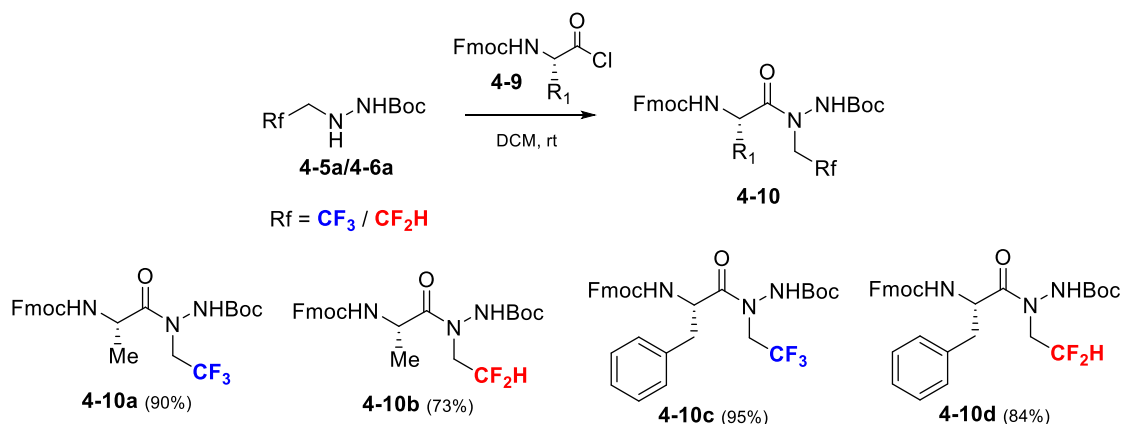
Unfortunately, no reaction occurred under classical peptide coupling between **4-5a/4-5b** and **4-6a/4-6b** and the amino-acids. This failure is undoubtedly due to the low nucleophilicity of the nitrogen, which carries the electron-withdrawing CF_3CH_2 group, and also the presence of the Boc group on the other nitrogen. So, we undertook another way involving the coupling with activated amino-acids which means acyl chloride amino acids. The acyl chloride derivatives **4-9** were easily prepared according to the conditions reported by the team of T. Brigaud.^[25] The Ala and PheAla amino acids were treated with thionyl chloride under sonication and then the crude was directly used for coupling without purification and after evaporation of solvent and excess of thionyl chloride (Scheme 4.3.2b).



Scheme 4.3.2b Preparation of acyl chloride derivatives 4-9a-b

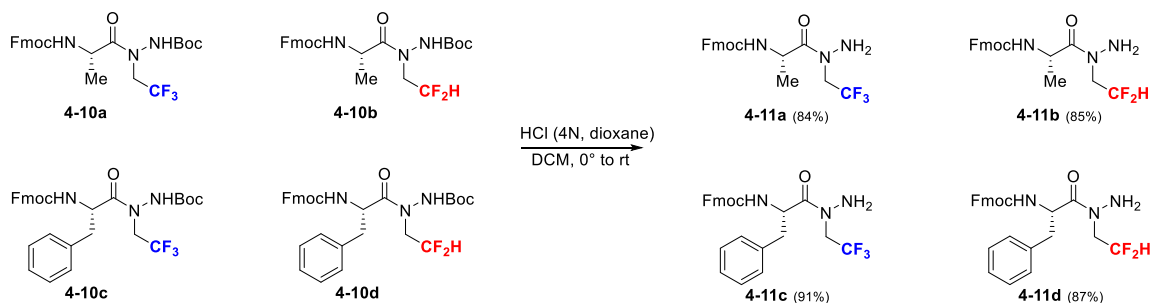
Thankfully, **4-9** mixed with fluorinated hydrazines **4-5a/4-6a** in DCM at room temperature without base led to **4-10** in 73% to 95% (Scheme 4.3.2c). It's interesting to

note that while the media is acidic, the Boc group was not removed.



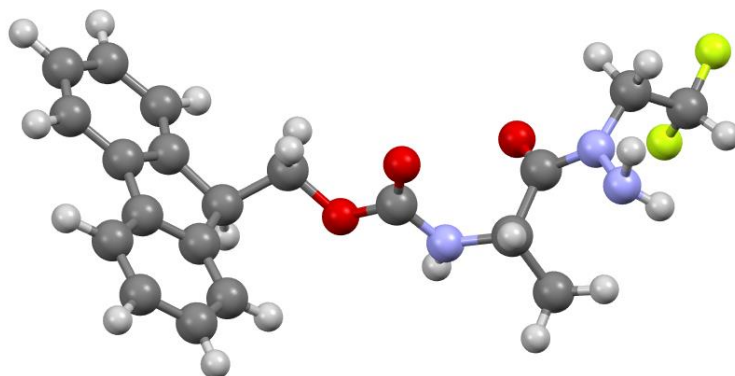
Scheme 4.3.2c Synthesis of 4-10a-d compounds

Then in order to deprotect the hydrazines, the reaction was carried out with HCl/dioxane in dichloromethane to afford **4-11** in excellent yields (84%-91%). In fact, the amine NH_2 is not basic and does not form a salt with HCl. It is, therefore, possible to purify the compounds on silica gel (Scheme 4.3.2d).

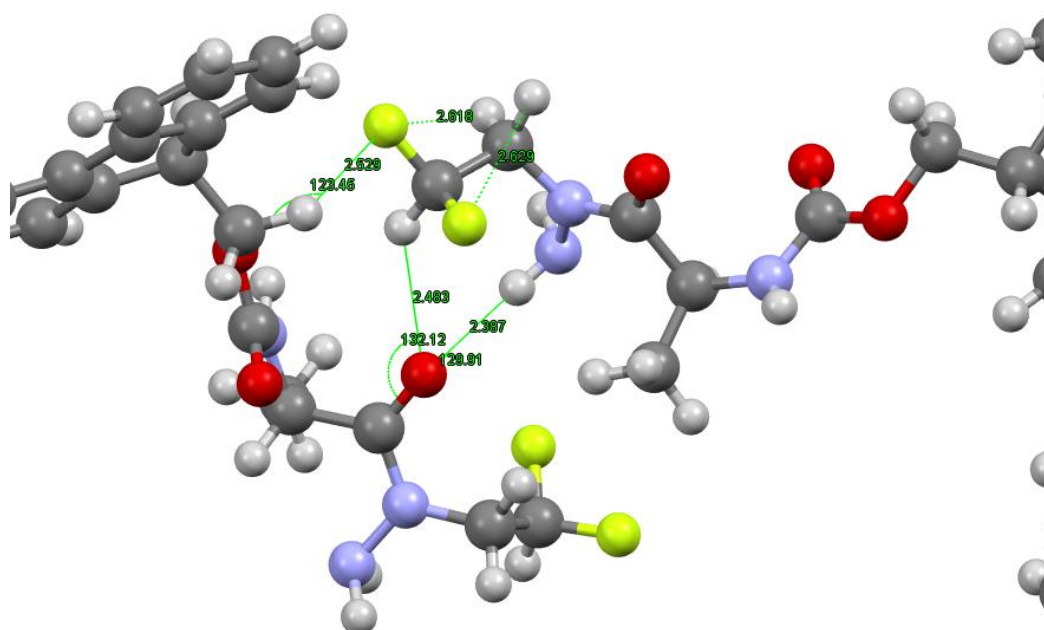


Scheme 4.3.2d Compounds 4-11a-d

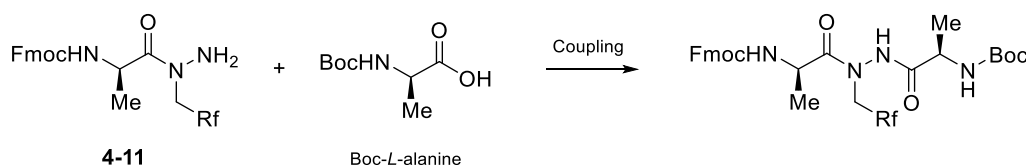
The structure of **4-11b** was determined by X-ray crystallographic analysis, performed by Pascal Retailleau of ICSN, as shown as Figure 4.3.2a.

Figure 4.3.2a X-ray crystallographic analysis of **4-11b**

We investigated the intramolecular and intermolecular interactions of the molecule **4-11b**. Both fluorines interact with their α CH₂ hydrogen (2.62 Å and 2.63 Å). The hydrogens of the HCF₂ and of the NH₂ formed strong intermolecular hydrogen-bonds with the carbonyl of another molecule. The distances are 2.48 Å for CF₂H---O and 2.39 Å for NH₂---O with angles of 132.12° and 129.91° respectively (Figure 4.3.2b). One fluorine atom clearly strongly interacts with the CH₂ proton of the Fmoc. The distance is of 2.53 Å and an angle of 123.45° (Figure 4.3.2b). We can suppose an intermolecular H-Bond.

Figure 4.3.2b H-bonding between C=O and HCF₂^[26]/H₂N and F---H-C

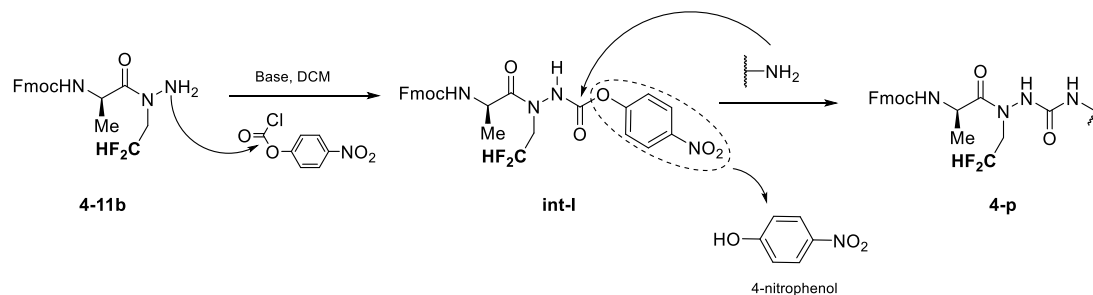
As an important part of azapeptoid construction, we directly investigated the coupling of **4-11** with Boc-L-alanine under classical conditions (Table 4.3.2). Unfortunately, the desired product did not appear when **4-11a** was coupled to alanine. Due to the influence of the CF_3CH_2 and carbonyl groups, the nucleophilicity of **4-11a** is relatively weaker. So we have tried other coupling conditions in difficult cases (entries 2-4), but unfortunately, there is also no reaction. We observed the same result with compound **4-11b**. Compounds **4-11** are recovered intact at the end of the reaction.



Conditions of coupling		Results
1	EDCI, HOBT, DIPEA, DCM, rt	No reaction
2	HATU, DIEA, DMF, rt	No reaction
3	Oxyma, DIC, Collidine, DCM	No reaction
4	EEDQ, DCM, rt	No reaction

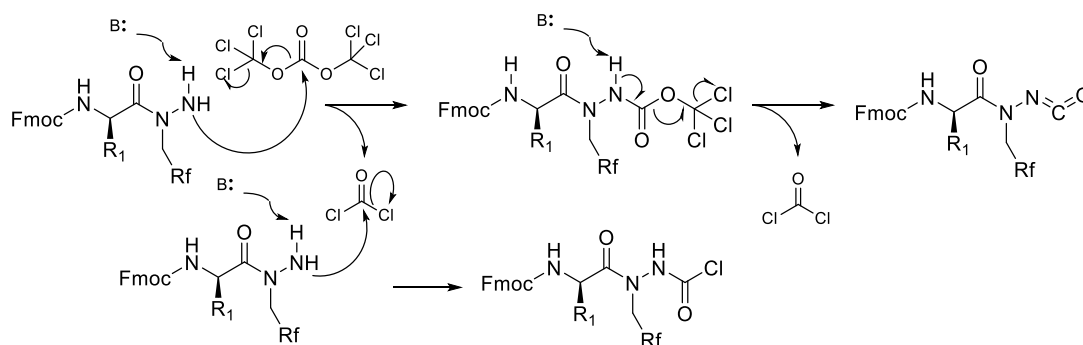
Table 4.3.2 Different coupling conditions

In order to circumvent this failure, we undertook to activate hydrazine. We introduced 4-nitrophenyl chloroformate on the structure of **4-11b** to obtain the carbamate **int-I**. Unfortunately, adding the NH_2 free amino acid to the 4-Nitrophenyl chloroformate failed (Scheme 4.3.2e).

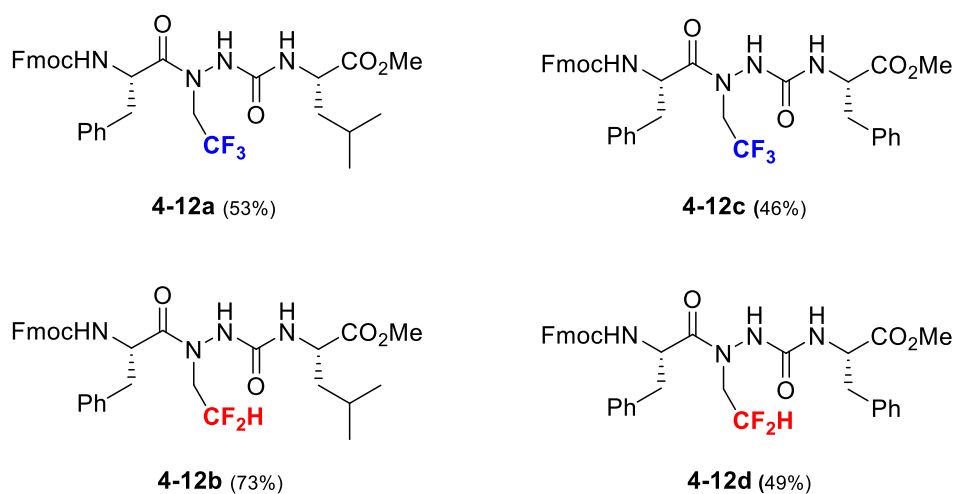


Scheme 4.3.2e Access to urea through formation of int-I with 4-nitrophenyl chloroformate

Consequently, another protocol^[27] was investigated by activating **4-11** with the bis (trichloromethyl) carbonate (BTC) to form activated intermediates -NHCOX (X=Cl, OCl₃, or isocyanate) and finally convert to desired ureas by employing *L*-Leucine methyl ester hydrochloride/ *L*-Phenylalanine methyl ester hydrochloride salt (Scheme 4.3.2f).



Formation of intermediates -NHCOX (X=Cl, OCl₃, or isocyanate)



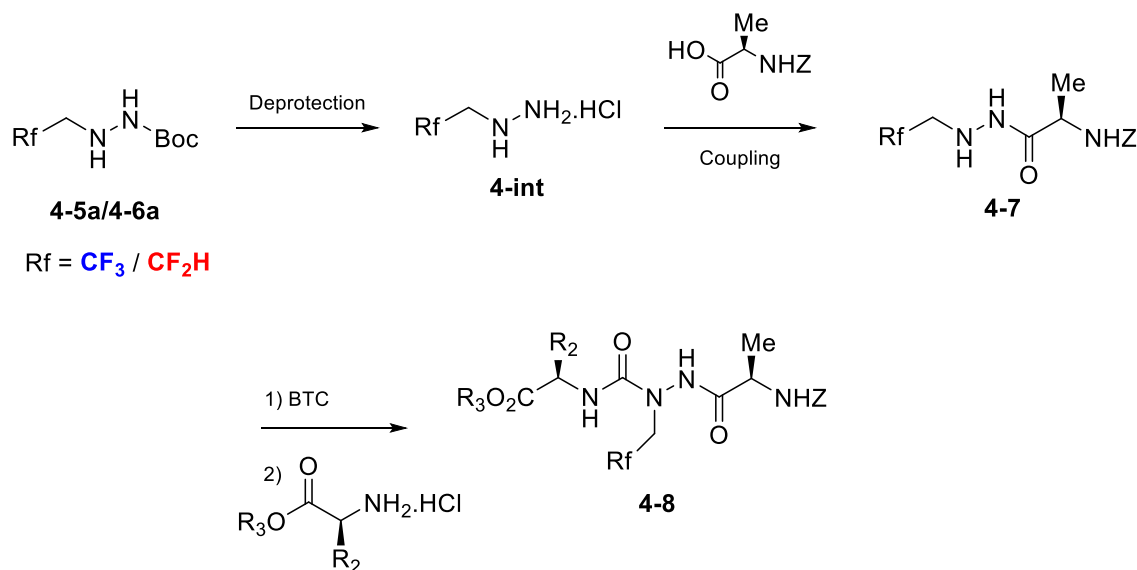
Scheme 4.3.2f Azapeptoid compounds **4-12a-d**

In two steps, the corresponding azapeptoids **4-12** were obtained in isolated yields of 46%-73% (Scheme 4.3.2f).

Subsequently, we undertook the synthesis of fluorinated azapeptides from the hydrazines prepared previously.

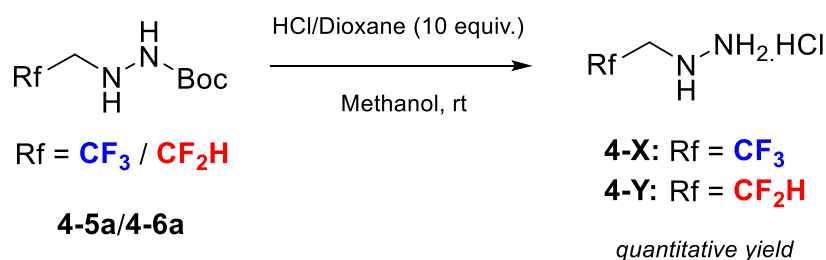
4.3.3 Access to *N*-trifluoro and difluoroethyl azapeptides

Next, we investigated the synthesis of azapeptides **4-8** according to the following Scheme 4.3.3a. After deprotection of the Boc group, the free hydrazine will be coupled with amino acids. Then, the second coupling step will involve the activation with the bis (trichloromethyl) carbonate (BTC) and addition of an amino acid.



Scheme 4.3.3a Synthesis of fluorinated azapeptides

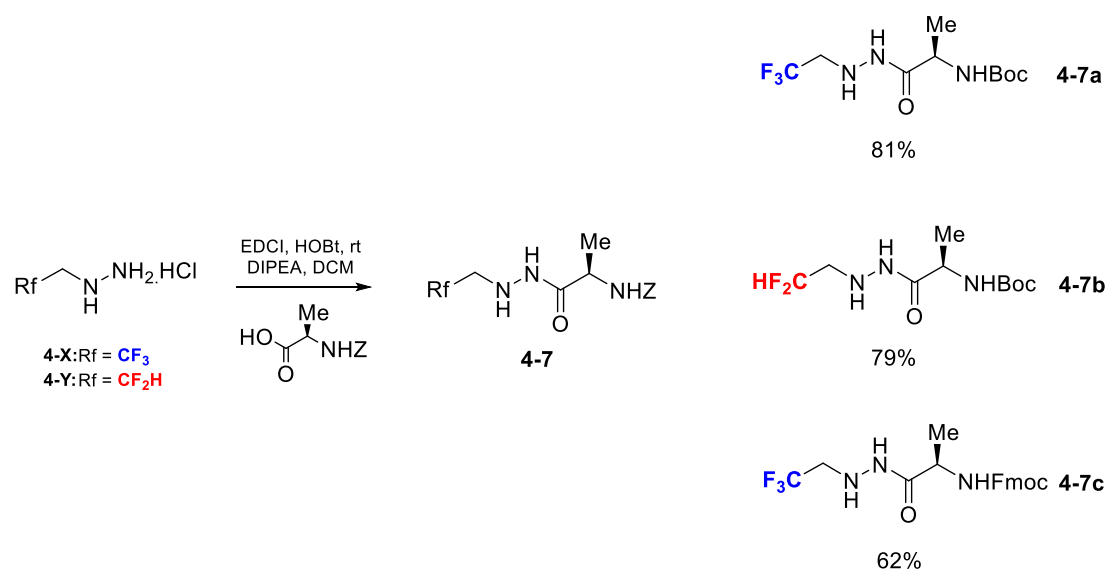
So after adding 10 equivalents of HCl/dioxane in methanol on **4-5a** and **4-6a**, **4-X/Y** were obtained as hydrochloride salt in quantitative yields (Scheme 4.3.3b).



Scheme 4.3.3b Deprotection of Boc group

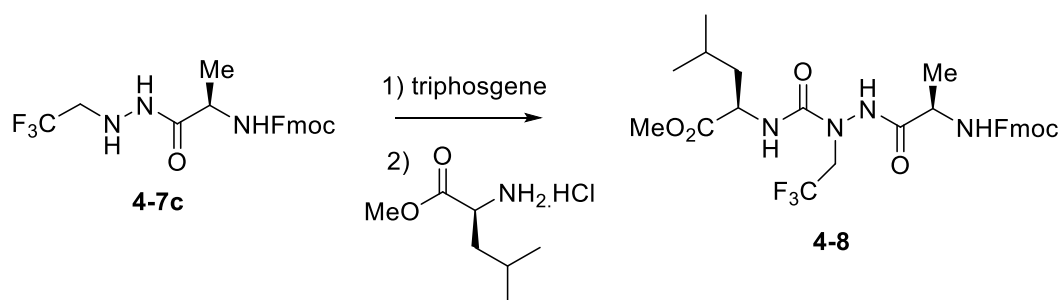
Then, having the appropriate CF_3 and CF_2H hydrazines **4-X**, **4-Y**, we first chose to evaluate the coupling with Boc-L-alanine under classical peptide conditions (EDCI,

HOBt, DIPEA). Fortunately, the corresponding peptidomimetics are obtained in excellent yields (**4-7a**, 81%; **4-7b**, 79%). Additionally, Fmoc-*L*-alanine underwent same reaction condition with **4-X** to afford **4-7c** (62%).

Scheme 4.3.3c Synthesis of compounds **4-7a-c**

Here, we can note that the hydrazine is sufficiently nucleophile to engage in the peptidic coupling.

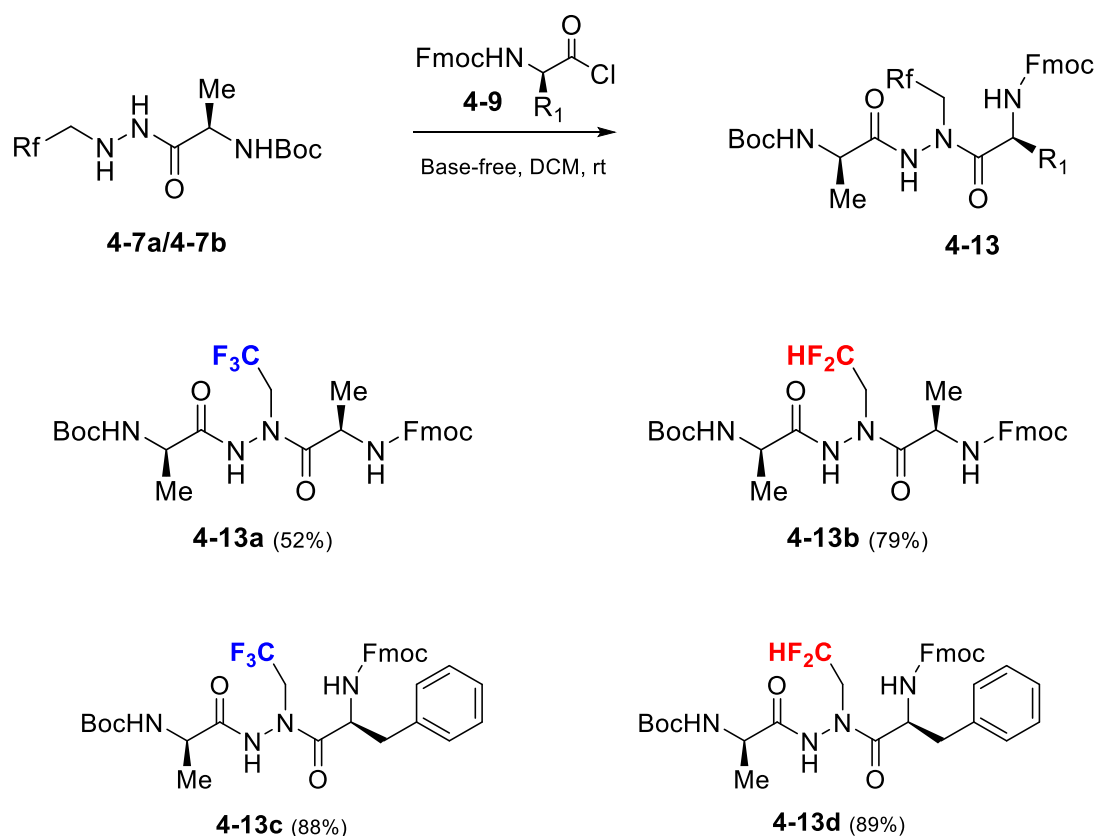
Next, a mixture of **4-7c** and base (DIEA) in DCM was treated with triphosgene at 0°C. After 40 minutes, the solution of *L*-Leucine methyl ester hydrochloride and DIEA in DCM was added in one portion to afford fluorinated azapeptide **4-8** in isolated yield 61% as white solid.



Scheme 4.3.3d Access to azapeptides

Other synthesis of fluorinated azapeptides

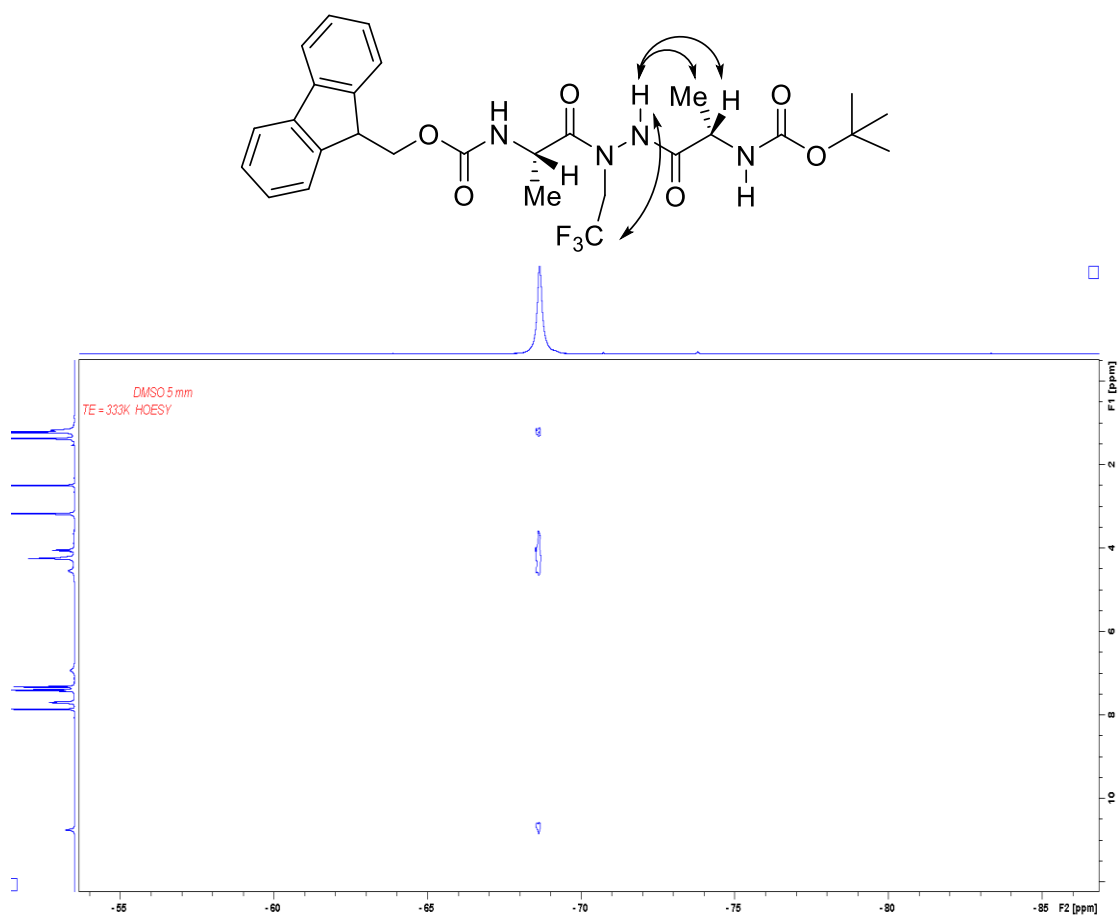
Moreover, while exploring the reactivity of these *N*-fluoroethyl hydrazines, we undertook the synthesis of new azapeptidic compounds **4-13**. In this case, the hydrazides **4-7** were treated directly with acyl chloride amino acids in dichloromethane at room temperature. In this way, a new family of trifluoromethyl and difluoromethyl azapeptides was obtained in good to excellent yields (52-89%) (Scheme 4.3.3e).



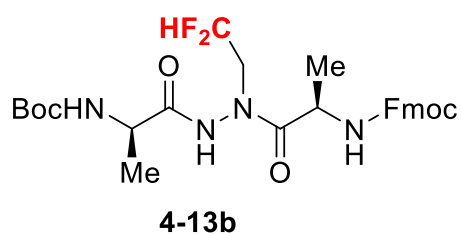
Scheme 4.3.3e Access to new azapeptides **4-13a-d**

Some of these azapeptides and azapeptoids are solids. We provided some to Pascal Retailleau's X-Ray department. Studies are in progress. We carried out some preliminary NMR analyzes such as HOESY, on two compounds **4-13a** and **4-13b**. But it was difficult at this step to give the conformation of these hydrazines in solution. For the compound **4-13a**, the HOESY in DMSO-*d*₆ showed that the CF₃ group correlates with the NH amide and the Me and group of the alanine close to the Boc group (Figure

4.3.3a).

Figure 4.3.3a. HOESY (^1H - ^{19}F) in DMSO- d_6 of compound **4-13a**

In the case of compound **4-13b**, there does not appear to be any correlations with groups other than $\text{CH}_2\text{CF}_2\text{H}$.



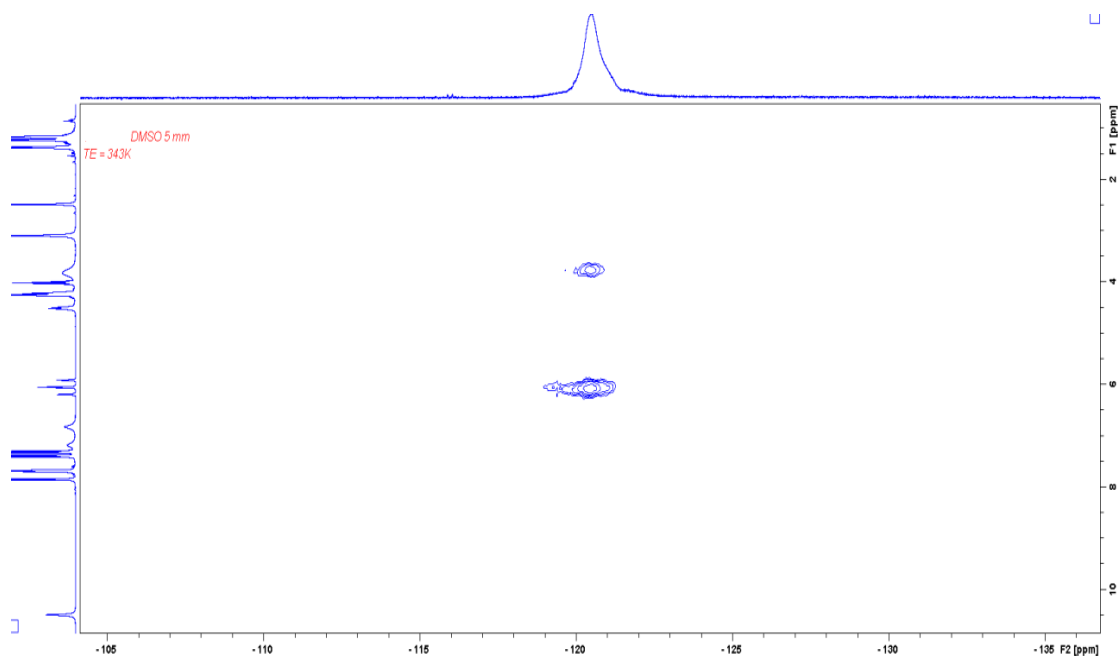


Figure 4.3.3b. HOESY (^1H - ^{19}F) in DMSO- d_6 of compound **4-13b**

4.4 Conclusion

In conclusion, a series of *N*-fluorinated azapeptoids and azapeptide were successfully prepared with *N*-fluorinated hydrazines as starting materials which are easy to access under simple reaction conditions in excellent yields. Additionally, some of the *N*-fluorinated products determined by X-Ray crystallographic analysis were proposed intermolecular and intramolecular Hydrogen Bonds.

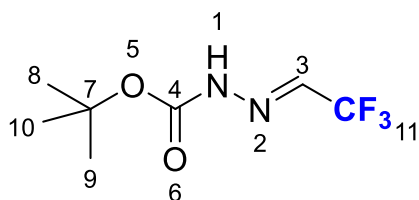
Experimental part

General Procedure (V) Preparation of *N*-trifluoro and difluoroethyl hydrazines

To a solution of Boc/Cbz/FmocNHNH₂ (1 equiv.) in toluene were added (0.05 equiv.) APTS and trifluoro or difluoromethyl acetaldehyde ethyl hemiacetal (1.2 equiv.). Then the reaction was warmed temperature to 90°C-reflux for 1-3h. The reaction was monitored by TLC. After complete reaction, solvent was evaporated and the hydrazones were used to next step directly.

Subsequently, the corresponding *N*-fluorinated hydrazines were prepared through reduction of the hydrazones with NaBH₄ (3 equiv.) in ethanol at room temperature. After complete reduction, a saturated aqueous solution of NH₄Cl was added and the mixture was stirred for 1h. After filtration, the product was extracted twice with dichloromethane. The organic phases were dried with Na₂SO₄, filtered and evaporated under vacuum to afford hydrazine as white solid.

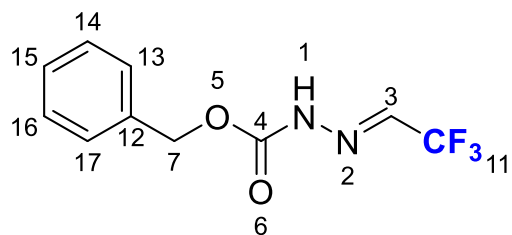
Tert-butyl (*E*)-2-(2,2,2-trifluoroethylidene)hydrazine-1-carboxylate [4-3a]



4-3a

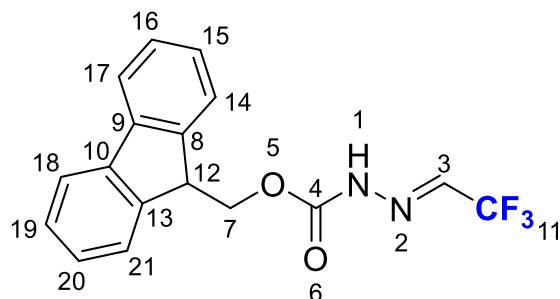
The title compound was prepared with *tert*-butyl carbazate (3.0 g, 22.73 mmol), trifluoroacetaldehyde ethyl hemiacetal (3.93 g, 27.27 mmol) and APTS (195 mg, 1.14 mmol) following general produce (V) (4.60 g, 95%). ¹H NMR (300 MHz, CDCl₃) δ (ppm) 8.42 (s, 1H, H₁), 7.80 (brs, 1H, H₃), 1.53 (s, 9H, H_{methyl}); ¹³C NMR (75 MHz, CDCl₃) δ (ppm) 151.5 (C₄), 131.8 (q, *J* = 42.5 Hz, C₃), 120.2 (q, *J* = 270.9 Hz, C₁₁), 83.0 (C₇), 28.1 (C_{methyl}); ¹⁹F NMR (188 MHz, CDCl₃) δ (ppm) -67.80 (s, CF₃); HRMS *m/z* C₇H₁₁F₃N₂O₂ [M+Na]⁺ cal. 235.0670, found. 235.0667.

Benzyl (*E*)-2-(2,2,2-trifluoroethylidene)hydrazine-1-carboxylate [4-3b]

**4-3b**

The title compound was prepared with benzyl carbazate (166 mg, 1 mmol), trifluoroacetaldehyde ethyl hemiacetal (173 mg, 1.2 mmol) and APTS (9 mg, 0.05 mmol) in toluene following general produce (V) (240 mg, 97%). **¹H NMR (300 MHz, CDCl₃)** δ (ppm) 9.08 (s, 1H, H₁), 7.62 (brs, 1H, H₃), 7.43-7.32 (m, 5H, H_{aryl}), 5.23 (s, 2H, H₇); **¹³C NMR (75 MHz, CDCl₃)** δ (ppm) 153.0 (C₄), 135.0 (C₁₂), 132.7 (q, J = 41.4 Hz, C₃), 128.7 (C_{arom}), 128.6 (C_{arom}), 128.4 (C_{arom}), 120.0 (q, J = 270.0 Hz, C₁₁), 68.2 (C₇); **¹⁹F NMR (188 MHz, CDCl₃)** δ (ppm) -67.8 (s, CF₃); **HRMS m/z** C₁₀H₉F₃N₂O₂ [M+Na]⁺ cal. 269.0514, found. 269.0514.

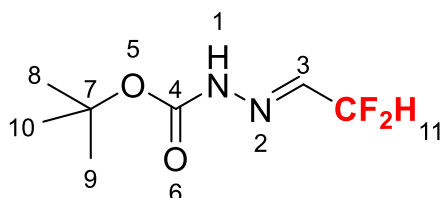
(9H-Fluoren-9-yl)methyl (E)-2-(2,2,2-trifluoroethylidene)hydrazine-1-carboxylate [4-3c]

**4-3c**

The title compound was prepared with 9-fluorenylmethyl carbazate (508 mg, 2 mmol), trifluoroacetaldehyde ethyl hemiacetal (317 mg, 2.2 mmol) and APTS (17 mg, 0.1 mmol) in 5 mL toluene following general produce (V) (579 mg, 87%). **¹H NMR (300 MHz, DMSO-*d*₆)** δ (ppm) 11.7 (s, 1H, H₁), 7.89 (d, J = 7.41 Hz, 2H, H_{arom}), 7.72 (d, J = 7.52 Hz, 2H, H_{arom}), 7.61 (q, J = 4.27 Hz, 1H, H₃), 7.45-7.32 (m, 4H, H_{arom}), 4.56 (d, J = 6.27 Hz, 2H, H₇), 4.32 (t, J = 6.69 Hz, 1H, H₁₂); **¹³C NMR (75 MHz, DMSO-*d*₆)** δ (ppm) 152.7 (C₄), 143.4 (C_{arom}), 140.8 (C_{arom}), 130.8 (q, J = 56.4 Hz, C₃), 127.7 (C_{arom}), 127.1 (C_{arom}), 125.0 (C_{arom}), 120.5 (q, J = 270.5 Hz, C₁₁), 120.1 (C_{arom}), 66.3 (C₇), 46.4

(C₁₂); ¹⁹F NMR (188 MHz, DMSO-*d*₆) δ (ppm) -65.98 (d, *J* = 4.12 Hz, CF₃); HRMS *m/z* C₁₇H₁₃F₃N₂O₂ [M+Na]⁺ cal. 357.0827, found. 357.0826.

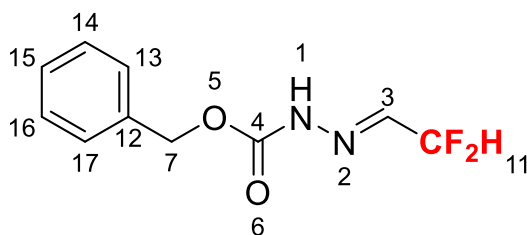
***Tert*-butyl (*E*)-2-(2,2-difluoroethylidene)hydrazine-1-carboxylate [4-4a]**



4-4a

The title compound was prepared with *tert*-butyl carbazate (2.0 g, 15.15 mmol), difluoroacetaldehyde ethyl hemiacetal (2.29 g, 18.18 mmol) and APTS (130 mg, 0.756 mmol) in 20 mL toluene following general procedure (V) (2.70 g, 92%). ¹H NMR (300 MHz, CDCl₃) δ (ppm) 9.00 (s, 1H, H₁), 7.41 (s, 1H, H₃), 6.13 (td, *J*₁ = 54.82 Hz, *J*₂ = 6.22 Hz, 1H, H₁₁), 1.50 (s, 9H, H_{methyl}); ¹³C NMR (75 MHz, CDCl₃) δ (ppm) 152.4 (C₄), 136.7 (t, *J* = 34.5 Hz, C₃), 113.3 (t, *J* = 233.3 Hz, C₁₁), 82.5 (C₇), 28.1 (C_{methyl}); ¹⁹F NMR (188 MHz, CDCl₃) δ (ppm) -116.14 (d, *J* = 54.10 Hz, 2F); HRMS *m/z* C₇H₁₂F₂N₂O₂ [M+Na]⁺ cal. 217.0765, found. 217.0758.

Benzyl (*E*)-2-(2,2-difluoroethylidene)hydrazine-1-carboxylate [4-4b]

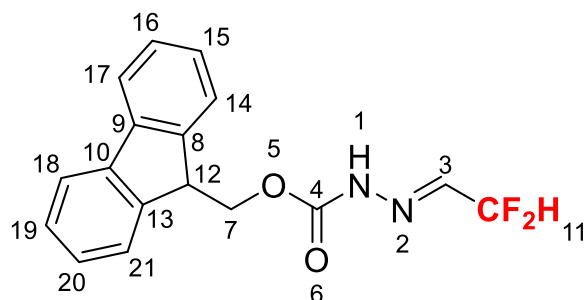


4-4b

The title compound was prepared with benzyl carbazate (830 mg, 5 mmol), difluoroacetaldehyde ethyl hemiacetal (756 mg, 6 mmol) and APTS (43 mg, 0.25 mmol) following general procedure (V) (1.097 g, 96%). ¹H NMR (300 MHz, CDCl₃) δ (ppm) 8.82 (s, 1H, H₁), 7.44-7.35 (m, 6H, H₃, H_{arom}), 6.16 (td, *J*₁ = 53.88 Hz, *J*₂ = 6.03 Hz, 1H, H₁₁), 5.25 (s, 2H, H₇); ¹³C NMR (75 MHz, CDCl₃) δ (ppm) 153.2 (C₄), 137.7 (t, *J* = 35.9 Hz, C₃), 135.1 (C₁₂), 128.7 (C_{arom}), 128.4 (C_{arom}), 112.9 (q, *J* = 234.4 Hz, C₁₁), 68.1

(C₇); ¹⁹F NMR (188 MHz, CDCl₃) δ (ppm) -116.36 (dd, *J*₁ = 54.02 Hz, *J*₂ = 2.48 Hz, 2F); HRMS *m/z* C₁₀H₁₀F₂N₂O₂ [M+Na]⁺ cal. 251.0608, found. 251.0605.

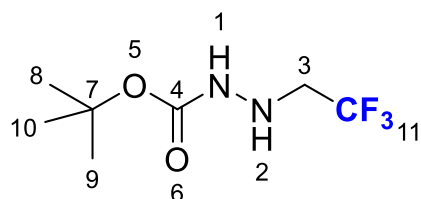
(9H-Fluoren-9-yl)methyl (E)-2-(2,2-difluoroethylidene)hydrazine-1-carboxylate [4-4c]



4-4c

The title compound was prepared with 9-fluorenylmethyl carbazate (254 mg, 1 mmol), difluoroacetaldehyde ethyl hemiacetal (189 mg, 1.2 mmol) and APTS (9 mg, 0.05 mmol) in 5 mL toluene following general procedure (V) (283 mg, 89%). ¹H NMR (300 MHz, DMSO-*d*₆) δ (ppm) 11.52 (s, 1H, H₁), 7.89 (d, *J* = 7.83 Hz, 2H, H_{arom}), 7.71 (d, *J* = 7.57 Hz, 2H, H_{arom}), 7.50-7.32 (m, 5H, H_{arom}, H₃), 6.49 (td, *J*₁ = 54.07 Hz, *J*₂ = 5.46 Hz, 1H, H₁₁), 4.55 (d, *J* = 6.39 Hz, 2H, H₇), 4.31 (t, *J* = 6.47 Hz, 1H, H₁₂); ¹³C NMR (75 MHz, DMSO-*d*₆) δ (ppm) 152.9 (C₄), 143.5 (C_{arom}), 140.8 (C_{arom}), 137.2 (t, *J* = 32.4 Hz, C₃), 127.7 (C_{arom}), 127.1 (C_{arom}), 124.9 (C_{arom}), 120.1 (C_{arom}), 113.3 (t, *J* = 233.4 Hz, C₁₁), 66.1 (C₇), 46.5 (C₁₂); ¹⁹F NMR (188 MHz, DMSO-*d*₆) δ (ppm) -116.05 (dd, *J*₁ = 54.29 Hz, *J*₂ = 3.42 Hz, 2F); HRMS *m/z* C₁₇H₁₄F₂N₂O₂ [M+Na]⁺ cal. 339.0921, found. 339.0921.

***Tert*-butyl 2-(2,2,2-trifluoroethyl)hydrazine-1-carboxylate [4-5a]**

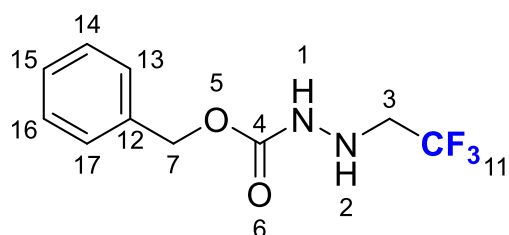


4-5a

NaBH₄ (152-228 mg, 4-6 mmol) was added into the mixture of **4-3a** (414 mg, 2 mmol)

and 20 mL ethanol to afford **4-5a** (405 mg, 95%) following the general procedure (V). **¹H NMR (300 MHz, CDCl₃)** δ (ppm) 6.31 (s, 1H, H₁), 4.20 (s, 1H, H₂), 3.36 (qd, $J = 9.2$ and 4.7 Hz, 2H, H₃), 1.40 (s, 9H, H_{methyl}); **¹³C NMR (75 MHz, CDCl₃)** δ (ppm) 156.6 (C₄), 124.8 (q, $J = 277.7$ Hz, C₁₁), 81.3 (C₇), 52.9 (q, $J = 30.7$ Hz, C₃), 28.2 (C_{methyl}); **¹⁹F NMR (188 MHz, CDCl₃)** δ -71.76 (t, $J = 9.12$ Hz, CF₃); **HRMS m/z** C₇H₁₃F₃N₂O₂ [M+Na]⁺ cal. 237.0827, found. 237.0825.

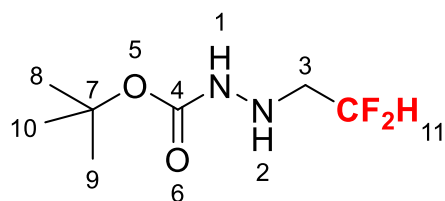
Benzyl 2-(2,2,2-trifluoroethyl)hydrazine-1-carboxylate [4-5b]



4-5b

The title compound was afforded with NaBH₄ (28.5 mg, 0.75 mmol), **4-3b** (61.6 mg, 0.25 mmol) and 3 mL ethanol. (60.8 mg, 98%). **¹H NMR (300 MHz, CDCl₃)** δ (ppm) 7.54-7.35 (m, 5H, H_{arom}), 6.62 (s, 1H, H₁), 5.17 (s, 2H, H₇), 4.35 (s, 1H, H₂), 3.44 (qd, $J = 9.2$ and 4.7 Hz, 2H, H₃); **¹³C NMR (75 MHz, CDCl₃)** δ (ppm) 157.2 (C₄), 135.7 (C₁₂), 128.6 (C_{arom}), 128.5 (C_{arom}), 128.2 (C_{arom}), 124.8 (q, $J = 278.5$ Hz, C₁₁), 67.6 (C₇), 52.8 (q, $J = 30.9$ Hz, C₃); **¹⁹F NMR (188 MHz, CDCl₃)** δ (ppm) -71.88 (t, $J = 9.32$ Hz, CF₃); **HRMS m/z** C₁₀H₁₁F₃N₂O₂ [M+Na]⁺ cal. 271.0670, found. 271.0665.

Tert-butyl 2-(2,2-difluoroethyl)hydrazine-1-carboxylate [4-6a]

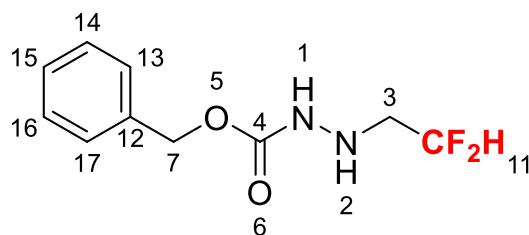


4-6a

The title compound was obtained with NaBH₄ (2.31 g, 60.87 mmol), **4-4b** (3.94 g, 20.29 mmol) and 150 mL ethanol. (3.29g, 83%). **¹H NMR (300 MHz, CDCl₃)** δ (ppm) 6.43 (s, 1H, H₁), 5.79 (tt, $J_1 = 55.88$ Hz, $J_2 = 4.29$ Hz, 1H, H₁₁), 4.17 (s, 1H, H₂), 3.12 (td, J_1

= 15.15 Hz, $J_2 = 4.26$ Hz, 2H, H₃), 1.39 (s, 9H, H_{methyl}); ¹³C NMR (75 MHz, CDCl₃) δ (ppm) 156.8 (C₄), 115.2 (t, $J = 240.0$ Hz, C₁₁), 81.0 (C₇), 53.9 (t, $J = 24.2$ Hz, C₃), 28.2 (H_{methyl}); ¹⁹F NMR (188 MHz, CDCl₃) δ (ppm) -122.39 (dt, $J_1 = 56.09$ Hz, $J_2 = 14.78$ Hz, 2F); HRMS m/z C₇H₁₄F₂N₂O₂ [M+Na]⁺ cal. 219.0921, found. 219.0929.

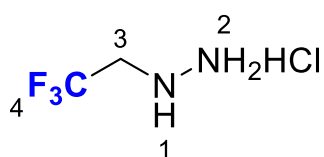
Benzyl 2-(2,2-difluoroethyl)hydrazine-1-carboxylate [4-6b]



4-6b

The title compound was afforded with NaBH₄ (114 mg, 3 mmol), **4-3b** (228 mg, 1 mmol) and 8 mL ethanol. (225 mg, 98%). ¹H NMR (300 MHz, CDCl₃) δ (ppm) 7.39-7.11 (m, 5H, H_{arom}), 6.54 (s, 1H, H₁), 5.76 (tt, $J_1 = 55.73$ Hz, $J_2 = 4.31$ Hz, 1H, H₁₁), 5.05 (s, 2H, H₇), 4.05 (s, 1H, H₂), 3.13 (td, $J_1 = 14.78$ Hz, $J_2 = 3.96$ Hz, 2H, H₃); ¹³C NMR (75 MHz, CDCl₃) δ (ppm) 157.4 (C₄), 135.8 (C₁₂), 128.6 (C_{arom}), 128.5 (C_{arom}), 128.3 (C_{arom}), 115.2 (t, $J = 241.3$ Hz, C₁₁), 67.5 (C₇), 53.7 (t, $J = 24.2$ Hz, C₃); ¹⁹F NMR (188 MHz, CDCl₃) δ (ppm) -122.25 (dt, $J_1 = 55.79$ Hz, $J_2 = 15.12$ Hz, 2F); HRMS m/z C₁₀H₁₂F₂N₂O₂ [M+Na]⁺ cal. 253.0764, found. 253.0761.

(2,2,2-Trifluoroethyl)hydrazine hydrochloride [4-int-1]

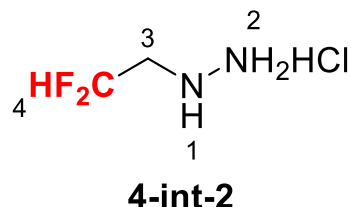


4-int-1

4-5a (856 mg, 4 mmol) was dissolved in 40 mL dichloromethane, followed by HCl/dioxane (4N) 10 ml drop by drop at 0°C. After that, the mixture was warmed to rt for overnight to afford quantitative yield title compound. ¹H NMR (300 MHz, CD₃OD) δ (ppm) 3.55 (q, $J = 9.27$ Hz, 2H, H₃); ¹³C NMR (75 MHz, CD₃OD) δ (ppm) 125.8 (q, $J = 276.9$ Hz, C₄), 57.0 (q, $J = 32.8$ Hz, C₃); ¹⁹F NMR (188 MHz, CD₃OD) δ (ppm) -

69.00 (t, $J = 9.09$ Hz, CF_3); **HRMS** m/z $\text{C}_2\text{H}_3\text{F}_3\text{N}_2$ $[\text{M}+\text{Na}]^+$ cal. 115.0483, found. 115.0480.

(2,2-Difluoroethyl)hydrazine hydrochloride [4-int-2]



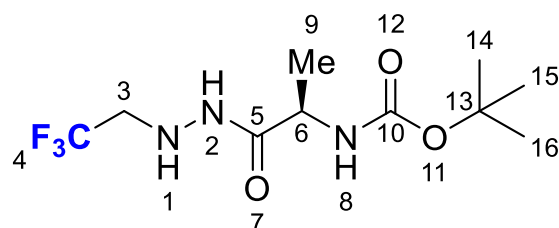
4-6a (784 mg, 4 mmol) was dissolved in 40 mL dichloromethane, followed by addition of HCl/dioxane (4N) 10 ml drop by drop at 0°C. Then, the mixture was warmed to rt for overnight to afford compound in quantitative yield. **^1H NMR (300 MHz, CD_3OD)** δ (ppm) 5.91 (tt, $J_1 = 55.19$ Hz, $J_2 = 4.14$ Hz, 1H, H_4), 3.20 (td, $J_1 = 15.07$ Hz, $J_2 = 4.14$ Hz, 2H, H_3); **^{13}C NMR (75 MHz, CD_3OD)** δ (ppm) 116.0 (t, $J = 239.3$ Hz, C_4), 52.3 (t, $J = 25.2$ Hz, C_3); **^{19}F NMR (188 MHz, CD_3OD)** δ (ppm) -123.70 (dt, $J_1 = 55.70$ Hz, $J_2 = 15.21$ Hz, 2F); **HRMS** m/z $\text{C}_2\text{H}_6\text{F}_2\text{N}_2$ $[\text{M}+\text{H}]^+$ cal. 97.0577, found. 97.0572.

General Procedure (VI): Access to azapeptides or azapeptoids

1. Peptide coupling

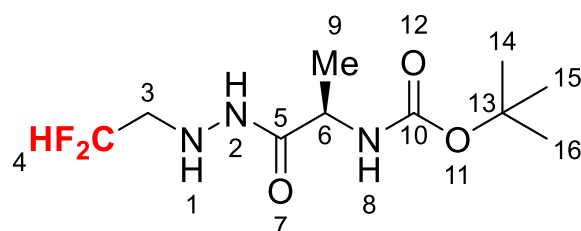
To a solution of **4-int** (1 equiv.), Boc-L-alanine (1.1 equiv.) and EDCI (1.1 equiv.), HOBt. H_2O (1.1 equiv.) in dichloromethane was added slowly DIPEA (2 equiv.) at 0°C slowly. The mixture was stirred at room temperature for 16h. The solvent was evaporated and the crude was diluted with ethyl acetate, and was washed by citric acid, H_2O , K_2CO_3 and brine successively. The products were obtained after evaporation of solvent and purification by chromatography column.

Tert-butyl (R)-(1-(2-(2,2,2-trifluoroethyl)hydrazineyl)-1-oxopropan-2-yl)carbamate [4-7a]

**4-7a**

4-7a was prepared following the general procedure (VI-1), **4-int-1** (530 mg, 3.53 mmol) in 35 mL of DCM, Boc-L-alanine (734, 3.88 mmol), EDCI (744 mg, 3.88 mmol), HOBT.H₂O (594 mg, 3.88 mmol) and DIPEA (1.51 mL, 7.06 mmol). Compound **4-7a** 811 mg, 81%. ¹H NMR (300 MHz, Acetone-*d*₆) δ (ppm) 8.91 (s, 1H, H₂), 6.05 (s, 1H, H₈), 5.22 (brs, 1H, NH₁), 4.13 (m, 1H, H₆), 3.47 (m, 2H, H₃), 2.79 (brs, 1H, NH₈), 1.40 (s, 9H, H_{methyl}), 1.30 (d, *J* = 7.04 Hz, 3H, H₉); ¹H NMR (300 MHz, CD₃OD) δ (ppm) 4.04 (q, *J* = 7.45 Hz, H₆), 3.41 (qd, *J* = 9.6 and 1.6 Hz, 2H, H₃), 1.34 (s, 9H, H_{methyl}), 1.29 (d, *J* = 7.53 Hz, 3H, H₉); ¹³C NMR (75 MHz, CD₃OD) δ (ppm) 175.4 (C₅), 157.6 (C₁₀), 126.7 (q, *J* = 277.2 Hz, C₄), 80.6 (C₁₃), 52.9 (q, *J* = 30.8 Hz, C₃), 50.3 (C₆), 28.7 (C_{methyl}), 18.2 (C₉); ¹⁹F NMR (188 MHz, Acetone-*d*₆) δ (ppm) -72.37 (t, *J* = 9.84 Hz, CF₃); HRMS *m/z* C₁₀H₁₈F₃N₃O₃ [M+Na]⁺ cal. 308.1198, found. 308.1195.

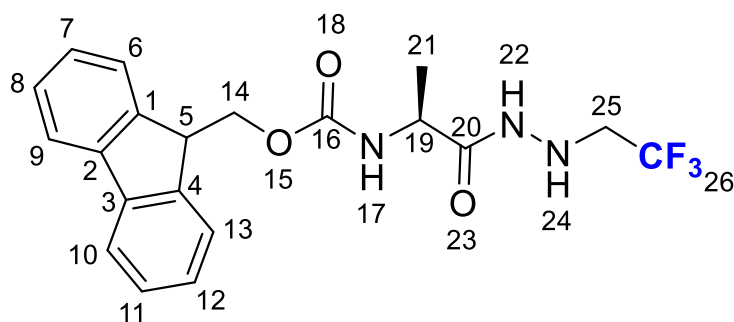
Tert-butyl (R)-(1-(2-(2,2-difluoroethyl)hydrazineyl)-1-oxopropan-2-yl)carbamate [4-7b]

**4-7b**

The title compound was prepared with **4-int-2** (602mg, 4 mmol), Boc-L-alanine (831, 4.4 mmol), EDCI (843 mg, 4.4 mmol), HOBT.H₂O (673 mg, 4.4 mmol) and DIPEA (1.71 mL, 8 mmol) in 35 mL DCM to afford **4-7b** following general procedure (VI-1) (840 mg, 79%). ¹H NMR (200 MHz, Acetone-*d*₆) δ (ppm) 8.86 (s, 1H, H₂), 6.09 (brs,

1H, H₈), 5.96 (tt, $J_1 = 56.28$ Hz, $J_2 = 4.47$ Hz, 1H, H₄), 5.05 (s, 1H, H₁), 4.10 (m, 1H, H₆), 3.16 (td, $J_1 = 15.20$ Hz, $J_2 = 4.52$ Hz, 2H, H₃), 1.41 (s, 9H, H_{methyl}), 1.31 (d, $J = 7.30$ Hz, 3H, H₉); ¹³C NMR (75 MHz, Acetone-*d*₆) δ (ppm) 173.5 (C₅), 156.1 (C₁₀), 116.8 (t, $J = 238.76$ Hz, C₄), 79.4 (C₁₃), 54.4 (t, $J = 25.40$ Hz, C₃), 49.7 (C₆), 28.5 (C_{methyl}), 18.5 (C₉); ¹⁹F NMR (188 MHz, Acetone-*d*₆) δ (ppm) -122.66 (dt, $J_1 = 55.64$ Hz, $J_2 = 15.36$ Hz, 2F); HRMS m/z C₁₀H₁₉F₂N₃O₃ [M+Na]⁺ cal. 290.1292, found. 290.1290.

(9H-fluoren-9-yl)methyl (S)-(1-oxo-1-(2-(2,2,2-trifluoroethyl)hydrazineyl)propan-2-yl)carbamate [4-7c]



4-7c

The title compound was prepared with **4-int-1** (2 mmol), Foc-L-alanine (653, 2.1 mmol), EDCI (403 mg, 2.1 mmol), HOBT.H₂O (321 mg, 2.1 mmol) and DIPEA (0.86 mL, 5 mmol) in 20 mL DCM to afford **4-7c** following general procedure (VI-1) (505 mg, 62%). ¹H NMR (200 MHz, Acetone-*d*₆) δ (ppm) 7.86 (d, $J = 6.67$ Hz, 2H, H_{arom}), 7.70 (d, $J = 7.30$ Hz, 2H, H_{arom}), 7.48-7.22 (m, 5H, H_{arom}, H₁₇), 4.40-4.14 (m, 5H, H₅, H₁₄, H₁₉, H₂₄), 3.48 (q, $J = 9.78$ Hz, 2H, H₂₅), 1.35 (d, $J = 7.05$ Hz, 3H, H₂₁); ¹⁹F NMR (188 MHz, Acetone-*d*₆) δ (ppm) -72.32 (t, $J = 9.62$ Hz, CF₃); HRMS m/z C₂₀H₂₀F₃N₃O₃ [M+Na]⁺ cal. 430.1349, found. 430.1354.

2. Preparation of the azapeptides from the aminoacid chlorides

Preparation of aminoacid chloride:

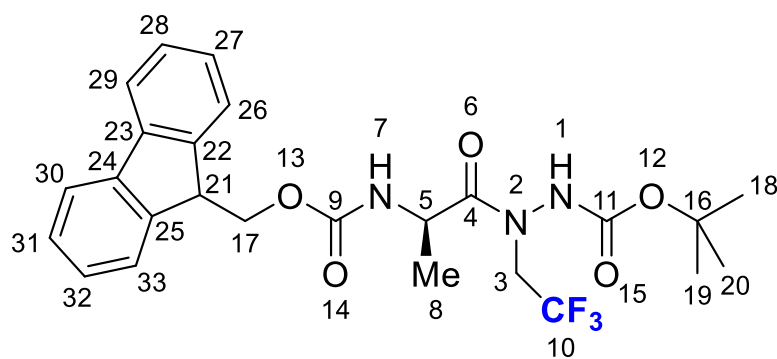
(1) Preparation of aminoacid chlorides **4-9** (General Procedure)

To a solution the Fmoc-Ala(Phe)-OH (1.2 mmol) suspended in 10 mL DCM under argon, was added SOCl₂ (15.6 equiv.). The mixture was sonicated at room temperature during 30 min-2h, and then solvent and excess of SOCl₂ were removed in vacuo. The crude was washed with DCM to give the Fmoc-Ala (Phe)-Cl as a solid directly used without further purification.

(2) The synthesis of the azapeptide **4-10**. (General procedure)

To a solution of **4-5a/6a** (1.0 equiv) in dichloromethane was added Fmoc-amino acid chloride (1.1 equiv). The reaction mixture was stirred for 24 h at room temperature under inert atmosphere, and then the solvent was evaporated under reduced pressure. Purification by flash chromatography gave pure compound.

Tert-butyl 2-(((9H-fluoren-9-yl)methoxy)carbonyl)-D-alanyl)-2-(2,2,2-trifluoroethyl)hydrazine-1-carboxylate [4-10a]

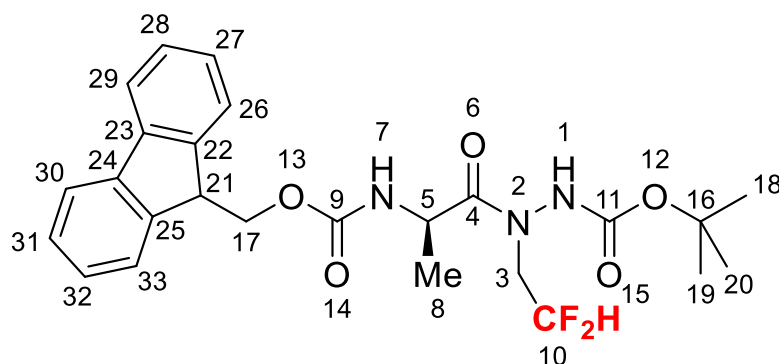
**4-10a**

Following the general procedures (VI-2). Fmoc-Ala-OH (342 mg, 1.1 mmol) was treated with SOCl₂ (14.3 mmol) to give Fmoc-Ala-Cl **4-9a**. Then the residue was mixed with **4-5a** (214 mg, 1 mmol) in 10 mL DCM to afford compound **4-10a** (458 mg, 90%).

¹H NMR (300 MHz, CDCl₃) δ (ppm) 7.66 (d, *J* = 7.44 Hz, 2H, H_{arom}), 7.55 (s, 1H, H₁), 7.49 (m, 2H, H_{arom}), 7.30 (t, *J* = 7.4 Hz, 2H, H_{arom}), 7.21 (t, *J* = 7.4 Hz, 2H, H_{arom}), 5.54 (s, 1H, H₇), 4.78 (brs, 2H, H_{3,5}), 4.26 (d, *J* = 7.08 Hz, 2H, H₁₇), 4.10 (t, *J* = 6.77 Hz, 1H, H₂₁), 3.65 (brs, 1H, H₃), 1.39 (s, 9H, H_{methyl}), 1.26 (d, *J* = 6.96 Hz, 3H, H₈); **¹³C NMR (75 MHz, CDCl₃)** δ (ppm) 175.9 (C₄), 155.8 (C₁₁), 153.6 (C₉), 143.8 and 143.7 (C₂₂,

C₂₅), 141.3 (C₂₃, C₂₄), 127.7 (C_{arom}), 127.1 (C_{arom}), 125.1 (C_{arom}), 124.0 (q, $J = 281.7$ Hz, C₁₀), 119.9 (C_{arom}), 83.1 (C₁₆), 67.2 (C₁₇), 47.1 (C₅), 47.0 (q, $J = 29.5$ Hz, C₃), 46.4 (C₂₁), 29.7 and 28.1 (C_{methyl}), 19.2 and 17.8 (C₈); **¹⁹F NMR (188 MHz, CDCl₃)** δ (ppm) -69.61 and -70.02 (brs, CF₃) mixture of rotamers; **HRMS** m/z C₂₅H₂₈F₃N₃O₅ [M+NH₄]⁺ cal. 525.2325, found. 525.2334.

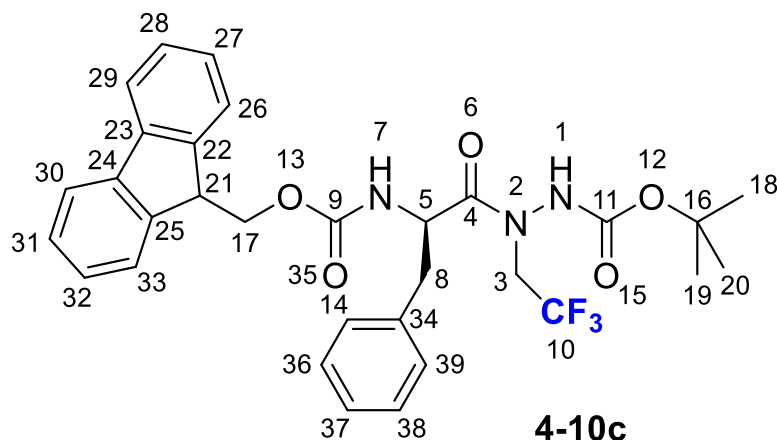
Tert-butyl 2-(((9H-fluoren-9-yl)methoxy)carbonyl)-D-alanyl)-2-(2,2-difluoroethyl)hydrazine-1-carboxylate [4-10b]



4-10b

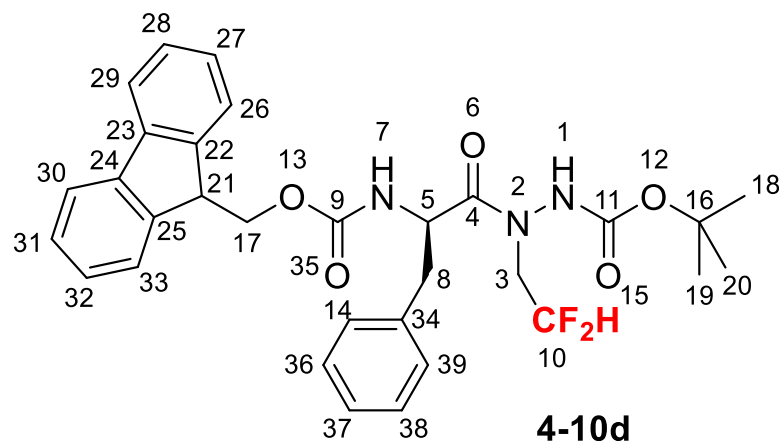
Following the general procedures (VI-2): Fmoc-Ala-OH (342 mg, 1.1 mmol) was firstly treated with SOCl₂ (14.3 mmol) to give Fmoc-Ala-Cl **4-9a**. Then the residue was mixed with **4-6a** (196 mg, 1 mmol) in 10 mL DCM to afford compound **4-10b** (356 mg, 73%). **¹H NMR (300 MHz, CDCl₃)** δ (ppm) 7.67 (d, $J = 7.47$ Hz, 2H, H_{arom}), 7.50 (m, 2H, H_{arom}), 7.31 (t, $J = 7.4$ Hz, 2H, H_{arom}), 7.22 (t, $J = 7.4$ Hz, 2H, H_{arom}), 7.24 (brs, 1H, H₁), 5.87 (tt, $J_1 = 55.85$ Hz, $J_2 = 4.29$ Hz, 1H, H₁₀), 5.46 (s, 1H, H₇), 4.74 (m, 1H, H₅), 4.28 (d, $J = 7.54$ Hz, 2H, H₁₇), 4.18 (brs, 1H, H₃), 4.11 (t, $J = 6.98$ Hz, 2H, H₂₁), 3.45 (brs, 1H, H₃), 1.41 (s, 9H, H_{methyl}), 1.26 (d, $J = 7.16$ Hz, 3H, H₈); **¹³C NMR (75 MHz, CDCl₃)** δ (ppm) 176.0 (C₄), 155.7 (C₁₁), 153.9 (C₉), 143.8 and 143.7 (C₂₂, C₂₅), 141.3 (C₂₃, C₂₄), 127.7 (C_{arom}), 127.1 (C_{arom}), 125.1 (C_{arom}), 119.9 (C_{arom}), 113.6 (t, $J = 242.1$ Hz, C₁₀), 83.0 (C₁₆), 67.1 (C₁₇), 50.2 (t, $J = 24.9$ Hz, C₃), 47.1 (C₅), 46.5 (C₂₁), 28.1 (C_{methyl}), 18.0 (C₈); **¹⁹F NMR (188 MHz, CDCl₃)** δ (ppm) -119.47 (dd, $J_1 = 280.66$ Hz, $J_2 = 60.14$ Hz, 1F), -122.23 (dd, $J_1 = 268.74$ Hz, 1F); **HRMS** m/z C₂₅H₂₉F₂N₃O₅ [M+Na]⁺ cal. 512.1972, found. 512.1969.

***Tert*-butyl 2-(((9H-fluoren-9-yl)methoxy)carbonyl)-*D*-phenylalanyl)-2-(2,2,2-trifluoroethyl)hydrazine-1-carboxylate [4-10c]**



Following the general procedures (VI-2): Fmoc-Phe-Cl was firstly prepared with SOCl_2 (42.9 mmol) and Fmoc-Phe-OH (1.28 g, 3.3 mmol) to give **4-9b**. Then the residue was mixed with **4-5a** (643 mg, 3 mmol) in 30 mL DCM to afford compound **4-10c** (1.66 g, 95%). **^1H NMR (300 MHz, CDCl_3)** δ (ppm) 7.66 (d, $J = 7.79$ Hz, 2H, H_{arom}), 7.45 (brs, 2H, H_{arom} , H_1), 7.36-6.69 (m, 10H, NH, H_{arom}), 5.49 (brs, 1H), 4.96 (brs, 1H), 4.70 (brs, 1H), 4.26 (brs, 2H), 4.08 (brs, 1H), 3.77-2.25 (m, 3H), 1.38 (s, 9H, H_{methyl}); **^{13}C NMR (75 MHz, CDCl_3)** δ (ppm) 174.6 (C_4), 155.3 (C_{11}), 153.5 (C_9), 143.8 (C_{22} , C_{25}), 141.3 (C_{23} , C_{24}), 135.8 (C_{34}), 129.4 (C_{arom}), 128.7 (C_{arom}), 127.7 (C_{arom}), 127.1 (C_{arom}), 125.1 (C_{arom}), 123.9 (q, $J = 280.8$ Hz, C_{10}), 83.3 (C_{16}), 67.1 (C_{17}), 52.1 (C_3), 48.1 (C_5), 47.1 (C_{21}), 37.3 (C_8), 28.1 (C_{methyl}); **^{19}F NMR (188 MHz, CDCl_3)** δ (ppm) -69.53 (s, CF_3); **HRMS m/z** $\text{C}_{31}\text{H}_{32}\text{F}_3\text{N}_3\text{O}_5$ [$\text{M}+\text{Na}$] $^+$ cal. 606.2192, found. 606.2204.

***Tert*-butyl 2-(((9H-fluoren-9-yl)methoxy)carbonyl)-*D*-phenylalanyl)-2-(2,2-difluoroethyl)hydrazine-1-carboxylate [4-10d]**

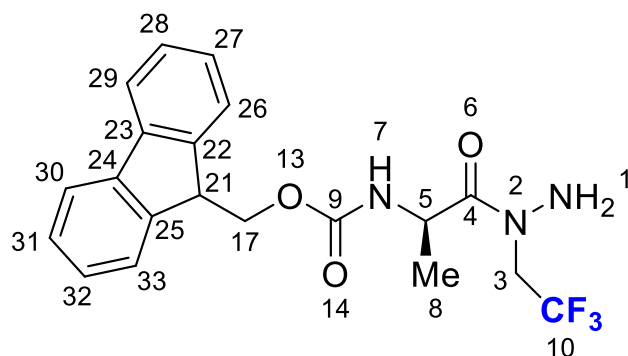


Following the general procedures (VI-2): Fmoc-Phe-Cl was firstly prepared with SOCl_2 (42.9 mmol) and Fmoc-Phe-OH (1.28 g, 3.3 mmol). Then the residue was mixed with **4-6a** (589 mg, 3 mmol) in 30 mL DCM to afford compound **4-10d** (1.42 g, 84%). **^1H NMR (300 MHz, CDCl_3)** δ (ppm) 7.79 (d, $J = 7.88$ Hz, 2H, H_{arom}), 7.57 (brs, 3H, H_1 , H_{arom}), 7.50-6.89 (m, 9H, H_{arom}), 5.93 (brt, $J = 55.20$ Hz, 1H, H_{10}), 5.64 (s, 1H, H_7), 5.09 (brs, 1H, H_5), 4.80-4.04 (m, 4H, H_{17} , H_{21} , H_3), 3.70 (brs, 1H, H_3), 3.09 (brs, 2H, H_8), 1.52 (s, 9H, H_{methyl}); **^{13}C NMR (75 MHz, CDCl_3)** δ (ppm) 174.7 (C_4), 155.7 (C_{11}), 153.6 (C_9), 143.8 (C_{22} , C_{25}), 141.3 (C_{23} , C_{24}), 136.0 (C_{34}), 129.4 (C_{arom}), 128.6 (C_{arom}), 127.7 (C_{arom}), 127.1 (C_{arom}), 125.1 and 125.0 (C_{arom}), 119.9 (C_{arom}), 113.5 (t, $J = 242.7$ Hz, C_{10}), 83.1 (C_{16}), 67.1 (C_{17}), 51.8 (C_5), 50.2 (t, $J = 32.8$ Hz, C_3), 47.1 (C_{21}), 37.8 (C_8), 28.1 (C_{methyl}); **^{19}F NMR (188 MHz, CDCl_3)** δ (ppm) -119.21 (m, 1F), -121.93 (m, 1F); **HRMS m/z** $\text{C}_{31}\text{H}_{33}\text{F}_2\text{N}_3\text{O}_5$ [$\text{M}+\text{Na}$] $^+$ cal. 588.2286, found. 588.2309.

Deprotection of Boc group (General procedure)

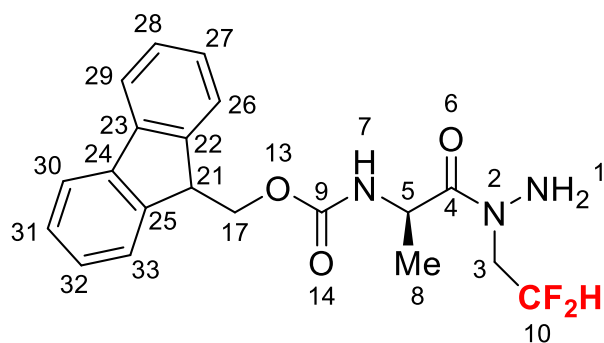
A solution of **4-10** in DCM was cooled down to 0 °C, followed by slow addition of HCl/dioxane (4N, 10 equiv.). Then, the mixture was stirred at room temperature overnight. Subsequently, the solvent was removed and the compound **4-11** was afforded after purification on silica gel.

(9H-fluoren-9-yl)methyl (R)-(1-oxo-1-(1-(2,2,2-trifluoroethyl)hydrazineyl)propan-2-yl)carbamate [4-11a]

**4-11a**

4-11a was prepared following the general procedure (VI-3) with **4-10a** (400 mg, 0.79 mmol) and HCl/dioxane (2 mL) in 8 mL DCM. **4-11a** was obtained in 84% (271 mg). **¹H NMR (300 MHz, CDCl₃)** δ (ppm) 7.65 (d, $J = 8.04$ Hz, 2H, H_{arom}), 7.48 (d, $J = 5.27$ Hz, 2H, H_{arom}), 7.29 (t, $J = 7.35$ Hz, 1H, H_{arom}), 7.20 (t, $J = 7.38$ Hz, 1H, H_{arom}), 5.57 (d, $J = 7.93$ Hz, 1H, H₇), 5.16 (q, $J = 7.4$ Hz, 1H, H₅), 4.47-4.29 (m, 1H, H₃), 4.26 (d, $J = 7.44$ Hz, 2H, H₁₇), 4.11 (t, $J = 7.06$ Hz, 1H, H₂₁), 4.01 (s, 2H, H₁), 3.91-3.58 (m, 1H, H₃), 1.28 (d, $J = 6.98$ Hz, 3H, H₈); **¹³C NMR (75 MHz, CDCl₃)** δ (ppm) 176.1 (C₄), 155.8 (C₉), 143.9 and 143.8 (C₂₂, C₂₂, C₂₅), 141.3 (C₂₃, C₂₄), 127.7 (C_{arom}), 127.1 (C_{arom}), 125.1 (C_{arom}), 124.3 (q, $J = 280.9$ Hz, C₁₀), 119.9 (C_{arom}), 66.9 (C₁₇), 50.7 (q, $J = 32.8$ Hz, C₃), 47.2 (C₅), 47.1 (C₂₁), 18.7 (C_{methyl}); **¹⁹F NMR (188 MHz, CDCl₃)** δ (ppm) -69.41 (t, $J = 8.87$ Hz, CF₃); **HRMS** m/z C₂₀H₂₀F₃N₃O₃ [M+H]⁺ cal. 408.1535, found. 408.1541.

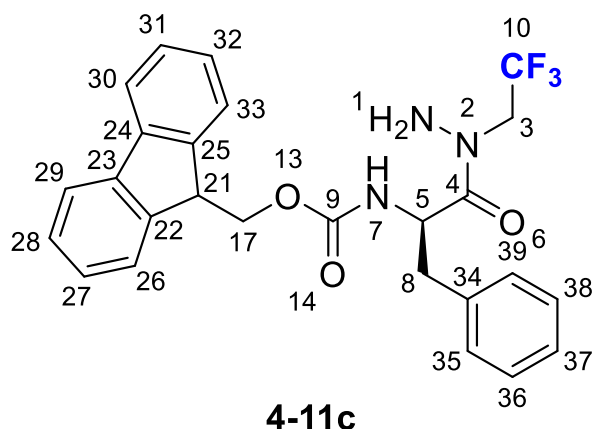
(9H-fluoren-9-yl)methyl (R)-1-(1-(2,2-difluoroethyl)hydrazineyl)-1-oxopropan-2-yl)carbamate [4-11b]

**4-11b**

4-11b was prepared following the general procedure (VI-3) with **4-10b** (593 mg, 1.21

mmol) and HCl/dioxane (3 mL) in 12 mL DCM. **4-11b** was obtained in 85% (400 mg). **¹H NMR (300 MHz, CDCl₃)** δ (ppm) 7.66 (d, J = 7.93 Hz, 2H, H_{arom}), 7.51 (d, J = 7.26 Hz, 2H, H_{arom}), 7.30 (t, J = 7.35 Hz, 1H, H_{arom}), -7.2 (t, J = 7.38 Hz, 1H, H_{arom}), 5.86 (tt, J_1 = 55.85 Hz, J_2 = 4.52 Hz, 1H, H₁₀), 5.54 (d, J = 7.72 Hz, 1H, H₇), 5.16 (q, J = 7.15 Hz, 1H, H₅), 4.27 (d, J = 7.16 Hz, 2H, H₁₇), 4.12 (t, J = 6.89 Hz, 1H, H₂₁), 3.98 (s, 2H, H₁), 3.93-3.83 (m, 1H, H₃), 3.77-3.62 (m, 1H, H₃), 1.29 (d, J = 6.78 Hz, 3H, H₈); **¹³C NMR (75 MHz, CDCl₃)** δ (ppm) 176.0 (C₄), 155.7 (C₉), 144.0 and 143.9 (C₂₂, C₂₅), 141.3 (C₂₃, C₂₄), 127.7 (C_{arom}), 127.1 (C_{arom}), 125.1 (C_{arom}), 119.9 (C_{arom}), 114.0 (t, J = 242.9 Hz, C₁₀), 66.9 (C₁₇), 52.7 (t, J = 24.9 Hz, C₃), 47.2 (C₅), 47.1 (C₂₁), 18.8 (C₈); **¹⁹F NMR (188 MHz, CDCl₃)** δ (ppm) -120.45 to -121.06 (m, 2F); **HRMS m/z** C₂₀H₂₁F₂N₃O₃ [M+Na]⁺ cal. 412.1449, found. 412.1445.

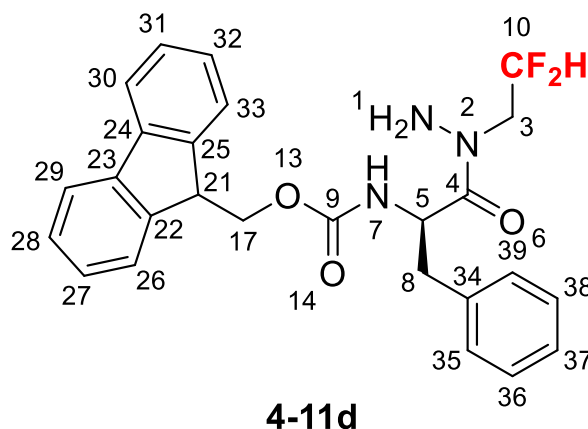
(9H-fluoren-9-yl)methyl (R)-(1-oxo-3-phenyl-1-(1-(2,2,2-trifluoroethyl)hydrazineyl)propan-2-yl)carbamate [4-11c]



4-11c was prepared following the general procedure (VI-3) with **4-10c** (1.5 g, 2.57 mmol) and HCl/dioxane (6.4 mL) in 30 mL DCM. **4-11b** was obtained in 91% (1.136 g). **¹H NMR (300 MHz, CDCl₃)** δ (ppm) 7.79 (d, J = 8.23 Hz, 2H, H_{arom}), 7.59 (dd, J = 7.33 Hz, 2H, H_{arom}), 7.43 (t, J = 7.45 Hz, 2H, H_{arom}), 7.38-7.18 (m, 7H, H_{arom}), 5.71-5.46 (m, 2H, H₅, H₇), 4.49-4.27 (m, 3H, H₃, H₁₇), 4.21 (t, J = 7.11 Hz, 1H, H₂₁), 3.86 (m, 1H, H₃), 3.72 (s, 2H, H₁), 3.08 (d, J = 6.39 Hz, 2H, H₈); **¹³C NMR (75 MHz, CDCl₃)** δ (ppm) 174.8 (C₉), 155.8 (C₄), 143.9 (C₂₂, C₂₅), 141.3 (C₂₃, C₂₄), 136.1 (C₃₄), 129.5 (C_{arom}), 128.8 (C_{arom}), 128.4 (C_{arom}), 127.7 (C_{arom}), 127.1 (C_{arom}), 125.1 (C_{arom}), 124.2 (q, J = 280.9 Hz, C₁₀), 119.9 (C_{arom}), 67.0 (C₁₇), 51.5 (C₅), 50.7 (q, J = 32.9 Hz, C₃),

47.2 (C₂₁), 39.7 (C₈); ¹⁹F NMR (188 MHz, CDCl₃) δ (ppm) -69.13 (t, *J* = 8.57 Hz, CF₃); HRMS *m/z* C₂₆H₂₄F₃N₃O₃ [M+Na]⁺ cal. 506.1667, found. 506.1670.

(9H-fluoren-9-yl)methyl (R)-(1-(1-(2,2-difluoroethyl)hydrazineyl)-1-oxo-3-phenylpropan-2-yl)carbamate [4-11d]



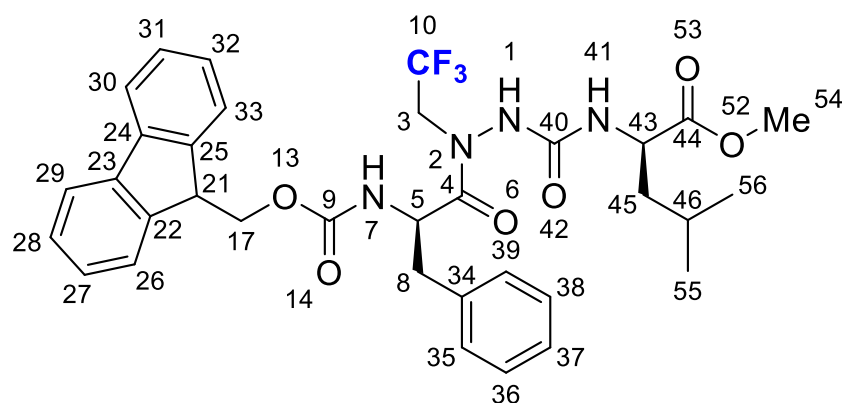
4-11d was prepared following the general procedure (VI-3) with **4-10d** (1.36 g, 2.40 mmol) and HCl/dioxane (6.0 mL) in 25 mL DCM. **4-11d** was obtained in 87% (970 mg). ¹H NMR (300 MHz, CDCl₃) δ (ppm) 7.79 (d, *J* = 8.44 Hz, 2H, H_{arom}), 7.66-7.53 (m, 2H, H_{arom}), 7.43 (t, *J* = 7.39 Hz, 2H, H_{arom}), 7.38-7.16 (m, 7H, H_{arom}), 5.86 (t, *J* = 59.58 Hz, 1H, H₁₀), 5.64 (brs, 2H, H₇, H₅), 4.49-4.27 (m, 2H, H₁₇), 4.22 (t, *J* = 7.05 Hz, 1H, H₂₁), 3.96 (m, 1H, H₃), 3.72 (s, 2H, H₁), 3.68-3.55 (m, 1H, H₃), 3.08 (brs, 2H, H₈); ¹³C NMR (75 MHz, CDCl₃) δ (ppm) 174.5 (C₄), 155.7 (C₉), 143.9 and 143.8 (C₂₂, C₂₅), 141.3 (C₂₃, C₂₄), 136.3 (C₃₄), 129.4 (C_{arom}), 129.3 (C_{arom}), 128.7 (C_{arom}), 128.3 (C_{arom}), 127.7 (C_{arom}), 127.3 (C_{arom}), 127.1 (C_{arom}), 125.1 (C_{arom}), 119.9 (C_{arom}), 113.9 (t, *J* = 243.9 Hz, C₁₀), 66.9 (C₁₇), 52.6 (t, *J* = 27.2 Hz, C₃), 51.6 (C₅), 47.2 (C₁₇), 39.6 (C₈), ¹⁹F NMR (188 MHz, CDCl₃) δ (ppm) -120.01 to 120.79 (m, 2F); HRMS *m/z* C₂₆H₂₅F₂N₃O₃ [M+Na]⁺ cal. 488.1762, found. 488.1764.

3. Synthesis of fluorinated azapeptoids (General procedure)

A mixture of **4-11** (1 equiv.) and DIPEA (1.2 equiv.) in DCM was slowly added into the stirred solution of triphosgene over a period of 10 min at 0°C. After that, this mixture was stirred at rt for 40 minutes, followed by the addition of the mixture of *L*-Leucine

methyl ester or *L*-Phenylalanine methyl ester hydrochloride salt (1 equiv.) and DIPEA (2.2 equiv.) in DCM. After 16h, the crude product was washed by H₂O one time. The organic phase was dried over NaSO₄ and filtered. After evaporation of the solvent, the crude was purified on silica gel to afford the desired compound.

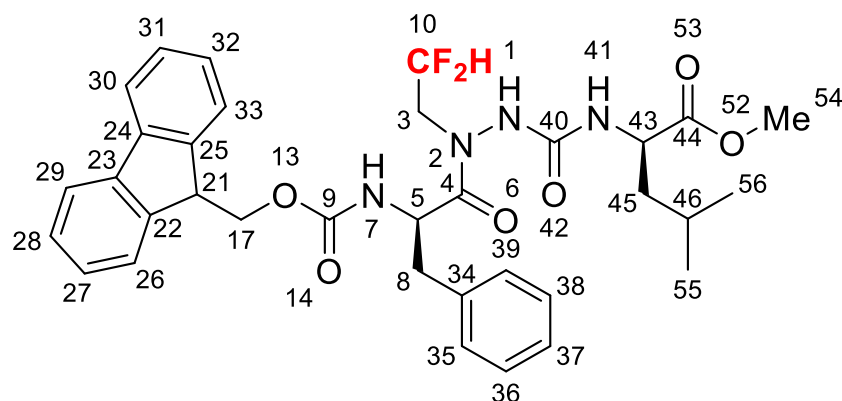
Methyl (2-(((9H-fluoren-9-yl)methoxy)carbonyl)-*D*-phenylalanyl)-2-(2,2,2-trifluoroethyl)hydrazine-1-carbonyl)-*D*-leucinate [4-12a]



4-12a

Following the general procedure: **4-11c** (242 mg, 0.5 mmol) and DIEPA (1.2 mmol) in 1.6 mL of DCM, triphosgene (59 mg, 0.2 mmol in 1.2 mL of DCM), *L*-Leucine methyl ester hydrochloride (91 mg, 0.5 mmol) and DIPEA (1.1 mmol) in 2 mL DCM. Compound **4-12a** was obtained in 53% (172 mg). Mixture of rotamers. ¹H NMR (300 MHz, CDCl₃) δ (ppm) 8.46 (brs, 1H), 7.62 (d, *J* = 7.05 Hz, 2H, H_{arom}), 7.49-6.77 (m, 12H, H_{arom}, H₁), 6.68-5.87 (brs, 1H, H₄₁), 5.69 (s, 1H, H₇), 4.99 (m, 1H, H₅), 4.46 (brs, 1H, H₁₁), 4.15 (brs, 2H, H₁₇), 4.09-3.85 (m, 2H, H₃, H₂₁), 3.47 (brs, 4H, H₃, H₅₄), 2.94 (m, 2H, H₈), 1.71-1.31 (m, 3H, H₄₅, H₄₆), 0.82 (d, *J* = 4.71 Hz, 6H, H₅₅, H₅₆); ¹³C NMR (75 MHz, CDCl₃) δ (ppm) 175.3 (C₄), 173.7 (C₄₄), 156.9 (C₄₀), 156.2 (C₉), 143.7 and 143.6 (C₂₂, C₂₅), 141.2 (C₂₃, C₂₄), 136.2 and 135.1 (C₃₄), 129.4 (C_{arom}), 128.8 (C_{arom}), 127.7 (C_{arom}), 127.5 (C_{arom}), 127.1 (C_{arom}), 125.1 (C_{arom}), 123.9 (q, *J* = 280.5 Hz, C₁₀), 119.9 (C_{arom}), 67.5 (C₁₇), 52.2 (C₅, C₄₃, C₅₄), 48.3 (q, *J* = 33.4 Hz, C₃), 46.9 (C₂₁), 41.4 and 40.1 (C₄₅), 37.5 (C₈), 24.9 (C₄₆), 22.9 and 21.3 (C₅₅, C₅₆); ¹⁹F NMR (188 MHz, CDCl₃) δ (ppm) -69.19 and -69.48 (s, CF₃); HRMS *m/z* C₃₄H₃₇F₃N₄O₆ [M+Na]⁺ cal. 677.2563, found. 677.2566.

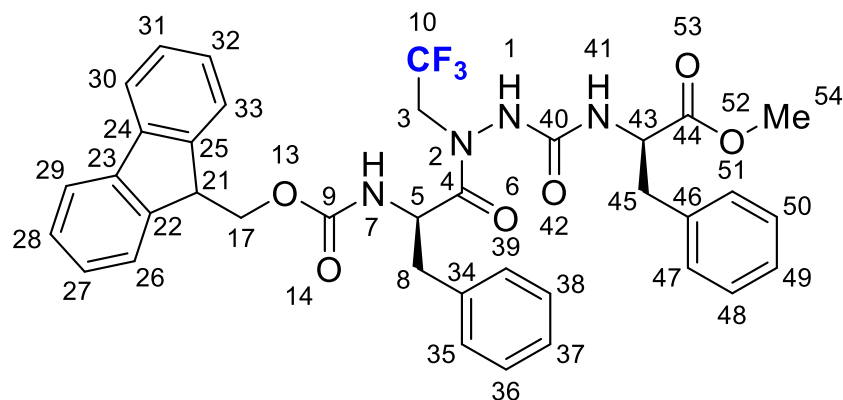
Methyl (2-(((9H-fluoren-9-yl)methoxy)carbonyl)-D-phenylalanyl)-2-(2,2-difluoroethyl)hydrazine-1-carbonyl)-D-leucinate [4-12b]



4-12b

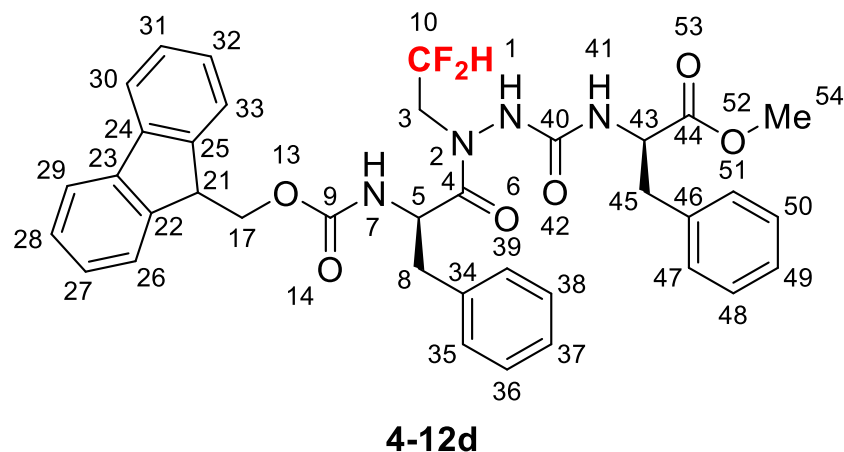
Following the general procedure: **4-11d** (233 mg, 0.5 mmol) and DIPEA (0.6 mmol) in 1.6 mL of DCM, triphosgene (59 mg, 0.2 mmol in 1.2 mL of DCM), *L*-Leucine methyl ester hydrochloride salt (91 mg, 0.5 mmol) and DIPEA (1.1 mmol) in 2 mL of DCM. The title compound was obtained (237 mg, 73%). ¹H NMR (300 MHz, CDCl₃) δ (ppm) 7.77 (d, *J* = 8.10 Hz, 2H, H_{arom}), 7.58-7.17 (m, 13H, H_{arom}, H₁), 6.26 (s, 1H, H₄₁), 5.92 (t, *J* = 51.87 Hz, 1H, H₁₀), 5.74 (s, 1H, H₇), 5.12 (brs, 1H, H₅), 4.64-4.0 (m, 5H, H₃, H₁₇, H₂₁), 3.63 (s, 3H, H₅₄), 3.04 (m, 2H, H₈), 1.89-1.39 (m, 3H, H₄₅, H₄₆), 0.94 (d, *J* = 5.58 Hz, 6H, H₅₅, H₅₆); ¹³C NMR (75 MHz, CDCl₃) δ (ppm) 175.4 (C₄), 173.7 (C₄₄), 157.0 (C₄₀), 156.5 (C₉), 143.7 (C₂₂, C₂₅), 141.2 (C₂₃, C₂₄), 135.5 (C₃₄), 129.3 (C_{arom}), 128.7 (C_{arom}), 127.8 (C_{arom}), 127.1 (C_{arom}), 125.1 and 125.0 (C_{arom}), 119.9 (C_{arom}), 113.3 (t, *J* = 244.5 Hz, C₁₀), 67.5 (C₁₇), 52.2 (C₅, C₄₃), 51.6 (C₅₄), 50.7 (t, *J* = 27.6 Hz, C₃), 46.9 (C₂₁), 40.1 (C₄₅), 37.5 (C₈), 24.9 (C₄₆), 22.9 (C₅₅), 21.4 (C₅₆); ¹⁹F NMR (188 MHz, CDCl₃) δ (ppm) -120.08 (dd, *J* = 50.89 Hz, 1F), -122.32 (dd, *J* = 54.07 Hz, 1F); HRMS *m/z* C₃₄H₃₈F₂N₄O₆ [M+Na]⁺ cal. 659.2657, found. 659.2659.

Methyl (2-(((9H-fluoren-9-yl)methoxy)carbonyl)-D-phenylalanyl)-2-(2,2,2-trifluoroethyl)hydrazine-1-carbonyl)-D-phenylalaninate [4-12c]

**4-12c**

Following the general procedure: **4-11c** (100 mg, 0.21 mmol) and DIPEA (0.25 mmol) in 0.8 mL of DCM, triphosgene (25 mg, 0.08 mmol in 0.6 mL of DCM), *L*-Phenylalanine methyl ester hydrochloride salt (45 mg, 0.21 mmol) and DIPEA (0.46 mmol) in 1 mL of DCM. The compound was obtained (65 mg, 46%). Mixture of rotamers. $^1\text{H NMR}$ (300 MHz, Acetone- d_6) δ (ppm) 8.58 and 8.10 (s, 1H, H₁), 7.84 (d, $J = 7.47$ Hz, 2H, H_{arom}), 7.61 (brs, 2H, H_{arom}, H₇), 7.39 (t, $J = 7.43$ Hz, 2H, H_{arom}), 7.34-7.15 (m, 13H, H_{arom}), 6.67 (brs, 1H, H₄₁), 5.20-4.0 (m, 5H, H₃, H₅, H₄₃, H₁₇, H₂₁), 3.62 (s, 3H, H₅₄), 3.58 (brs, 1H, H₃), 3.21 (dd, $J = 13.9, 5.1$ Hz, 1H, H₄₅), 3.06 (dd, $J = 13.6, 7.6$ Hz, 1H, H₄₅), 2.78 (s, 2H, H₈); $^{13}\text{C NMR}$ (75 MHz, CDCl₃) δ (ppm) 176.1 (C₄), 172.8 (C₄₄), 156.8 (C₄₀), 156.3 (C₉), 144.9 (C₂₂, C₂₅), 142.1 (C₂₃, C₂₄), 138.8 (C₃₄), 137.7 (C₄₆), 130.3 (C_{arom}), 129.2 (C_{arom}), 129.1 (C_{arom}), 128.5 (C_{arom}), 127.9 (C_{arom}), 127.6 (C_{arom}), 127.3 (C_{arom}), 126.2 (C_{arom}), 126.1 (C_{arom}), 125.5 (q, $J = 279.7$ Hz, C₁₀), 120.8 (C_{arom}), 67.3 (C₁₇), 55.3 (C₅), 53.4 (C₁₁), 52.5 (C₅₄), 48.4 (q, $J = 31.6$ Hz, C₃), 47.9 (C₂₁), 38.9 (C₈), 38.2 (C₄₅); $^{19}\text{F NMR}$ (188 MHz, CDCl₃) δ (ppm) -70.34, -70.46 and -70.63 (brs, CF₃), mixture of rotamers; HRMS m/z C₃₇H₃₅F₃N₄O₆ [M+Na]⁺ cal. 711.2406, found. 711.2406.

Methyl (2-(((9H-fluoren-9-yl)methoxy)carbonyl)-*D*-phenylalanyl)-2-(2,2-difluoroethyl)hydrazine-1-carbonyl)-*D*-phenylalaninate [4-12d]

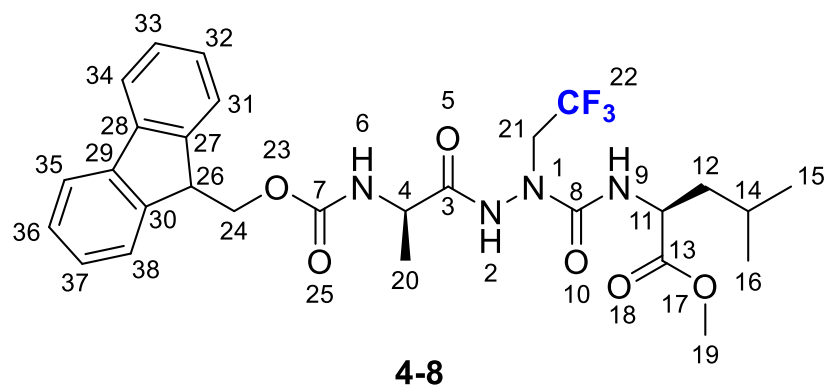


Following the general procedure: **4-11d** (233 mg, 0.5 mmol) and DIPEA (0.6 mmol), triphosgene (59 mg, 0.2 mmol in 1.2 mL of DCM), *L*-Phenylalanine methyl ester hydrochloride salt (108 mg, 0.5 mmol) and DIPEA (1.1 mmol) in 2 mL of DCM. The title compound was obtained (164 mg, 49%). **¹H NMR (200 MHz, CDCl₃)** δ (ppm) 7.73 (d, $J = 7.18$ Hz, 2H, H_{arom}), 7.55 (d, $J = 7.18$ Hz, 2H, H_{arom}), 7.48-7.04 (m, 15H, H_{arom}, H₇), 6.99-5.81 (brs, 1H, H₄₁), 5.75-5.26 (m, 2H), 5.22-4.87 (m, 1H, H₅), 4.88-4.47 (brs, 1H), 4.41-3.84 (m, 4H), 3.67 (s, 3H, H₅₄), 3.31-2.85 (m, 4H, H₈, H₄₅); **¹⁹F NMR (188 MHz, CDCl₃)** δ (ppm) -119.77 (dd, $J_1 = 281.81$ Hz, $J_2 = 60.49$ Hz, 1F), -122.35 (dd, $J_1 = 290.74$ Hz, $J_2 = 64.61$ Hz, 1F); **HRMS** m/z C₃₇H₃₆F₂N₄O₆ [M+Na]⁺ cal. 693.2495, found. 693.2503.

4. Synthesis of fluorinated aza peptides 4-8 and 4-13a-d

Preparation of 4-8: To a solution of triphosgene (44 mg, 0.15 mmol) in 0.8 mL of DCM was added a mixture of DIPEA (0.45 mmol) and **4-7c** (150 mg, 0.37 mmol) in x mL of DCM. After 40 minutes, the mixture of DIPEA (0.81 mmol) and *L*-Leucine methyl ester hydrochloride salt (67 mg, 0.37 mmol) were added in one portion to afford **4-8** (131 mg, 61%).

Methyl (2-(((9H-fluoren-9-yl)methoxy)carbonyl)-*D*-alanyl)-1-(2,2,2-trifluoroethyl)hydrazine-1-carbonyl)-*L*-leucinate [4-8]

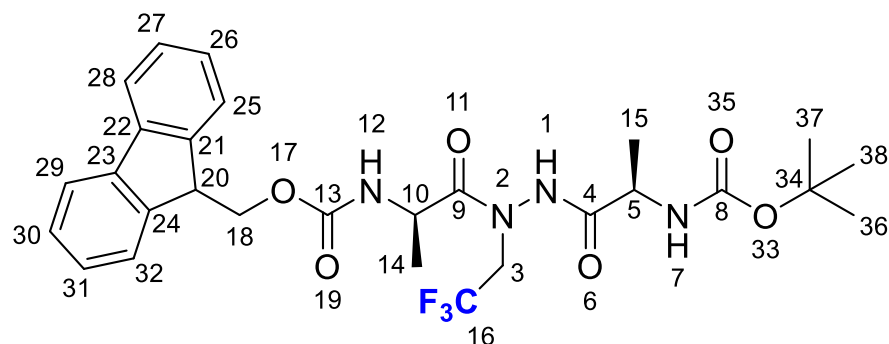


¹H NMR (300 MHz, CDCl₃) δ (ppm) 7.69 (d, *J* = 8.15 Hz, 2H, H_{arom}), 7.49 (d, *J* = 6.87 Hz, 2H, H_{arom}), 7.37-7.16 (m, 4H, H_{arom}), 5.11 (d, *J* = 9.99 Hz, 1H, H₆), 4.99 (d, *J* = 9.09 Hz, 1H, H₉), 4.85-4.68 (brs, 1H, H₄), 4.47-4.29 (m, 3H, H₁₁, H₂₄), 4.27-4.09 (m, 3H, H₂₁, H₂₆), 3.60 (s, 3H, H₁₉), 1.73-1.31 (m, 6H, H₁₂, H₁₄, H₂₀), 0.86 (d, *J* = 3.00 Hz, 3H, H₁₅), 0.84 (d, *J* = 2.76 Hz, 3H, H₁₆); **¹³C NMR (75 MHz, CDCl₃)** δ (ppm) 174.8 (C₁₃), 156.9 and 156.8 (C₃), 155.3 (C₈), 153.1 (C₇), 143.6 (C₂₇, C₃₀), 141.3 (C₂₈, C₂₉), 127.8 (C_{arom}), 127.1 (C_{arom}), 124.9 (C_{arom}), 122.6 (q, *J* = 279.9 Hz, C₂₂), 120.0 (C_{arom}), 67.3 (C₂₄), 52.1 (C₄, C₁₁), 51.6 (C₁₉), 47.1 (C₂₆), 46.8 (q, *J* = 36.6 Hz, C₂₁), 42.2 (C₁₂), 24.8 (C₁₄), 22.8 (C₁₅), 22.0 (C₁₆), 18.3 (C₂₀); **¹⁹F NMR (188 MHz, CDCl₃)** δ (ppm) -71.03 (td, *J* = 16.69 Hz, CF₃).

General procedure for the preparation of compounds 4-13a-d

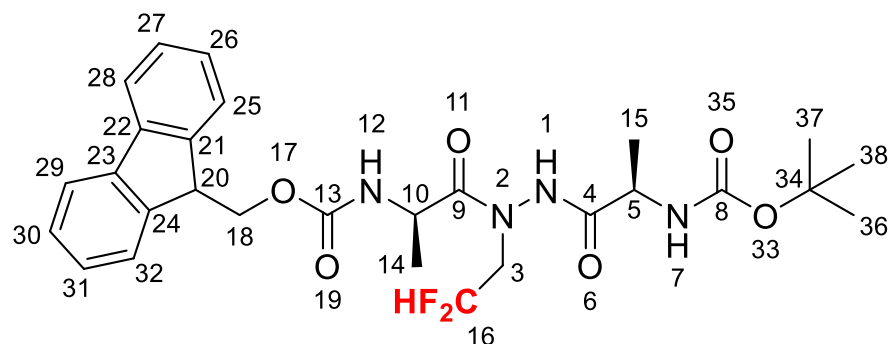
To a solution of **4-7a/7b** (1.0 equiv) in dichloromethane was added Fmoc-amino acid chloride (1.1 equiv). The reaction mixture was stirred for 16h at room temperature under inert atmosphere, and then the solvent was evaporated under reduced pressure. Purification by flash chromatography gave pure compound.

***Tert*-butyl ((*R*)-1-(2-(((9H-fluoren-9-yl)methoxy)carbonyl)-*D*-alanyl)-2-(2,2,2-trifluoroethyl)hydrazineyl)-1-oxopropan-2-yl)carbamate [4-13a]**

**4-13a**

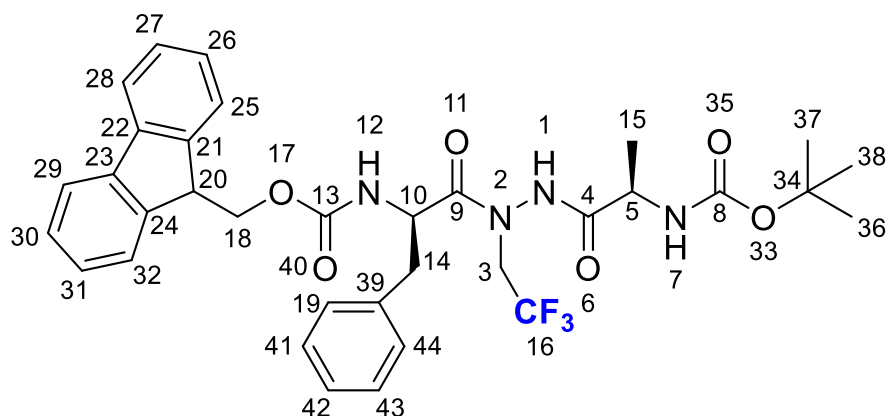
Following the general procedure: **4-7a** (285 mg, 1 mmol) and **4-9a** (362 mg, 1.1 mmol) were employed in 10 mL DCM to afford **4-13a**. (303 mg white solid, 52%). Mixture of rotamers. $^1\text{H NMR}$ (400 MHz, $\text{DMSO-}d_6$) δ (ppm) 11.00 and 10.83 (s, 1H, H_1), 7.88 (d, $J = 7.52$ Hz, 2H, H_{arom}), 7.72 (t, $J = 6.8$ Hz, 2H, H_{arom}), 7.65 (s, 1H, H_7), 7.43 (t, $J = 7.3$ Hz, 2H, H_{arom}), 7.3 (t, $J = 7.3$ Hz, 2H, H_{arom}), 7.15 (d, $J = 6.05$ Hz, 1H, H_{12}), 4.78 (brs, 1H, H_3), 4.62 (brs, 1H, H_{10}), 4.41 (t, $J = -4.14$ (m, 3H, H_{18} , H_{20}), 4.02 (q, $J = 7.0$ Hz, 1H, H_5), 3.72 (brs, 1H, H_3), 1.37 (s, 9H, H_{36} , H_{37} , H_{38}), 1.21 and 1.09 (brs, 6H, H_{14} , H_{15}); $^{13}\text{C NMR}$ (100 MHz, $\text{DMSO-}d_6$) δ (ppm) 175.7 (C_9), 172.6 (C_4), 155.2 (C_8 , C_{13}), 143.8 and 143.7 (C_{21} , C_{24}), 140.7 (C_{22} , C_{23}), 127.6 (C_{arom}), 127.0 (C_{arom}), 125.5 (C_{arom}), 124.2 (q, $J = 280.5$ Hz, C_{16}), 120.0 (C_{arom}), 78.1 (C_{34}), 65.7 (C_{18}), 48.3 (C_{10}), 47.0 (C_5), 46.6 (C_{20}), 46.4 (C_3), 28.1 (C_{36} , C_{37} , C_{38}), 17.6 (C_{14}), 16.6 (C_{15}); $^{19}\text{F NMR}$ (376 MHz, $\text{DMSO-}d_6$) δ (ppm) -68.61 and -69.12 (s, CF_3); **HRMS** m/z $\text{C}_{28}\text{H}_{33}\text{F}_3\text{N}_4\text{O}_6$ $[\text{M}+\text{Na}]^+$ cal. 601.2250, found. 601.2259.

***Tert*-butyl ((*R*)-1-(2-(((9H-fluoren-9-yl)methoxy)carbonyl)-*D*-alanyl)-2-(2,2-difluoroethyl)hydrazineyl)-1-oxopropan-2-yl)carbamate [4-13b]**

**4-13b**

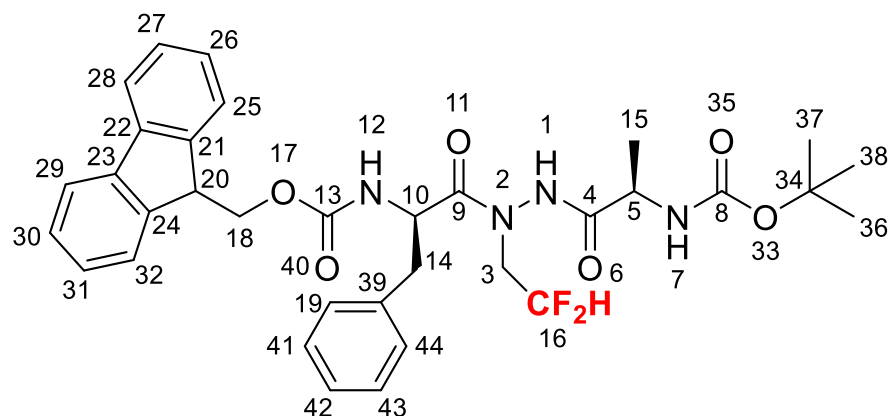
Following the general procedure: **4-7b** (267 mg, 1 mmol) and **4-9a** (362 mg, 1.1 mmol) were employed in 10 mL DCM to afford **4-13b**. (427 mg white solid, 76%). ¹H NMR (400 MHz, CDCl₃) δ (ppm) 9.48 (s, 1H, H₁), 7.74 (d, *J* = 7.49 Hz, 2H, H_{arom}), 7.55 (m, 2H, H_{arom}), 7.38 (t, *J* = 7.4 Hz, 2H, H_{arom}), 7.29 (t, *J* = 7.25 Hz, 2H, H_{arom}), 5.92 (t, *J* = 55.57 Hz, 1H, H₁₆), 5.64 (d, *J* = 7.82 Hz, 1H, H₁₂), 5.16 (brs, 1H, H₁₀), 4.7 (brs, 1H, H₅), 4.40-4.10 (m, 4H, H₁₈, H₂₀, H₃), 3.73 (brs, 1H, H₃), 1.42 (s, 9H, H₃₆, H₃₇, H₃₈), 1.39 (d, *J* = 7.19 Hz, 3H, H₁₄), 1.30 (d, *J* = 6.24 Hz, 3H, H₁₅); ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 175.4 (C₉), 172.4 (C₄), 156.0 (C₈), 155.9 (C₁₃), 143.9 and 143.8 (C₂₁, C₂₄), 141.4 (C₂₂, C₂₃), 127.9 (C_{arom}), 127.2 (C_{arom}), 125.2 (C_{arom}), 120.1 (C_{arom}), 113.7 (t, *J* = 242.5 Hz, C₁₆), 80.9 (C₃₄), 67.3 (C₁₈), 49.9 (t, *J* = 27.1 Hz, C₃), 49.1 (C₁₀), 47.1 (C₅), 46.4 (C₂₀), 29.8 and 28.3 (C₃₆, C₃₇, C₃₈), 18.2 (C₁₄), 17.2 (C₁₅); ¹⁹F NMR (376 MHz, CDCl₃) δ (ppm) -120.47 to -121.40 (m, 2F); HRMS *m/z* C₂₈H₃₄F₂N₄O₆ [M+Na]⁺ cal. 583.2344, found. 583.2339.

***Tert*-butyl((*R*)-1-(2-(((9H-fluoren-9-yl)methoxy)carbonyl)-*D*-phenylalanyl)-2-(2,2,2-trifluoroethyl)hydrazineyl)-1-oxopropan-2-yl)carbamate [4-13c]**

**4-13c**

Following the general procedure: **4-7a** (285 mg, 1 mmol) and **4-9b** (445 mg, 1.1 mmol) were employed in 10 mL DCM to afford **4-13c**. (574 mg, 88%). ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.75 (d, *J* = 7.52 Hz, 2H, H_{arom}), 7.51 (brs, 2H, H_{arom}), 7.38 (t, *J* = 7.5 Hz, 2H, H_{arom}), 7.35-7.16 (m, 8H, H_{arom}, H₇), 5.62 (d, *J* = 8.49 Hz, 1H, H₁₂), 5.03 (brs, 1H, H₁₀), 4.95 (brs, 1H, H₅), 4.45-4.04 (m, 5H, H₂₀, H₃, H₁₈), 3.15-2.90 (m, H₁₄), 1.52-1.33 (m, 12H, H₁₅, H₃₆, H₃₇, H₃₈); ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 174.0 (C₉), 171.8 (C₄), 155.9 (C₈), 143.8 and 143.7 (C₂₁, C₂₄, C₁₃), 141.4 (C₂₂, C₂₃), 135.8 (C₃₉), 129.5 (C_{arom}), 128.7 (C_{arom}), 127.8 (C_{arom}), 127.3 (C_{arom}), 127.2 (C_{arom}), 125.2 (C_{arom}), 125.1 (C_{arom}), 123.9 (q, *J* = 280.1 Hz, C₁₆), 120.1 (C_{arom}), 81.0 (C₃₄), 67.4 (C₁₈), 51.4 (C₁₀), 48.8 (C₅), 47.5 (q, *J* = 33.5 Hz, C₃), 47.1 (C₂₀), , 28.3 (C₃₆, C₃₇, C₃₈), 16.9 (C₁₅); ¹⁹F NMR (376 MHz, CDCl₃) δ (ppm) -69.75 (s, CF₃); HRMS *m/z* C₃₄H₃₇F₃N₄O₆ [M+Na]⁺ cal. 677.2563, found. 677.2557.

***Tert*-butyl ((R)-1-(2-(((9H-fluoren-9-yl)methoxy)carbonyl)-D-phenylalanyl)-2-(2,2-difluoroethyl)hydrazineyl)-1-oxopropan-2-yl)carbamate [4-13d]**

**4-13d**

Following the general procedure: **4-7b** (267 mg, 1 mmol) and **4-9b** (445 mg, 1.1 mmol) was employed in 10 mL DCM to afford **4-13d**. (569 mg, 89%). **¹H NMR (400 MHz, DMSO-*d*₆)** δ (ppm) 10.86 (s, 1H, H₁), 7.87 (d, $J = 7.53$ Hz, 2H, H_{arom}), 7.65 (t, $J = 8.5$ Hz, 2H, H_{arom}), 7.40 (td, $J = 7.2, 2.45$ Hz, 2H, H_{arom}), 7.35-7.11 (m, 11H, H_{arom}, H₇, H₁₂), 6.14 (t, $J = 55.44$ Hz, 1H, H₁₆), 4.63 (brs, 1H, H₁₀), 4.45-3.80 (m, 5H, H₃, H₅, H₁₈, H₂₀), 3.55 (brs, 1H, H₃), 3.18-2.65 (m, 2H, H₁₄), 1.37 (s, 9H, H₃₆, H₃₇, H₃₈), 1.25 (d, $J = 7.81$ Hz, 3H, H₁₅); **¹³C NMR (100 MHz, DMSO-*d*₆)** δ (ppm) 174.2 (C₉), 172.8 (C₄), 155.3 (C₈, C₁₃), 143.7 (C₂₁, C₂₄), 140.6 (C₂₂, C₂₃), 137.6 (C₃₉), 129.3 (C_{arom}), 128.1 (C_{arom}), 127.9 (C_{arom}), 127.6 (C_{arom}), 127.0 (C_{arom}), 126.2 (C_{arom}), 125.3 and 125.2 (C_{arom}), 120.0 (C_{arom}), 114.0 (t, $J = 240.7$ Hz, C₁₆), 78.3 (C₃₄), 65.7 (C₁₈), 52.1 (C₁₀), 49.0 (t, $J = 26.4$ Hz, C₃), 48.5 (C₅), 46.5 (C₂₀), 36.6 (C₁₄), 28.1 (C₃₆, C₃₇, C₃₈), 17.1 (C₁₅); **¹⁹F NMR (376 MHz, DMSO-*d*₆)** δ (ppm) -119.39 to -123.12 (m, 2F); **HRMS** m/z C₃₄H₃₈F₂N₄O₆ [M+Na]⁺ cal. 659.2657, found. 659.2653.

References

- [1] A. Henninot, J. C. Collins, J. M. Nuss, *J. Med. Chem.* **2018**, 61, 1382–1414.
- [2] S. S. Timur, R. N. Gürsoy, *J. Drug. Target.* **2021**, 29, 1048–1062.
- [3] D. J. Craik, D. P. Fairlie, S. Liras, D. Price, *Chem. Biol. Drug. Des.* **2013**, 81, 136–147.
- [4] E. Lenci, A. Trabocchi, *Chem. Soc. Rev.* **2020**, 49, 3262.
- [5] Y. D. Wu, S. Gellman, *Acc. Chem. Res.* **2008**, 41, 1231–1232.
- [6] A. Grauer, B. König, *Eur. J. Org. Chem.* **2009**, 2009, 5099–5111.
- [7] R. M. J. Liskamp, D. T. S. Rijkers, J. A. W. Kruijtzter, J. Kemmink, *ChemBioChem.* **2011**, 12, 1626–1653.
- [8] C. Adessi, C. Soto, *Curr. Med. Chem.* **2002**, 9, 963–978.
- [9] S. Sagan, P. Karoyan, O. Lequin, G. Chassaing, S. Lavielle, *Curr. Med. Chem.* **2004**, 11, 2799–2822.
- [10] K. Luthman, U. Hacksell, *Textb. Drug Des. Discovery* (3rd Ed) **2002**, 459–485.
- [11] A. F. Spatola, *Chemistry and Biochemistry of Peptides and Proteins*, Marcel Dekker: New York, 1983.
- [12] C. Proulx, D. Sabatino, R. Hopewell, J. Spiegel, Y. G. Ramos, W. D. Lubell, *Future Med. Chem.* **2011**, 3, 1139–1164.
- [13] C. Proulx, J. Zhang, D. Sabatino, S. Chemtob, H. Ong, W. D. Lubell, *Biomedicines.* **2020**, 8, 241.
- [14] Y. Zhang, R. M. Malamakal, D. M. Chenoweth, *J. Am. Chem. Soc.* **2015**, 137, 12422–12425.
- [15] Y. Zhang, M. Herling, D. M. Chenoweth, *J. Am. Chem. Soc.* **2016**, 138, 9751–9754.
- [16] A. J. Kasznel, Y. Zhang, Y. Hai, D. M. Chenoweth, *J. Am. Chem. Soc.* **2017**, 139, 9427–9430.
- [17] S. D. Melton, E. A. E. Brackhahn, S. J. Orlin, P. Jin, D. M. Chenoweth, *Chem. Sci.* **2020**, 11, 10638–10646.
- [18] A. S. Dutta, M. B. Giles, Polypeptides. Part XIV. *J. Chem. Soc. Perkin Trans. 1* **1976**, 244–248.
- [19] K. Baruah, B. Sahariah, S. S. Sakpal, Jugal Kishore Rai Deka, Arun Kumar Bar, S. Bagchi, Bani Kanta Sarma, *Org. Lett.* **2021**, 23, 13, 4949–4954.

- [20] a) Z. Benatalah, A. Aubry, G. Boussard, M. Marraud, *Int. J. Pept. Protein Res.* **1991**, 38, 603–605. (b) M. Thormann, H. J. Hofmann, *J. Mol. Struct.* **1999**, 469, 63–76. (c) H. J. Lee, I. A. Ahn, S. Ro, K. H. Choi, Y. S. Choi, K. B. Lee, *J. Pept. Res.* **2000**, 56, 35–46. (d) H. J. Lee, K. H. Choi, I. A. Ahn, S. Ro, H. G. Jang, Y. S. Choi, K. B. Lee, *J. Mol. Struct.* **2001**, 569, 43–54. (e) C. Hemmerlin, M. T. Cung, G. Boussard, *Tetrahedron Lett.* **2001**, 42, 5009–5012. (f) D. Sabatino, C. Proulx, S. Klocek, C. B. Bourguet, D. Boeglin, H. Ong, W. D. Lubell, *Org. Lett.* **2009**, 11, 3650–3653. (g) D. Sabatino, C. Proulx, P. Pohankova, H. Ong, W. D. Lubell, *J. Am. Chem. Soc.* **2011**, 133, 12493–12506. (h) C. Proulx, É. Picard, D. Boeglin, P. Pohankova, S. Chemtob, H. Ong, W. D. Lubell, *J. Med. Chem.* **2012**, 55, 6502–6511.
- [21] C. Gibson, S. L. Goodman, D. Hahn, G. Hölzemann, H. Kessler, *J. Org. Chem.* **1999**, 64, 7388–7394.
- [22] M. O. Bowles, C. Proulx, *Org. Lett.* **2022**, 24, 1768–1773.
- [23] M. D. Bailey, T. Halmos, N. Goudreau, E. Lescop, M. Llinàs-Brunet, *J. Med. Chem.* **2004**, 47, 3788–3799.
- [24] D. Enders, K. Funabiki, *Org. Lett.* **2001**, 3, 1575–1577.
- [25] C. A. Sanchez, C. Gadais, G. Chaume, S. Girard, E. Chelain, T. Brigaud, *Org. Lett.* **2021**, 23, 382–387.
- [26] C. D. Sessler, M. Rahm, S. Becker, J. M. Goldberg, F. Wang, S. J. Lippard, *J. Am. Chem. Soc.* **2017**, 139, 9325–9332.
- [27] F. Andre, M. Marraud, T. Tsouloufis, S. J. Tzartos, G. Boussard, *J. Pept. Sci.* **1997**, 3, 429–441.

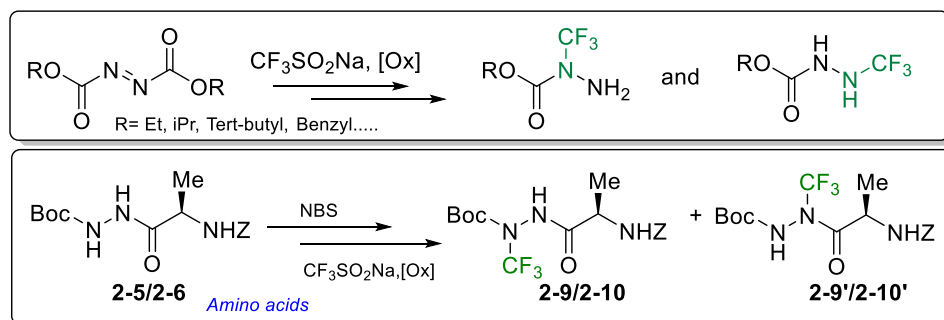
General conclusion

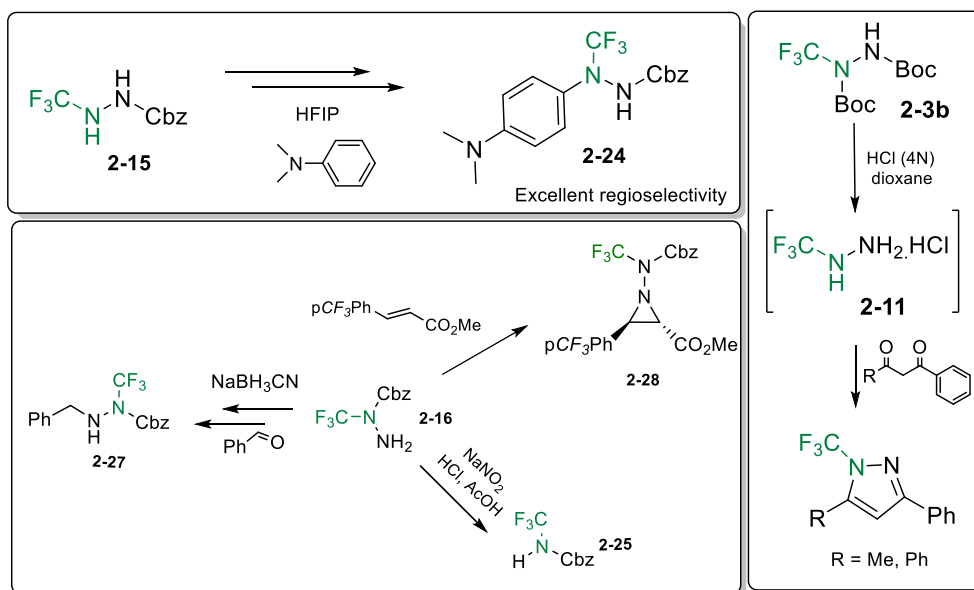
During my PhD, we achieved significant results in developing an efficient methodology to synthesize *N*-trifluoromethylated hydrazines through the radical reaction from azodicarboxylates. The study of their reactivity allowed access to new peptidomimetics and fluorinated compounds. Then direct access to a series of fluorinated sulfonyl hydrazides has been performed in a mild and effective condition in good to excellent yields. The trifluoromethyl sulfonyl hydrazide showed its excellent reactivity as the SCF₃ source with a copper catalyst in the thiolation reaction on indoles. Additionally, we also synthesized *N*-di and trifluoromethylated hydrazines and coupled them with amino acids to access new fluorinated azapeptides/azapeptoids.

1. Synthesis of *N*-CF₃ hydrazines through radical trifluoromethylation of azodicarboxylates

In the first chapter, a new approach to accessing *N*-CF₃ hydrazines was developed. By carrying out the radical reaction of the CF₃ group on azodicarboxylate compounds, families of molecules could be synthesized very efficiently. Studies of the deprotection and reactivity of these building blocks have also been carried out. Thus, new *N*-CF₃ hydrazino peptidomimetics have been prepared in reasonable yields. Also, heterocyclic compounds, substituted *N*-CF₃ hydrazine, aziridine and the protected *N*-CF₃ amine have been synthesized in excellent yields in few steps. Some products were determined by X-Ray crystallographic analysis.

This methodological study gave rise to a publication: **Tingting Cao**, Pascal Retailleau, Thierry Milcent, Benoît Crousse, *Chem. Commun.* **2021**, 57, 10351-10354.



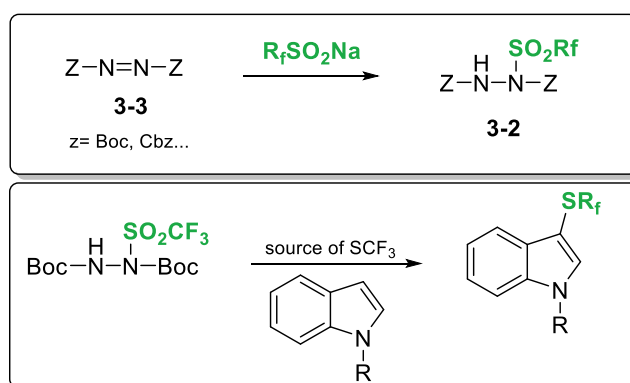


Scheme 1. Synthesis of *N*-CF₃ hydrazines and access to new family of *N*-CF₃

2. Direct access to fluorinated sulfonylhydrazides and study of their reactivity in trifluoromethylthiolation of indoles

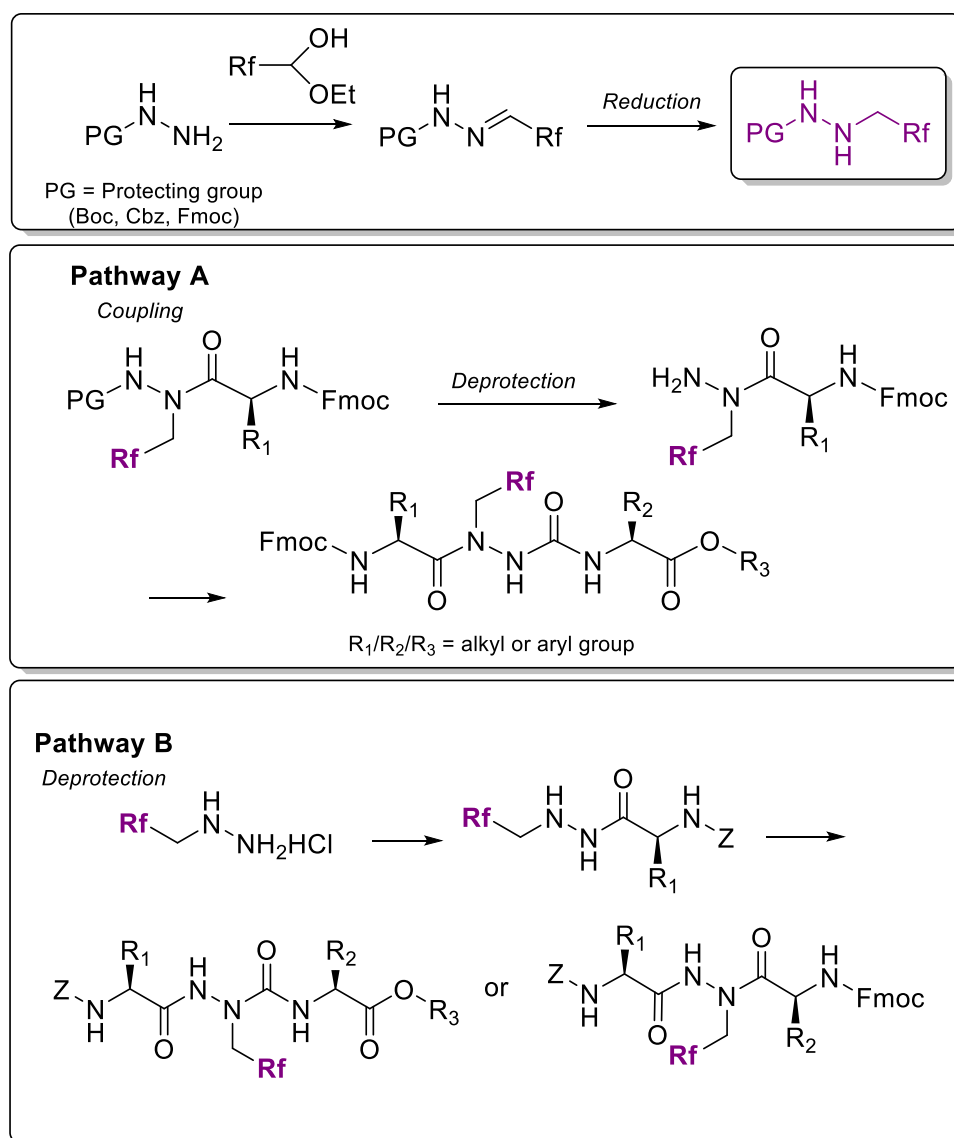
A wide range of families of new fluorinated sulfonyl hydrazides were prepared from accessible and inexpensive sulfinates and azodicarboxylates in excellent yields. Meanwhile, we showed that the trifluoromethylsulfonyl hydrazide (Tf(Boc)N-NHBoc) is an efficient source of SCF₃ in the trifluoromethylthiolation of indoles and is an alternative to the TfNHNHBoc reagent.

This work has led to a publication: **Tingting Cao**, Benoît Crousse, *Helv. Chim. Acta.* **2021**, 105, e202100196.



Scheme 2. Direct access to fluorinated sulfonylhydrazides and application in trifluoromethylthiolation of indoles

In later research, we disclosed some simple reaction conditions to access a series of *N*-fluorinated azapeptoids and azapeptides. After reduction of hydrazones, hydrazines, obtained in good yields, are coupled with amino acids to generate corresponding aza-derivatives. Finally, some products were determined by X-Ray crystallographic analysis.



Scheme 3. Synthesis of aza-derivatives

Résumé

Grâce à des propriétés physico-chimiques particulières, le fluor prend de plus en plus d'importance dans la chimie médicinale. Les hydrazines sont essentielles pour la synthèse de composés fonctionnalisés N-hétérocycliques et pour leurs nombreuses applications dans les domaines des matériaux, de la pharmacie et de l'agrochimie. Dans ce mémoire, nous sommes particulièrement focalisés sur la synthèse d'hydrazines fluorées et en particulier des hydrazines *N-N*-CF₃, *N-N*-CH₂CF₃ et *N-N*-CH₂CF₂H.

Dans la première partie, une étude de préparation d'hydrazines *N*-CF₃ a été réalisée par voie radicalaire, faisant intervenir le réactif de Langlois, le triflinate (CF₃SO₂Na) et des azodicarboxylates. Les conditions réactionnelles sont douces et efficaces. Cette réaction a pu également être effectuée sur des diazènes comprenant des acides aminés pour donner des peptidomimétiques *N*-CF₃-hydrazines. Les produits *N*-CF₃ avec des groupes protecteurs tels que Boc et Cbz ont généré des hydrazines RCO-*N*(CF₃)-NH₂ et H-*N*(CF₃)-NHCOR. Ces derniers ont conduit après plusieurs réactions de nouveaux composés d'intérêts. Egalement en parallèle de cette étude, nous avons pu exploité un produit secondaire, le trifluorométhyl sulfonyl hydrazide (Boc-NH-N(Boc)SO₂CF₃) dans la réaction de trifluorométhylthiolation d'indoles.

Dans la seconde partie, de nouveaux peptidomimétiques comportant des groupements *N-N*-CH₂CF₃ et *N-N*-CH₂CF₂H ont été conçus et synthétisés. Nous avons particulièrement synthétisé des azapeptides et des azapeptoïdes qui ont été incorporés dans des peptides. Des études de RMN ont été réalisées afin de voir l'impact des groupes fluorés dans la conformation des peptidomimétiques et peptides.

Titre : titre (en français) : Conception et Synthèse de Nouvelles Hydrazines Fluorées

Mots clés : peptidomimétiques, fluor, *N*-fluoroalkyles, hydrazines, azodicarboxylates, trifluoromethylthiolation

Résumé : Dans la première partie, une étude de préparation d'hydrazines *N*-CF₃ a été réalisée par voie radicalaire, faisant intervenir le réactif de Langlois, le triflinate (CF₃SO₂Na) et des azodicarboxylates. Les conditions réactionnelles sont douces et efficaces. Cette réaction a pu également être effectuée sur des diazènes comprenant des acides aminés pour donner des peptidomimétiques *N*-CF₃-hydrazines. Les produits *N*-CF₃ avec des groupes protecteurs tels que Boc et Cbz ont généré des hydrazines RCO-*N*(CF₃)-NH₂ et H-*N*(CF₃)-NHCOR. Ces derniers ont conduit après plusieurs réactions de nouveaux composés d'intérêts.

Egalement en parallèle de cette étude, nous avons pu exploité un produit secondaire, le trifluorométhyl sulfonyl hydrazide (Boc-NH-N(Boc)SO₂CF₃) dans la réaction de trifluorométhylthiolation d'indoles.

Dans la seconde partie, de nouveaux peptidomimétiques comportant des groupements *N*-*N*-CH₂CF₃ et *N*-*N*-CH₂CF₂H ont été conçus et synthétisés. Nous avons particulièrement synthétisé des azapeptides et des azapeptoides qui ont été incorporés dans des peptides. Des études de RMN ont été réalisées afin de voir l'impact des groupes fluorés dans la conformation des peptidomimétiques et peptides.

Title : titre (en anglais): Design and Synthesis of New Fluorinated Hydrazines.

Keywords : fluorine, *N*-fluoroalkyles, hydrazines, azodicarboxylates, peptidomimetics, trifluoromethylthiolation

Abstract : Thanks to particular Physico-chemical properties, fluorine is becoming increasingly important in medicinal chemistry. Hydrazines are essential for synthesising *N*-heterocyclic functionalised compounds and for their many applications in many areas of synthetic chemistry in materials, pharmaceuticals and agrochemicals, dyes, and directing groups important in catalysis. This thesis mainly focused on synthesising fluorinated hydrazines, particularly the hydrazines *N*-*N*-CF₃, *N*-*N*-CH₂CF₃ and *N*-*N*-CH₂CF₂H. In the first part, a study of the preparation of *N*-CF₃ hydrazines was carried out by the radical route, involving Langlois' reagent, triflinate (CF₃SO₂Na) and azodicarboxylates. The reaction conditions are mild and efficient. This reaction could also be carried out on diazenes comprising amino acids to give peptidomimetics *N*-CF₃-hydrazines.

N-CF₃ products with protecting groups such as Boc and Cbz generated RCO-*N*(CF₃)-NH₂ and H-*N*(CF₃)-NHCOR hydrazines. The latter has led, after several reactions, to new compounds of interest. Also, in parallel with this study, we exploited a secondary product, trifluoromethyl sulfonyl hydrazide (Boc-NH-N(Boc)SO₂CF₃), in the trifluoromethylthiolation reaction of indoles.

In the second part, new peptidomimetics comprising *N*-*N*-CH₂CF₃ and *N*-*N*-CH₂CF₂H groups were designed and synthesized. We have synthesized azapeptides and azapeptoids, which have been incorporated into peptides. NMR studies have been carried out to see the impact of fluorinated groups on the conformation of peptidomimetics and peptides.