# New synthetic approaches for the introduction of pentafluorosulfanyl group (SF5) into heterocycles

Ewelina Falkowska

**ÉCOLE DOCTORALE NORMANDE DE CHIMIE**

**THÈSE**

Présentée à

**L'Institut National des Sciences Appliquées de Rouen**

Pour l'obtention du grade de

**DOCTEUR EN CHIMIE ORGANIQUE**

Par

**Ewelina FALKOWSKA**

# New Synthetic Approaches for the Introduction of Pentafluorosulfanyl Group ($SF_5$) into Heterocycles

**le 16 décembre 2015**

**Devant le jury composé de:**

| | | |
|---|---|---|
| Dr. Julien PYTKOWICZ | Université de Cergy-Pontoise | Rapporteur |
| Dr. Stéphane LEBRUN | Université Lille 1 | Rapporteur |
| Dr. Petr BEIER | Academy of Sciences of the Czech Republic | Examinateur |
| Pr. Jean-Philippe BOUILLON | Université de Rouen | Examinateur |
| Pr. Philippe JUBAULT | INSA de Rouen | Examinateur |
| Pr. Xavier PANNECOUCKE | INSA de Rouen | Examinateur |

**Acknowledgement**

First of all, I would like to thank Dr. Petr Beier (Academy of Sciences of the Czech Republic), Dr. Stéphane Lebrun (Université Lille 1) and Dr. Julien Pytkowicz (Université de Cergy-Pontoise) for kindly accepting to examine my thesis.

I am very thankfull to my supervisors Pr. Jean-Philippe Bouillon and Pr. Philippe Jubault for their guidance, patience and the support that I received from them trough last three years. I am also very grateful to Pr. Xavier Pannecoucke for giving me the opportunity to carry out my thesis in the team of "Synthesis of Fluorinated Biomolecules".

I would like to thank Dr. Morgane Sanselme for X-ray analyses; Dr. Albert Marcual and Dr. Dominique Harakat (Reims University) for HRMS analyses; Laetitia Bailly and Emilie Petit for their help with chromatography techniques; Dr. Vincent Tognetti and Pr. Laurent Joubert for the theoretical calculations.

I would also like to thank Dr. Petr Beier, Dr. Mathieu Laurent (Université du Maine) and Dr. Pavel Mykhailiuk (Enamine Company) for the collaboration and the valuable advises.

Many thanks to Elisabeth Roger (Babette) for her help and kindness. I also thank to all the former and current team members, and to all people from IRCOF.

Finally, I would like to thank to my parents and to my future husband Szymek for their love and encouragement. They have been going trough the hardest moments together with me, especially during the final stages of this PhD, and I am deeply grateful for that.

Dziękuję Wam kochani Rodzice i Szymku.

# Contents

# Abbreviations

**1,3-DC** – 1,3-dipolar cycloaddition

**5-HT** – 5-hydroxytryptamine

**Ac** – acetyl

**ACN** – acetonitrile

**AcOEt –** ethyl acetate

**AcOH –** acetic acid

**Alk** – alkyl

**Ar** – aryl

**Boc** – *tert*-butyloxycarbonyl

**Bn** – benzyl

**COSY** – correlation spectroscopy

**CAN** – cerium (IV) ammonium nitrate

**Cy** – cyclohexyl

**DCC** – *N,N′*-dicyclohexylcarbodiimide

**DCE** – 1,2-dichloroethane

**DDQ** – 2,3-dichloro-5,6-dicyano-1,4-benzoquinone

**DEAD** – diethyl azidocarboxylate

**DIPC** – *N,N'*-diisopropylcarbodiimide

**DMAP** – 4-dimethylaminopyridine

**DMF –** dimethylformamide

**DMSO** – dimethyl sulfoxide

***dr* –** diastereoisomeric ratio

**$EC_{50}$ –** half maximal effective concentration

**EDG** – electron donating group

***ee*** – enantiomeric excess

**equiv –** equivalent

**EWG –** electron withdrawing group

**FMO –** frontier molecular orbitals

**h –** hour

**HetAr** – heteroaryl

**HMBC** – heteronuclear multiple bond correlation

**HOBt** – hydroxybenzotriazole

**HOMO** – the highest occupied molecular orbital

**HRMS –** high resolution mass spectroscopy

**$IC_{50}$** – inhibitory concentration 50 (50% response)

**IR** – infrared

**IBX** – 2-iodoxybenzoic acid

***J*** – spin-spin soupling constance

**LUMO –** the lowest unoccupied molecular orbital

***m*-CPBA** – *meta*-chloroperoxybenzoic acid

**MS** – molecular sieves

**M.p.** – melting point

**NMO** – N-methylmorpholine N-oxide

**NMR –** nuclear magnetic resonance

**NOESY –** nuclear Overhauser effect spectroscopy

**PCC** – pyridinium chlorochromate

**Ph** – phenyl

**Pin** - pinacole

**PMB** – *p*-methoxybenzyl

**PTSA** – *p*-toluenesulfonic acid

**Pyr** – pyridine

***(R)*-BINAP** – *(R)*-(2,2'-bis(diphenylphosphino)-1,1'-binaphthyl)

**rt** – room temperature

**$T_3P$** – propylphosphonic anhydride

**TBAF** – tetrabutylammonium fluoride

**TFA** – trifluoroacetic acid

**THF –** tetrahydrofuran

**TIPS** – triisopropylsilyl

**TLC** – Thin Layer Chromatography

**TMAF –** tetramethylamounium fluoride

**TMS –** trimethylsilyl

**Tol** – tolyl

**TPAP** – tetrapropylammonium perruthenate

**UV** - ultraviolet

## Abstract

Due to its unique properties, the pentafluorosulfanyl ($SF_5$) group has recently reached much attention. This bulky, highly lipophilic and electron-withdrawing substituent is often called as a "super-trifluoromethyl group". Currently, the $SF_5$-chemistry is becoming a fast growing field of the fluorine chemistry and the new pentafluorosulfanylated building-blocks are under continuous development. Nevertheless, the methods for the introduction of the $SF_5$-group into heterocycles remain still quite limited.

The aim of this thesis was to synthesize new pentafluorosulfanylated building-blocks, on the one hand, and to develop new synthetic approaches leading to original pentafluorosulfanylated nitrogen-containing heterocyles, on the other hand.

In the first part of our work, we have developed an efficient four-step synthesis of new $SF_5$-acrylic esters and amides, starting from commercially available allyl acetate derivatives. Using the same strategy, several new pentafluorosulfanylated allylsilanes were synthesized. We have also developed an In-mediated allylation reaction of aldehydes, using the $SF_5$-allyl bromide, leading to the corresponding pentafluorosulfanylated $\alpha$- and $\gamma$-homoallylic alcohols.

In the second part, two different strategies for the synthesis of new $SF_5$-substituted heterocycles were explored. The first one was the direct fluorination of heterocyclic thiols or disulfides, according to the Umemoto's procedure. The second approach was based on the cycloaddition reactions of our pentafluorosulfanylated building-blocks. As a result, we have successfully developed the synthesis of the first $SF_5$-substituted pyrrolidines and isoxazolidines. Finally, post-functionalizations of $SF_5$-pyrrolidines were performed, leading to several pentafluorosulfanylated scaffolds which could be easily introduce into molecules of biological interest.

## Résumé

Grâce à ses propriétés uniques, le groupement pentafluorosulfanyle ($SF_5$) a récemment retenu beaucoup d'attention. Ce substituant encombrant, hautement lipophile et électro-attracteur est souvent considéré comme un "super groupement trifluorométhyl". Aujourd'hui, la chimie de groupement $SF_5$ est un domaine de la chimie du fluor qui se développe rapidement, et les méthodologies de synthèse des nouveaux « building-blocks » pentafluorosulfanylés sont constamment développées. Néanmoins, les méthodes permettant l'introduction du groupement $SF_5$ dans les hétérocycles restent encore assez limitées.

L'objectif de cette thèse était de synthétiser des nouveaux « building-blocks » pentafluorosulfanylés, d'une part, et de développer des nouvelles approches synthétiques, conduisant à des hétérocycles azotés originaux, substitués par un groupement $SF_5$, d'autre part.

Dans la première partie de notre travail, nous avons développé une synthèse en 4 étapes, conduisant à de nouveaux esters et amides acryliques substitués par un groupement $SF_5$, à partir des dérivés commerciaux de l'acetate allylique. En utilisant la même stratégie, quelques nouveaux allylsilanes pentafluorosulfanylés ont été synthétisés. Nous avons aussi développé une réaction d'allylation des aldéhydes, catalysée par indium, en utilisant le bromure $SF_5$-allylique, conduisant aux alcools $\alpha$- et $\gamma$-homoallyliques correspondants.

Dans la deuxième partie, deux stratégies différentes pour la synthèse de nouveaux hétérocycles $SF_5$-substitués, ont été explorées. La première était la fluoration directe des thiols ou disulfures hétérocycliques, suivant la procédure de Umemoto. La deuxième approche était basée sur les réactions de cycloaddition de nos "building-blocks" pentafluorosulfanylés. Ainsi, nous avons développé avec succès la synthèse des premières pyrrolidines et isoxazolidines pentafluorosulfanylées. Enfin, des post-fonctionnalisations des $SF_5$-pyrrolidines ont été effectuées, conduisant aux plusieurs "plateformes" pentafluorosulfanylées qui pourraient être facilement incorporées dans les molécules d'intérêt biologique.

# Chapter I

# Introduction

# 1. General introduction

Since the discovery of the elemental fluorine by Henri Moissan in 1886,[1] a number of organofluorine compounds were applied in various domains, such as agrochemistry, medicinal chemistry, materials or polymers. The interest in the fluorine chemistry is due to the physico-chemical characteristics of the fluorine atom, including its high electronegativity and small size, as well as its influence on the acidity of the neighbouring functional groups.[2] It is well known that the C–F bond can successfully replace the C–H or C–O bonds, retaining comparable activities of the molecule, but changing some properties. Because of this special nature of the fluorine atom, its presence in drugs or agrochemicals is usually crucial for their activity. Fluorine substitution is often used to increase metabolic stability, enhance binding interactions or increase the blood brain barrier permeability.[3] Nowadays, approximately 25% of new commercially available pharmaceuticals contain at least one fluorine atom.[4]

A number of methods for the incorporation of one or several fluorine atoms into organic molecules were efficiently developed.[5] The introduction of the polyfluorinated groups, such as $CF_3$, $OCF_3$, $SCF_3$ or $CF_2CF_3$, is described as well.[6] Among these substituents, the bulky and highly electronegative trifluoromethyl group has been of a special interest of researchers, since several decades.[7] The pentafluorosulfanylated group ($SF_5$) – another interesting fluorinated substituent, often called as the "super-trifluoromethyl group", particularly attracted our attention. The $SF_5$-group has been introduced into organic

[1] Moissan, H. *R. Acad. Sciences* **1886**, *102*, 1543.
[2] For some general reviews, see: (a) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (b) Bégué, J.-P.; Bonnet-Delpon, D. *Bioorganic and Medicinal Chemistry of Fluorine*, Wiley-VCH, Weinheim, **2008**. (c) Hagmann, W. K. *J. Med. Chem***. 2008**, *51*, 4359. (d) Gilmour, R.; Seebach, D. *Chimia* **2014**, *68*, 345. (e) Wang, J.; Sanchez-Rosello, M.; Acena, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H *Chem. Rev.* **2014**, *114*, 2432.
[3] (a) Kirk, K. L *J. Fluorine Chem.* **2006**, *127*, 1013. (b) Purser, S.; Moore, P. R.; Swallow, S.; Gouverner, V. *Chem. Soc. Rev*. **2008**, *37*, 320.
[4] (a) Murphy, C. D.; Sandford, G. *Chim. Oggi Chem. Today* **2012**, *30*, 16. (b) Thayer, A. M. *Chem. Eng. News* **2006**, *84*, 15.
[5] (a) Kirk, K. L. *Org. Process Res. Dev.* **2008**, *12*, 305. (b) Hu, J.; Zhang, W.; Wang, F. *Chem. Commun.* **2009**, *48*, 7465. (c) Belhomme, M.-C.; Besset, T.; Poisson, T.; Pannecoucke, X. *Chem. Eur. J.* **2015**, *21*, 12836. (d) Besset, T.; Poisson, T.; Pannecoucke, X. *Chem. Eur. J.* **2014**, *20*, 16830.
[6] For some selected review, see: (a) Macé, Y.; Magnier, E. *Eur. J. Org. Chem.* **2012**, *13*, 2479. (b) Roy, S.; Gregg, B.T.; Gribble, G. W.; Le, V. –D.; Roy, S. *Tetrahedron* **2011**, *67*, 2161. (c) Besset, T.; Poisson, T.; Pannecoucke, X. *J. Fluorine Chem.* **2015**, *178*, 225. (d) Landelle, G; Panossian, A.; Pazenok, S.; Vors, J.-P.; Leroux, F. *Beilstein J. Org. Chem.* **2013**, *9*, 2476.
[7] For some selected review, see: (a) Barata-Vallejo, S.; Lantano, B.; Postigo, A. *Chem. Eur. J.* **2014**, 20, 16806. (b) Liu, X.; Xu, C.; Wang, M.; Liu, Q. *Chem. Rev.* **2015**, *115*, 683. (c) Egami, H.; Sodeoka, M. *Ang. Chem. Int. Ed.* **2014**, *53*, 8294.

molecules for the first time by Sheppard in 1960;[8] however, this substituent reached more attention only in the last two decades. Currently, the $SF_5$-chemistry is becoming a fast growing field of the fluorine chemistry, as new pentafluorosulfanylated building-blocks and reagents are under continuous development.[9]

The physicochemical properties of the pentafluorosulfanyl group, as well as the methods for its introduction into organic compounds, will be presented in this chapter, in order to better understand the context of this study. The applications of the pentafluorosulfanylated, aryl- or heteroaryl-containing compounds, and the influence of the $SF_5$-group on their activities, will be also discussed.

# 2. Physicochemical properties of the pentafluorosulfanyl group

## 2.1. Structure and steric hindrance of the $SF_5$-group

Because of the presence of the hypervalent hexacoordinated sulfur atom, the pentafluorosulfanylated compounds are considered as organic derivatives of the sulfur hexafluoride ($SF_6$). In both cases, the octahedral geometry of the ligands around the sulfur is observed.[9a] Fluorine atoms of the $SF_5$-group constitute a typical $AB_4$ system, in which one axial and four equatorial fluorine atoms are present (Figure 1).[10] Because of the square pyramidal array of fluorines, the $SF_5$-substituent has a reduced rotation barrier, which allows its better interactions with receptor.[9g] This geometry is in contrast with the tetrahedral geometry presented by the $CF_3$-group (Figure 1).

[8] Sheppard, W. A. *J. Am. Chem. Soc.* **1960**, *82*, 4751.
[9] For general reviews, see: (a) Kirsch P. *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*. Wiley-VCH: Weinhein; **2004**. (b) Winter, R. W.; Dodean, R. A.; Gard, G. L.; Soloshonok, V. A. in *Fluorine Containing Synthons.* Soloshonok, V. A., Ed. American Chemical Society: Washington, DC; **2005**, 87. (c) Gard, G. L. *Chem. Today* **2009**, *27*, 10. (d) P. Wipf, T. Mo, S. J. Geib, D. Caridha, G. S. Dow, L. Gerena, N. Roncal, E. E. Milner *Org. Biomol. Chem.*, **2009**, *7*, 4163. (e) Altomonte, S.; Zanda, M. *J. Fluorine Chem.* **2012**, *143*, 57. (f) Welch, J. T. in *Fluorine in Pharmaceutical and Medicinal Chemistry*. Gouverneur, V.; Muellen, K., Eds. Imperial College Press; **2012**, Vol. 6, 175. (g) Savoie, P. R.; Welch, J. T. *Chem. Rev.* **2015**, *115*, 1130.
[10] Dolbier, W. R. *Guide to Fluorine NMR for Organic Chemists*; John Wiley & Sons, Inc.: Hoboken, New Jersey, 2009.

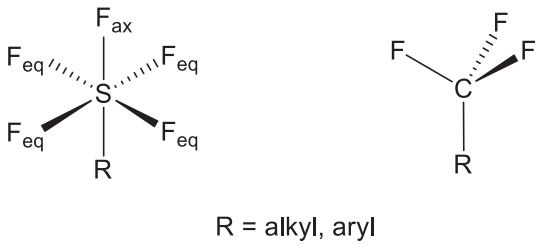



**Figure 1: Structures of $SF_5$- and $CF_3$-derivatives.**

The steric hindrance of the pentafluorosulfanyl group is often compared with that of *tert*-butyl group. The "volumes" of $SF_5$- and $CF_3$- relative to *t*-Bu-substituents were recently calculated ($\Delta V = V_{substituent} - V_{t\text{-Bu}}$), and are as follows: $\Delta V\,(CF_3) = -34.9$ Å$^3$ < $\Delta V\,(SF_5) = -11.1$ Å$^3$ < $\Delta V$ (*t*-Bu) = 0 Å$^3$).[11] The pentafluorosulfanyl group is therefore much bigger than the trifluoromethyl one, but smaller than the *tert*-butyl one.

## 2.2. Electronic properties

From the charge distributions and molecular size points of view, the electrostatic surface of the $SF_5$-substituent is comparable to that of the $CF_3$-group (Figure 2). Both of these two moieties present highly fluorinated surfaces.[12]

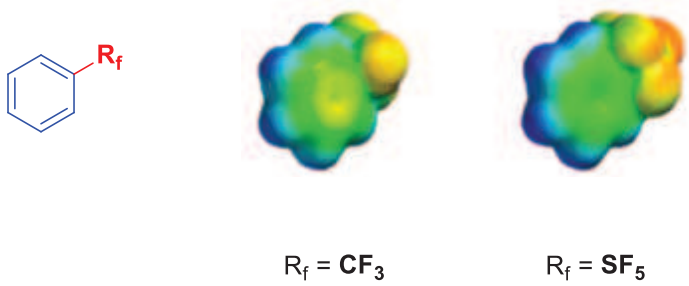



**Figure 2: Electrostatic potential maps of $CF_3$-Ph and $SF_5$-Ph.**

However, it has been shown that the pentafluorosulfanyl group is more electron-withdrawing than the trifluoromethyl one, approaching rather the nitro group in its inductive

[11] Westphal, M. V.; Wolfstädter, B. T.; Plancher, J.-M.; Gatfield, J.; Carreira, E. M. *ChemMedChem* **2015**, *10*, 461.
[12] Matsuzaki, K.; Okuyama, K.; Tokunaga, E.; Saito, N.; Shiro, M.; Shibata, N. *Org. Lett.* **2015**, *17*, 3038.

power (Hammet substituent constants: $\sigma_1(SF_5)$ = 0.55 and $\sigma_1(CF_3)$ = 0.39).[13] As a consequence, the $SF_5$-substituent has greater influence on the acidity of the molecule than the $CF_3$ one. The electronegativity of $SF_5$-group has been measured as well, and its value is 3.65, compared to 3.36 for the trifluoromethyl substituent.[14] The presence of two additional fluorine atoms in $SF_5$ enhances also the dipole moment of the pentafluorosulfanylated derivatives ($\mu$ = 3.44 D for Ph-$SF_5$, compared to $\mu$ = 2.60 D for Ph-$CF_3$).[13]

## 2.3. Lipophilicity

The measurments of Hansch hydrophobicity constants for $CF_3$- and $SF_5$-substituents proved higher lipophilicity of the latter one ($\pi$ ($CF_3$) = 1.09 and $\pi$ ($SF_5$) 1.51, respectively).[15] It is worth noting that the high electronegativity and high lipophilicity are usually "in conflict". Nevertheless, the $SF_5$-group possesses both of these properties, similarly as $CF_3$, $OCF_3$ and $SCF_3$ substituents.

## 2.4. Chemical stability

The pentafluorosulfanyl group is considered as chemically stable (Table 1). A set of experiments testing the stability of Ph-$SF_5$ was performed by Sheppard.[16] When the pentafluorosulfanylated benzene was treated with 1 N $NaOH_{aq.}$ solution, the release of fluoride ion was not detected even after 4 h of heating at 94°C. Another test proved that the $SF_5$-substituent is relatively stable under the acidic conditions as well – when heating in the presence of 98% $H_2SO_4$ solution, Ph-$SF_5$ started to decompose into Ph-$SO_2F$ only at 100°C. Though, in the same conditions, the trifluoromethylated benzene was totally hydrolysed within 5 minutes at 90°C.

[13] Sheppard, W. A. *J. Am. Chem. Soc.* **1962**, *84*, 3072.
[14] Saethre, L. J.; Berrah, N.; Bozek, J. D.; Boerve, K. J.; Carroll, T. X.; Kukk, E.; Gard, G. L.; Winter, R.; Thomas, T. D. *J. Am. Chem. Soc.* **2001**, *123*, 10729.
[15] (a) Bégué, J.-P.; Bonnet-Delpon, D. *Bioorganic and Medicinal Chemistry of Fluorine*; Wiley: Hoboken, 2008. (b) Hansch, C.; Muir, R. M.; Fujita, T.; Maloney, P. P.; Geiger, F.; Streich, M. *J. Am. Chem. Soc.* **1963**, *85*, 2817.
[16] Sheppard, W. A. *J. Am. Chem. Soc.* **1962**, *84*, 3064.

More recently, another study confirmed the higher chemical resistance of the $SF_5$-group relative to $CF_3$ one. [17] Indeed when the *p*-$SF_5$-aniline was treated with 1 N $NaOH_{aq.}$ solution at room temperature, it was recovered in 90%, whereas the corresponding $CF_3$-compound was totally hydrolysed in these conditions.

| Parameter | | **$SF_5$**-group | **$CF_3$**-group |
|---|---|---|---|
| "Volume" relative to *t*-Bu | | -11.1 Å | -34.9 Å |
| Hammet substituent constant ($\sigma_1$) | | 0.55 | 0.39 |
| Electronegativity | | 3.65 | 3.36 |
| Dipole moment ($\mu$) | | 3.44 D (for **Ph-$SF_5$**) | 2.60 D (for **Ph-$CF_3$**) |
| Hansch hydrophobicity constant ($\pi$) | | 1.51 | 1.09 |
| Chemical stability | 98% $H_2SO_4$, 90-100°C | **Ph-$SF_5$**: start of decomposition | **Ph-$CF_3$**: hydrolysis within 5 min. |
| | 1N $NaOH_{aq.}$, rt | ***p*-$SF_5$-aniline**: recovery in 90% | ***p*-$CF_3$-aniline**: hydrolysis |

**Table 1: Comparison of the properties of the $SF_5$- and $CF_3$-groups.**

# 3. Synthesis of pentafluorosulfanylated compounds

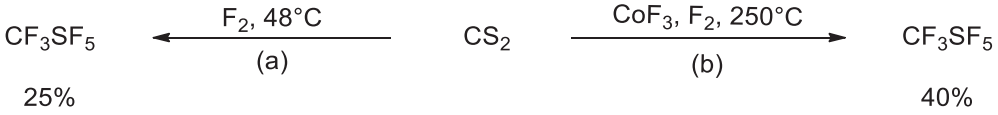
## 3.1. Introduction of the $SF_5$-group into aliphatic compounds

In this section, general methods for the introduction of the $SF_5$-group into the aliphatic compounds will be presented. We will focus on two main methodologies: the direct fluorination of sulfur containing precursors on the one hand, and the radical addition of the $SF_5X$ reagents to unsaturated compounds on the other hand.

[17] Bowden, R. D.; Comina, P. J.; Greenhall, M. P.; Kariuki, B. M.; Loveday, A.; Philp, D. *Tetrahedron* **2000**, *56*, 3399.

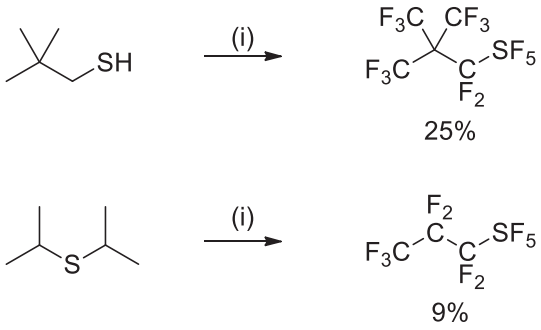
### 3.1.1. Direct fluorination of sulfur containing compounds

The first report on the direct fluorination leading to a pentafluorosulfanylated molecule dates from 1950.[18] The smallest $SF_5$-containing compound ($SF_5CF_3$) was synthesized in 25% yield, by the direct fluorination of $CS_2$ with molecular $F_2$, at 48°C (Scheme 1 (a)). When the reaction was performed in the presence of $CoF_3$, $SF_5CF_3$ was obtained in significantly better yield (40%) (Scheme 1 (b)).[18,19]




**Scheme 1: Fluorination of carbon disulfide with: (a) $F_2$ or (b) $F_2$ and $CoF_3$.**

The reaction of alkyl thiols or dialkyl sulfides with $F_2$ allowed the synthesis of some larger perfluoroalkyl-$SF_5$ derivatives as well; however, the yields of these reactions were low. In all cases only primary pentafluorosulfanylated compounds were obtained, regardless the structure of the starting products (Scheme 2).[20]



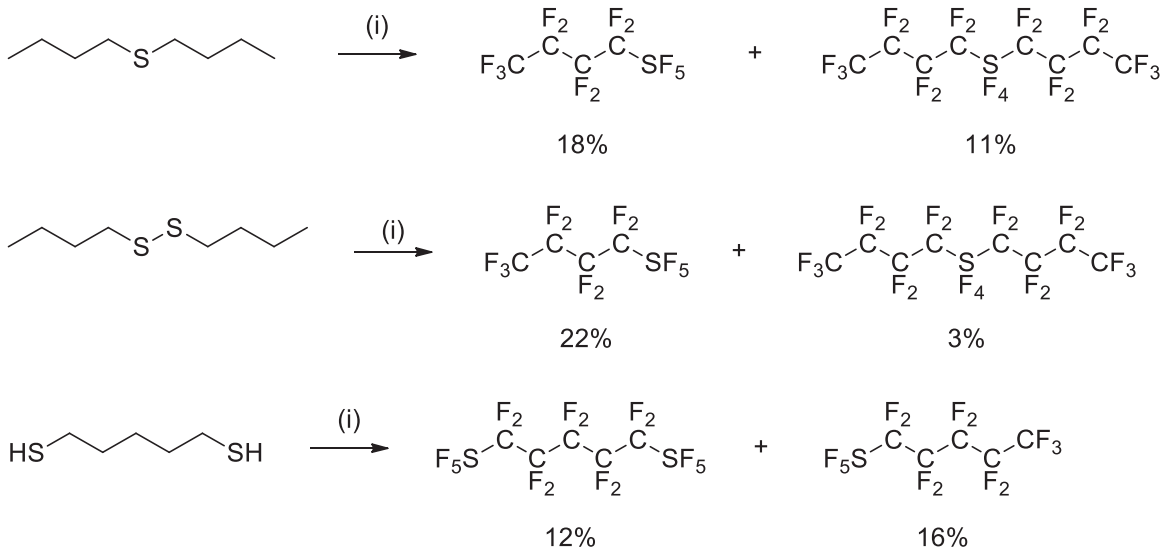

**Scheme 2: Fluorination of alkyl thiol and dialkyl sulfide with $F_2$.**
**Reagents and conditions: (i) 2-20% $F_2$/He, -120°C to 25°C.**

In addition to molecular fluorine other fluorinating agents, such as ClF, $AgF_2$, $CoF_3$ or $SF_4$ were reported.[21] When the above mentioned fluorine sources were reacted with various

[18] Silvey, G. A.; Cady, G. H. *J. Am. Chem. Soc.* **1950**, *72*, 3624.
[19] Silvey, G. A.; Cady, G. H. U.S. Patent US2697726, 1954; *Chem. Abstr*. **1954**, *49*, 30129.
[20] Huang, H. N.; Lagow, R. J.; Roesky, H. *Inorg. Chem.* **1991**, *30*, 789.
[21] Fischer, J.; Jaenckner, W. *Angew. Chem.* **1929**, *42*, 810.

sulfur-containing compounds under thermal conditions, the pentafluorosulfanylated derivatives were obtained in moderate to good yields.[22]

Finally, the $SF_5$-containing compounds could be also synthesized using HF. The pentafluorosulfanylated derivatives were obtained from organic thiols,[23] sulfides[24] and disulfides,[23a,25] under electrochemical conditions, similar to those described by Simons *et al*.[26] In all cases the fluorination of chain carbons took place as well (Scheme 3).




**Scheme 3: Electrochemical fluorination of organic sulfides, disulfides and thiols. Reagents and conditions: (i) HF, $e^-$ (5-6 V, 9 A), 120 h.**

### 3.1.2. Radical addition of $SF_5X$ to unsaturated compounds

As the scope of the direct fluorination was quite limited and pentafluorosulfanylated compounds were often obtained in moderate yields together with other fluorinated by-products, other methods have been developed. The reaction of $SF_5X$ (X = Br, Cl or $SF_5$)

[22] (a) Abe, T.; Shreeve, J. M. *J. Fluorine Chem*. **1973**, *3*, 187. (b) Alam, K.; Shreeve, J. M.; Mack, H. G.; Oberhammer, H. *J. Mol. Struct.* **1988**, *178*, 207. (c) Waterfeld, A.; Mews, R. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 1017. (d) Hoefer, R.; Glemser, O. *Z. Naturforsch., B: Chem. Sci.* **1975**, *30B*, 458. (e) Gombler, W. *J. Fluorine Chem.* **1977**, *9*, 233.

[23] (a) Haszeldine, R. N.; Nyman, F. *J. Chem. Soc.* **1956**, 2684. (b) Baba, H.; Kodaira, K.; Nagase, S.; Abe, T. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 1891.

[24] (a) Hoffmann, F. W.; Simmons, T. C.; Beck, R. B.; Holler, H. V.; Katz, T.; Koshar, R. J.; Larsen, E. R.; Mulvaney, J. E.; Rogers, F. E.; Singleton, B.; Sparks, R. S. *J. Am. Chem. Soc.* **1957**, *79*, 3424. (b) Dresdner, R. D.; Reed, T. M., III; Taylor, T. E.; Young, J. A. *J. Org. Chem*. **1960**, *25*, 1464.

[25] Abe, T.; Nagase, S.; Kodaira, K.; Baba, H. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 1812.

[26] Simons, J. H.; Francis, H. T.; Hogg, J. A.; Harland, W. J.; Pearlson, W. H.; Brice, T. J.; Wilson, W. A.; Dresdner, R. D. *Trans. Electrochem. Soc.* **1949**, *95*, 47.

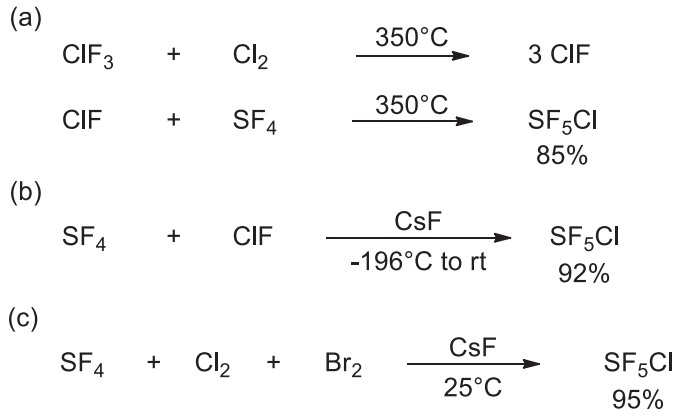
reagents with unsaturated compounds turned out to be a more efficient pathway for the introduction of the $SF_5$-substituent into organic molecules. As the highly toxic $SF_5$ dimer ($S_2F_{10}$) is the low reactive one; therefore, in this chapter, we will focus our attention only on $SF_5Br$ and $SF_5Cl$ agents.

#### 3.1.2.1. Preparation of $SF_5Cl$ and $SF_5Br$

Pentafluorosulfanylating agents ($SF_5X$) were prepared for the first time about half a century ago.[27] The initial methods for the synthesis of $SF_5Cl$ consisted on the addition of fluorine to $SCl_2$, or the reaction of $Cl_2$ or $BCl_3$ with $S_2F_{10}$. The first method gave low yield, while the latter one depended on the poorly available disulfur decafluoride, prepared from sulfur and fluorine.[27,28]

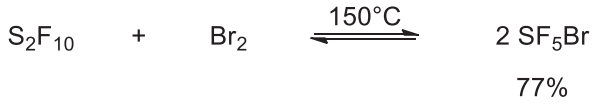
Alternative methods of $SF_5Cl$ synthesis were based on the reactions with toxic gaseous $SF_4$. The use of ClF (prepared *in situ* from $Cl_2$ and $FCl_3$) was reported by Nyman in 1962.[29] Its addition to $SF_4$ in a batch process at 350°C afforded the desired product in 85% (Scheme 4, (a)). Further optimisation showed that the temperature of the reaction could be decreased to ambient in the presence of CsF, which probably formed a complex with $SF_4$ and rendered it more susceptible to oxidation by ClF (Scheme 4, (b)).[30] It has been also proved that ClF could be replaced by inexpensive and easy accessible $Cl_2$.[30a] More recently, Winter[31] has improved this methodology by introducing bromine to the reaction (Scheme 4, (c)); however, the role of this additive was not explained.

[27] (a) George, J. W. ; Cotton F.A. *Proc. Chem. Soc.* **1959**, 317. (b) Cohen, B.; MacDiarmid, A. G. *Chem. Ind. (London, U. K.)* **1962**, 1866. (c) Roberts, H.L.; Ray, N.H. *J. Chem. Soc.*, **1960**, 665.
[28] Cohen, B.; MacDiarmid, A. G.; *Inorg. Chem.* **1965**, *4*, 1782.
[29] Nyman, F.; Roberts, H. L. *J. Chem. Soc*. **1962**, 3180.
[30] (a) Schack, C. J.; Wilson, R. D.; Warner, M. G. *J. Chem. Soc. D* **1969**, 1110. (b) Jonethal, U.; Kuschel, R.; Seppelt, K. *J. Fluorine Chem.* **1998**, *88*, 3.
[31] Winter, R. WO Patent WO2009152385A2, 2009; *Chem. Abstr*. **2009**, 152, 59210.




**Scheme 4: Preparation of $SF_5Cl$.**

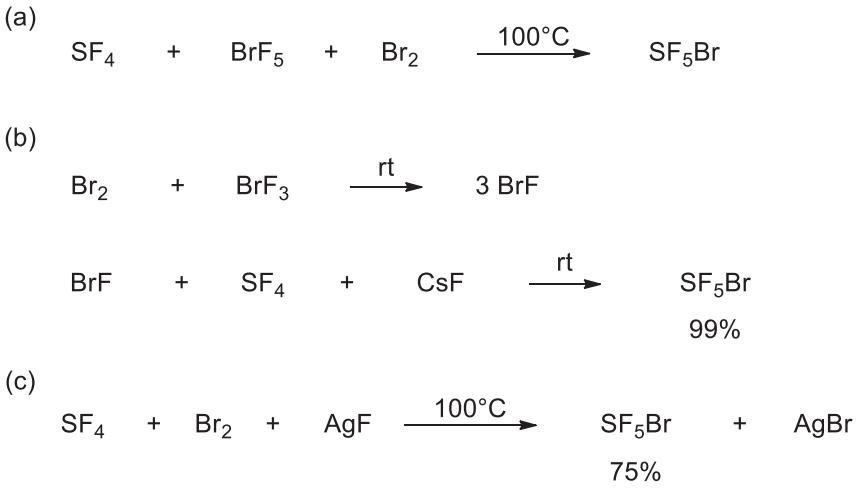
Pentafluorosulfanyl bromide is generally less studied and more difficult to prepare, compared to the chlorinated reagent. $SF_5Br$ was first synthesized in 1962[27b] from $S_2F_{10}$ and $Br_2$ by the analogous method as reported for $SF_5Cl$. Nevertheless, the reaction was not complete even in the presence of a large excess of $Br_2$ at 150°C, the brominated derivative being obtained in 77% yield (Scheme 5). Apparently, this reaction might be reversible because of the decomposition of $SF_5Br$ at high temperature. By using Monel reactors and re-using unreacted $Br_2$, the yield exceeded 80%.[32]




**Scheme 5: Synthesis of $SF_5Br$ from $S_2F_{10}$ and $Br_2$.**

Once again, the attention of researchers was turned on sulfur tetrafluoride as a starting product for the synthesis of pentafluorosulfanylated agent. The reaction of $SF_4$ with $BrF_5$ and bromine in a Monel tube was reported to be efficient at 100°C (Scheme 6, (a)).[33] In 1998, an important improvement in the $SF_5Br$ synthesis was made by Gard *et al*.[34] who reported the reaction of $Br_2$, $BrF_3$, CsF and $SF_4$, carried out in a single reaction vessel, without heating (Scheme 6, (b)). Under these conditions, the pentafluorosulfanyl bromide was obtained in 99% yield (relative to $SF_4$). A recent patent[30] also described the synthesis of $SF_5Br$ from $SF_4$, $Br_2$ and dried AgF or $AgF_2$, at 100°C, in 75% yield (Scheme 6, (c)).

[32] Kovacina, T. A.; Berry, A. D.; Fox, W. B. *J. Fluorine Chem.* **1976**, *7*, 430.
[33] Merrill, C. I.; Lustig, M.; Cady, G. H. *Sulfur bromide pentafluoride and preparation and properties of difluorofluorosulfato amine, $NF_2OSO_2F$;* University of Washington: Seattle, WA, 1962.
[34] Winter, R.; Terjeson, R. J.; Gard, G. L. *J. Fluorine Chem.* **1998**, *89*, 105.



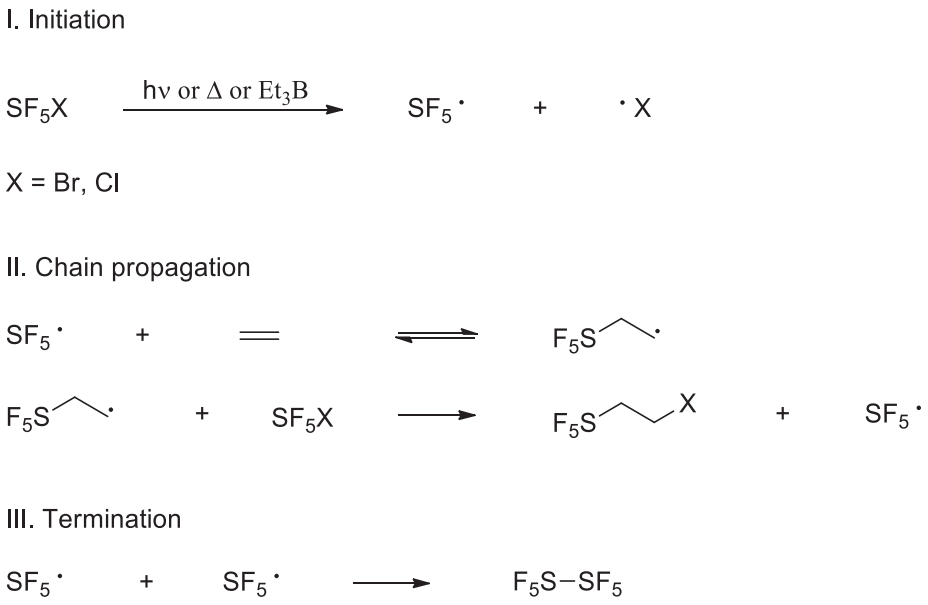

**Scheme 6: Preparation of $SF_5Br$.**

### 3.1.2.2. Chemistry of $SF_5Br$ and $SF_5Cl$

Pentafluorosulfanyl bromide is known to be more reactive than its chlorinated analogue; however, it has lower thermal stability, with the decomposition starting at 150°C. Slightly less reactive, $SF_5Cl$ is thermally stable up to 400°C in inert vessel and it does not undergo hydrolysis in the presence of water or aqueous acids. Nevertheless, it decomposes in lower temperature in the presence of UV light or in alkaline solutions.[9e]

Both of these reagents are known to undergo radical additions to unsaturated bonds. This way of $SF_5$ introduction into an organic compound is very advantageous, because of the broader scope and better yields of such reaction, compared to direct fluorination. The mechanism of the radical addition of $SF_5X$ to alkene is depicted on Scheme 7.[35] In the first step, the $SF_5^{\cdot}$ radical is formed under photochemical or thermal conditions or in the presence of radical initiator, such as $Et_3B$, in the presence of dioxygen. The next step is the addition of the $SF_5^{\cdot}$ radical to the double (or triple) bond, followed by the reaction with $X^{\cdot}$ (from the second molecule of $SF_5X$). The termination step takes place when two $SF_5^{\cdot}$ radicals react together, leading to $S_2F_{10}$.

[35] Sidebottom, H. W.; Tedder, J. M.; Walton, J. C. *Trans. Faraday Soc.* **1969**, *65*, 2103.



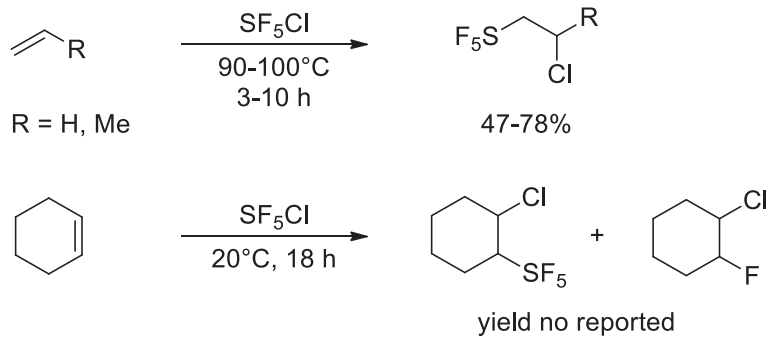

**Scheme 7: General mechanism for the radical addition of $SF_5X$ (X = Br or Cl) to an alkene.**

Nowadays only the pentafluorosulfanyl chloride is commercially available. As it undergoes generally clean additions to various unsaturated compounds, the $SF_5Cl$ is currently the principal reagent used for the preparation of $SF_5$-substituted building-blocks.

### 3.1.2.3. Addition of $SF_5X$ to double bond

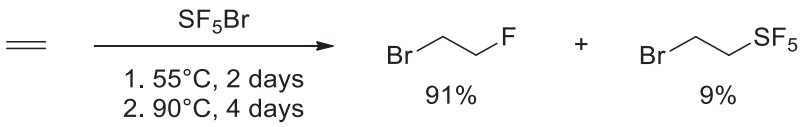
The radical addition of $SF_5Cl$ to alkenes, under thermal and photochemical conditions was first reported by Case *et al*. in 1961.[36] Most alkenes gave the corresponding pentafluorosulfanylated products in moderate to good yields (48-78%) (Scheme 8). However, some of unsaturated derivatives, such as 2-methylpropene or styrene, afforded exclusively the polymerization product under these conditions.

[36] Case, J. R.; Ray, N. H.; Roberts, H. L. *J. Chem. Soc*. **1961**, 2066.




**Scheme 8: First $SF_5Cl$ additions to alkenes.**

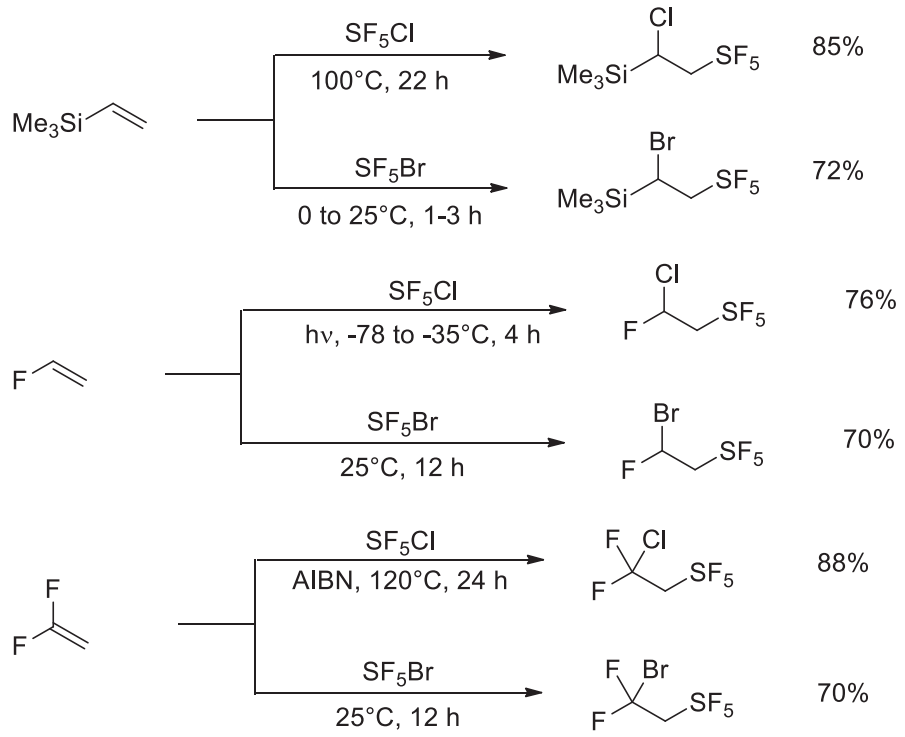
The $SF_5Br$ addition to ethylene under thermal conditions turned out to be more complicated, as all attempts led to the mixture of fluorinated and pentafluorosulfanylated products. The desired $SF_5$-product was obtained in only 9% yield (Scheme 9).[37]




**Scheme 9: Early attempt of $SF_5Br$ addition to ethylene.**

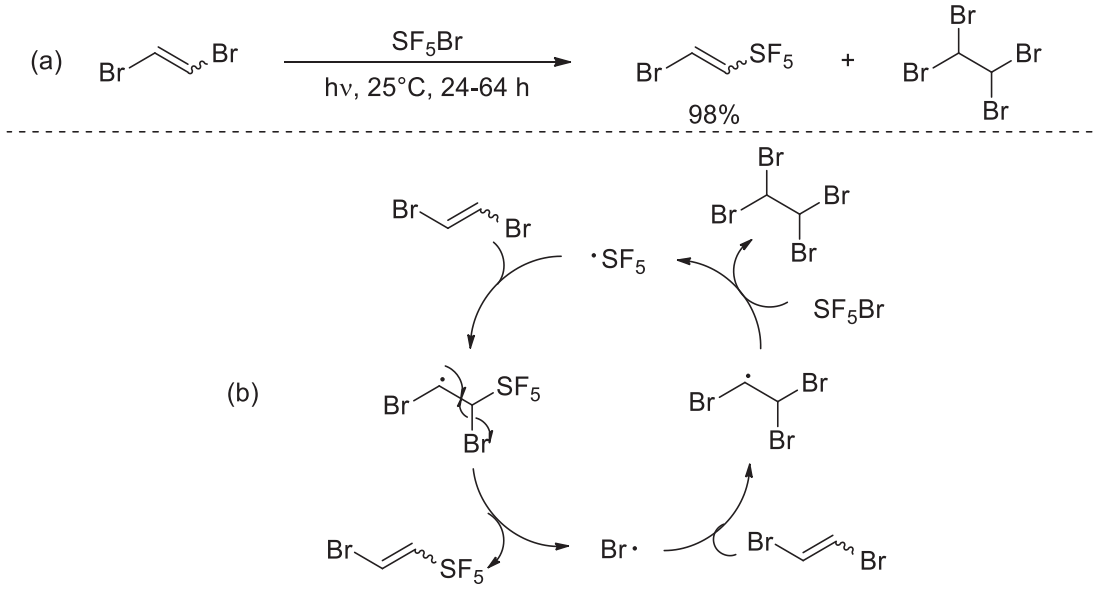
In the following years, various examples of the introduction of $SF_5$ into olefins, using $SF_5X$, were reported in the literature. For example, the additions to vinyl silanes,[38] mono- or poly-haloethylenes[39] or terminal dienes[40]. The general trend shows that the additions of $SF_5Cl$ to vinylsilanes and haloalkenes gave slightly better yields than the analogous reactions with $SF_5Br$; however, the latter one proved to be more reactive and the additions were usually possible at lower temperatures (Scheme 10).

[37] Terjeson, R. J.; Gard, G. L. *J. Fluorine Chem.* **1987**, *35*, 653.
[38] Berry, A. D.; Fox, W. B. *J. Fluorine Chem*. **1975**, *6*, 175.
[39] (a) Banks, R. E.; Haszeldine, R. N.; Morton, W. D. *J. Chem. Soc. C* **1969**, 1947. (b) De Marco, R. A.; Fox, W. B. *J. Fluorine Chem.* **1978**, *12*, 137. (c) Grelbig, T.; Pötter, B.; Seppelt, K. *Chem. Ber*. **1987**, *120*, 815. (d) Steward, J.; Kegley, L.; White, H. F.; Gard, G. L. *J. Org. Chem.* **1969**, *34*, 760.
[40] Brel, V. K. *Synthesis* **2005**, 1245.



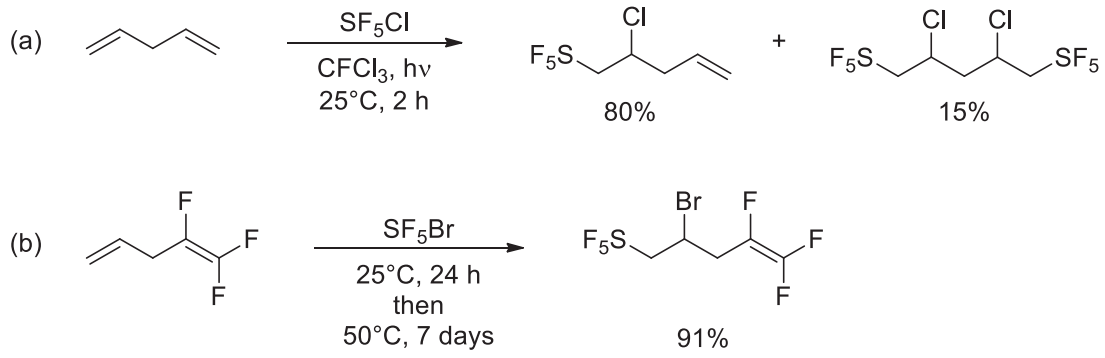

**Scheme 10: Additions of $SF_5X$ to vinylsilanes and haloalkenes.**

Interestingly, in the reaction of $SF_5Br$ with 1,2-dibromoethylene, the unexpected mixture of $SF_5$-substituted alkene and 1,1,2,2-tetrabromoethylene was obtained (Scheme 11, (a)). This phenomenon was explained by a possible radical exchange reaction (Scheme 11, (b)).




**Scheme 11: Reaction of $SF_5Br$ with 1,2-dibromoethene.**

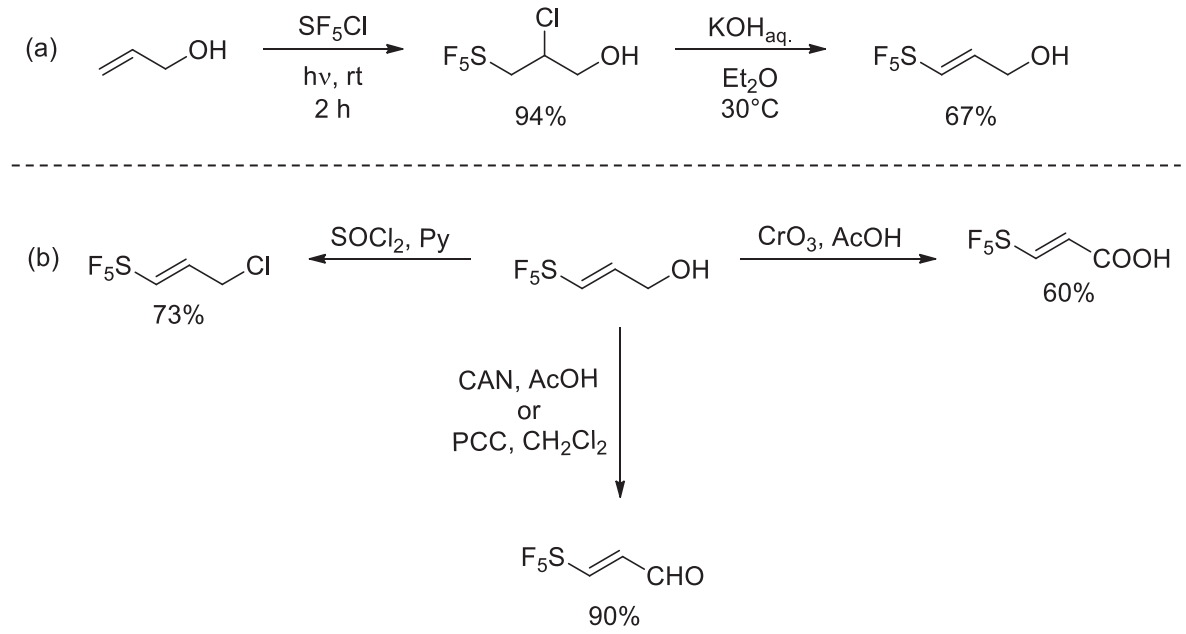
It is also worth mentioning that when the pentafluorosulfanyl chloride was reacted with dienes, containing two terminal double bonds, the monoaddition products were dominating (Scheme 12, (a)).[40] When one of the diene's double bonds was substituted with three fluorine atoms, the $SF_5Br$ added regioselectively to the $CH_2$=$CH_2$ bond, leading to the corresponding product in 91% (Scheme 12, (b)). This result was explained by a better stability of the radical created when the $SF_5$ added to the more electron-rich double bond.[41]




**Scheme 12: Addition of $SF_5Cl$ to penta-1,4-diene derivatives.**

More recently, the radical addition of $SF_5Cl$ was also used for the synthesis of the $SF_5$-substituted allyl alcohol (Scheme 13, (a)). This versatile synthon underwent a set of transformations, leading to new $SF_5$-substituted building blocks, such as $SF_5$-allyl chloride, $SF_5$-acrylic aldehyde or $SF_5$-acrylic acid and other pentafluorosulfanylated derivatives (Scheme 13, (b)).[42]

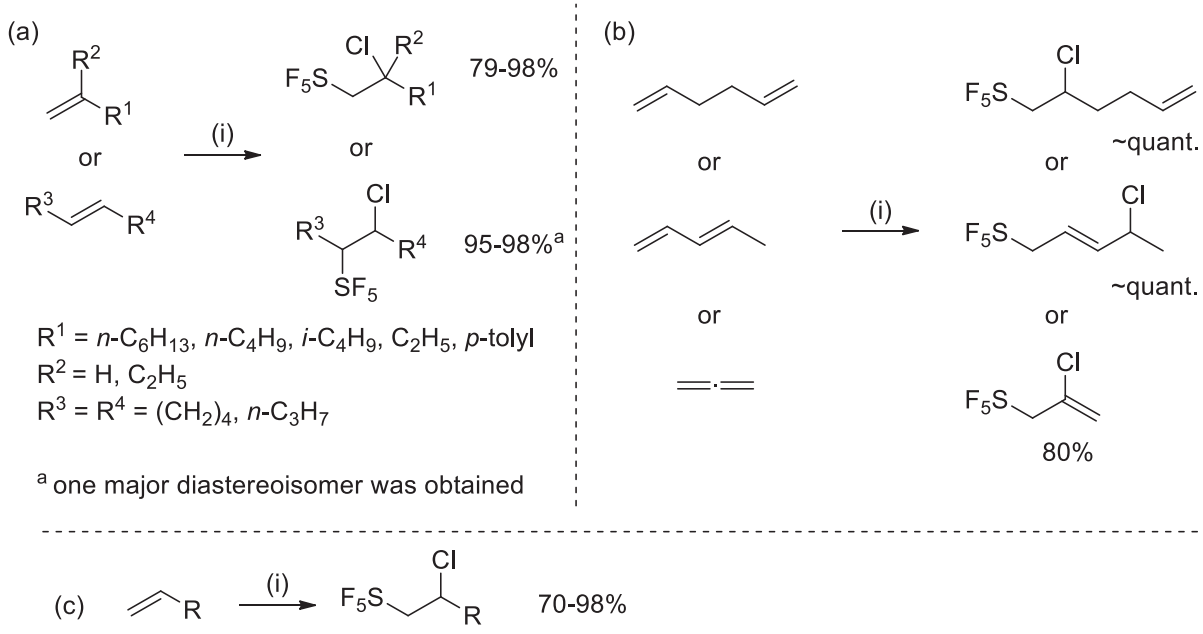
[41] Nixon, P. G.; Renn, J.; Terjeson, R. J.; Choi, Y. S.; Winter, R.; Gard, G. L. *J. Fluorine Chem*. **1998**, *91*, 13.
[42] (a) Trushkov, I. V.; Brel, V. K. *Tetrahedron Lett.* **2005**, *46*, 4777. (b) Brel, V. K. *Synthesis* **2006**, 339. (c) Brel, V. K. *J. Fluorine Chem.* **2007**, *128*, 862. (d) Husstedt, W. S.; Thrasher, J. S.; Haufe, G. *Synlett* **2011**, 1683.




**Scheme 13: Synthesis of $SF_5$-allyl alcohol and its further transformations.**

In 2002, an important improvement of the $SF_5$-addition was made by Dolbier and co-workers.[43] After testing several radical initiators, they discovered that the $SF_5Cl$ could successfully undergo the radical additions to unsaturated bonds, in the presence of $Et_3B$ and oxygen. According to this procedure, the low boiling $SF_5Cl$ could be directly condensed into a cooled (-40°C) solution of the unsaturated substrate, followed by the addition of the $Et_3B$ initiator, at -30°C. This method allowed the synthesis of a variety of pentafluorosulfanylated building blocks in excellent yields (Scheme 14).[43,44] The addition of $SF_5Cl$ was efficient with long-chain alkenes (Scheme 14, (a)), non-conjugated, conjugated or cumulated dienes (Scheme 14, (b)), as well as with alkenes bearing various functional groups, those being usually not conjugated with the double bond (Schemen 14, (c)). For most of the substrates the reaction was complete within 30 minutes. The Dolbier's method was then successfully applied by other researchers, who prepared by this way a variety of functionalized pentafluorosulfanylated derivatives.[45]

[43] Aït-Mohand, S.; Dolbier, W. R. *Org. Lett.* **2002**, *4*, 3013.
[44] Dolbier, W. R.; Aït-Mohand, S.; Schertz, T. D.; Sergeeva, T. A.; Cradlebaugh, J. A.; Mitani, A.; Gard, G. L.; Winter, R. W.; Thrasher, J. S. *J. Fluorine Chem.* **2006**, *127*, 1302.
[45] (a) Ponomarenko, M. V.; Serguchev, Y. A.; Röschenthaler, G. V *Synthesis* **2010**, 3906. (b) Dreier, A.-L.; Matsnev, A. V.; Thrasher, J. S.; Haufe, G. *J. Fluorine Chem.* **2014**, *167*, 84.

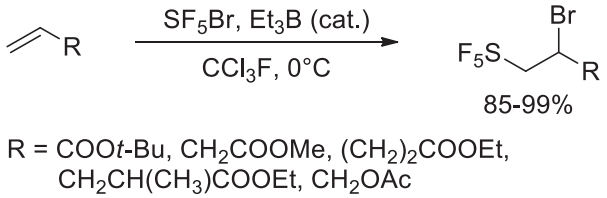



**Scheme 14: $Et_3B$ catalyzed additions of $SF_5Cl$ to unsaturated compounds. Reagents and conditions: (i) $SF_5Cl$, $Et_3B$ (cat.), hexane, -30°C to rt.**

It was reported that $SF_5Br$ could also undergo the radical addition in the presence of $Et_3B$; however, this reagent gave good results only when electron-deficient alkenes were engaged. With other substrates (especially with nucleophilic ones), pentafluorosulfanyl bromide reacted rather in an electrophilic manner, via the attack of the olefin double bond on the bromide, to form $Br^+$ and $SF_5^-$. The latter one liberated a fluoride anion; therefore, instead of $SF_5Br$, the BrF addition took place.[44]

An improved procedure for the addition of the pentafluorosulfanyl bromide was reported by Welch.[46] When a non-polar solvent, such as $CCl_3F$, was used, the $SF_5Br$ addition afforded the pentafluorosulfanylated compounds in high yields and no BrF addition product was observed (Scheme 15).

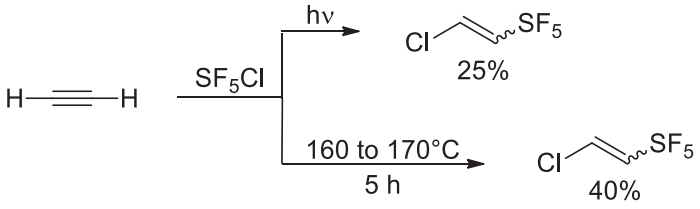
[46] Lim, D. S.; Ngo, S. C.; Lal, S. G.; Minnich, K. E.; Welch, J. T. *Tetrahedron Lett.* **2008**, *49*, 5662.




**Scheme 15: $Et_3B$ catalyzed addition of $SF_5Br$ to olefins.**

### 3.1.2.4. Addition of $SF_5X$ to triple bond

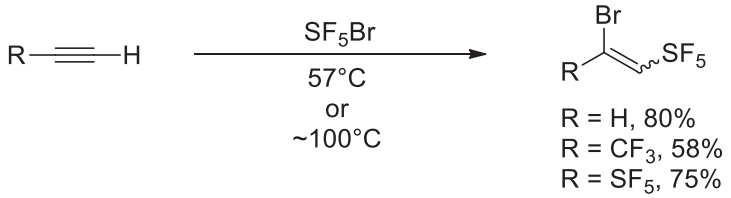
First examples of the $SF_5X$ addition to alkynes were described at the same time as the analogous reactions with alkenes. Pentafluorosulfanyl chloride was reported to react with acetylene under photochemical[36] or thermal[47] conditions, leading to the corresponding pentafluorosulfanylated ethylene in 25% and 40% yield, respectively (Scheme 16).




**Scheme 16: Photochemical and thermal additions of $SF_5Cl$ to acetylene.**

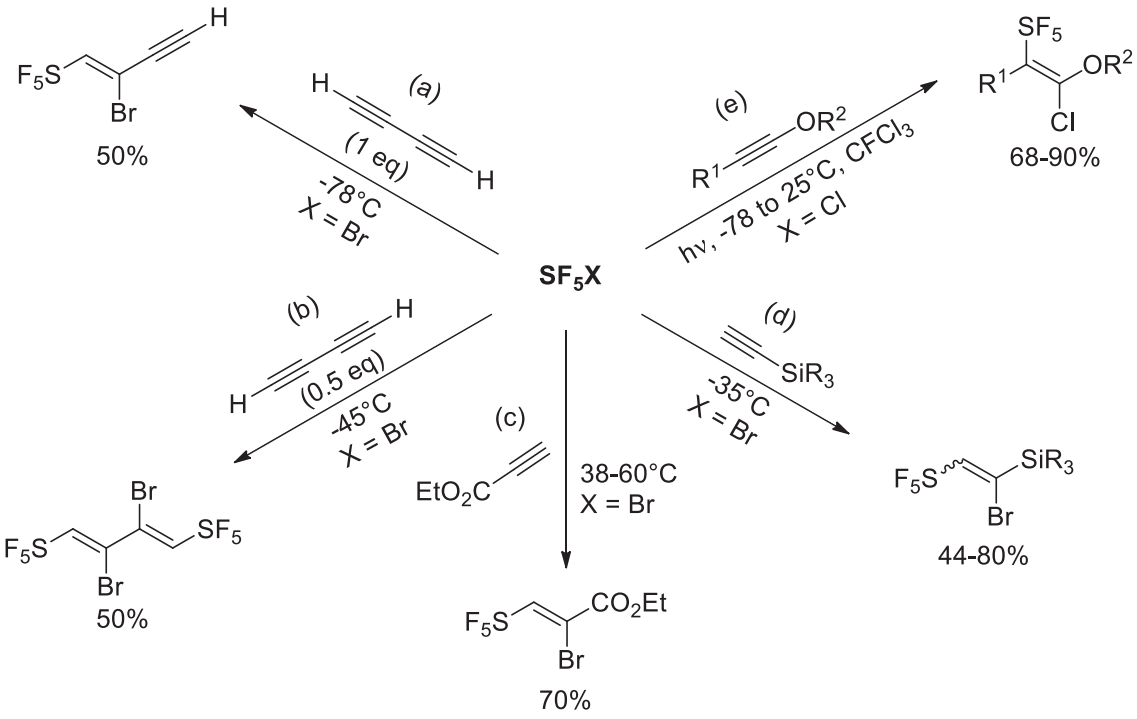
Further replacement of $SF_5Cl$ by $SF_5Br$ reagent allowed the reaction to occur at lower temperature (57°C instead of 160°C) leading to 80% yield.[48] The addition of $SF_5Br$ to $CF_3$- or $SF_5$-substituted acetylenes afforded the corresponding $SF_5$-products in 58% and 75% yields, respectively. However, in the two latter cases higher temperature (~100°C) was required (Scheme 17).[49]

[47] Hoover, F. W.; Coffman, D. D. *J. Org. Chem.* **1964**, *29*, 3567.
[48] Canich, J. A. M.; Ludvig, M. M.; Paudler, W. W.; Gard, G. L.; Shreeve, J. M. *Inorg. Chem.* **1985**, *24*, 3668.
[49] (a) Wang, Q. C.; White, H. F.; Gard, G. L. *J. Fluorine Chem.* **1979**, *13*, 455. (b) Berry, A. D.; De Marco, R. A.; Fox, W. B. *J. Am. Chem. Soc*. **1979**, *101*, 737.




**Scheme 17: Additions of $SF_5Br$ to acetylenic derivatives.**

Later, reactions of the $SF_5X$ reagents with various substituted alkynes were reported in the literature. The pentafluorosulfanyl bromide underwent the thermal additions to diynes,[50] alkynyl esters[51] or alkynyl silanes[52] (Scheme 18, (a-d)), while the $SF_5Cl$ reacted with alkynyl ethers under photochemical conditions (Scheme 18, (e)). The resulting pentafluorosulfanylated derivatives were generally obtained in good yields (50-90%).

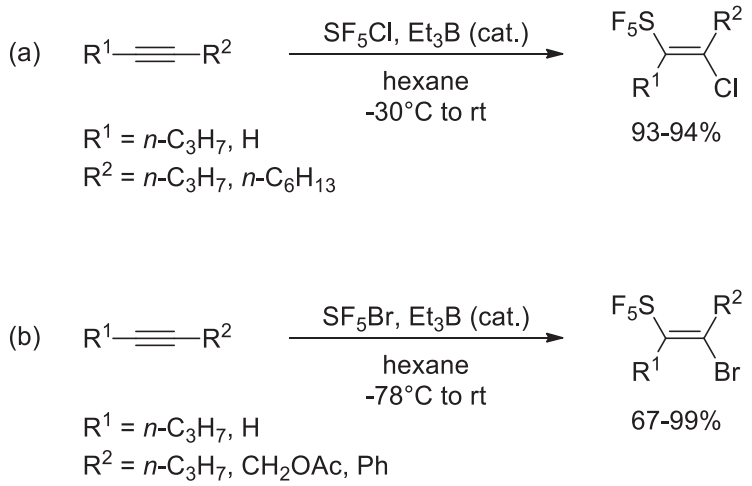



**Scheme 18: Thermal and photochemical $SF_5X$ additions to various substituted alkynes.**

The method based on the use of $Et_3B$ radical initiator, was also successfully applied to alkynes.[43] The reactions of $SF_5Cl$ with alkynes, containing long alkyl-chains, afforded the corresponding $SF_5$-substituted products in high yields, as single diastereoisomers (Scheme

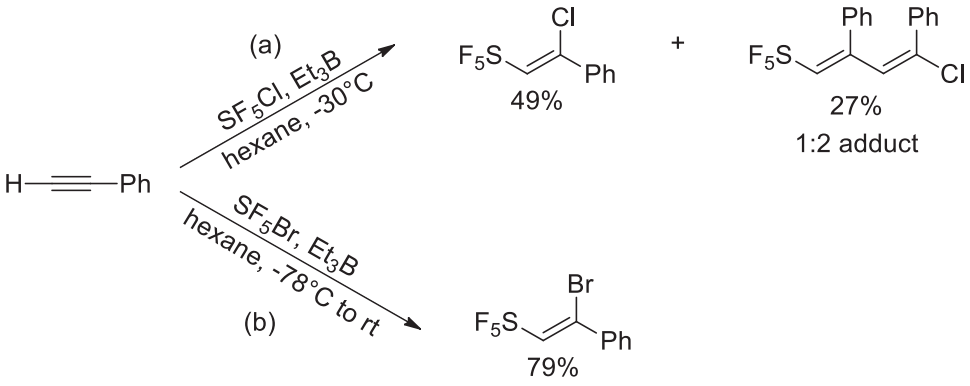
[50] (a) Kovacina, T. A.; De Marco, R. A.; Snow, A. W. *J. Fluorine Chem.* **1982**, *21*, 261. (b) Kovacina, T. A.; De Marco, R. A.; Snow, A. W. US4535011A, 1985; *Chem. Abstr.* **1985**, 104, 90558. (c) Kovacina, T. A.; De Marco, R. A.; Snow, A. W. *Ind. Eng. Chem. Prod. Res. Dev.* **1983**, *22*, 170.
[51] Winter, R. W.; Dodean, R.; Holmes, L.; Gard, G. L. *J. Fluorine Chem.* **2004**, *125*, 37.
[52] Lal, G. S.; Minnich, K. E. U.S. Patent US6479645B1, 2002; *Chem. Abstr.* **2002**, 137, 353172.

19, (a)), whereas the radical addition of $SF_5Br$ led to the pentafluorosulfanylated products in up to 99% yields (Scheme 19, (b)).




**Scheme 19: $Et_3B$ catalyzed additions of $SF_5X$ to alkynes.**

In the reaction of phenyl acetylene with $SF_5Cl$, the expected product was accompanied by the 1:2 adduct (Scheme 20, (a)). This phenomenon could be explained by the addition of the propagating radical intermediate to a second molecule of phenyl acetylene. It was reported that the use of a larger excess of pentafluorosulfanyl chloride minimized the formation of this by-product. On the other hand, $SF_5Br$ showed to be more reactive toward phenyl acetylene, giving the pentafluorosulfanylated product in higher yield (79%). Another advantage of the use of this reagent was its ability to react with phenyl acetylene without forming the 1:2 adduct (Scheme 20, (b)).[43]




**Scheme 20: $Et_3B$ catalyzed additions of $SF_5X$ to phenyl acetylene.**

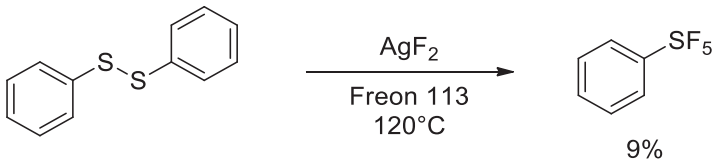
## 3.2. Introduction of the $SF_5$-group into aromatic compounds

In this part, the methods for the synthesis of pentafluorosulfanylated aromatic derivatives will be presented. The $SF_5$-substituent can be introduced into the aromatic compounds using three general approaches. The first one is based on the fluorination reactions of various sulfur-containing substrates, such as diaryl disulfides or aryl thiols. The second approach consists on the introduction of the $SF_5$-group into alkynes or cycloalkenes, using the previously described addition methods, followed by cycloaddition or aromatization reactions of these pentafluorosulfanylated building-blocks. The last strategy for the synthesis of $SF_5$-substituted aryl compounds is the approach based on the transformations of benzene derivatives, already containing the $SF_5$-group.

As in this project, we will investigate the synthesis of $SF_5$-derivatives via the direct fluorination of sulfur-containing compounds or via the cycloaddition reactions of $SF_5$-building-blocks; therefore, we were especially interested in the first two approaches. Herein we will primarily discuss the first two methodologies; nevertheless, the latter approach will be also briefly presented.

### 3.2.1. Fluorination of sulfur containing aromatic compounds

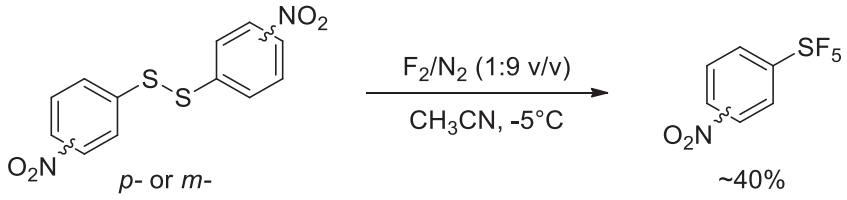
In 1962, Sheppard reported the first synthesis of phenylsulfur pentafluoride, by the fluorination of diphenyl disulfide with silver difluoride (Scheme 21).[16,53] Many researchers used these conditions in order to prepare pentafluorosulfanylated aromatic derivatives;[54] however, this method suffered from low yields and required an excess of the expensive $AgF_2$.




**Scheme 21: First synthesis of phenylsulfur pentafluoride.**

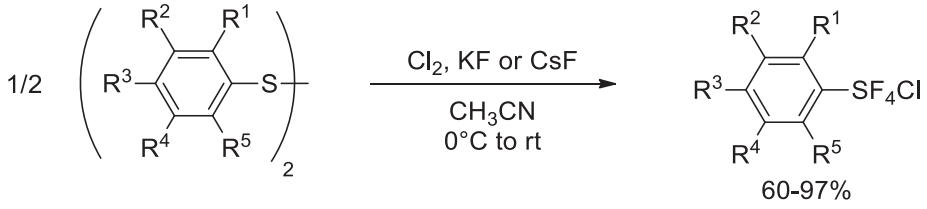
[53] Sheppard, W. *J. Am. Chem. Soc.* **1962**, *85*, 1310.
[54] (a) Reiffenrath, V.; Eidenschink, R.; Weber, G. WO-A8810251A1, 1987; *Chem. Abstr.* **1993**, 110, 240329. (b) Williams, A.; Foster N. WO9422817, 1995; *Chem. Abstr.* **1995**, 122, 58831. (c) Crowley, P. J.; Mitchell, G.; Salmon, R.; Worthington, P. A. *Chim. Int. J. Chem.* **2004**, *58*, 138.

Later, the direct fluorination using molecular fluorine, instead of silver difluoride, was reported.[55] The reaction of bis(*p*- or *m*-nitrophenyl) disulfide with $F_2$ in nitrogen atmosphere ($F_2/N_2$ = 1/9) afforded the pentafluorosulfanylated product in ca. 40% (Scheme 22). The drawbacks of this method were: the low yield, the use of the toxic and explosive gaseous $F_2$, and the scope was limited only to highly electron-deficient aromatic substrates. Alternatively, the use of the expensive xenon difluoride in the reaction with diphenyl disulfide was reported, giving the corresponding $SF_5$-substituted product in a low 25% yield.[56]




**Scheme 22: Synthesis of *m*- or *p*-nitrophenylsulfur pentafluoride using molecular fluorine.**

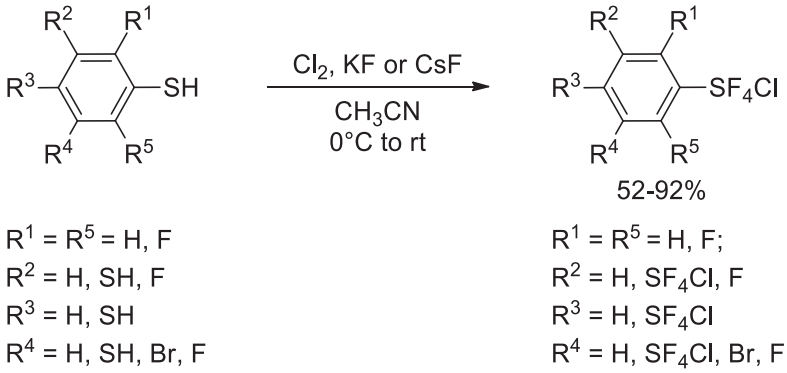
Quite recently, Umemoto group[57] developed a new practical and economical 2-step procedure leading to pentafluorosulfanylated aromatic derivatives. Arylsulfur chlorotetrafluorides were first prepared in high yields by the reaction of diaryldisufides with chlorine, in the presence of fluoride source (KF or CsF) (Scheme 23). Many $SF_4Cl$-substituted aromatic derivatives, bearing different electron-donating and electron-withdrawing substituents on the aryl ring, were prepared by this method in moderate to good yields.




**Scheme 23: Synthesis of arylsulfur chlorotetrafluorides starting from the corresponding disulfides.**

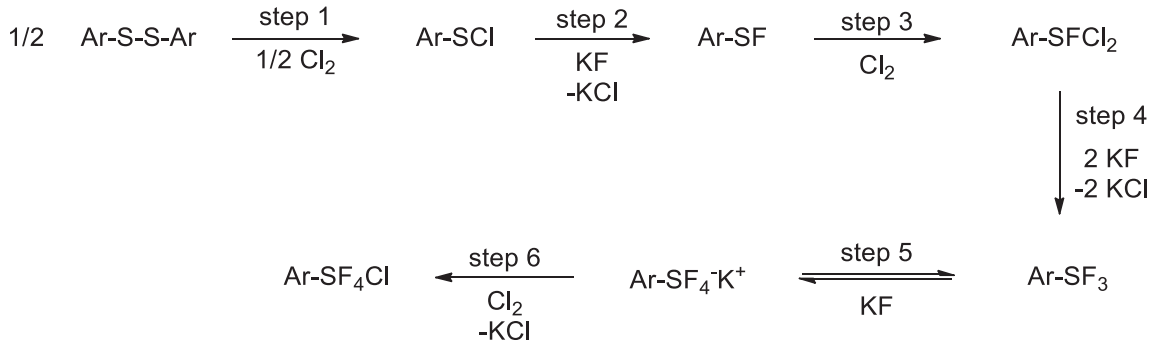
[55] (a) Bowden, R. D.; Greenhall, M. P.; Moillet, J. S.; Thomson, J. WO97/05106, 1987; *Chem. Abstr.* **1997**, 126, 199340. (b) Bowden, R. D.; Comina, P. J.; Greenhall, M. P.; Kariuki, B. M.; Loveday, A.; Philip, D. *Tetrahedron* **2000**, *56*, 3399.
[56] Ou, X.; Janzen, A. F. *J. Fluorine Chem.* **2000**, *101*, 279.
[57] For a recent review, see : Umemoto, T.; Garrick, L. M.; Saito, N. *Beilstein J. Org. Chem.* **2012**, *8*, 461.

Aryl thiols also reacted smoothly under these conditions, affording arylsulfur chlorotetrafluorides in 52% to 98% yields (Scheme 24).




**Scheme 24: Synthesis arylsulfur chlorotetrafluorides starting from the corresponding thiols.**

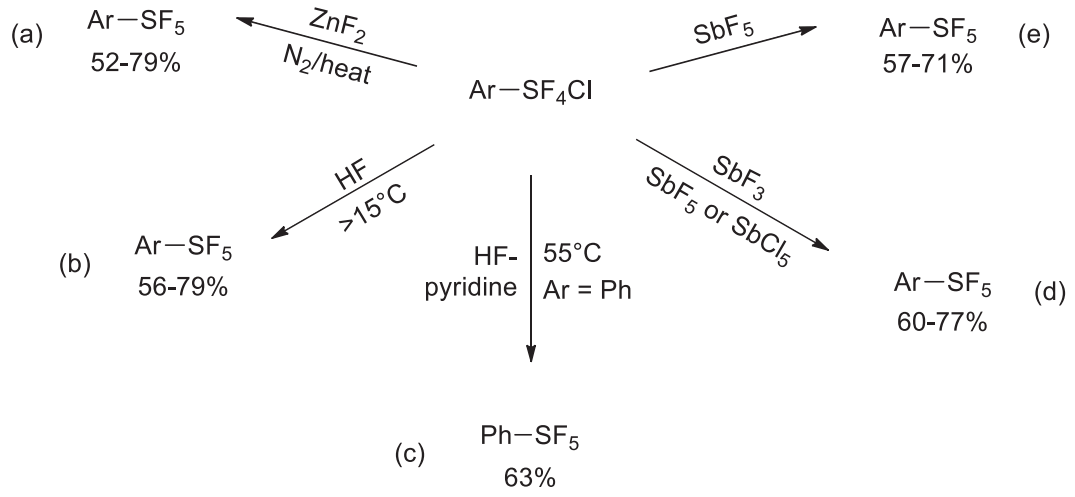
The mechanism of the chlorination-fluorination reactions, proposed by Umemoto, consists of six steps sequence, as depicted on the Scheme 25. After the introduction of chlorine to the reaction mixture, its fast reaction takes place leading to the formation of $ArSF_3$ in four steps (steps 1-4). The presence of this intermediate was confirmed by the $^{19}F$ NMR of the reaction mixture. The next two steps, leading to the final $SF_4Cl$-product, are slower, probably due to equilibrium in step 5. The reaction of thiols was explained by the same mechanism.




**Scheme 25: Proposed mechanism for the formation of the $SF_4Cl$-substituted aromatics.**

In order to transform the $SF_4Cl$-intermediates into the corresponding pentafluorosulfanylated derivatives, various conditions were screened. The reaction with the inexpensive $ZnF_2$ afforded the desired products with good yields (Scheme 26, (a)). It was reported that the electron-withdrawing substituents on the aryl ring increased the reactivity of Ar-$SF_4Cl$ derivatives under these conditions, whereas the electron-donating groups decreased

it. Interestingly, in the presence of $Cl_2$ the reactions were faster and gave better yields for most of the products; however, the role of the chlorine remained unclear. Other fluoride sources, such as HF, HF-pyridine, $SbF_3$ or $SbF_5$ were also reported to react efficiently with the $SF_4Cl$-intermadiates, leading to pentafluorosulfanylated products with good yields (Scheme 26, (b-e)).



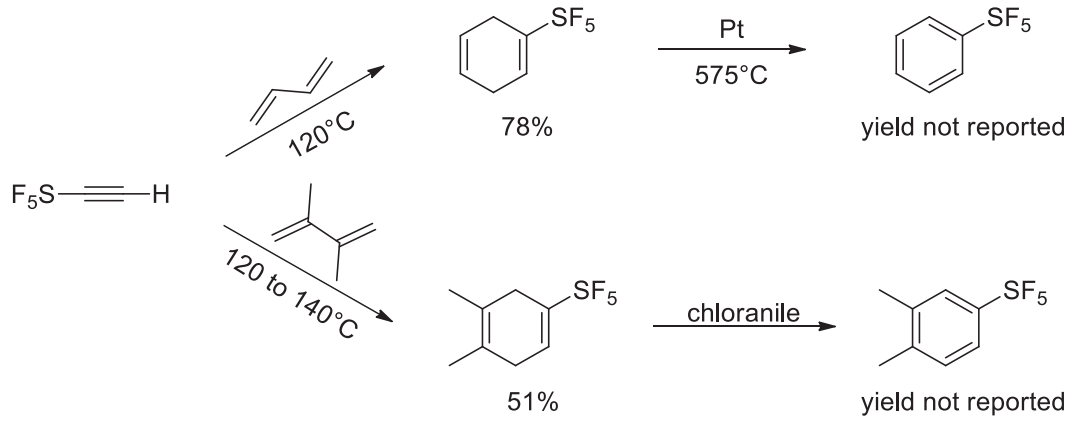

**Scheme 26: Synthesis of $SF_5$-substituted aromatics from $SF_4Cl$-derivatives.**

### 3.2.2. Approach based on the $SF_5X$ addition to unsaturated compounds

This approach to pentafluorosulfanylated aromatic compounds includes two methodologies, both based on the radical addition of $SF_5X$ to unsaturated compounds, and their further transformations (Diels-Alder reactions or aromatizations).

#### 3.2.2.1. Diels-Alder reaction of $SF_5$-building-blocks

The synthesis of the $SF_5$-aromatic compounds based on the cycloaddition reactions was reported in the literature, as an alternative to the inefficient direct fluorination. Indeed, $SF_5$-acetylene underwent Diels-Alder cycloadditions with buta-1,3-diene or 2,3-dimethylbuta-1,3-diene, followed by the dehydrogenation of the corresponding cycloadducts, leading to phenylsulfur pentafluoride derivatives (Scheme 27).[47]

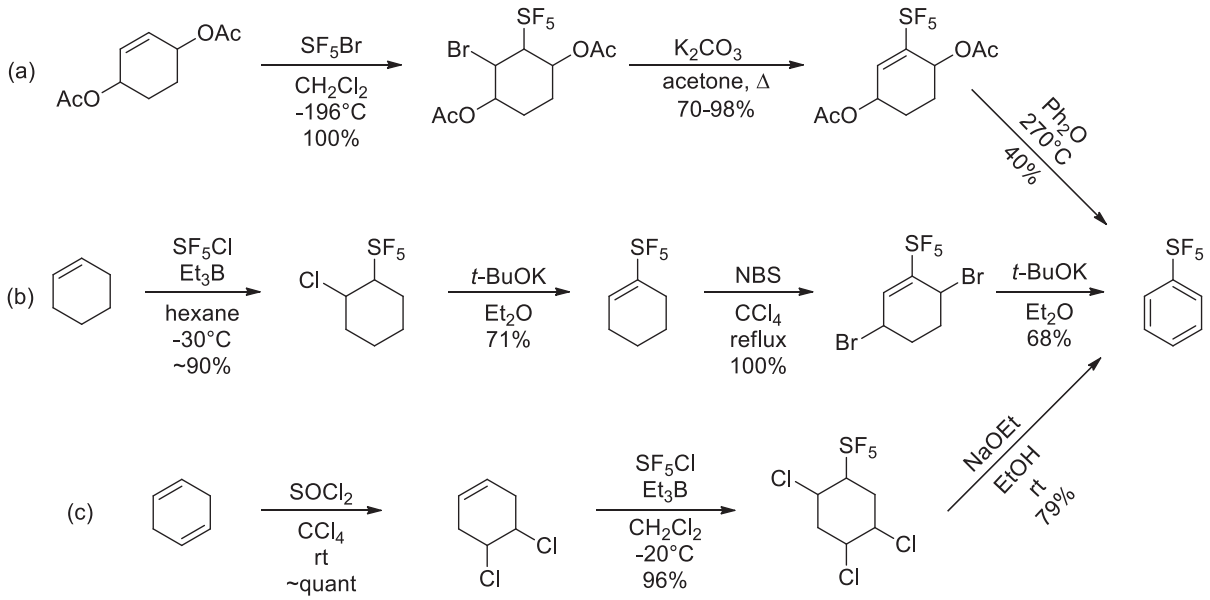



**Scheme 27: Diels-Alder cycloadditions of $SF_5$-acetylene and further dehydrogenations.**

### 3.2.2.2. $SF_5X$ introduction-aromatization approach

In 2004, two papers reporting the synthesis of $SF_5$-benzene, using $SF_5X$ additions on cycloalkenes or related derivatives appeared. On the one hand, $SF_5Cl$ and $SF_5Br$ underwent additions to cyclohexene and its diacetoxy derivative, respectively. After further transformations, the pentafluorosulfanylated product was obtained with moderate overall yields (Scheme 28, (a) and (b)).[58] On the other hand, Dolbier and collaborators[59] reported the addition of $SF_5Cl$ to 4,5-dichlorocyclohexene, according to his previously described method,[43] followed by the HCl elimination (Scheme 28, (c)). This procedure allowed the synthesis of phenylsulfur pentafluoride in a high overall yield (>70%).

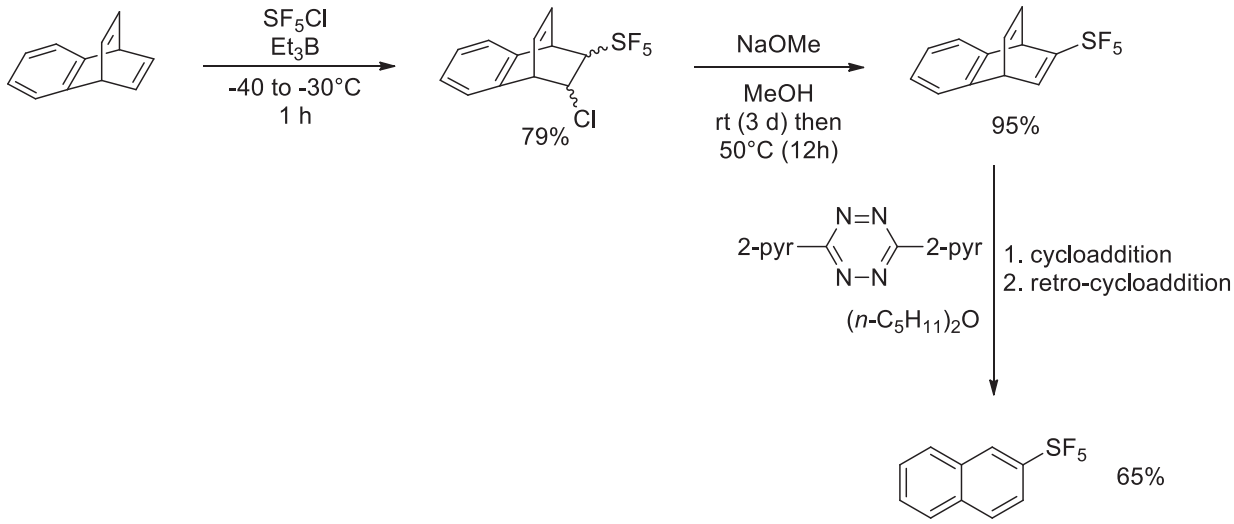
[58] Winter, R. W.; Gard, G. L. *J. Fluorine Chem.* **2004**, *125*, 549.
[59] Sergeeva, T. A.; Dolbier, W. R. *Org. Lett.* **2004**, *6*, 2417.




**Scheme 28: Synthesis of $SF_5$-substituted aromatics via $SF_5X$ addition and aromatization.**

The same concept of $SF_5X$ introduction into unsaturated cyclic compound and subsequent aromatisation, was used for the synthesis of the first $SF_5$-naphthalene, reported few years later.[60] The addition of $SF_5Cl$ to benzobarralene was followed by the dehydrochlorination to form the $SF_5$-substituted benzobarralene. The ethylene bridge was then eliminated by the reaction with 3,6-bis-(2-pyridyl)-1,2,4,5-tetrazine, via a sequence of cycloaddition and retro-cycloaddition reactions, to form the 2-$SF_5$-naphtalene in 65% (Scheme 29).

[60] Dolbier, W. R.; Mitani, A.; Warren, R. D. *Tetrahedron Lett.* **2007**, *48*, 1325.



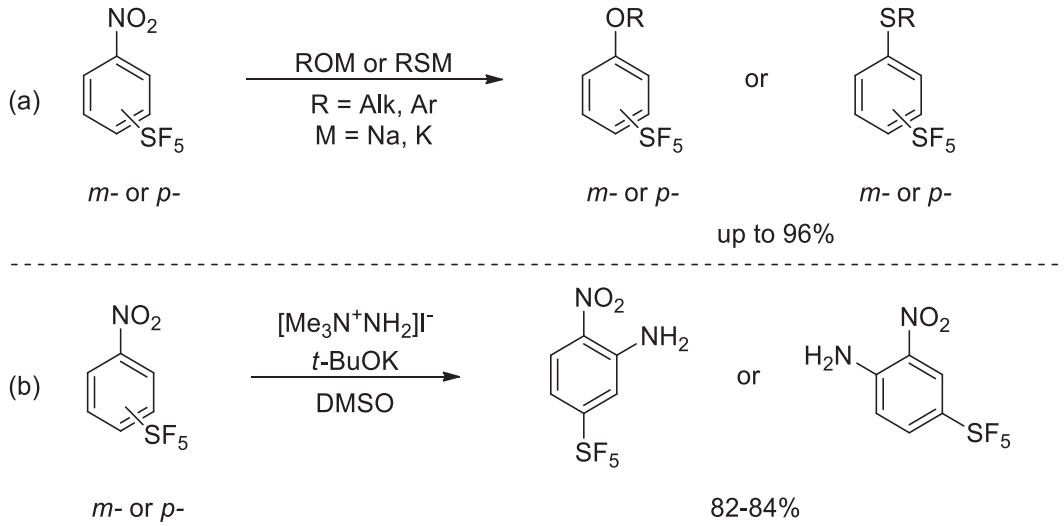

**Scheme 29: Three-step synthesis of 2-pentafluorosulfanyl naphthalene.**

### 3.2.3. Approach based on the reactions of novel Ar-$SF_5$ building-blocks

A more modern pathway for the introduction of the pentafluorosulfanyl group into aromatic compounds is the use of benzene derivatives, already containing the $SF_5$-group. In this sub-section, few selected examples of reactions engaging the Ar-$SF_5$ building-blocks, will be shortly presented.

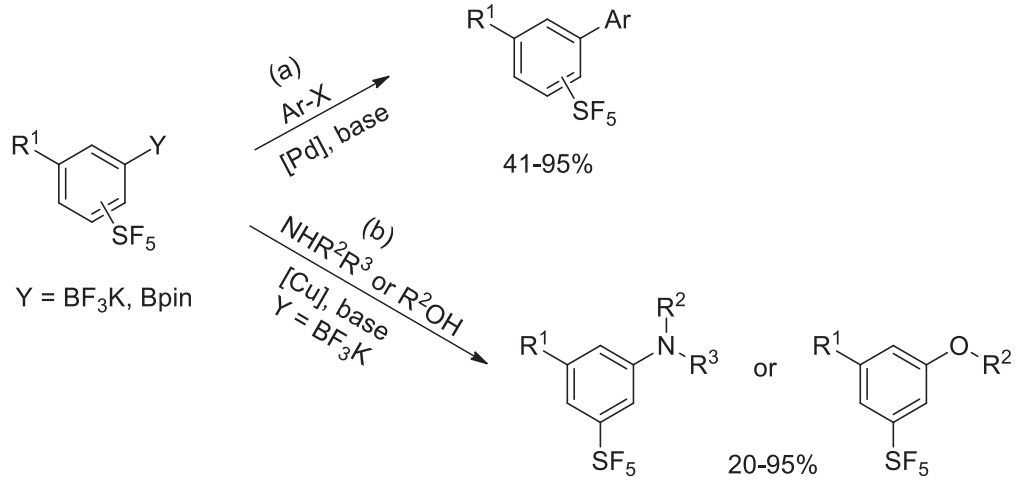
Among various transformations of $SF_5$-aryl building-blocks, Beier *et al.* have quite recently reported a series of nucleophilic aromatic substitution reactions, giving the access to a variety of unknown $SF_5$-benzene derivatives.[61] For example, the $S_NAr$ reaction of *p*- or *m*-nitro(pentafluorosulfanyl)benzene with alkoxides or thiolates, led to the corresponding substitution products in high yields (Scheme 30, (a)).[61a] On the other hand, the vicarious nucleophilic substitution with 1,1,1-trimethylhydrazinium iodide in the presence of potassium tert-butoxide allowed the direct amination of *p*- and *m*-nitro(pentafluorosulfanyl)benzene (Scheme 30, (b)).[61d] The same strategy was previously used in the reactions with carbon or oxygen nucleophiles.[61b,c]

[61] (a) Beier, P.; Pastyrikova, T.; Vida, N.; Iakobson, G. *Org. Lett.* **2011**, *13*, 1466. (b) Beier, P.; Pastyrikova, T.; Iakobson, G. *J. Org. Chem.* **2011**, *76*, 4781. (c) Beier, P.; Pastyrikova, T. *Tetrahedron Lett*. **2011**, *52*, 4392. (d) Pastyrikova, T.; Iakobson, G.; Vida, N.; Pohl, R.; Beier, P. *Eur. J. Org. Chem.* **2012**, 2123. (e) Iakobson, G.; Beier, P. Beilstein *J. Org. Chem.* **2012**, *8*, 1185. (f) Vida, N.; Beier, P. *J. Fluorine Chem*. **2012**, *143*, 130. (g) Beier, P.; Pastyrikova, T. *Beilstein J. Org. Chem*. **2013**, *9*, 411.




**Scheme 30: Selected examples of aromatic nucleophilic substitution reactions of Ar-$SF_5$.**

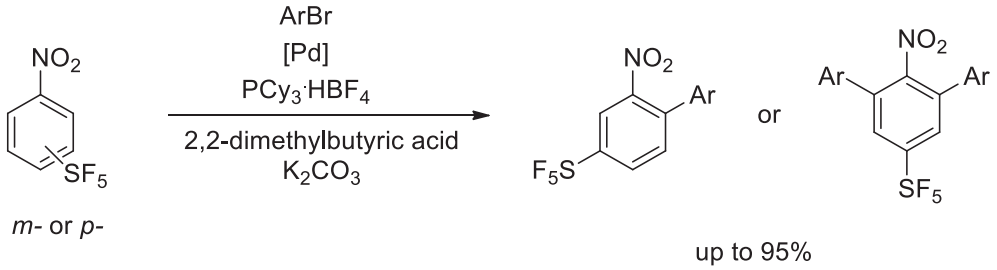
Other recently developed methods for the transformation of easily accessible Ar-$SF_5$ compounds, are mainly based on the Pd- or Cu-catalyzed coupling reactions. The synthesis of several $SF_5$-aryl trifluoroborates and boronates has been recently reported.[62] These new derivatives have been subjected to the Pd-catalyzed Suzuki-Miyaura reaction with various aryl halides, leading to the pentafluorosulfanylated biaryl products, in moderate to good yields (Scheme 31, (a)).[62a,b] The $SF_5$-substituted aryl trifluoroborates underwent also the Cu-catalyzed coupling reactions with amines and alcohols, affording the original 3-$SF_5$-substituted anilines and aryl ethers (Scheme 31, (b)).[62c]




**Scheme 31: Pd- and Cu-catalyzed couplings of novel $SF_5$-aryl trifluoroborates and boronates.**

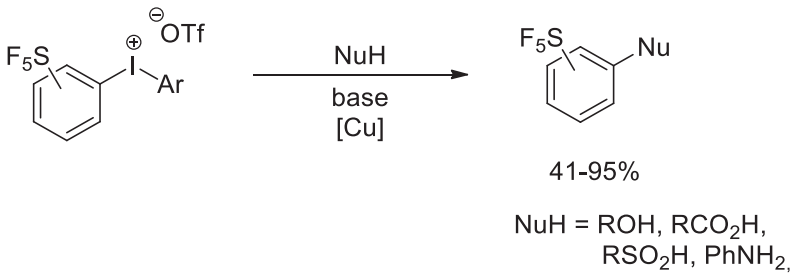
[62] (a) Iakobson, G.; Du, J.; Slawin, A. M. Z.; Beier, P. *Beilstein J. Org. Chem.* **2015**, *11*, 1494. (b) Joliton, A.; Carreira, E. M.; Hci, H. *Org. Lett.* **2013**, *7*, 5147. (c) Joliton, A.; Carreira, E. *Synlett* **2015**, *26*, 737.

The Pd-catalyzed direct arylation of nitro(pentafluorosulfanyl)benzenes with aryl bromides was reported as well.[63] This method led to a variety of $SF_5$-containing aryl derivatives in high yields and with good regioselectivities (Scheme 32).




**Scheme 32: Pd-catalyzed direct arylation using nitro(pentafluorosulfanyl)benzenes.**

Very recently, Matsuzaki *et al.*[12] has reported the synthesis of $SF_5$-arene containing diaryliodonium salts, which turned out to be efficient reagents for the electrophilic $SF_5$-arylation of various nucleophiles. Reaction of these new unsymmetrical diaryliodonium salts with alcohols, phenols, carboxylic acids, sulfonic acids, or anilines in the presence of base or copper catalyst, led to a wide variety of $SF_5$-aromatic compounds, in moderate to good yields (Scheme 33).




**Scheme 33: Electrophilic arylations using $SF_5$-arene containing diaryliodonium salts.**

## 3.3. Preparation of $SF_5$-heterocycles

Pentafluorosulfanylated heterocycles can be generally divided into two types, depending on the location of the $SF_5$-group on their rings. On the one hand, there is a group of derivatives, in which the $SF_5$-substituent is located on the aryl moiety (Figure 3, (a)). On

[63] Wang, C.; Yu, Y.-B.; Fan, S.; Zhang, X. *Org. Lett.* **2013**, *15*, 5004.

the other hand, the $SF_5$-group can be also directly attached to the heterocyclic ring, as depicted on Figure 3, (b).

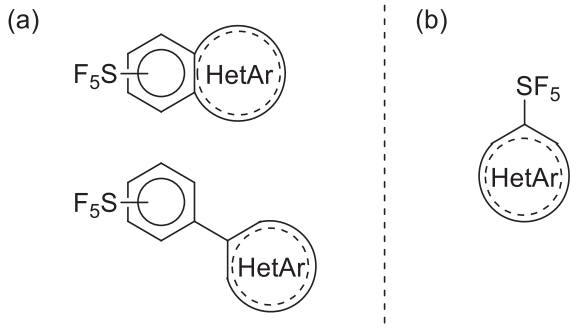



**Figure 3: Presentation of pentafluorosulfanylated heterocycles, depending on their structures.**

The methods for the synthesis of both types of pentafluorosulfanylated heterocyclic derivatives were exhaustively described in the Welch's revue.[9g] The access to $SF_5$-heterocycles of the first type appears to be easier, as the aromatic $SF_5$-containing building blocks are usually commercially available, whereas the synthesis of derivatives bearing the $SF_5$-group directly on the heteroaryl part is more challenging. Therefore, in the following sections, we will only shortly present the first type of $SF_5$-containing heterocycles, but we will discuss in details the examples of the second type of pentafluorosulfanylated heterocycles.

### 3.3.1. Derivatives bearing the $SF_5$-group on the aryl moiety

Among the pentafluorosulfanylated heterocycles bearing the $SF_5$-group on the aryl moiety, one can distinguish derivatives composed exclusively of monocyclic rings (Figure 4, (a)),[54c,64] and those, containing fused bicyclic rings (Figure 4, (b)).[61d,g,65] Several examples of both types of $SF_5$-compounds are depicted on Figure 4.

[64] (a) Coteron, J. M.; Marco, M.; Esquivias, J.; Deng, X.; White, K. L.; White, J.; Koltun, M.; El Mazouni, F.; Kokkonda, S.; Katneni, K.; Bhamidipati, R.; Shackleford, D. M.; Angulo-Barturen, I.; Ferrer, S. B.; Jiménez-Díaz, M. B.; Gamo, F. J.; Goldsmith, E. J.; Charman, W. N.; Bathurst, I.; Floyd, D.; Matthews, D.; Burrows, J. N.; Rathod, P. K.; Charman, S. A.; Phillips, M. A. *J. Med. Chem.* **2011**, *54*, 5540. (b) Gujjar, R.; El Mazouni, F.; White, K. L.; White, J.; Creason, S.; Shackleford, D. M.; Deng, X.; Charman, W. N.; Bathurst, I.; Burrows, J.; Floyd, D. M.; Matthews, D.; Buckner, F. S.; Charman, S. A; Phillips, M. A; Rathod, P. K. *J. Med. Chem.* **2011**, *54*, 3935. (c) Sun, L.; Li, J.; Bera, H.; Dolzhenko, A. V.; Chiu, G. N. C.; Chui, W. K. *Eur. J. Med. Chem.* **2013**, *70*, 400.

Such $SF_5$-derivatives are attractive, since they can be used in agrochemistry, medicinal chemistry or in chemistry of materials. Examples of biologically active pentafluorosulfanylated heterocycles with the $SF_5$-group attached to the aryl moiety will be discussed in details in Section 4.1 of this chapter.

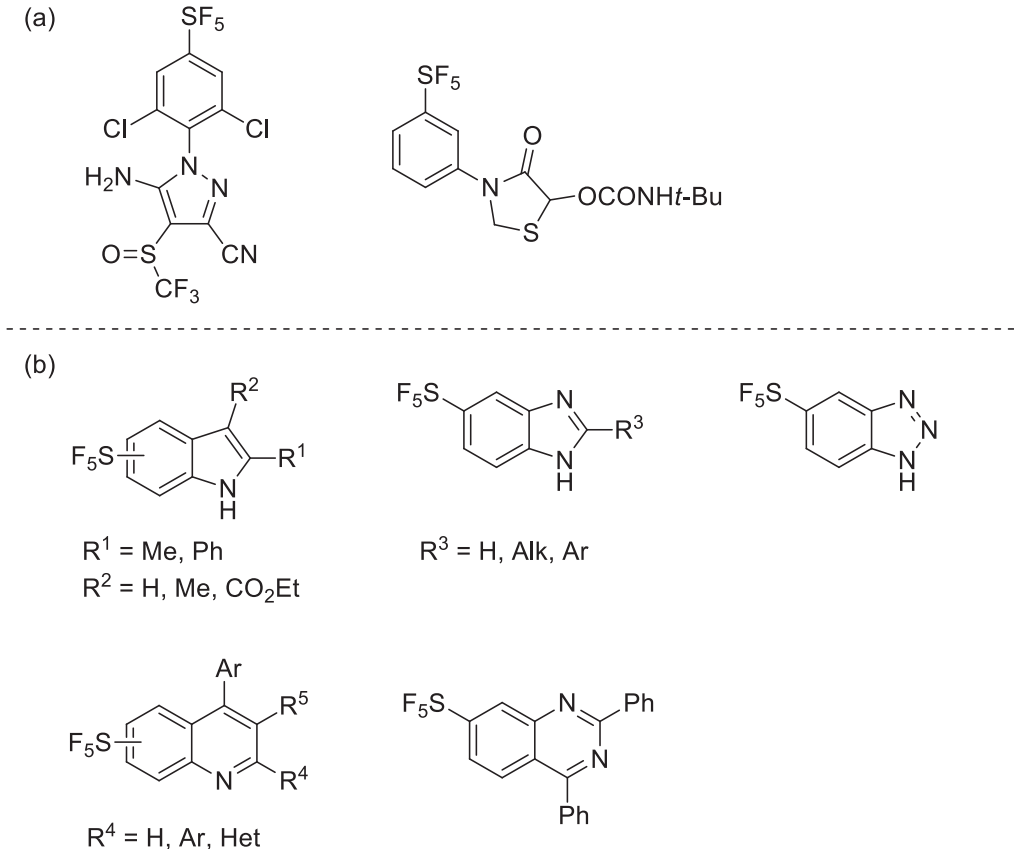



**Figure 4: Heteroaromatic derivatives, bearing the $SF_5$-group on the aryl moiety.**

### 3.3.2. Derivatives bearing the $SF_5$-group directly on the heteroaryl moiety

The examples of pentafluorosulfanylated heterocycles, having the $SF_5$-substitutent directly fixed on the heterocycle moiety are quite limited. Since the $SF_5$-acetylene was prepared for the first time, in 1961,[36,47] the main methodology for the introduction of the $SF_5$-

[65] (a) Vida, N.; Pastyrikova, T.; Klepetarova, B.; Beier, P. *J. Org. Chem.* **2014**, *79*, 8906. (b) Chen, J.; Xu, L.; Mi, X. *Tetrahedron Lett.* **2015**, *56*, 4204. (c) Mi, X.; Chen, J.; Xu, L. *Eur. J. Org. Chem.* **2015**, *2015*, 1415. (d) Frischmuth, A.; Unsinn, A.; Groll, K.; Stadtmuller, H.; Knochel, P. *Chem. Eur. J.* **2012**, *18*, 10234. (e) Iakobson, G.; Posta, M.; Beier, P. *Synlett* **2013**, 855. (f) Sipyagin, A. M.; Enshov, V. S., Kashtanov, S. A.; Bateman, C. P.; Mullen, B. D.; Tan, Y.-T.; Thrasher, J. S. *J. Fluorine Chem.* **2004**, *125*, 1305.

substituent into the heterocyclic compounds were based on the cycloaddition reactions of $SF_5$-alkynes with various partners. Several oxygen-,[66] sulfur-[67a] or nitrogen-containing[47,67,68,69] five-membered unsaturated heterocycles were prepared by this methodology (Figure 5). Recently, the direct fluorination of sulfur-containing heterocyclic compounds, leading to first 2-pentafluorosulfanylated pyridines, has been reported by Dolbier.[70] Nevertheless, the saturated five-membered heterocycles have remained undiscovered so far.

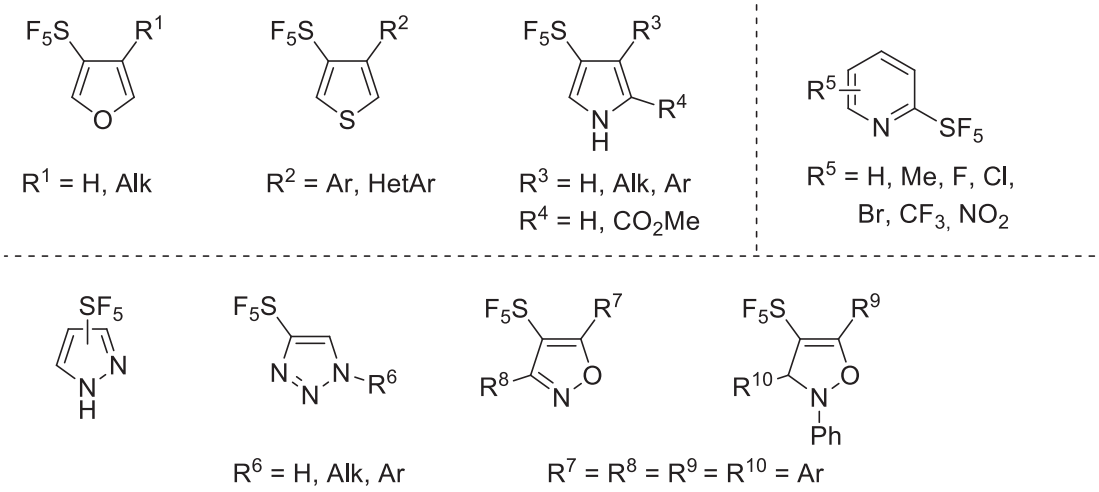



**Figure 5: Heteroaromatic derivatives, bearing the $SF_5$-group on the heteroaryl moiety.**

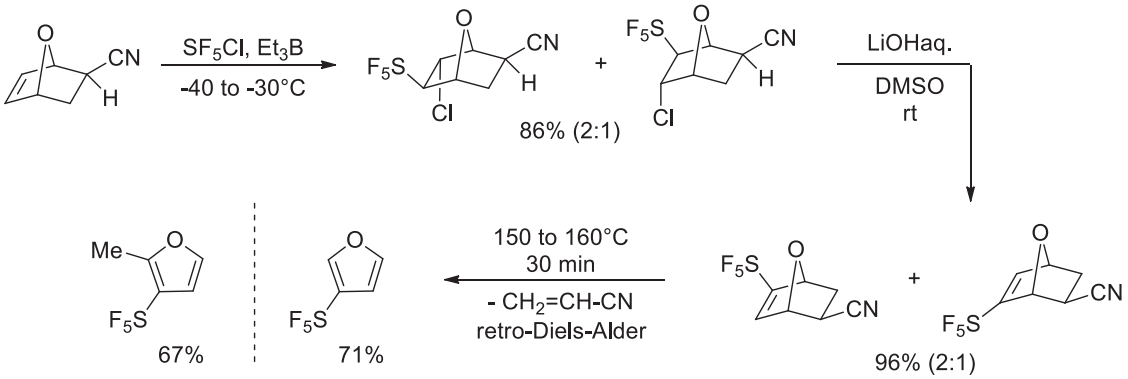
In the following sub-sections, different methods for the synthesis of above presented pentafluorosulfanylated heterocycles (Figure 5) will be described in details.

### 3.3.2.1. Synthesis of unsaturated five-membered heterocycles by cycloaddition reactions

The preparation of $SF_5$-substituted furans, using two different retro-Diels-Alder strategies, was reported by Dolbier.[66] First, the 3-pentafluorosulfanylfuran was synthesized, using the furan-acrylonitrile *exo*-adduct, as the starting product (Scheme 34). The first step of

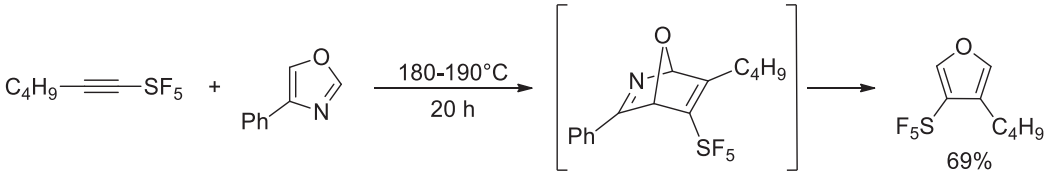
[66] Dolbier, W. R.; Mitani, A.; Xu, W.; Ghiviriga, I. *Org. Lett.* **2006**, *8*, 5573.
[67] (a) Dolbier, W. R.; Zheng, Z. *J. Fluorine Chem.* **2011**, *132*, 389. (b) Dolbier, W. R.; Zheng, Z. *J. Org. Chem.* **2009**, *74*, 5626.
[68] (a) Ye, C.; Gard, G. L.; Winter, R. W.; Syvret, R. G.; Twamley, B.; Shreeve, J. M. *Org. Lett.* **2007**, *9*, 3841. (b) Abe, T.; Tao, G. H.; Joo, Y. H.; Winter, R. W.; Gard, G. L.; Shreeve, J. M. *Chem. Eur. J.* **2009**, *15*, 9897.
[69] Lopez, S. E.; Mitani, A.; Pena, P.; Ghiviriga, I.; Dolbier, W. R. *J. Fluorine Chem.* **2015**, *176*, 121.
[70] Kanishchev, O. S.; Dolbier, W. R. *Angew. Chem. Int. Ed.* **2015**, *54*, 280.

this sequence was the usual $Et_3B$-initiated addition of $SF_5Cl$, leading to two regioisomeric products. After the HCl elimination and the subsequent retro-Diels-Alder reaction (release of acrylonitrile), the expected $SF_5$-furan was obtained in the overall yield of 59%. The same method was also used for the preparation of the corresponding 2-methylated derivative, in 67% yield.




**Scheme 34: Synthesis of 3-pentafluorosulfanylfurans.**

Another 3-substituted pentafluorosulfanylated furan was obtained via tandem cycloaddition/retrocycloaddition reactions. The 1-pentafluorosulfanylhex-1-yne was shown to be a good dienophile and reacted with 4-phenyloxazole, leading to the corresponding cycloadduct (as one regioisomer). The latter one underwent retro-Diels-Alder reaction to give the desired pentafluorosulfanylated product in a good yield (Scheme 35).

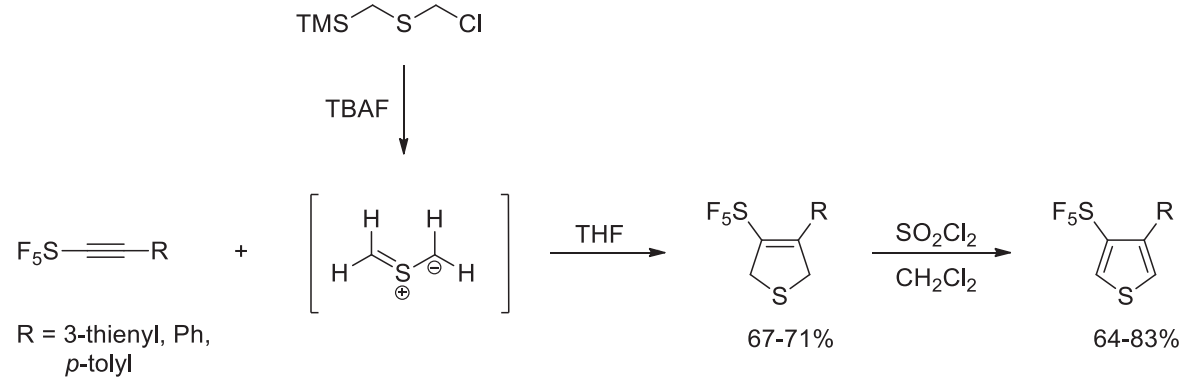



**Scheme 35: Synthesis of 4-(*n*-butyl)-3-pentafluorosulfanylfuran.**

Other five-membered unsaturated $SF_5$-heterocycles, such as tiophenes, pyrroles, pyrazoles, triazoles, isoxazoles or isoxazolines, were also synthesized by 1,3-dipolar cycloaddition reactions starting from $SF_5$-acetylenic derivatives.

The reactions of $SF_5$-substituted alkynes with *in situ*-generated thiocarbonyl ylide led to the pentafluorosulfanylated 2,5-dihydrothiophenes, in ca. 70% yield. The subsequent reaction with sulfuryl chloride gave access to the corresponding thiophenes (Scheme 36). As the $SF_5$-

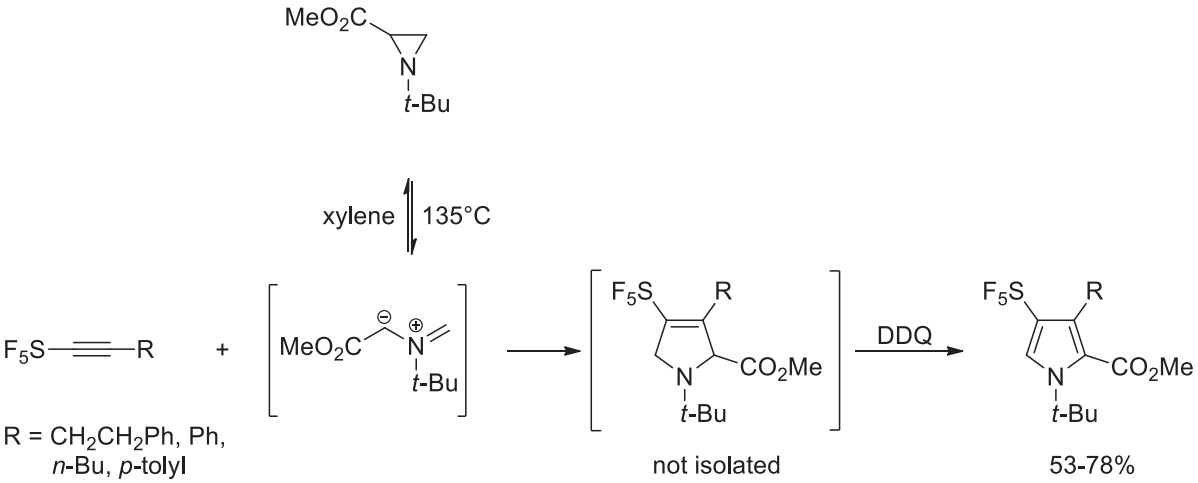
substrates bearing an alkyl group on the triple bond did not react under these conditions, the scope of this reaction was limited to the aryl-substituted alkynes.[67a]




**Scheme 36: Synthesis of 3-pentafluorosulfanylated thiophenes.**

1,3-Dipolar cycloadditions of $SF_5$-acetylenic derivatives with two different azomethine ylide precursors were reported as well. Both reactions allowed the synthesis of a few pentafluorosulfanylated pyrroles in moderate to high yields.

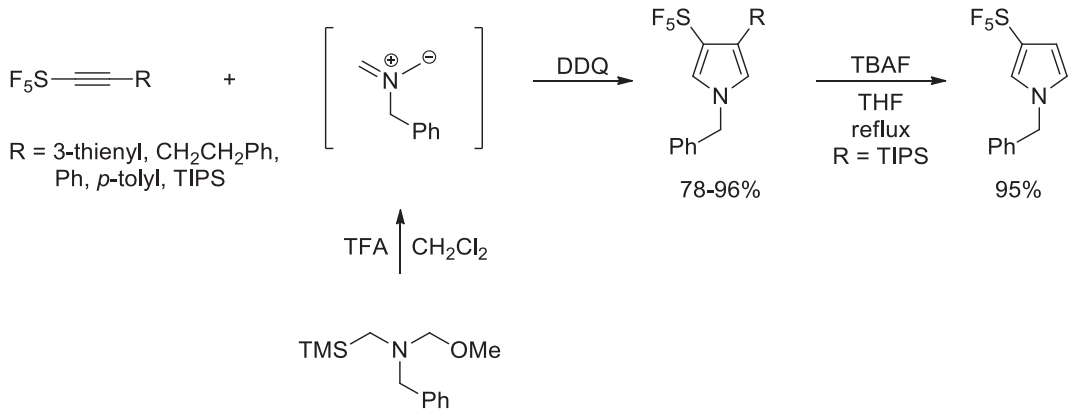
Reacting the $SF_5$-alkynes with N-(*t*-butyl) aziridine ester, followed by the oxidation of the intermediate pyrrolines, afforded the 4-$SF_5$-substituted pyrrole derivatives (Scheme 37). The removal of the *tert*-butyl group was possible in the presence of a catalytic amount of the triflic acid.[67b]




**Scheme 37: Synthesis of pentafluorosulfanylated pyrrole carboxylic acid esters.**

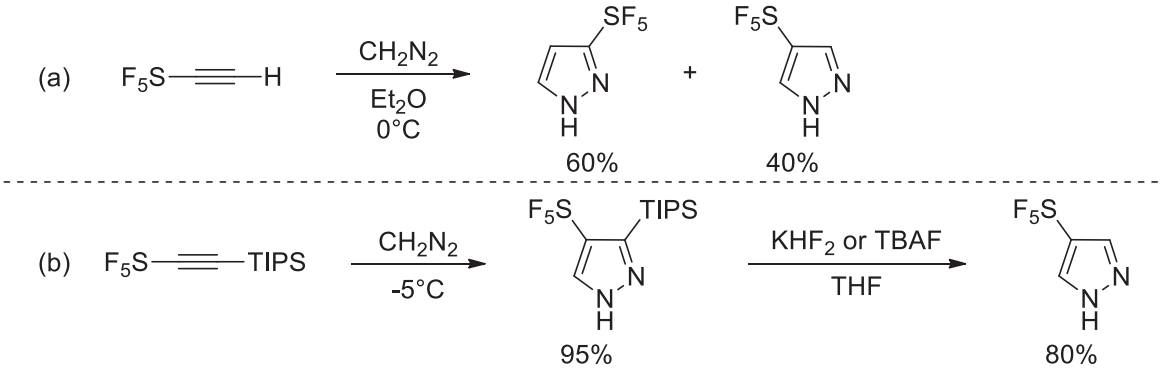
Alternatively, pentafluorosulfanylated pyrroles were synthesized in good yields from the $SF_5$-alkynes and N-(methoxymethyl)-N-[(trimethylsilyl)methyl]-N-benzylamine, as a

dipole precursor (Scheme 38). The $SF_5$-pyrrolines, obtained from 1,3-dipolar cycloaddition reactions of azomethine ylide and $SF_5$-alkynes, were converted *in-situ* to the corresponding pyrroles, using DDQ as an oxydizing reagent. When the triisopropyl substituted $SF_5$-alkyne was used as the starting material, the pyrrole could be easily desilylated by the use of TBAF.[67a]




**Scheme 38: Synthesis of 3-pentafluorosulfanylated pyrroles.**

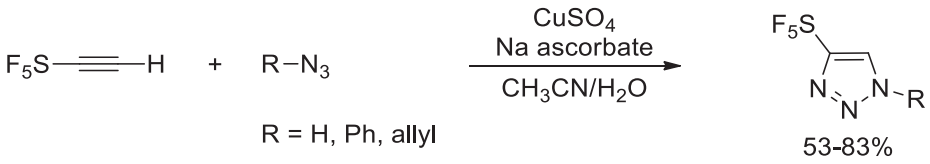
The first synthesis of $SF_5$-pyrrazoles was reported in 1964, together with the first preparation of the $SF_5$-acetylene. The latter showed to be reactive toward diazomethane, leading to a mixture of non-separable regioisomeric cycloadducts (Scheme 39 (a)).[47] This procedure was improved more recently, by using the TIPS-substituted $SF_5$-acetylene, as the starting product. The only obtained regioisomer underwent an easy desilylation to give the 4-pentafluorosulfanylated pyrazole in 80% yield (Scheme 39 (b)).[68a]




**Scheme 39: Synthesis of pentafluorosulfanylpyrazoles.**

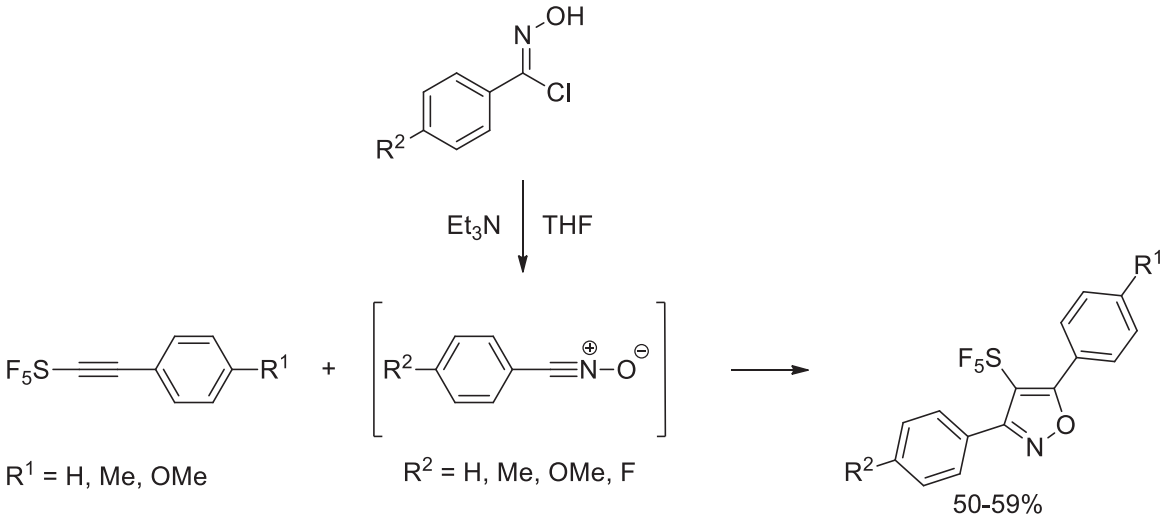
Several examples of 4-$SF_5$-substituted 1,2,3-triazoles were reported. Such heterocycles were prepared from pentafluorosulfanylacetylene and various azides, in the presence of Cu(I)

catalyst, formed *in-situ* from $CuSO_4$/sodium ascorbate (Scheme 40). These typical "click chemistry" conditions allowed a straightforward synthesis of the 4-pentafluorosulfanylated 1,2,3-triazoles in moderate to good yields.[68]



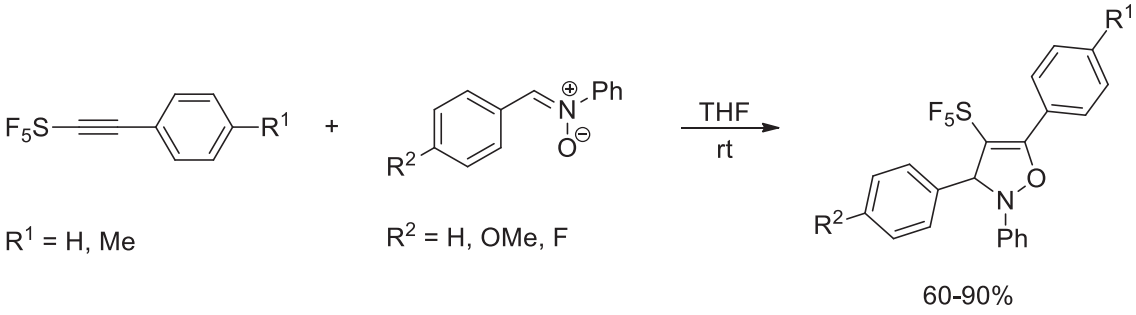

**Scheme 40: Synthesis of 4-pentafluorosulfanyl-1,2,3-triazoles.**

Very recently, Dolbier and coworkers have described the synthesis of the first pentafluorosulfanylated heterocycles, containing both nitrogen and oxygen atoms.[69] They reported the 1,3-dipolar cycloadditions of aryl-substituted $SF_5$-acetylenes with *in-situ* generated nitrile oxides, affording regioselectively the 4-pentafluorosulfanyl isoxazoles (Scheme 41). Nevertheless, a large excess of the nitrile oxide, as well as a long reaction time (36 h), were required to give the desired $SF_5$-heterocycles, in rather moderate yields.




**Scheme 41: Synthesis of 4-pentafluorosulfanylated isoxazoles.**

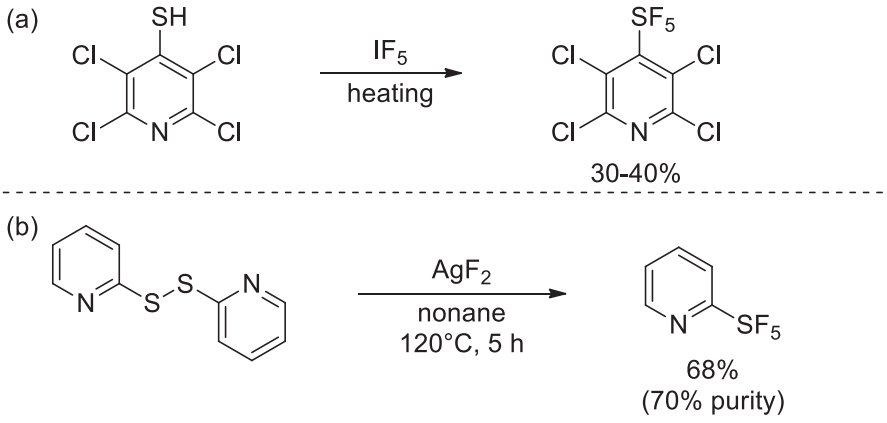
$SF_5$-Isoxazolines were synthesized in better yields (60-90%), by reacting the same $SF_5$-acetylenic building-blocks with several nitrones (Scheme 42).[69] The structures of 4-$SF_5$-regioisomers were assigned on the basis of 2D NMR experiments; however, no explanation for the total regioselectivity of these reactions was given.




**Scheme 42: Synthesis of 4-pentafluorosulfanylated isoxazolines.**

### 3.3.2.2. Synthesis of 2-$SF_5$-pyridines by Umemoto's method

Until recently, the preparation of pentafluorosulfanylated pyridines was very limited. The synthesis of 4-$SF_5$-2,3,5,6-tetrachloropyridine was achieved by heating the corresponding thiol with $IF_5$ (Scheme 43, (a)); nevertheless, the yield of the reaction was low (30-40%) and no experimental or characterization details of the new compound were described.[71a] A patent described also the synthesis of 2-$SF_5$-pyridine by oxidative fluorination of 2,2'-dipyridyl disulfide with $AgF_2$, in nonane for 5 hours at 120°C (Scheme 43, (b)); nevertheless, the latter method appeared to be very limited.[71b]

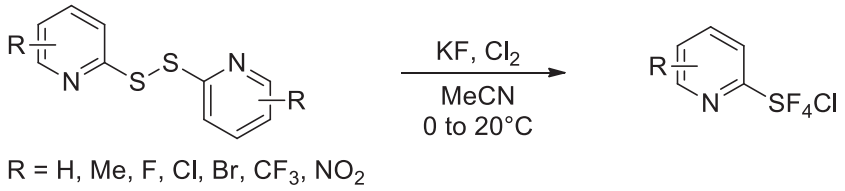



**Scheme 43: First reported synthetic routes for $SF_5$-substituted pyridines.**

Another approach for the synthesis of 2-$SF_5$-pyridines, was developed very recently.[70] It was reported that the Umemoto's procedure, previously reported for the aryl series, can be

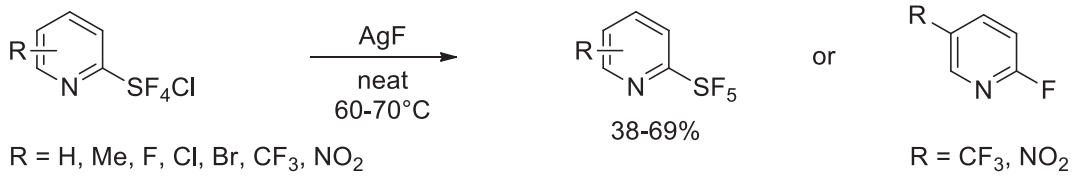
[71] (a) Sipyagin, A. M.; Pomytkin, I. A.; Paltsun, S. V.; Aleinikov, N. N.; Kartsev, V. G. *J. Fluorine Chem.* **1991**, *54*, 115. (b) Williams, A. G., Foster, N. R. WO1994/22817, 1994.

applied to some sulfur-containing heterocyclic compounds, as well. Indeed, a variety of substituted 2,2'-dipyridyl disulfides underwent a two-step transformation into the corresponding 2-$SF_5$-pyridines. The oxidative fluorination of the disulfides with an excess of KF and $Cl_2$ led to the formation of 2-pyridylsulfur chlorotetrafluorides (Scheme 44). This first step proceeded through the same mechanism as in the case of aromatic substrates (Scheme 25), which was proved by the formation of the pyridylsulfur trifluoride ($SF_3$-Pyr) intermediate, confirmed by the $^{19}F$ NMR. The efficiency of this reaction was highly dependent on the aryl-substituent size – it was indeed noticed that with the more hindered *ortho*-substituents, the conversion rate of the $SF_3$-intermediate into the corresponding $SF_4Cl$-product decreased dramatically.




**Scheme 44: Synthesis of 2-pyridylsulfur chlorotetrafluorides.**

The transformation of the $SF_4Cl$-intermediates into the desired $SF_5$-pyridines was further investigated. The screening of widely used fluorinating agents revealed that in most cases the $SF_4Cl$-products decomposed. Only the silver (I) fluoride showed to be a very efficient reagent for the halogen-exchange reaction, leading to the desired 2-pentafluorosulfanylated pyridines (Scheme 45). It is worth noting that in the reactions of $SF_4Cl$-pyridines bearing a very electron-withdrawing substituent (such as a $CF_3$ or $NO_2$ group) in the 5-postition, mainly the 2-fluoropyridines were formed. This was explained by the activating effect of these substituents, toward the $S_NAr$ reaction with fluoride anions, competing with the desired Cl-F exchange process. The moderate yields (38-69%) of this 2-step transformation were probably due to a high volatility of the final products.




**Scheme 45: Transformation of 2-pyridylsulfur chlorotetrafluorides into 2-$SF_5$-pyridines.**

# 4. Applications of $SF_5$-derivatives

The interesting properties of $SF_5$-group, prompted some researchers to synthesize new $SF_5$-containing active compounds. A large majority of such derivatives was very recently reviewed by Welch;[9g] thus in this section, only selected examples, possessing agrochemical or pharmaceutical activities, will be presented. The first sub-section includes the active compounds containing exclusively aromatic rings in their structures. In the second sub-section, the $SF_5$-derivatives, containing one or more heterocyclic rings, will be presented. It is worth noting that, in all cases the $SF_5$-substituent is placed on the aryl part of these active compounds.

## 4.1. Active pentafluorosulfanylated aryl-containing derivatives

### 4.1.1. Agrochemistry

In 2007, Welch group synthesized the pentafluorosulfanylated analogue of the herbicide trifluraline (Figure 6, **II**), starting from the commercially available 1-nitro-4-pentafluorosulfanylbenzene.[72] The herbicidal activity of this $SF_5$-substituted aryl compound was tested against a representative panel of plant species, in pre- and post-emergence applications. The replacement of $CF_3$- by the $SF_5$-group did not bring any significant improvement in the post-emergence applications; however, it turned out to be advantageous in pre-emergence use. The $SF_5$-analogue caused less crop injury compared to the parent trifluraline. For example, only 10% growth inhibition was observed for corn treated with **II** at 2.68 kg/ha, whereas the application of trifluoraline at 4 and 1 kg/ha resulted by 100% and

[72] Lim, D. S.; Choi, J. S.; Pak, C. S.; Welch, J. T. *J. Pestic. Sci.* **2007**, *32*, 255.

20% damage, respectively. Furthermore, the $SF_5$-derivative was also reported to have greater herbicidal activity – the control of several weeds was efficient at 4 kg/ha application rate for trifluralin, and already at 0.67 kg/ha for the $SF_5$-analogue. The mechanism of action of these herbicides was explained by the interactions of their electron dense areas ($CF_3$-group for **I** and $SF_5$-group for **II**) with charged arginase enzyme.

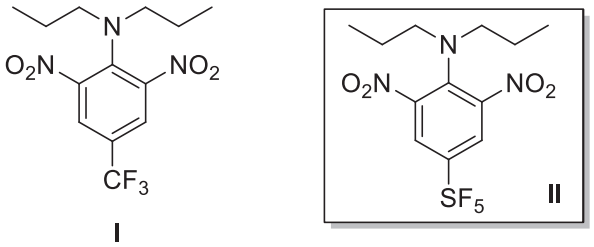



**Figure 6: Trifluraline (I) and its $SF_5$-analogue (II).**

### 4.1.2. Medicinal chemistry

In the same laboratory, $SF_5$-analogues of fluoxetine (Figure 7, **III**), fenfluramine (Figure 7, **IV**) and norfenfluramine (Figure 7, **V**) were synthesized.[73] The well known fluoxetine is an anti-depressive drug, whereas the fenfluramine and its metabolite – norfenfluramine, are used in the treatment of obesity. All of these compounds are acting by binding the serotonin (5-HT) receptors. The synthesis of the fluoxetine $SF_5$-analogue started from 1-nitro-4-pentafluorosulfanylbenzene, while the analogues of fenfluramine and norfenfluramine were prepared starting from $SF_5$-benzene. The initial screening at 10 μmol/L concentrations, showed that all the $SF_5$-derivatives inhibited the binding of selected 5-HT receptors. In addition, the secondary screening demonstrated that fenfluramine and norfenfluramine $SF_5$-analogues had almost ten-fold enhanced affinity to 5-$HT_{2b}$ and 5-$HT_6$ receptors, than the parent $CF_3$-compounds.

[73] Welch, J. T.; Lim, D. S. *Bioorganic Med. Chem.* **2007**, *15*, 6659.

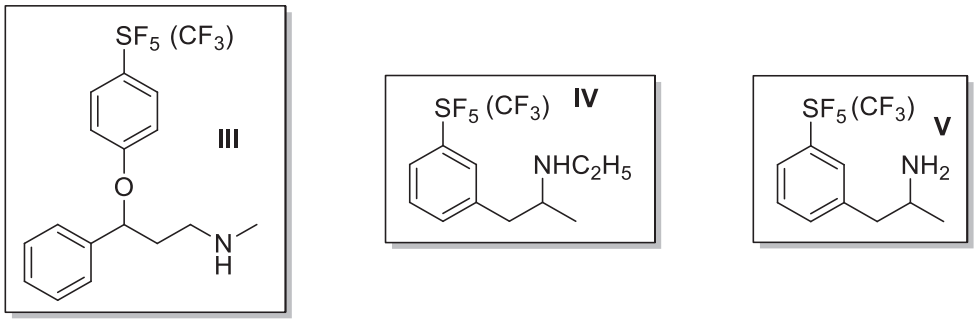



**Figure 7: $SF_5$-Analogues of fluoxetine (III), fenfluramine (IV) and norfenfluramine (V).**

The $SF_5$-group was reported to be a suitable substituent for diarylamine-based tryptanothione reductase (TR) inhibitor (Figure 8).[74] This compound was synthesized, by hydrogenation of the commercially available 1-nitro-4-pentafluorosulfanylbenzene to the corresponding aniline, followed by further post-transformations. Compound **VI** was reported to show a mixed competitive-uncompetitive inhibition of *Trypanosoma cruzi* TR. The binding conformation of this derivative in the receptor site is depicted on Figure 8 – the $SF_5$-phenylamine moiety occupies the hydrophobic binding side, framed by Trp21, Tyr110 and Met113 amino acid residues. The highly electron-withdrawing nature of $SF_5$-group probably strengthens the interaction of **VI** with the electron-reach amino acids, present in the binding site. Further investigations showed also lower cytotoxicity of **VI**, relative to the corresponding $CF_3$-analogue. The $SF_5$-derivative displayed also a good membrane permeability, with the logarithmic distribution coefficient lying in the desirable range (log*D* = 3.56 at pH 7.4).

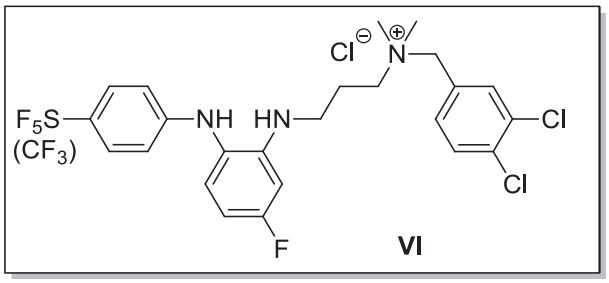



**Figure 8: Pentafluorosulfanylated inhibitor of tryptanothione reductase.**

[74] Stump, B.; Eberle, C.; Schweizer, W. B.; Kaiser, M.; Brun, R.; Krauth-Siegel, R. L.; Lentz, D.; Diederich, F. *ChemBioChem* **2009**, *10*, 79.

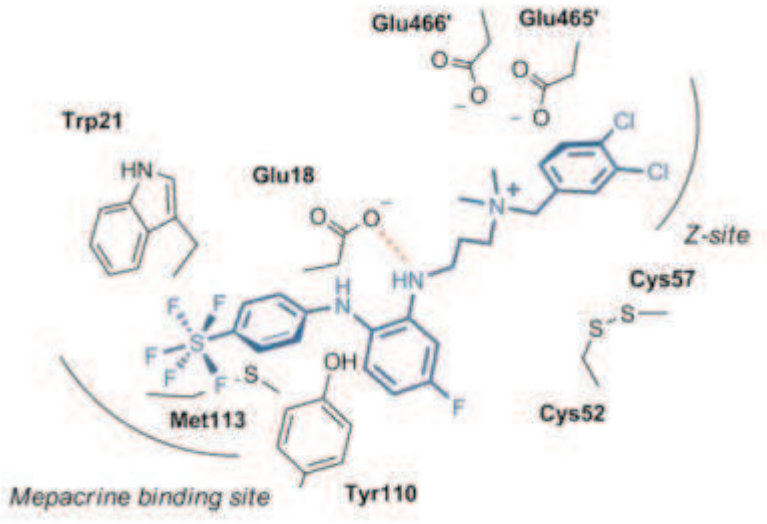



**Figure 9: The binfing conformation of compound VI in the receptor.**

The pentafluorosulfanylated flufenamic acid analogues were very recently reported by Hendriks *et al.* (Figure 10).[75] The parent $CF_3$-substituted compound is known to inhibit aldo-keto reductase 1C3 (AKR1C3) – an enzyme over-expressed in prostate cancer. Compounds **VII-X** were efficiently prepared by a two-step procedure, starting from pentafluorosulfanylanilines. All the $SF_5$-derivatives displayed good biological activities and selectivities; however, the best results were reported for analogues **VIII** and **IX**. High inhibitory potency ($IC_{50}$ < 100 nM) and selectivity for AKR1C3 over AKR1C2 ($IC_{50}$ ratio > 150) make them potential new drug candidates for prostate cancer.

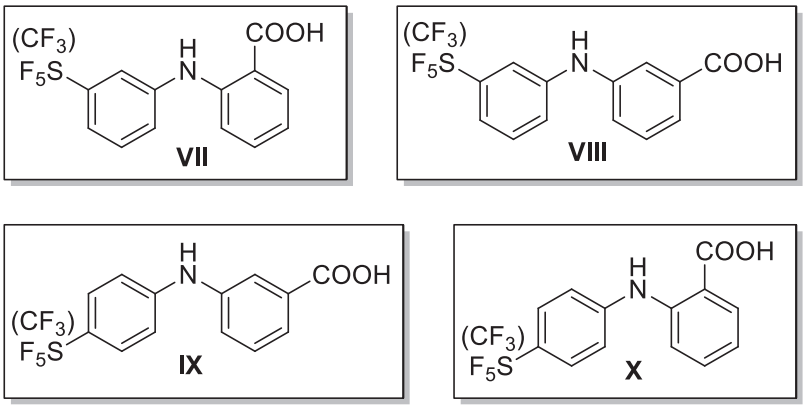



**Figure 10: Pentafluorosulfanylated analogues of flufenamic acid.**

[75] Hendriks, C. M. M.; Penning, T. M.; Zang, T.; Wiemuth, D.; Gründer, S.; Sanhueza, I. A.; Schoenebeck, F.; Bolm, C. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 4437.

## 4.2. Active pentafluorosulfanylated heterocycle-containing derivatives

### 4.2.1. Agrochemistry

$SF_5$-Insecticides, containing pyrimidinone and pyrazole rings (Figure 11), were synthesized from polysubstituted pentafluorosulfanylated benzenes.[54c] Their biological activities, compared to the corresponding trifluoromethyl analogues, were evaluated. On the one hand, compounds **XI** were more active against houseflies (*Musca domestica*) and German cockroaches (*Blatella germanica*), than their $CF_3$-analogues ($EC_{50}$ ($SF_5$) = 0.3-1 ppm vs. $EC_{50}$ ($CF_3$) = 1-17 ppm). Nevertheless, their activity against resistant strain of housefly was low. On the other hand, the $SF_5$-analogue **XII** was reported to be more active against houseflies and cockroaches, than the parent $CF_3$-containing fipronil. Moreover, the $SF_5$-derivative showed no loss of potency against the housefly resistant strain (Table 2).

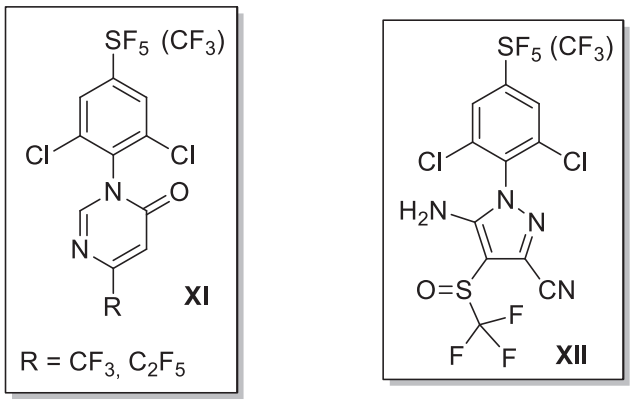



**Figure 11: Pentafluorosulfanylated insecticides: N-aryl pyrimidinones (XI) and N-aryl pyrazoles (XII).**

| $SF_5$ Analogue (XII) Relative potency | | Fipronil Relative potency | | $SF_5$ Analogue (XII) Relative potency | Fipronil Relative potency |
|---|---|---|---|---|---|
| *Musca* (S)[a] | *Musca* (R)[a] | *Musca* (S)[a] | *Musca* (R)[a] | *Blattella* (S)[a] | *Blattella* (S)[a] |
| 1 | 1 | 0.1 | 0.01 | 1 | 0.5 |

[a](R) indicates a strain resistant to dieldrin and (S) is a susceptible strain.

**Table 2: Comparison of the insecticidal activity of the $SF_5$-derivative XII and the parent fipronil.**

In the same paper, the synthesis of the pyridine-containing herbicide (Figure 12), starting from the $SF_5$-substituted sodium phenoxide and a 3-chloro substituted pyridine, was described. It was reported that the pentafluorosulfanylated derivative **XIII** showed the same level of potency and selectivity in pre-emergence applications, as the commercial $CF_3$-containing diflufenican.

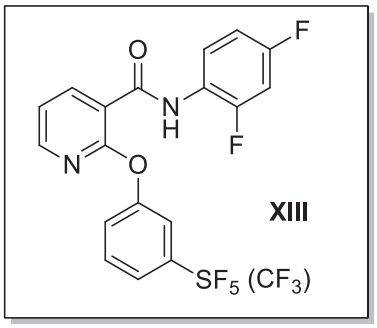



**Figure 12: $SF_5$-Analogue of the herbicide diflufenican.**

### 4.2.2. Medicinal chemistry

Three pentafluorosulfanylated analogues of the antimalarial agent mefloquine were reported by Wipf *et al.* (Figure 13).[76] The $SF_5$-substituent in these compounds was attached to the phenyl part of the quinoline. The 6-, 7- and 8-$SF_5$-derivatives were synthesized starting from the respective *p*-, *m*- and *o*-$SF_5$-anilines, through five steps, in 10-23% overall yields. Compounds **XIV** and XV displayed the biological mimicry of the trifluoromethyl group. Both of them exhibited equivalent or lower values of $IC_{50}$ and $IC_{90}$ against drug resistant strains of *Plasmodium falciparum*, compared to the $CF_3$-analogues and mefloquine. In addition, compound **XIV** was reported to have greater selectivity than mefloquine. Thus, 6- and 7-$SF_5$-derivatives could be considered as potential antimalarial drug candidates. As for the 8-$SF_5$-analogue, its biological activity has not been reported yet.

[76] (a) Wipf, P.; Mo, T.; Geib, S. J.; Caridha, D.; Dow, G. S.; Gerena, L.; Roncal, N.; Milner, E. E. *Org. Biomol. Chem.* **2009**, *7*, 4163. (b) Mo, T.; Mi, X.; Milner, E. E.; Dow, G. S.; Wipf, P. *Tetrahedron Lett.* **2010**, *51*, 5137.

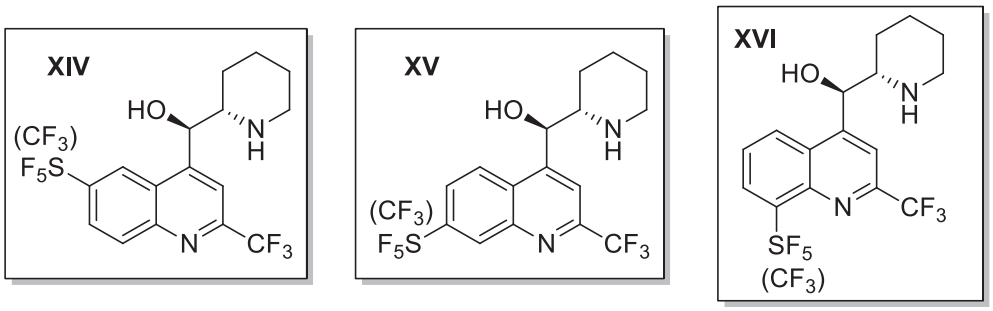



**Figure 13: $SF_5$-Substituted mefloquine analogues.**

Other heterocycle-containing pentafluorosulfanylated compounds, with potential antimalarial activity, were reported in 2011 (Figure 14).[64a,b] Compounds **XVII** and **XVIII** were synthesized from $SF_5$-aniline and chloro-substituted triazolopyrimidine derivatives. The biological studies demonstrated that compound **XVII** had 2-3 fold greater activity against *Plasmodium falciparum* dihydroorotate dehydrogenase (*Pf*DHODH), than its trifluoromethylated analogue. Even if the $EC_{50}$ values against *Plasmodium berghei* was higher than those reported for the well-known antimalarial drugs, the $SF_5$-derivative showed a good balance between potency and metabolic stability. Compound **XVIII** was also efficient against *P. falciparum* and it displayed an activity against drug resistant parasite strains.

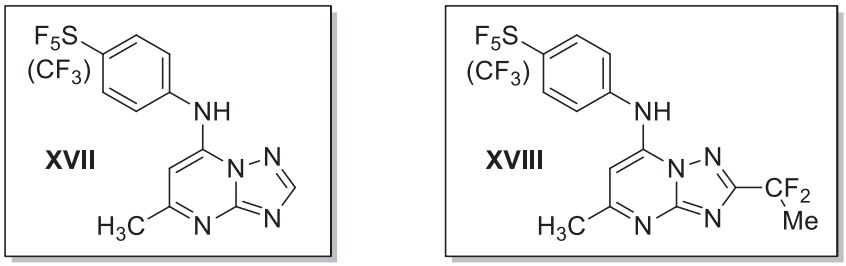



**Figure 14: $SF_5$-Substituted antimalarial arylamine-based triazolopyrimidines.**

The last presented example was designed as a potential thymidine phosphorylase (TP) inhibitor (Figure 15).[64c] As it is known that TP has some functions related to cancer biology, the inhibitors of this enzyme might be used as potential anticancer agents. The pentafluorosulfanylated derivative **XIX** displayed a high inhibitory activity ($IC_{50}$ ($SF_5$) = 0.36 μM) against this enzyme. The mixed-type inhibition mechanism was reported for this compound, suggesting that it could bind at two sites of the enzyme. Finally, the preliminary cytotoxicity studies indicated that $SF_5$-derivative **XIX** did not exhibit severe cytotoxic effects; thus it could be a potential drug candidate.

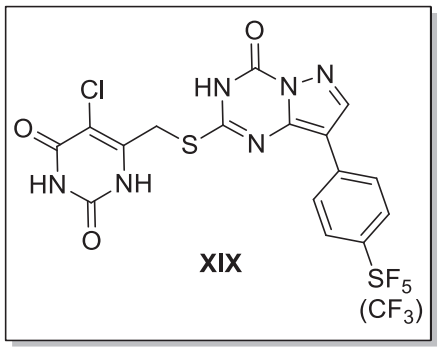



**Figure 15: New $SF_5$-substituted thymidine phosphorylase inhibitor.**

# 5. Presentation of the PhD project

The aim of this PhD thesis is to develop new methodologies for the synthesis of original pentafluorosulfanylated building-blocks, on the one hand, and to get the access to new pentafluorosulfanylated nitrogen-containing heterocycles, on the other hand. Given quite limited examples of simple pentafluorosulfanylated building-blocks, the preparation of new $SF_5$-derivatives could contribute to a faster development in $SF_5$-chemistry. Finally, thanks to the unique properties of the $SF_5$-group, its introduction into heterocycles should give us the access to new potential biologically active compounds.

In the first part of the project, we will concentrate on the preparation of various unsaturated pentafluorosulfanylated building-blocks. The synthesis of $SF_5$-substituted allylic and acrylic derivatives (Figure 16, (a)), based on the radical addition of $SF_5Cl$, will be presented. The attempts of the synthesis of original pentafluorosulfanylated homoallylic alcohols (Figure 16, (b)), by the allylation reactions of aldehydes, will be discussed as well.

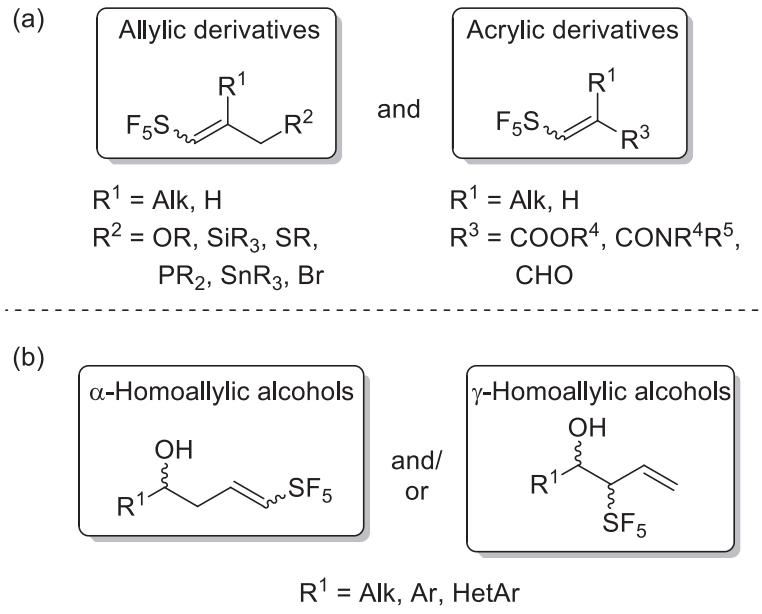



**Figure 16: Targeted pentafluorosulfanylated building-blocks.**

The next part of the project will include the development of new methods for the introduction of the $SF_5$-group into nitrogen-containing heterocycles. Our attention will be especially focused on the synthesis of $SF_5$-containing pyridines, on the one hand, and various $SF_5$-substituted saturated or unsaturated five-membered heterocycles, such as pyrrolidines,

isoxazolidines, isoxazolines or pyrazolines, on the other hand. In order to achieve our objective, two different approaches will be explored. The first one will be based on the direct fluorination of heterocyclic thiols or disulfides, leading to pentafluorosulfanylated pyridines (Figure 17, (a)). Alternatively, we will also investigate the use of previously prepared pentafluorosulfanylated building-blocks in cycloaddition reactions. A special attention will be paid to the Diels Alder reaction with oxazoles, and 1,3-dipolar cycloaddition with various dipoles, such as azomethine ylides, nitrones, nitrile oxides or diazomethane derivatives. The latter approach is very attractive, as it should allow to access a large variety of original $SF_5$-containing heterocycles in one step (Figure 17, (b)).

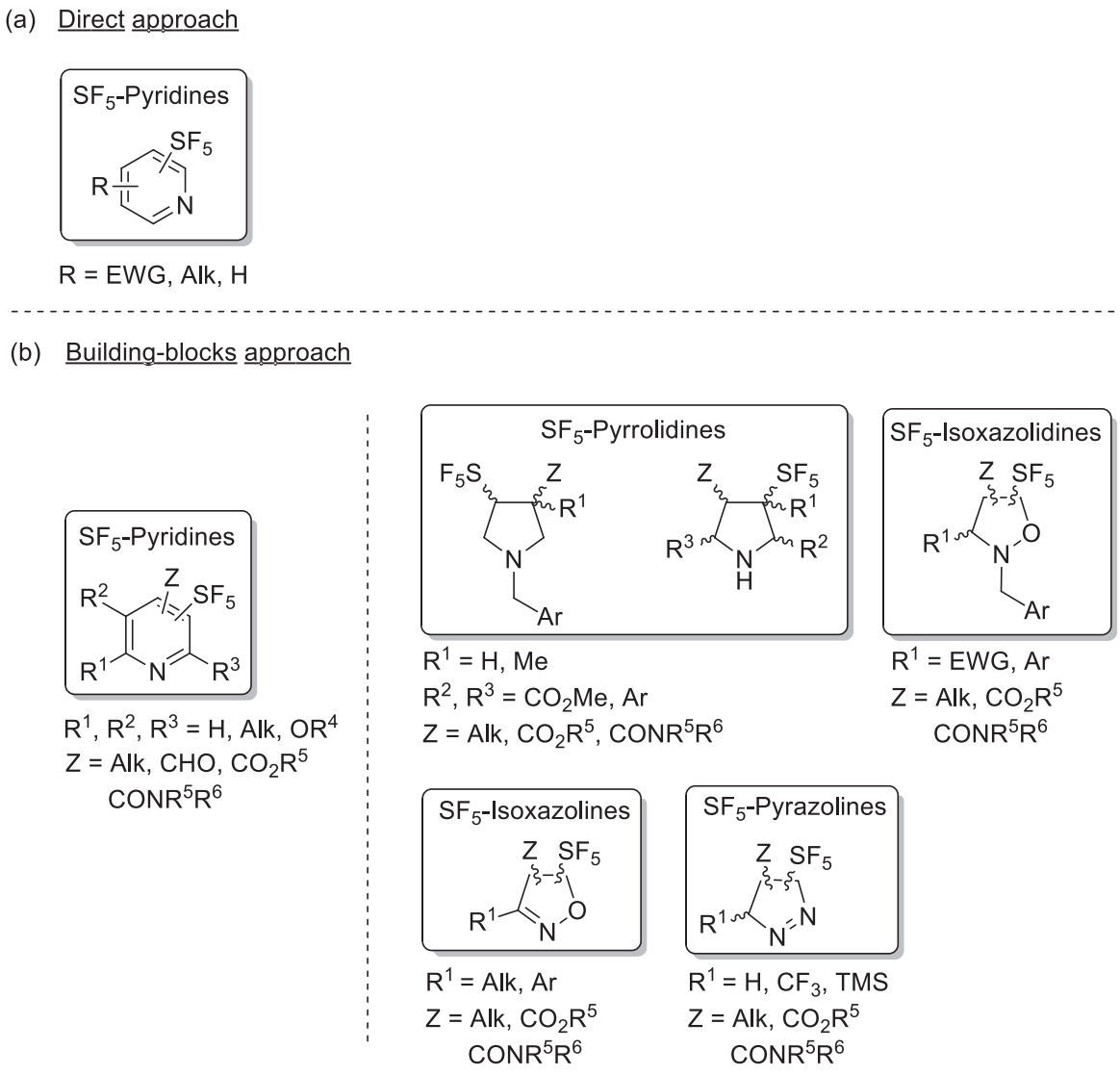
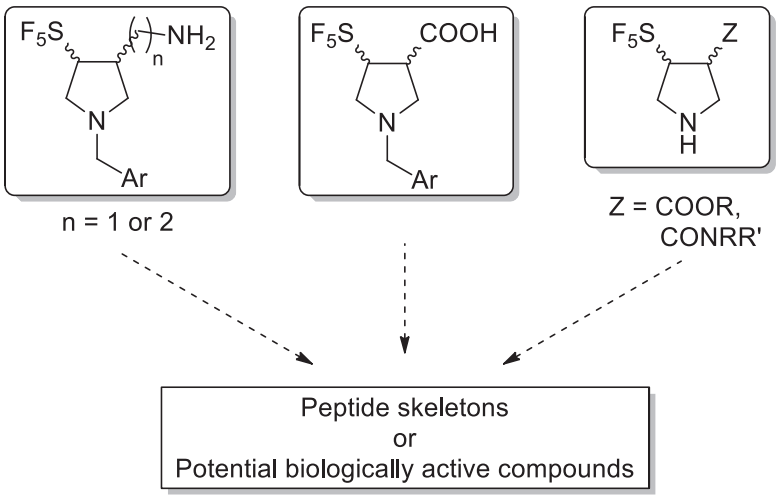



**Figure 17: Targeted pentafluorosulfaylated nitrogen-containing heterocycles.**

As part of our work on the development of new pentafluorosulfanylated heterocycles, we envisage also to perform a post-functionalization studies of some of newly synthesized pyrrolidines. For example, chemical transformations of $SF_5$-containing pyrrolidines should give us the access to the various cyclic amines or acids, which could be incorporate into more complex structures, leading to new pentafluorosulfanylated compounds of biological interest (Scheme 46).




**Scheme 46: Post-functionalizations of $SF_5$-pyrrolidines.**

# Chapter II

# Preparation of Pentafluorosulfanylated Building-Blocks

In the first part of our project, we were working on the synthesis of various pentafluorosulfanylated building-blocks. These simple compounds could be used for the introduction of $SF_5$-group into more complexed structures. First, the preparation of $SF_5$-allyl alcohols, as well as their further transformations, leading to a variety of pentafluorosulfanylated acrylic derivatives, will be presented. We will also discuss in this chapter, the first synthesis of $SF_5$-allylsilanes, and the attempts of their use in allylation reactions. The In-mediated allylations using allylic $SF_5$-bromide will be presented, as an alternative pathway leading to original $SF_5$-substituted homoallylic alcohols. Finally, we will present several attempts of $SF_5Cl$ radical additions to allylic and propargylic derivatives, which have never been presented before.

# 1. Synthesis of $SF_5$-substituted allylic and acrylic derivatives

## 1.1. Synthetic sequence leading to $SF_5$-allyl alcohols 5a-c and acetate 6

At the beginning, we focused our attention on the preparation of previously described pentafluorosulfanylated allyl alcohol **5a**[42] and its new derivatives **5b** and **5c** (Figure 18). We were interested in these versatile and quite easily accessible scaffolds, as their chemical transformations could give access to a large variety of other more complex $SF_5$-containing compounds. Previously described methodologies afforded the alcohol **5a** in 53% and 63% overall yields, starting from allyl acetate **1a** or allyl alcohol **2**,[77,42] respectively (Scheme 47).

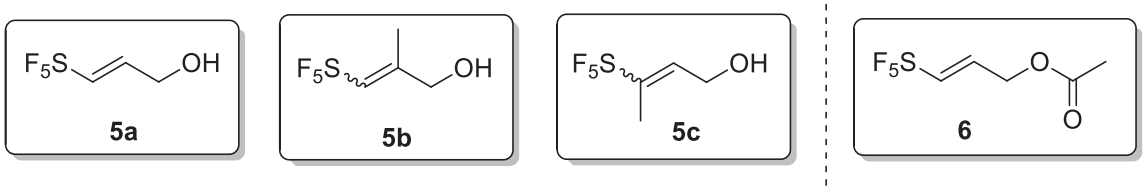
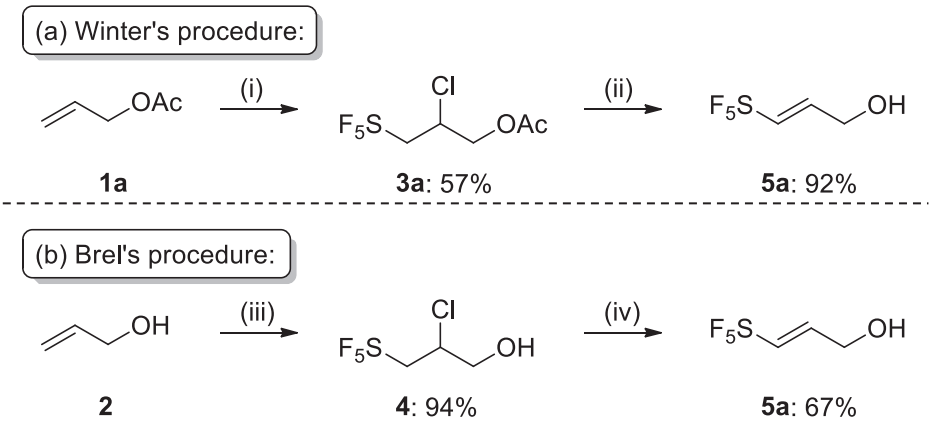



**Figure 18: $SF_5$-Alcohols 5a-c and $SF_5$-acetate 6.**

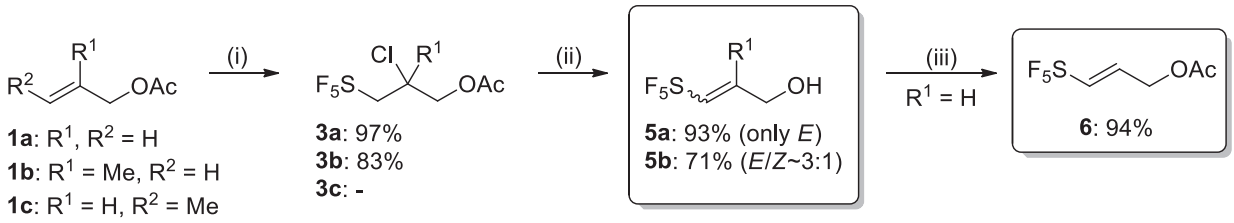
[77] Winter, R.; Gard, G. L. *J. Fluorine Chem.* **1994**, *66*, 109.




**Scheme 47: Previously described syntheses of $SF_5$-alcohol 5a.**
**Reagents and conditions : (i) $SF_5Cl$ (1.1 equiv), $CCl_3F$, 15 d, 95°C; (ii) KOH (2.2 equiv), $H_2O$, 18 h, rt or 60°C; (iii) $SF_5Cl$ (excess), hν, 2 h, rt; (iv) $KOH_{(aq.)}$ (excess), $Et_2O$, 30°C.**

In order to synthesize compound **5a**, we decided to use a modified Winter's method.[77] In the first step, we performed the radical addition of $SF_5Cl$ to the commercially available allyl acetate **1a**, according to Dolbier's procedure (Scheme 48, (i)).[43] The corresponding product **3a** was obtained in a high yield (97%). The next step was a *one pot* dehydrochlorination/ ester hydrolysis sequence, using $KOH_{(aq.)}$ solution, which afforded the desired alcohol **5a** in 93% yield as *E*-stereoisomer (Scheme 48, (ii)). The latter one was protected by acetylation with acetyl chloride, in the presence of pyridine, leading to the corresponding pentafluorosulfanylated allyl acetate **6** in 94% yield (Scheme 48, (iii)).

We then decided to extend this methodology to other $SF_5$-substituted derivatives, by engaging 2-methylprop-2-enyl acetate **1b** or but-2-enyl acetate **1c**, as starting materials. When compound **1b** was used, good yields were obtained for both steps; however, the elimination/ hydrolysis step required a higher temperature (60°C), leading to a ~3:1 mixture of *E/Z*-isomers **5b** (Scheme 48, (ii)). Unfortunately, all attempts of $SF_5Cl$ addition to crotyl acetate **1c** did not give the expected product.




**Scheme 48: Preparation of alcohols 5a,b and acetate 6.**

**Reagents and conditions: (i) $SF_5Cl$ (1.3 equiv), $Et_3B$ (0.1 equiv), hexane, 1 h, -50°C to -30°C; (ii) KOH (2.2 equiv), $H_2O$, 18 h, rt or 60°C; (iii) $CH_3COCl$ (1.1 equiv), Pyr (1.1 equiv), $CH_2Cl_2$, 6 h, 0°C.**

This two-step methodology proved to be an efficient pathway, leading to pentafluorosulfanylated allyl alcohols **5a** and **5b** in 59-90% overall yields. It could successfully replace the previously described methodologies (Scheme 47).[42a-c,77]

## 1.2. Oxidation of $SF_5$-allyl alcohols 5a and 5b to aldehyde 7 and acids 8a and 8b

Having in hands pentafluorosulfanylated allyl alcohols **5a** and **5b**, we were interested in their oxidation to the corresponding aldehyde **7** or acids **8a** and **8b** (Figure 19). These acrylic $SF_5$-derivatives could either undergo further useful transformations to afford other $SF_5$-building-blocks, or be engaged in cycloaddition reactions, to give new pentafluorosulfanylated heterocycles.

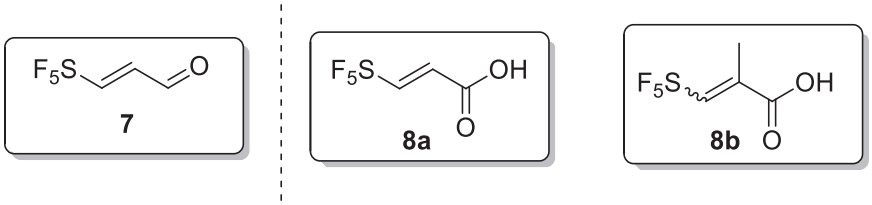
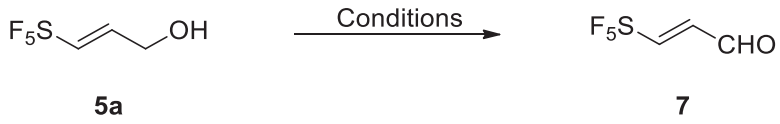



**Figure 19: $SF_5$-aldehyde 7 and $SF_5$-acrylic acids 8a and 8b.**

We have first tried to prepare pentafluorosulfanylated aldehyde **7**, by oxidizing the alcohol **5a** with cerium (IV) ammonium nitrate (CAN) in acetic acid, as previously described by Brel (Table 3, Entry 1).[42c] Unfortunately, this method did not work in our hands; the purification was difficult, and despite several attempts, only traces of the desired product were obtained. The standard Swern oxidation conditions turned out to be inefficient as well,

leading to aldehyde **7**, contaminated by the starting product **5a** and other fluorinated compounds (Table 3, Entry 2). Therefore, we decided to use silica gel supported pyridinium chlorochromate (PCC), which was reported to improve the yield and simplify the work-up and purification of the final product.[42d] Indeed, under these conditions, 3-pentafluorosulfanylpropenal **7** was isolated in 44% yield, without further optimisation (Table 3, Entry 3).

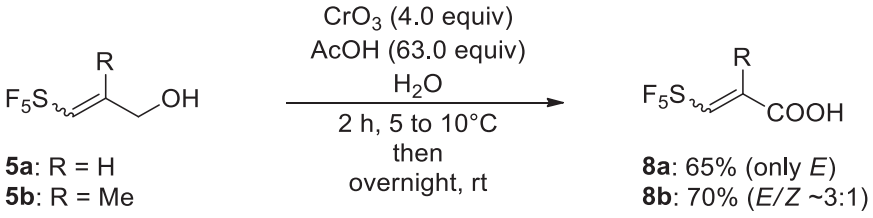



**5a** **7**

| Entry | Conditions | Yield (%) |
|---|---|---|
| 1 | CAN (6.5 equiv), 50% AcOH, 3 h, 90°C | traces |
| 2 | 1. $(COCl)_2$ (1.4 equiv), DMSO (2.8 equiv), $CH_2Cl_2$, 25 min, -75°C<br>2. $Et_3N$ (5.0 equiv), overnight, rt | traces |
| 3 | PCC/$SiO_2$ (2.0 equiv), $CH_2Cl_2$, 2.5 h, rt | 44 |

**Table 3: Screening of various conditions for the preparation of 3-pentafluorosulfanylpropenal 7.**

We then turned our attention on the synthesis of pentafluorosulfanylated acrylic acids **8a** and **8b** (Scheme 49). Oxidation of $SF_5$-allyl alcohol **5a**, using a mixture of chromium trioxide in acetic acid and water,[42b] afforded the desired product **8a** in 65% yield, as exclusively *E*-isomer. When $SF_5$-derivative **5b** was engaged as a starting material, the corresponding α-methylated acrylic acid **8b** was obtained in 70% yield. Compound **8b** was isolated as a mixture of *E/Z* isomers in a ~3:1 ratio determined by $^{19}F$ NMR, which was in accordance with the stereochemistry of the starting material **5b**.




**Scheme 49: Synthesis $SF_5$-acrylic acids 8a and 8b**

## 1.3. Synthesis of $SF_5$-acrylic esters 9,10 and amides 11,12

Having in hands pentafluorosulfanylated acrylic acids **8a,b** our aim was to prepare the corresponding esters **9,10** and amides **11,12** (Figure 20). These $SF_5$-unsaturated building-blocks were especially interesting from our point of view, as they could act as potential dieno- or dipolarophiles in cycloaddition reactions. Nevertheless, the examples of such simple compounds in the literature are quite limited and their preparation remains a challenge.

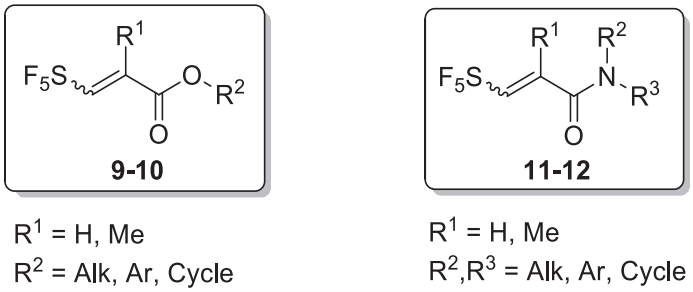
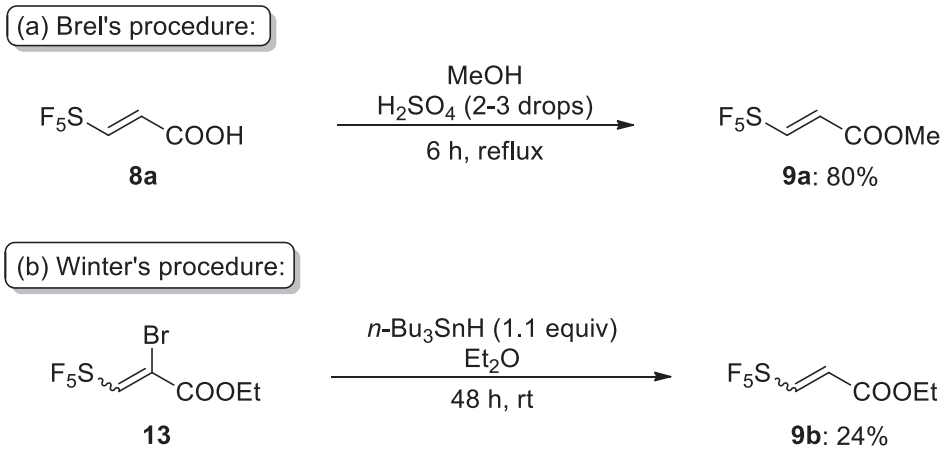



**Figure 20: Targeted $SF_5$-acrylic esters and amides.**

### 1.3.1. State of the art

The only pentafluorosulfanylated α,β-unsaturated esters reported so far in the literature, were methyl and ethyl β-$SF_5$-acrylates. Brel synthesized the compound **9a** by esterification of the corresponding $SF_5$-acid **8a**, under classical acidic conditions (Scheme 50, (a)).[42c,78] Ethyl acrylate **9b** was also prepared by Winter, from the corresponding 2-bromo derivative **13**, using tributyltin hydride (Scheme 50, (b)).[51] Nevertheless, the latter method gave the desired product **9b** in a poor yield, which was attributed to its high volatility.

[78] Brel, V. K. *Phosphorus. Sulfur. Silicon Relat. Elem.* **2011**, *186*, 1284.




**Scheme 50: Previously described syntheses of β-$SF_5$-acrylic esters 8a and 8b.**

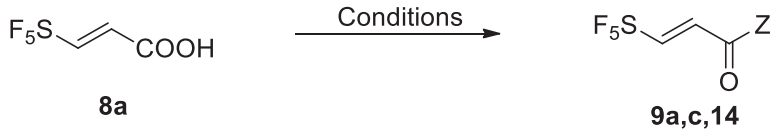
Concerning $SF_5$-substituted acrylic amides, only a few examples were mentioned in two patents. However, neither experimental procedure, nor experimental data of these compounds, were reported.[79]

### 1.3.2. Optimization and scope of esterification reactions

In order to prepare pentafluorosulfanylated acrylic esters **9** and **10**, we have first tested Brel's procedure (MeOH, $H_2SO_4$(cat.), reflux).[42c, 78] Unfortunately, this method did not work in our hands – only degradation of starting material was observed (Table 4, Entry 1). Therefore, we decided to develop our own methodology for the synthesis of $SF_5$-unsaturated esters **9** and **10**.

We started our study by using acidic (Table 4, Entry 2) or neutral (Table 4, Entry 3) conditions. Nevertheless, both of these methods were unsuccessful; the starting material was quantitatively recovered. Therefore, we decided to synthesize esters **9**,**10** via the preparation of 3-pentafluorosulfanylpropenoic acid chloride **14**, and further reacting it with alcohols. Indeed, the treatment of acid **8a** with thionyl chloride (Table 4, Entry 4) or oxalyl chloride (Table 4, Entry 5) afforded the corresponding product **14**; however, the yields of these reactions were very low (12-13%).

[79] (a) Berger, M.; Kern, C.; Eck, M.; Schroeder, J. PCT Int. Appl. 2012 WO 2,012,041,873. (b) Berger, M.; Kern, C.; Eck, M.; Schroeder, J. PCT Int. Appl. 2012 WO 2,012,041,872.



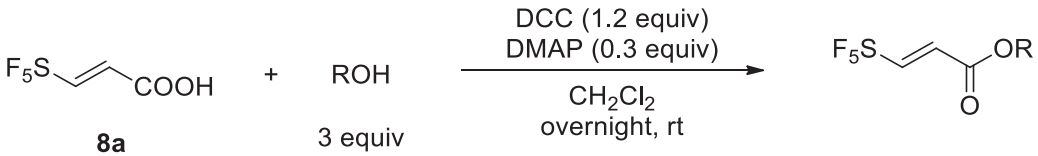

**8a** **9a,c,14**

| Entry | Conditions | Z (product) | Yield (%) |
|---|---|---|---|
| 1 | MeOH (25.0 equiv), $H_2SO_{4(cat.)}$, reflux, 6 h | OMe (**9a**) | degradation |
| 2 | BnOH (3.7 equiv), PTSA (1.6 equiv), toluene, reflux, overnight | OBn (**9c**) | 0 |
| 3 | TMS-$CHN_2$ (2.7 equiv), MeOH, 0°C, 2 h | OMe (**9a**) | 0 |
| 4 | $SOCl_2$ (5 equiv), 80°C, 5 h | Cl (**14**) | 13[a] |
| 5 | $(COCl)_2$ (2 equiv), $CH_2Cl_2$, reflux, overnight | Cl (**14**) | 12[a] |

[a] Isolated yield

**Table 4: Screening of conditions for the synthesis of esters 9a,c and chloride 14.**

Then we turned our attention to the use of coupling agents.[80] When $SF_5$-acrylic acid **8a** was treated with MeOH or *n*-BuOH, in the presence of DCC and DMAP, the corresponding esters **9a** or **9d** were detected by $^1H$ and $^{19}F$ NMR, in the reaction mixtures (Scheme 51). However, these compounds were lost during the work-up, probably due to their high volatility. In order to avoid this problem, we decided to decrease the volatility of final ester, by using benzyl alcohol as a coupling partner.




**8a**

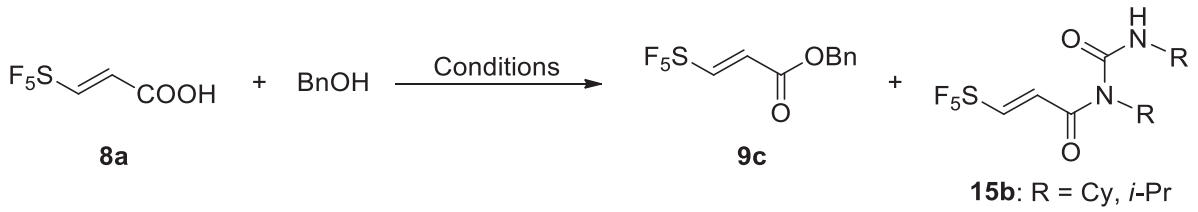
**9a[a]**: R = Me
**9d[a]**: R = *n*-Bu

**Scheme 51: Synthesis of methyl and *n*-butyl $SF_5$-acrylic esters (9a and 9d).**
**[a] The product was not isolated.**

Treating acid **8a** with benzyl alcohol, in the presence of DCC/DMAP system in $CH_2Cl_2$, led to ester **9c** in 44% isolated yield (Table 5, Entry 1). The purification of this

[80] For reviews, see : (a) Prasad, K. V. S. R. G.; Bharathi, K.; Haseena, B. B. *Int. J. Pharm. Sc. Rev. Res.* **2011**, *8*, 108. (b) Albericio, F. *Curr. Opin. Chem. Biol.* **2004**, *8*, 211.

compound was quite difficult, due to the presence of *N*-acylurea side product **15b**, whose polarity was very close to the ester's one. The formation of compound **15b** could be explained by the spontaneous rearrangement of the very reactive *O*-acylisourea intermediate **15a**, obtained from the reaction of carboxylic acid **8a** with DCC (Scheme 52). Such phenomenon was already reported in the literature, for the reactions engaging this type of coupling agents.[81] Further screening showed that replacing DCC by DIPC did not solve this problem, and in addition the yield decreased to 30% (Table 5, Entry 2). The use of $T_3P$-reagent, known for its low toxicity and easy work-up,[82] was inefficient as well, affording the desired product **9c** in only 28% isolated yield (Table 5, Entry 3). Finally, we found that addition of HOBt to previously tested DCC/DMAP system, allowed to reach 64% yield, without forming the by-product **15b** (Table 5, Entry 4). The use of HOBt enabled probably a fast capture of *O*-acylisourea intermediate **15a**, preventing its further transformation into the unreactive side-product **15b**.



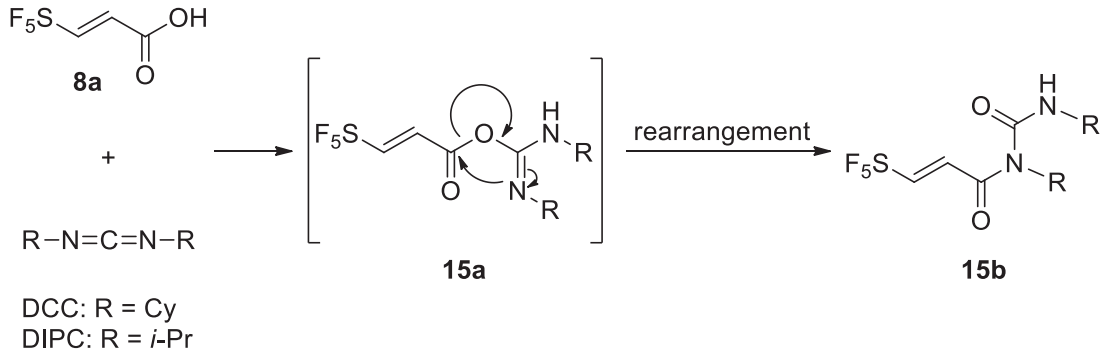

| Entry | Conditions | Yield[a] (%) |
|---|---|---|
| 1 | DCC (1.2 equiv), DMAP (0.3 equiv), $CH_2Cl_2$, rt, overnight | 44 |
| 2 | DIPC (1.3 equiv), DMAP (1.5 equiv), $CH_2Cl_2$, 0°C, overnight | 30 |
| 3 | $T_3P$ (1.5 equiv), $Et_3N$ (2.0 equiv), $CH_2Cl_2$, 0°C, 2 h | 28 |
| 4 | DCC (2.0 equiv), HOBt (1.1 equiv), DMAP (1.0 equiv), $CH_2Cl_2$, 0°C, 1 h | 64 |

[a] Isolated yield.

**Table 5: Optimization of esterification reactions.**

[81] (a) Hegarty, A. F.; McCormak, M. T.; Ferguson, G.; Roberts, P. J. *J. Am. Chem. Soc.* **1977**, *99*, 2015. (b) Rohrich, T.; Thaher, B. A.; Manicone, N.; Otto, H.-H. *Monatsh. Chem.* **2004**, *135*, 979. (c) Lauria, A.; Patella, C.; Dattolo, G.; Almerico, A.M. *J. Med. Chem.* **2008**, *51*, 2037.

[82] (a) Wissmann, H.; Kleiner, H.-J. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 133. (b) Escher, R.; Bünning, P. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 277. (c) Glauder, J. *Speciality Chemicals Magazine* **2004**, *24*, 30.




**Scheme 52: Formation of the unreactive *N*-acylurea side-product 15b.**

Having established optimal conditions, we tested the scope of esterification reactions. DCC/DMAP/HOBt system allowed the synthesis of esters **9c-g** and **10a,b** in low to moderate yields (Figure 22).[83] When the esterification was performed with primary aliphatic or allylic alcohols, the corresponding esters (**9c-f**) were obtained in up to 71% yield. Reaction with a secondary alcohol (menthol) was more difficult, affording the product **9g** in only 27% yield. When metacrylic acid **8b** was used as a starting material, the corresponding products **10a,b** were obtained as mixtures of *E/Z* isomers; their separation was possible by silica gel flash column chromatography. All of the esters were isolated as oils.

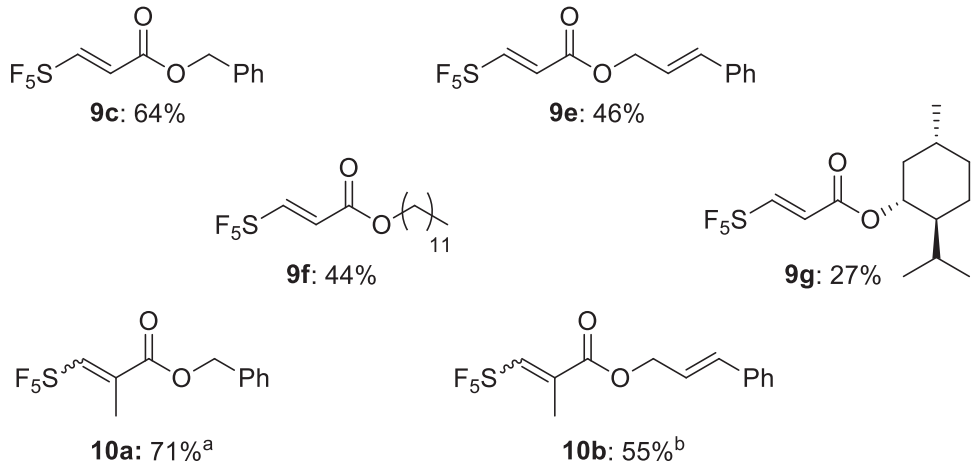
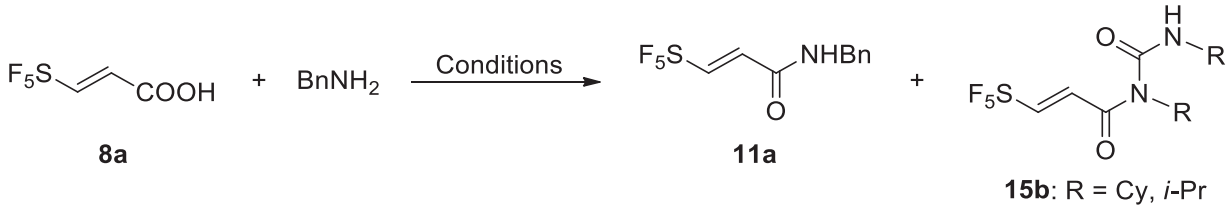



**Figure 22: Scope of pentafluorosulfanylated acrylic esters.**
**[a] *E/Z* isomers (ratio ~3:1) determined in the crude mixture. Only *E* isomer was isolated after purification.**
**[b] *E/Z* isomers (ratio ~3:1) were separated by silica gel column chromatography.**

[83] Falkowska, E.; Suzenet, F.; Jubault, P.; Bouillon, J.-P.; Pannecoucke, X. *Tetrahedron Lett.* **2014**, *55*, 4833.

### 1.3.3. Optimization and scope of amidification reactions

After preparing novel pentafluorosulfanylated esters, we focused our attention on the synthesis of analogous $SF_5$-amides. Benzylamine was selected as a model amine for the screening of amidification conditions. In the presence of DCC/DMAP system the desired product **11a** was isolated in only 15% yield, and the side-product **15b** (R = Cy) was detected as well (Table 6, Entry 1). In contrast, both DCC/HOBt and $T_3P/Et_3N$ systems (Table 6, Entries 2 and 3) turned out to be efficient, leading to the compound **11a** in high yields (85% and 93%, respectively).




| Entry | Conditions | Yield[a] (%) |
|---|---|---|
| 1 | DCC (1.5 equiv), DMAP (0.3 equiv), $CH_2Cl_2$, rt, overnight | 15 |
| 2 | DCC (2.0 equiv), HOBt (1.1 equiv), $CH_2Cl_2$, 0°C, 1 h | 85 |
| 3 | $T_3P$ (1.5 equiv), $Et_3N$ (2.0 equiv), $CH_2Cl_2$, 0°C, 2 h | 93 |

[a] Isolated yield.

**Table 6: Optimization of amidification reactions.**

With the optimal conditions in hand, we have investigated the scope of the amidification reactions. Two selected methods (DCC/HOBt and $T_3P/Et_3N$) allowed the synthesis of a variety of secondary and tertiary $SF_5$-substituted amides (Figure 21).[83] All of them were isolated as solids. DCC/HOBt procedure was generally used for the preparation of non-polar amides, affording the desired products in good to excellent yields (57-98%). Indeed, reactions proceeded smoothly with primary benzylic (product **11a,h**), aromatic (product **11b**), aliphatic (product **11c**) and allylic (product **11d**) amines, as well as with secondary ones (product **11j-l**). Chiral amino ester and amino alcohols also reacted under these conditions, leading to the corresponding products (**11f-i**) in moderate yields. Compound **12**, derived from α-methylated acrylic acid **8b**, was obtained as *E/Z* isomers mixture in the

reaction mixture; however, only the *E* isomer was isolated. For the preparation of more polar amides, such as compounds **11e,f**, $T_3P/Et_3N$ system was selected, because of the easier purification process. It is worth nothing that the latter two reactions, with 2-aminoethanol and phenylglycinol were fully chemoselective, leading only to the corresponding amides.

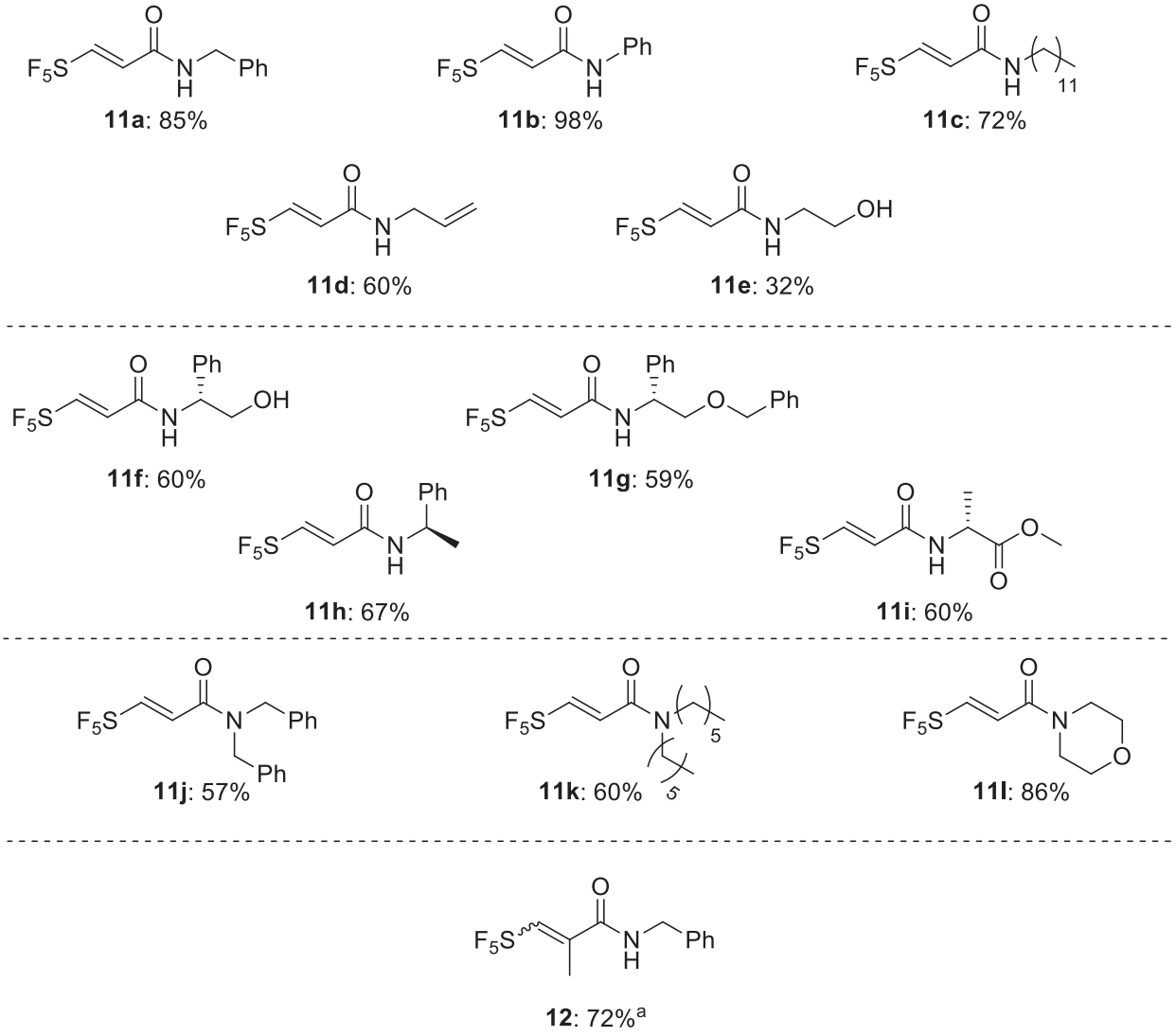



**Figure 21: Scope of pentafluorosulfanylated acrylic amides.**
**[a] *E/Z* isomers (ratio ~3:1) were separated by silica gel column chromatography.**

# 2. Attempts for the synthesis of new $SF_5$-substituted homoallylic alcohols

Continuing our studies on the synthesis of pentafluorosulfanylated building blocks, homoallylic alcohols gained our interest. These versatile compounds are considered as key building blocks in organic synthesis. Their double bond can be used in a number of synthetically useful transformations, giving the access to a large variety of functionalized compounds (Figure 23).[84]

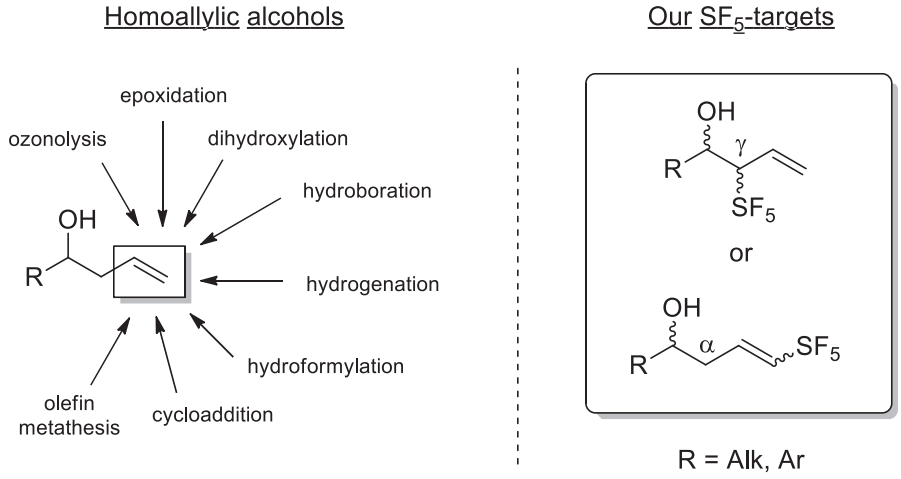
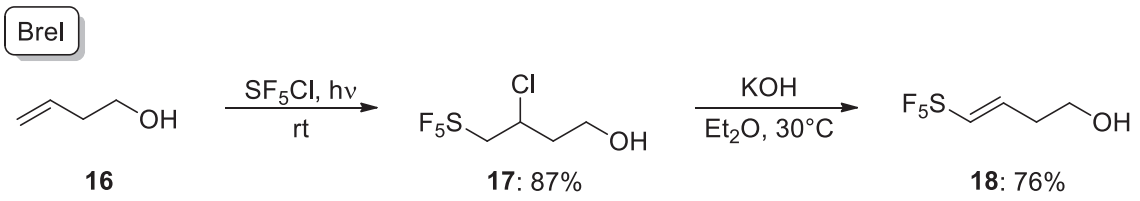



**Figure 23: Synthetic transformations of homoallylic alcohols and our $SF_5$-targets.**

Concerning homoallylic $SF_5$-alcohols, Brel reported the synthesis of *E*-4-pentafluorosulfanylbut-3-en-1-ol **18**, by a two-step procedure, including a radical addition of $SF_5Cl$ to but-3-en-1-ol **16** (Scheme 53).[42b,78] To our knowledge this is the only reported example of such compound and the synthesis of substituted $SF_5$-containing homoallylic alcohols remains a scientific challenge.




**Scheme 53: Reported synthesis of $SF_5$-homoallylic alcohol 18.**

[84] Selected examples : (a) Makita, N.; Hoshino, Y.; Yamamoto, H. *Angew. Chem., Int. Ed. Engl.* **2003**, *42*, 941. (b) Blanc, A.; Toste, F. D. *Angew. Chem., Int. Ed. Engl.* **2006**, *45*, 2096. (c) Malkov, A. V.; Barlog, M.; Miller-Potucka; Kabeshov, L. M. A.; Farrugia, L. J.; Kocovsky, P. *Chem. Eur. J.* **2012**, *18*, 6873.

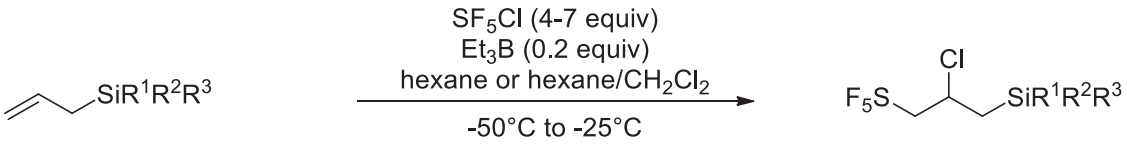
We decided therefore, to develop a methodology, giving the access to these novel pentafluorosulfanylated building-blocks. Among commonly used methods, we were particularly interested in the allylation reactions using allylsilanes, on the one hand, and the In-mediated allylation reactions of allylhalides, on the other hand.

## 2.1. Allylation reactions using new pentafluorosulfanylated allylsilanes

### 2.1.1. Preparation of $SF_5$-allylsilanes

We have first turned our attention on the synthesis of pentafluorosulfanylated allylsilanes. Taking into account that $SF_5Cl$ radical addition on terminal alkenes worked well (Scheme 48, (a)), these new $SF_5$-building blocks seemed to be relatively easy accessible, by previously used two-step procedure.

$Et_3B$-Catalyzed addition of $SF_5Cl$ to allylsilanes **19a-d**, afforded corresponding pentafluorosulfanylated products **20a-d** in good to excellent yields (Scheme 54), except for the trimethylsilyl derivative **19a**. Poor yield of the latter one was probably due to its high volatility. Compared to the reaction of allyl acetate **1a**, a large excess (4-7 equiv) of $SF_5Cl$ was necessary to fully convert allyl silanes **19a-d** into the corresponding $SF_5$-products **20a-d**.



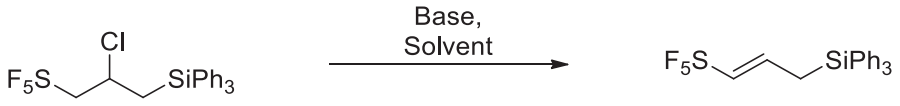

**19a**: $R^1 = R^2 = R^3 =$ Me
**19b**: $R^1 = R^2 = R^3 =$ Ph
**19c**: $R^1 = R^2 =$ Me, $R^3 =$ Ph
**19d**: $R^1 = R^2 = R^3 =$ *i*-Pr

**20a**: 14%
**20b**: 97%
**20c**: 79%
**20d**: 84%

**Scheme 54: Radical addition of $SF_5Cl$ to allylsilanes 19.**

First attempts of dehydrochlorination of trimethylsilyl derivative **20a** failed. Presuming the possible high volatility of the expected product, we selected triphenylsilyl derivative **20b** for further optimisation (Table 7). Various bases were investigated (Entries 1-6), however the desired product **21a** was exclusively detected in the presence of aqueous solution of KOH (Entry 6). When 1,4-dioxane was used as a solvent, better conversions were observed, than in

water or $Et_2O$ (Entries 6-8). Finally, we found that the base concentration played a crucial role on the efficiency of the reaction (Entry 10). Applying the optimal conditions (6.0 M KOH (8 equiv), in 1,4-dioxane, rt, 25 min.), compound **21a** was isolated in 87% yield.




**20b** **21a**

| Entry | Base | | Solvent | Temperature (°C) | Concentration (M) | Time (h) | Conversion[a] (%) |
|---|---|---|---|---|---|---|---|
| | Type | equiv | | | | | |
| 1 | $K_2CO_3$ | 5 | DMF | 50 | 1.0 | 24 | 0 |
| 2 | $Cs_2CO_3$ | 5 | 1,4-dioxane | 60 | 0.3 | 14 | 0 |
| 3 | DBU | 1 | *n*-heptane/$CH_2Cl_2$ | rt | 0.3 | 2 | desilylation |
| 4 | NaOMe | 2 | MeOH | rt | 0.6 | 2 | desilylation |
| 5 | LiOH | 10 | DMSO | rt | 1.0 | 1 | desilylation |
| 6 | KOH | 4 | $H_2O$ | 60 | 2.0 | 2 | 20 |
| 7 | KOH | 4 | $Et_2O$ | rt | 2.0 | 2 | 50 |
| 8 | KOH | 4 | 1,4-dioxane | rt | 2.0 | 45 min | 50 |
| 9 | KOH | 8 | 1,4-dioxane | rt | 2.0 | 45 min | 65 |
| 10 | KOH | 8 | 1,4-dioxane | rt | 6.0 | 25 min | 90 (87)[b] |

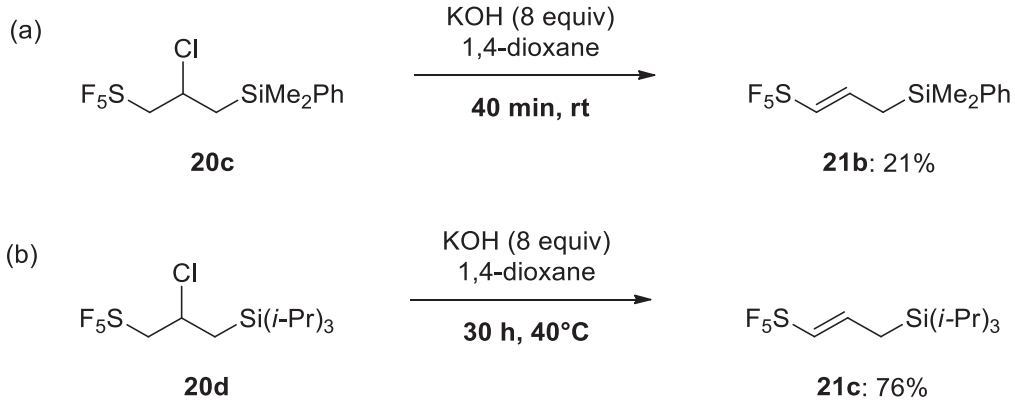
[a] According to $^{19}F$ NMR of the reaction mixture.

[b] Isolated yield.

**Table 7: Screening of conditions for the synthesis of (3-pentafluorosulfanylallyl)triphenylsilane 21a.**

The above method (Entry 10) was then extended to pentafluorosulfanylated allylsilanes bearing different silyl substituents. Elimination step turned out to be more complicated in the case of compound **20c**. Despite several attempts of optimizing reaction conditions, $SF_5$-allylsilane **21b** was isolated in only 21% yield (Scheme 55, (a)). Derivative **21c** was obtained

in 76% yield; however, longer reaction time (30 h) and heating at 40°C were necessary to fully convert the starting material (Scheme 55, (b)). It is worth nothing that compounds **21a-c** are, to our knowledge, the first examples of pentafluorosulfanylated allylsilanes reported so far.

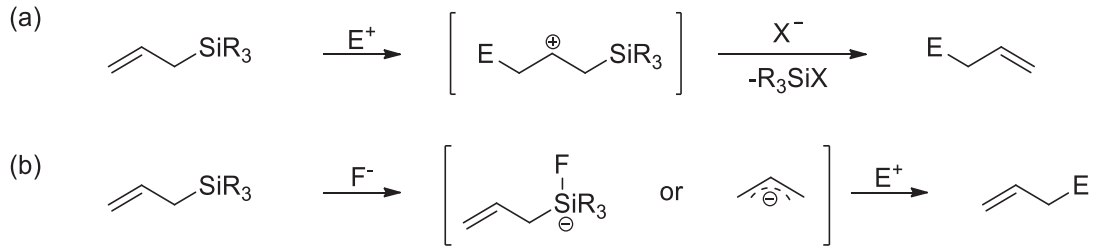



**Scheme 55: Synthesis of $SF_5$-allylsilanes 21b and 21c.**

### 2.1.2. Attempts of allylation reactions using $SF_5$-allylsilanes

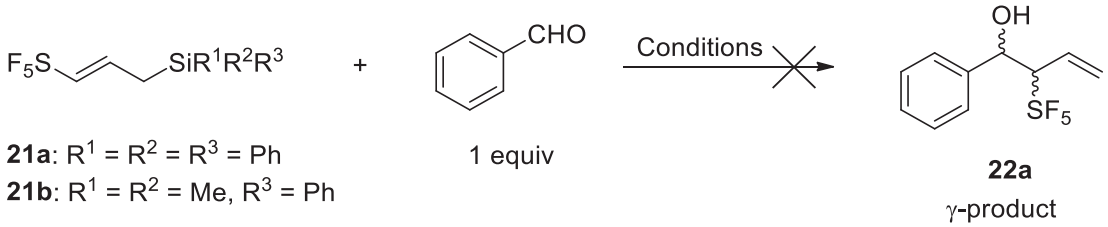
Having new pentafluorosulfanylated building-blocks **21a-c** in hand, we were investigating their reactivity. Allylsilanes are commonly known to undergo electrophilic substitution with various electrophiles. Such reactions are catalysed either by Lewis acids (Scheme 56, (a)) or by fluoride ions (Scheme 56, (b)). In the first case, only γ-products are obtained, whereas the latter reaction leads to both, γ- and α-products, depending on the substitution of allylsilanes.[85] Among frequently used electrophiles, our attention was especially attracted by reactions with aldehydes.

[85] For general reviews, see: (a) Fleming, I.; Dunoguès, J.; Smithers, R. *Org. React.* **2004**, *1948*, 57. (b) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763. (c) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207. (d) Sakurai, H. *Pure Appl. Chem.* **1982**, *54*, 1. (e) Fleming, I.; Langley, J. A. *J. Chem. Soc., Perkin Trans. 1,* **1981**, 1421.




**Scheme 56: Electrophilic substitution of allylsilanes catalysed by Lewis acids (a) or fluoride ions (b).**

We started our investigations using benzaldehyde as a model substrate, in the presence of various Lewis acids (Table 8). Unfortunately, reaction of triphenylsilyl derivative **21a** with aldehyde was unsuccessful, regardless of Lewis acid type (Entries 1-3). The starting material was completely recovered, even when the reaction mixture was heated at reflux for several hours (Entry 3). Engaging pentafluorosulfanylated allylsilane **21b** as a starting product, also did not afford the desired homoallylic alcohol **22a** (Entry 4).



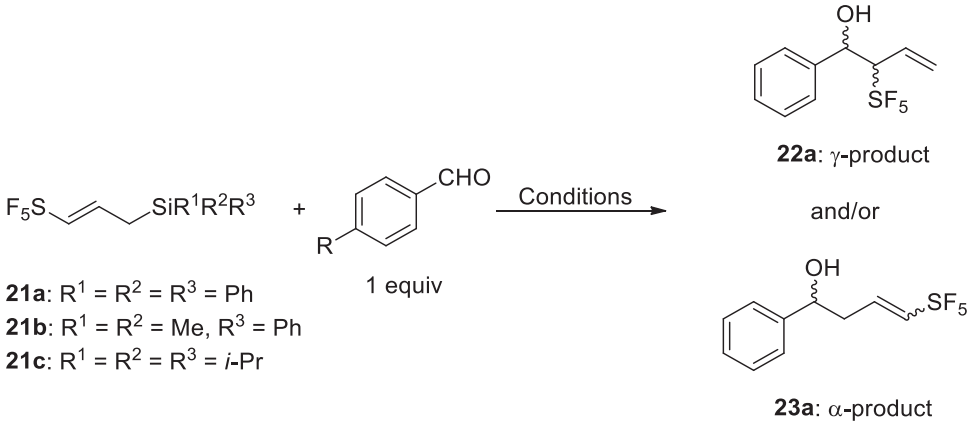

| Entry | $SF_5$-Allylsilane | Conditions | Conversion[a] (%) |
|---|---|---|---|
| 1 | **21a** | $TiCl_4$ (1 equiv), $CH_2Cl_2$, -78°C | 0 |
| 2 | **21a** | $Ti(O\text{-}i\text{-}Pr)_4$ (2 equiv), $CH_2Cl_2$, -78°C to rt | 0 |
| 3 | **21a** | $BF_3.Et_2O$ (2 equiv), $CH_2Cl_2$, -78°C to reflux | 0 |
| 4 | **21b** | $BF_3.Et_2O$ (2 equiv), $CH_2Cl_2$, -78°C to reflux | 0 |

[a] According to $^{19}F$ NMR of the reaction mixture.

**Table 8: Screening of few Lewis acids for allylation reactions of compounds 21a-b with benzaldehyde.**

We then turned our attention to the use of fluoride ion, as catalyst for the allylation reaction (Table 9). We performed reactions of allylsilanes **21a-c** with benzaldehyde in the presence of several fluoride sources, such as TBAF, TMAF or CsF. Nevertheless, all the attempts failed, giving either desilylation of starting product (Entries 1-2 and 4), or no

conversion (Entries 3 and 5-6). Use of a more electrophilic aldehyde brought no improvement (Entry 4).




| Entry | $SF_5$-Allylsilane | R | Conditions | Conversion[a] (%) |
|---|---|---|---|---|
| 1 | **21a** | H | TBAF (0.1 equiv), MS 3 Å, THF, 0°C to reflux | desilylation |
| 2 | **21a** | H | TMAF (0.1 equiv), MS 3 Å, THF, 0°C to reflux | desilylation |
| 3 | **21a** | H | CsF (0.1 equiv), MS 3 Å, THF, 0°C to reflux | 0 |
| 4 | **21a** | $CF_3$ | TBAF (0.1 equiv), MS 3 Å, THF, 0°C to reflux | desilylation |
| 5 | **21b** | H | TBAF (0.1 equiv), MS 3 Å, THF, 0°C to reflux | 0 |
| 6 | **21c** | H | TBAF (0.1 equiv), MS 3 Å, THF, 0°C to reflux | 0 |

[a] According to $^{19}F$ NMR of the reaction mixture.

**Table 9: Screening of few fluoride sources for allylation reactions of compounds 21a-c with different substituted benzaldehydes.**

Discouraged by these unsuccessful attempts, we changed our strategy to access to new $SF_5$-homoallylic alcohols. We turned our attention to In-mediated reaction, which will be discussed in the following section.

## 2.2. Indium-mediated allylation reactions

### 2.2.1. State of the art

Indium-mediated reactions are quite advantageous over other carbon-carbon bond formation methods. They are known to be low toxic, insensitive to air and oxygen at ambient temperature and they can be performed in water.[86] It has been established that in the reactions of allyl halides, under aqueous conditions, allylindium intermediate containing indium (I), was formed (Figure 24).[87]

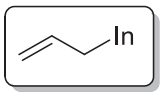
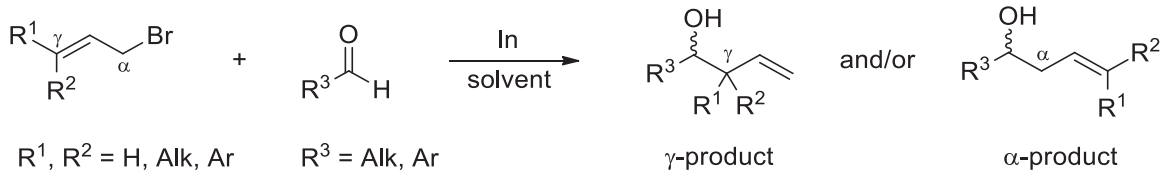



**Figure 24: Allylindium intermediate formed in the reaction under aqueous conditions.**

In-mediated allylations of aldehydes usually afford γ-branched homoallylic alcohols. However, when allyl halides bearing bulky substituents are used, α-products are often formed predominately (Scheme 57).[86] It has been also proved, that in some cases, the regioselectivity of In-mediated allylations could be dependent on the nature of solvent.[86b]




**Scheme 57: In-mediated allylations of aldehydes.**

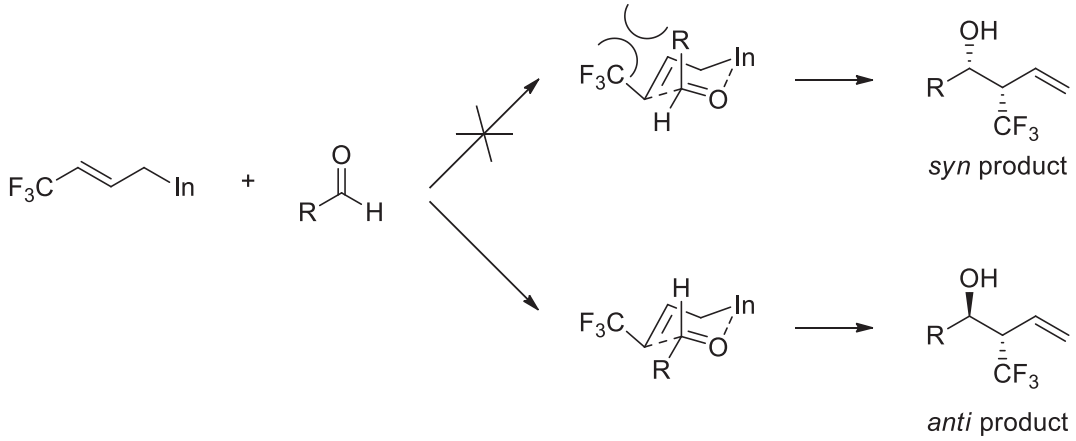
Concerning the diastereoselectivity, the steric and chelating effects of substitutents on both allylic halide and aldehyde, play a key role. For example in allylations using crotyl bromide, no diastereoselectivity was observed.[88] On the other hand, when allyl bromide bearing a bulky $CF_3$-group was used, corresponding γ-homoallyl alcohols were obtained with

[86] (a) Nair, V.; Ros, S.; Jayan, C. N.; Pillai, B. S. *Tetrahedron* **2004**, *60*, 1959. ; (b) Cheng, H.-S.; Loh, T.-P. *Pure Appl. Chem.* **2005**, *77*, 1199. (c) Postigo, A.; Nudelman, N. S. *Coord. Chem. Rev.* **2011**, *255*, 2991. (d) Lemonnier, G.; Van Hijfte, N.; Sebban, M.; Poisson, T.; Couve-Bonnaire, S.; Pannecoucke, X. *Tetrahedron* **2014**, *70*, 3123. (e) Lemonnier, G.; Poisson, T.; Couve-Bonnaire, S.; Pannecoucke, X. *Tetrahedron Lett.* **2013**, *54*, 2821.

[87] Chan, T. H.; Yang, Y. *J. Am. Chem. Soc.* **1999**, *121*, 3228.

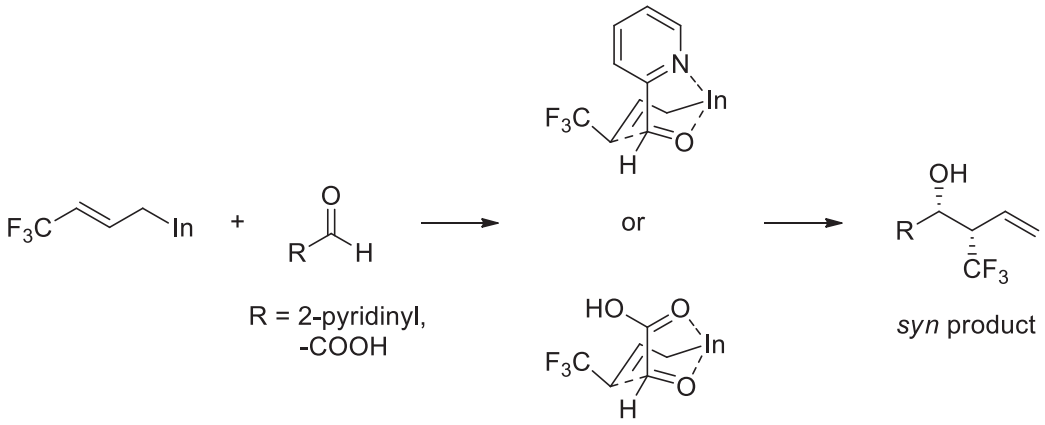
[88] (a) Li, X. R.; Loh, T.-P. *Tetrahedron: Asymmetry* **1996**, *7*, 1535. (b) Araki, S.; Ito, H.; Butsugan, Y. *J. Org. Chem.* **1988**, *53*, 1831. (c) Isaac, M. B.; Chan, T.-H. *Tetrahedron Lett.* **1995**, *36*, 8957.

excellent *anti* diastereoselectivity, for most aldehydes.[89] Such behaviour was explained by the six-membered ring transition state (Zimmerman-Traxler), in which both $CF_3$ and R substitutents adopted equatorial positions, leading to *anti* product (Scheme 58).




**Scheme 58: Diastereoselectivity of In-mediated allylations using $CF_3$-allyl bromide.**

In contrast, when 2-pyridinylcarboxaldehyde or glyoxylic acid were engaged in the allylation reactions with 4-bromo-1,1,1-trifluorobut-2-ene, *syn* adducts were predominately formed. It would indicate that in these cases, 2-pyridinyl or COOH group adopted an axial position in the six-membered transition state, probably due to the chelatation with indium, as depicted on Scheme 59.[89]

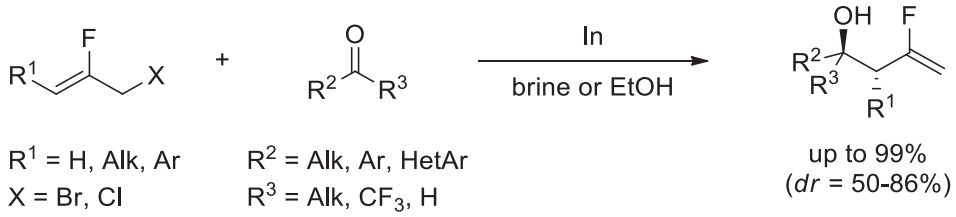



**Scheme 59: S*yn*-diastereoselective In-mediated allylations using $CF_3$-allyl bromide.**

Quite recently, a straightforward access to fluorinated homoallylic alcohols by means of an indium mediated allylation reaction was developed in our laboratory.[86d,e] The method

[89] (a) Loh, T.-P.; Li, X. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 980. (b) Loh, T.; Li, X. *Tetrahedron Lett.* **1997**, *38*, 869. (c) Loh, T.; Li, X. *Eur. J. Org. Chem.* **1999**, *8*, 1893.

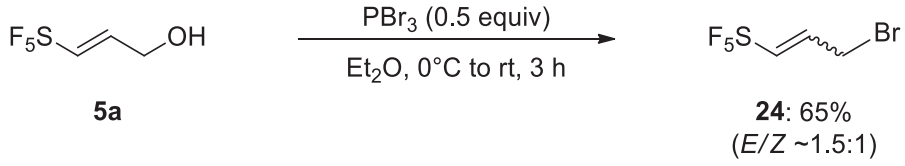
was applied to a broad range of highly functionalized aldehydes and ketones, providing the γ-addition products in good yields and moderate to good diastereoselectivities (Scheme 60). Encouraged by these results, we desired to apply this methodology to the $SF_5$-allylic derivatives.




**Scheme 60: In-mediated synthesis of fluorinated homoallylic alcohols.**

### 2.2.2. Preparation of $SF_5$-allyl bromide 24

Since allyl bromides are known to be more reactive than the corresponding chlorides, under In-mediated conditions, we were interested in the preparation of a new $SF_5$-substituted allyl bromide **24**. Compound **24** was easily synthesized from previously prepared pentafluorosulfanylated allyl alcohol **5a**. Indeed, when the latter one was treated with $PBr_3$ in $Et_2O$, the expected product **24** was formed within 3 h, as a mixture of *E/Z* isomers (ratio ~1.5:1) (Scheme 61). Because of its high volatility, it was not possible to completely remove the solvent after the work-up; therefore, bromide **24** was used for further reactions as an ethereal solution.




**Scheme 61: Synthesis of pentafluorosulfanylated allyl bromide 24.**

### 2.2.3. Optimisation of allylation conditions

The reactivity of pentafluorosulfanylated allyl bromide **24** toward *p*-chlorobenzaldehyde, in the presence of indium, was then investigated (Table 11). As In-

mediated reactions of fluorinated allylic derivatives were already successfully developed in our laboratory,[86d,e] we decided to begin our study using our optimal conditions. When an excess of $SF_5$-allyl bromide **24** was used in the presence of equimolar quantity of indium, in water, two regioisomeric pentafluorosulfanylated allylic alcohols, **22a** and **23a**, were formed in 30% overall yield (Entry 1). It is worth noting that α-product **23a** was obtained as a mixture of *E/Z* isomers (~1:1), regardless the stereochemistry of the starting bromide **24**; whereas, the γ-product **22a** was formed as exclusively *anti* diastereoisomer. In addition to the expected homoallylic alcohols, another pentafluorosulfanylated compound was observed. According to $^{19}F$ and $^{1}H$ NMR, this compound could be the $SF_5$-allylindium intermediate **25** (Figure 25).

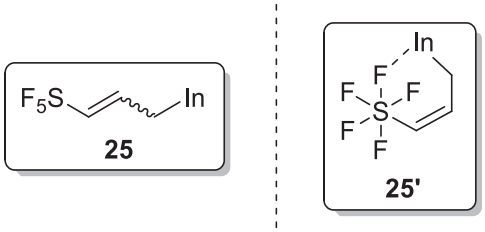



**Figure 25: Possible pentafluorosulfanylated allylindium intermediates.**

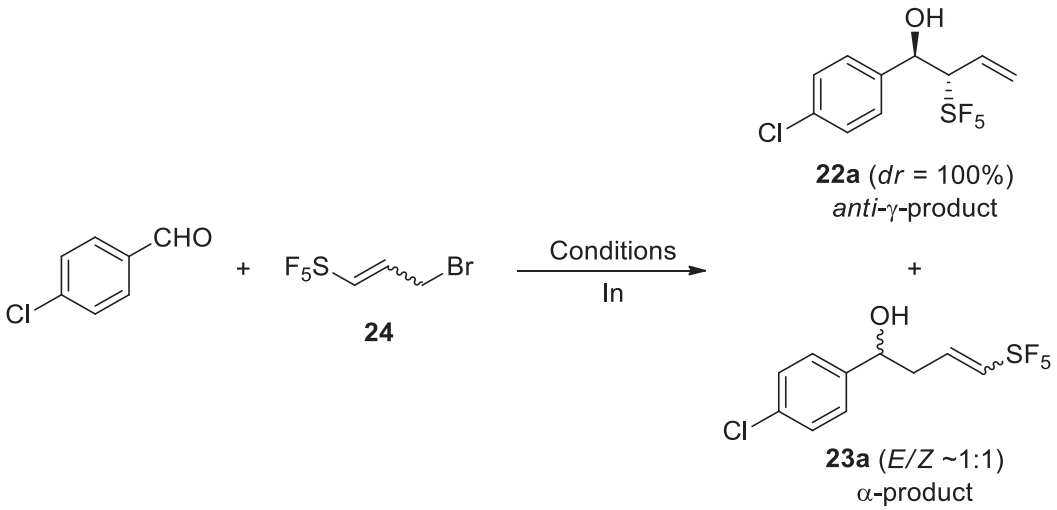
When the reaction was performed at higher temperature (50°C), α-isomer **23a** was selectively obtained; nevertheless, the yield of reaction was lower (Entry 2). Increasing the reaction time to 3 days brought no significant improvement, compared to the standard time (18 h, Entry 1), but interestingly, the ratio of γ- and α-products (**22a** and **23a**) changed from ~2:1 to ~1:5, respectively (Entry 3). In contrary, when we shortened the reaction time to 9 h, the desired products were obtained in only 13% yield (Entry 4). In all these attempts, the formation of product **25** was observed as well.

We then performed several reactions, using other solvents than water. Unfortunately, all attempts of allylation in brine (Entry 5), EtOH (Entry 6) or EtOH/$H_2O$ mixture (Entry 7) brought no improvement. In brine or EtOH/$H_2O$, the desired $SF_5$-homoallylic alcohols were formed in low yields. In EtOH, the product **25** was exclusively obtained. In order to confirm the possible formation of $SF_5$-allylindium intermediate **25**, we removed the ethanol from the reaction mixture and we added *p*-chlorobenzaldehyde in water to the residue. However, we observed no conversion into the corresponding homoallylic alcohols. As possible explanation, we could assume that fluorine atoms in the allylindium species could coordinate

to the indium (**25'**, Figure 25), rendering this intermediate unreactive. Unfortunately, we were not able to confirm this theory.

Keeping in mind that $SF_5$-allyl bromide **24** represents a greater value than the aldehyde, we decided to check the influence of the ratio of starting materials. To our delight, we found that the excess of pentafluorosulfanylated derivative **24** was not required. In fact, a slightly better yield was obtained, when the reagents were used in equimolar quantities (Entry 1 vs. Entry 8). On the other hand, using an excess of aldehyde led to products **22a** and **23a** in 27% overall yield (Entry 9), but the purification turned out to be difficult, due to similar polarities of *p*-chlorobenzaldehyde and γ-homoallylic alcohol **22a**.

Despite varying reaction parameters, we were not able to significantly improve the allylation yield. *p*-Chlorobenzaldehyde was converted in 90% in the best of case (Entry 1); nevertheless, the overall yield remained quite low (30%), which could be explained by the presence of the side product **25**. Therefore, we selected the Entry 8 conditions as the optimal ones.




| Entry | Stoichiometry (equiv) | | | Solvent | Temperature (°C) | Time (h) | Yield (%)[b] | | |
|---|---|---|---|---|---|---|---|---|---|
| | Aldehyde | **24** | In | | | | Total | γ-**22a** | α-**23a** |
| 1[a] | 1 | 2 | 2 | $H_2O$ | rt | 18 | **30** | 19 | 11 |
| 2[a] | 1 | 2 | 2 | $H_2O$ | 50 | 18 | **19** | 0 | 19 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 3[a] | 1 | 2 | 2 | $H_2O$ | rt | 72 | **32** | 5 | 27 |
| 4[a] | 1 | 2 | 2 | $H_2O$ | rt | 9 | **13** | 7 | 6 |
| 5[a] | 1 | 2 | 2 | $NaCl_{(aq.,sat.)}$ | rt | 18 | **21** | 16 | 5 |
| 6[a] | 1 | 2 | 2 | EtOH | rt | 18 | **0** | 0 | 0 |
| 7[a] | 1 | 2 | 2 | EtOH/$H_2O$ (1:1) | rt | 18 | **6** | 5 | 1 |
| 8[a] | 1 | 1 | 1 | $H_2O$ | rt | 18 | **34** **(31)**[c] | 21 (19)[c] | 13 (12)[c] |
| 9[a] | 2 | 1 | 1 | $H_2O$ | rt | 18 | **27** | 20 | 7 |

[a] Compound **25** or **25'** was observed in the crude mixture.

[b] Determined by $^1H$ NMR on the crude mixture using 1,1,2,2-tetrachloroethane as internal standard.

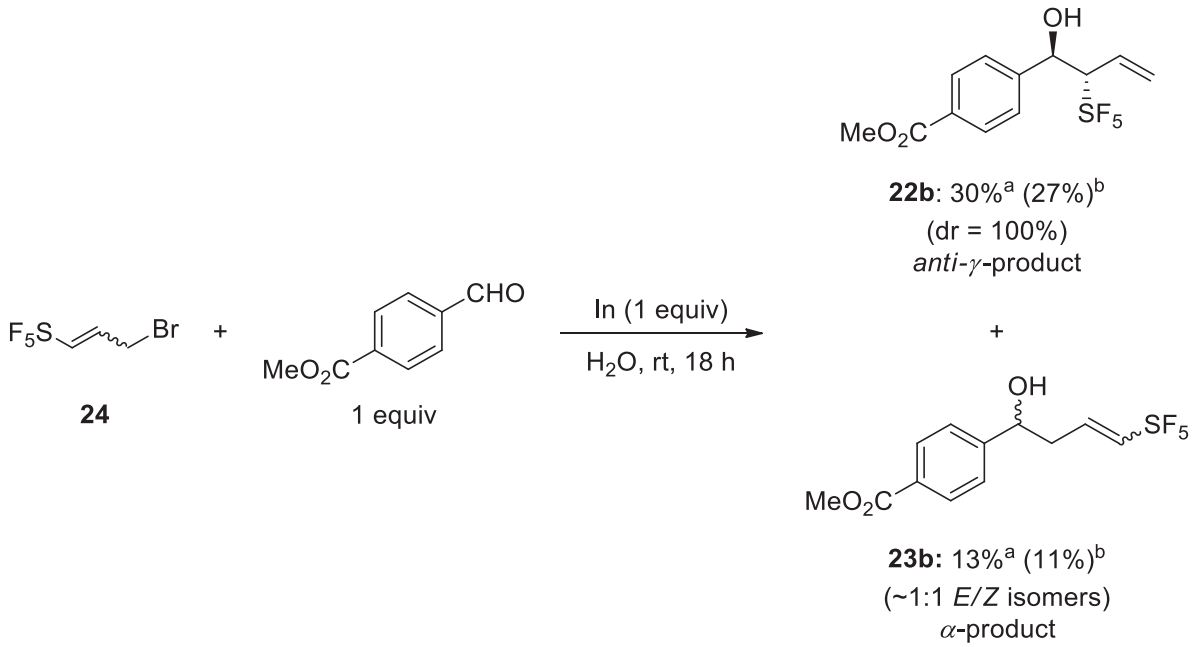
[c] Isolated yield.

**Table 11: Optimisation of In-mediated allylation conditions.**

### 2.2.4. Scope of allylation reaction

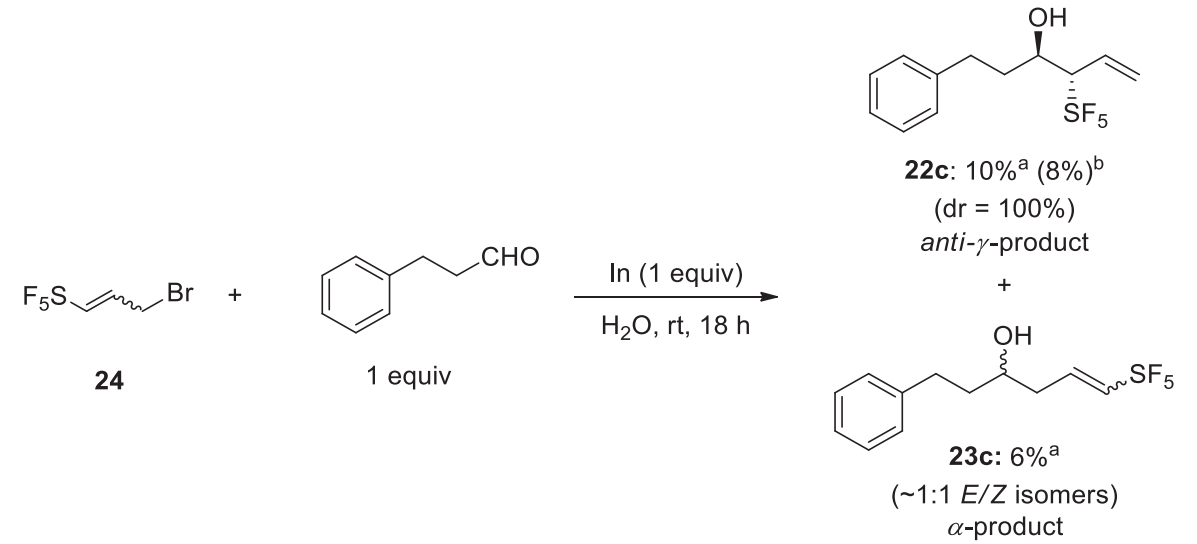
Taking into account the previous results (Table 11), we performed the reaction of $SF_5$-allyl bromide **24** with other aldehydes. For this purpose, we selected methyl 4-formylbenzoate and 3-phenylpropanal as partners.

To our delight, reaction of methyl 4-formylbenzoate with bromide **24**, using our "optimized" conditions (Table 11, Entry 8), led to the corresponding $SF_5$-homoallylic alcohols **22b** and **23b**, in 43% NMR yield (Scheme 62). After the purification, we obtained the separated α- and γ-products, in 11% and 27% yields, respectively. As in the case of compounds **22a** and **23a**, γ-product **22b** was obtained as only *anti* diastereoisomer, whereas α-homoallylic alcohol **23b** showed a mixture of *E/Z* isomers (~1:1).




**Scheme 62: In-mediated allylation of methyl 4-formylbenzoate.**
**[a] $^1$H NMR yields; [b] Isolated yields.**

When the aliphatic type aldehyde (3-phenylpropanal) was used in the In-mediated reaction with allyl bromide **24**, the NMR yield of the corresponding products was much lower – 10% for the γ-product **22c** and only 6% for the α-product **23c** (Scheme 63). After purification, only the γ-alcohol **22c** was recovered, in 8% yield, as *anti* diastereoisomer. The loss of α-product **23c** during the purification was probably due to its minor proportion in the crude mixture.




**Scheme 63: In-mediated allylation of 3-phenylpropanal.**

**[a] $^1$H NMR yields; [b] Isolated yields.**

Having synthesized several new pentafluorosulfanylated homoallylic alcohols, we stopped our investigations of In-mediated allylations at this stage. We then focused our attention on the preparation of novel $SF_5$-allylic and $SF_5$-propargylic building-blocks.

# 3. Attempts for the synthesis of new $SF_5$-allylic and propargylic derivatives

Encouraged by the efficiency of previously performed radical additions of $SF_5Cl$ to unsaturated compounds, we decided to extend this reaction to several other derivatives. Our idea was to introduce the $SF_5$-substituent on a functionalized double or triple bond, and to study further transformation into more complexe pentafluorosulfanylated derivatives.

## 3.1. Attempts for the radical addition of $SF_5Cl$ to functionalized allylic derivatives

In the context of our research for new $SF_5$-building blocks, we were interested in the synthesis of several pentafluorosulfanylated allylic derivatives, depicted on Figure 26. These versatile compounds could undergo a number of interesting chemical transformations. For example, allyl sulfides could be easily oxidized into the corresponding allylsulfones, the latter ones being versatile synthetic intermediates (for example, use in Julia's olefination).[90] On the other hand, allyl stannanes are known to undergo Lewis acid catalysed allylations (similar as previously presented for allylsilanes), leading to the homoallylic alcohols.[86b,c,91] Finally, allylphosphines can be transformed into the corresponding allylphosphine oxides, which are key intermediates for the preparation of biologically active compounds.[92]

[90] (a) Fernández, I.; Khiar, N. *Chem. Rev.* **2003**, *103*, 3651. (b) Kowalski, P.; Mitka, K.; Ossowska, K.; Kolarska, Z. *Tetrahedron* **2005**, *61*, 1933. (c) Wojaczynska, E.; Wojaczynski, J. *Chem. Rev.* **2010**, *110*, 4303.
[91] Gung, B. W. *Org. React.* **2004**, *64*, 1.
[92] (a) Brunner, H.; Limmer, S. *J. Organomet. Chem.* **1991**, *417*, 173. (b) Brunner, H.; Limmer, S. *J. Organomet. Chem.* **1991**, *413*, 55. (c) Nicolaou, K. C.; Maligres, P.; Shin, J.; de Leon, E.; Rideout, D. *J. Am. Chem. Soc.* **1990**, *112*, 7825. (d) Haynes, R. K.; Loughlin, W. A.; Hambley, T. W. *J. Org. Chem.* **1991**, *56*, 5785.

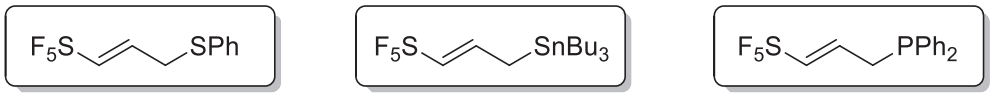
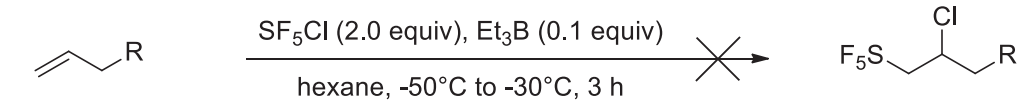



**Figure 26: Targeted $SF_5$-substituted functionalized allylic compounds.**

In order to prepare new functionalized pentafluorosulfanylated building-blocks, we envisaged to use our two-step sequence, including $SF_5Cl$ addition to allylic compounds, and then subsequent HCl elimination. We performed several attempts of the radical addition of $SF_5Cl$ to compounds **26-28**, under $Et_3B$-catalyzed conditions (Scheme 64). Nevertheless, in all cases we recovered quantitavely the starting materials. Discouraged by these unsuccessful attempts, we turned our attention to the synthesis of pentafluorosulfanylated acetylenic derivatives.




**26**: R = SPh
**27**: R = $SnBu_3$
**28**: R = $PPh_2$

**Scheme 64: Attempts of $SF_5Cl$ radical addition to allylic derivatives 26-28.**

## 3.2. Attempts for the synthesis of new $SF_5$-propargylic derivatives

Our attention was attracted by pentafluorosulfanylated propargyl alcohol and the corresponding acid (Figure 27, (a)). Using our previously developed methodology[83], acid could give also access to a new class of $SF_5$-propargylic esters and amides (Figure 27, (b)). Even if the radical addition of $SF_5X$ to acetylene derivatives was already reported,[36,43,47-52] to our knowledge, above mentioned propargylic derivatives remain unknown.

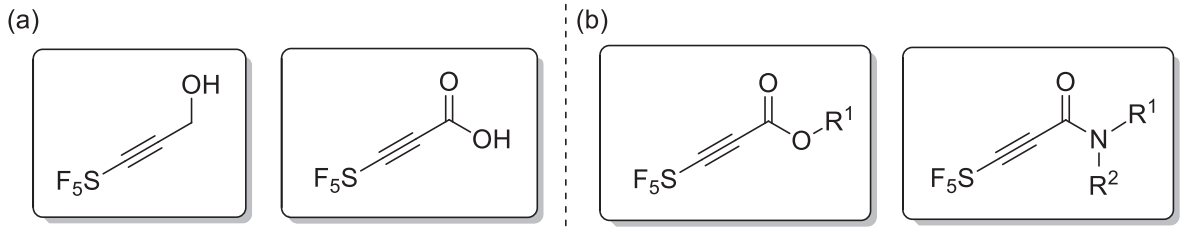
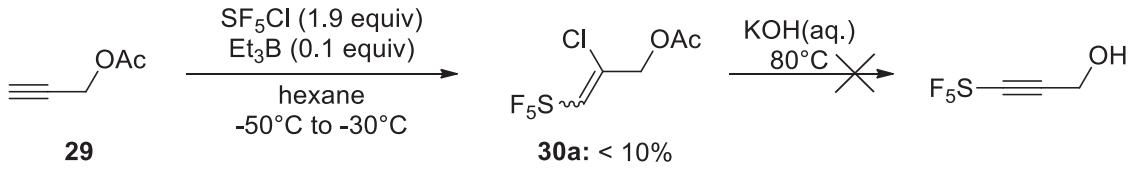



**Figure 27: Targeted pentafluorosulfanylated propargylic derivatives.**

In order to access to new $SF_5$-derivatives, we have first performed $Et_3B$-catalyzed addition of $SF_5Cl$ to propargylic acetate **29** (Scheme 65). After several hours, the starting material was fully converted; however, a complex mixture of at least five $SF_5$-products was obtained, according to $^{19}F$ NMR spectra. The presence of so many $SF_5$-compounds in the reaction crude could be probably explained by the possible formation of different regioisomeric 1:1 and 2:1 adducts, as proposed on Figure 28. Compounds **31a-d** would be obtained via the addition of the propagating radical intermediate to a second molecule of propargylic acetate **29**. Moreover, all of proposed products (**30a,b** and **31a-d**) could be formed as mixtures of diastereoisomers. The purification of the crude mixture by a flash chromatography, afforded a fraction containing mainly two $SF_5$-compounds (probably the stereoisomers **30a**), contaminated by other adducts (yield < 10%).




**Scheme 65: Attempt for the synthesis of $SF_5$-propargyl alcohol.**

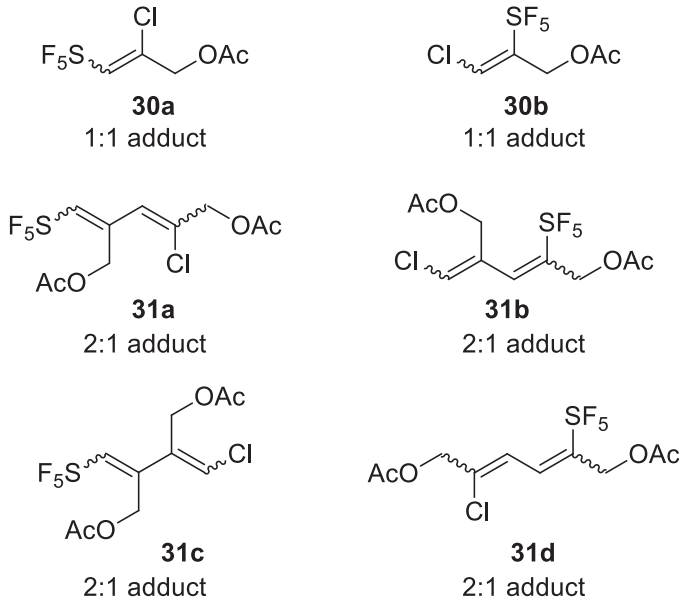



**Figure 28: Possible products of the $SF_5Cl$ addition to propargyl acetate 29.**

We next performed few attempts of dehydrochlorination/ester hydrolysis of compound **30a**; nevertheless, all of them failed (Scheme 65). When the acetate **30a** was heated at 80°C in aqueous solution of KOH, for several hours, only deacetylation reaction was observed. Using LiOH in DMSO at room temperature resulted in the degradation of the starting material **30a**. Given the complexity of $SF_5Cl$ addition to propargyl acetate **29**, and the failure of subsequent elimination step, we abandoned this approach.

# 4. Conclusion

A variety of unsaturated pentafluorosulfanylated building-blocks was synthesized. We have successfully developed a new methodology leading to $SF_5$-acrylic esters **9**,**10** and amides **11**,**12**, which are promising synthetic intermediates. Several pentafluorosulfanylated allyl silanes (**21a-c**) were synthesized as well; however, these novel building-blocks showed to be unreactive in allylation reactions of aldehydes. As an alternative, few $SF_5$-homoallyl alcohols (**22a-c** and **23a-c**) were synthesized in low to moderate yields, by the In-mediated allylations of aldehydes, using the $SF_5$-allyl bromide **24**.

Unfortunately, all attempts of the synthesis of new more functionalized $SF_5$-allylic building-blocks failed, as the derivatives **26-28** showed to be unreactive toward $SF_5Cl$, under $Et_3B$-catalyzed conditions. On the other hand, the reaction of propargyl acetate **29** with $SF_5Cl$ afforded a complex mixture of products. Concerning the latter result, the use of $SF_5Br$ instead of $SF_5Cl$ could be to be an interesting alternative, as the brominated reagent is known to be a better partner in the radical additions to triple bond.[43]

# Chapter III

# Synthesis of Pentafluorosulfanylated Heterocycles

The aim of this part of the project was to develop efficient methodologies for the synthesis of new pentafluorosulfanylated nitrogen-containing aromatic or non-aromatic heterocycles. Our discussion will begin by the attempts of the synthesis of $SF_5$-pyridines. Both, reactions of dipyridyl disulfides according to Umemoto procedure,[57] as well as Diels-Alder approach, using our previously prepared $SF_5$-building blocks, will be presented. We will further investigate the synthesis of various five-membered heterocycles, by 1,3-dipolar cycloaddition reactions of the $SF_5$-building blocks. Synthesis of pentafluorosulfanylated pyrrolidines, isoxazolidines, isoxazolines or pyrazolines, as well as further post-functionalisation of these new $SF_5$-heterocycles, will be discussed.

# 1. Attempts for the synthesis of $SF_5$-pyridines

The pyridine ring is one of the most common scaffolds present in alkaloids, drugs and agrochemicals.[93] According to the literature, on the beginning of our project, the reports concerning the synthesis of $SF_5$-pyridines were very limited (see Chapter I, section 3.3.2.2.).[71a,b] As a consequence, we first focused our attention on the development of a new and efficient methodology for the direct introduction of $SF_5$-group into these interesting heterocycles (Figure 29).

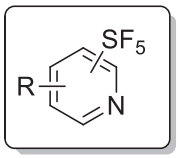


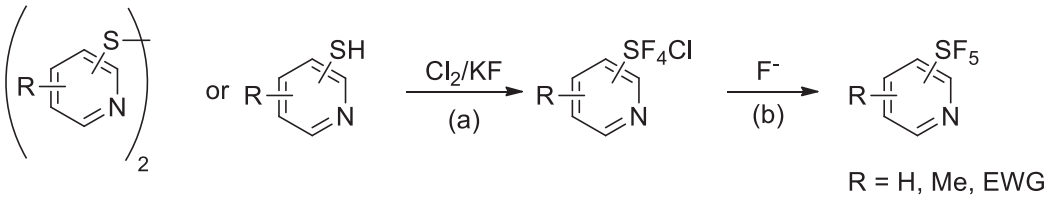

**Figure 29: Targeted pentafluorosulfanylated pyridines.**

## 1.1. Direct fluorination approach

Our first idea was to use the Umemoto procedure, previously developed for the aromatic compounds.[57] We envisaged a two-step synthesis, including chlorination of a

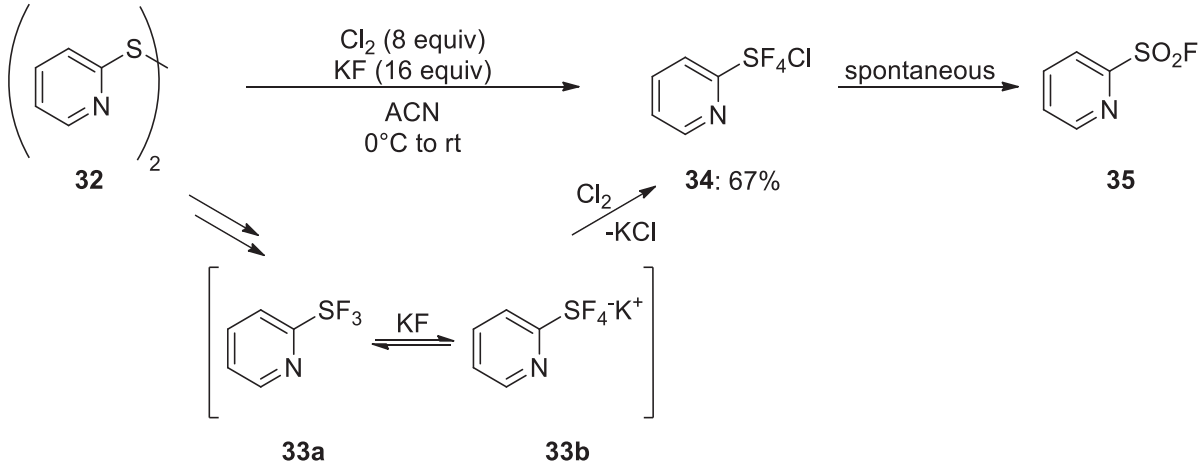
[93] (a) Qiao, J. X. in *Heterocyclic Chemistry in Drug Discovery*; Li, J. J. (Ed.), Wiley, Hoboken, 2013; p. 175. (b) Kiuru, P.; Yli-Kauhaluoma, J. in *Heterocycles in Natural Product Synthesis*; Majumdar, K.; Chattopadhyay, S. K. (Eds.), Wiley-VCH, Weinheim, 2011; p. 267.

heteroaromatic thiol or disulfide (Scheme 66, (a)), followed by the reaction with a fluoride, to afford the desired $SF_5$-pyridines (Scheme 66, (b)).



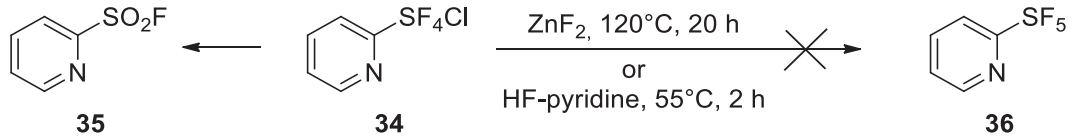

**Scheme 66: Direct fluorination approach to $SF_5$-pyridines.**

We have first performed the chlorination-fluorine substitution step, using the commercially available 2,2'-dithiodipyridine **32**, as starting material. The reaction was performed in acetonitrile (ACN), from 0°C to room temperature (Scheme 67). The $^{19}F$ NMR analysis on the beginning of the reaction, confirmed the formation of the $SF_3$-intermediate **33a**. The latter one was fully converted into the corresponding $SF_4Cl$-pyridine **34**, within 24 h. Nevertheless, a quick spontaneous decomposition of compound **34** into the corresponding 2-fluorosulfonyl derivative **35** was observed. Therefore, the $SF_4Cl$-pyridine **34** had to be stored in Teflon reactor, under the argon atmosphere; nevertheless, its stability remained very low.




**Scheme 67: Chlorination-fluorine substitution of disulfide 32.**

In the next step, two different fluoride sources were tried: $ZnF_2$ at 120°C, or HF-pyridine at 55°C. Nevertheless, all the attempts to transform compound **34** into the desired pentafluorosulfanylated pyridine **36** failed, because of the quick decomposed of the starting material **34** (Scheme 68).



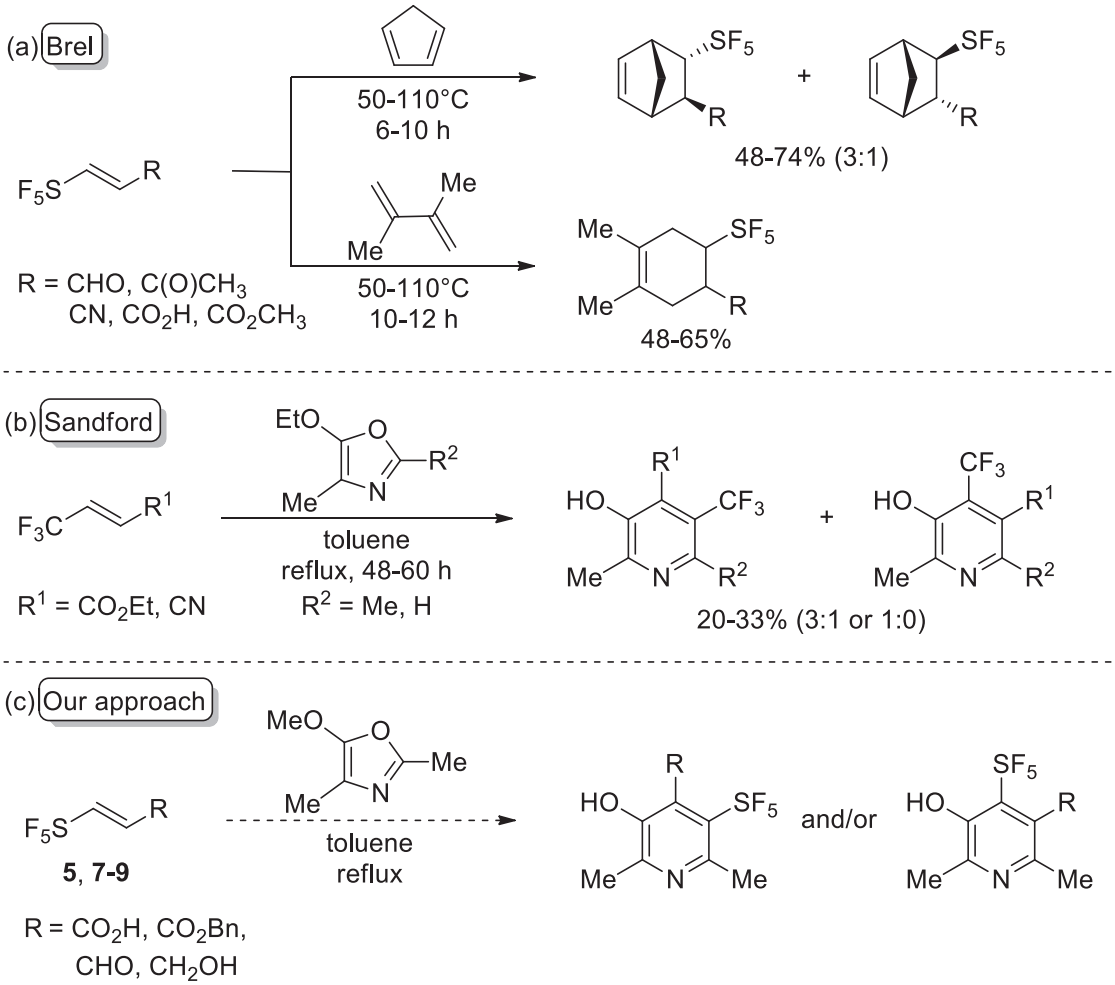

**Scheme 68: Attempts of transformation of compound 34 into $SF_5$-pyridine 36.**

In the meantime, Dolbier's group succeeded to synthesize pentafluorosulfanylated pyridine derivatives, using the Umemoto procedure.[70] The transformation of the $SF_4Cl$-pyridine into the corresponding pentafluorosylfanylated derivative was carried out in the presence of silver (I) fluoride; nevertheless, this methodology was limited only to 2-$SF_5$-pyridine derivatives. Thus, we turned our attention to the Diels-Alder reactions of our $SF_5$-building-blocks, which could give us the access to other $SF_5$-substituted pyridines.

## 1.2. Diels-Alder approach

Pentafluorosulfanylated acrylic derivatives were already reported to efficiently undergo Diels-Alder reactions with 1,3-dienes (Scheme 69, (a)).[42b,c] On the other hand, Sandford *et al.*[94] developed cycloaddition reactions of $CF_3$-substituted electron-deficient alkenes with 5-ethoxyoxazoles, leading to the corresponding trifluoromethylated pyridines (Scheme 69, (b)). Thus, we decided to apply Sandford's conditions in the reactions of our pentafluorosulfanylated building-blocks, expecting the formation of original $SF_5$-pyridines (Scheme 69, (c)).

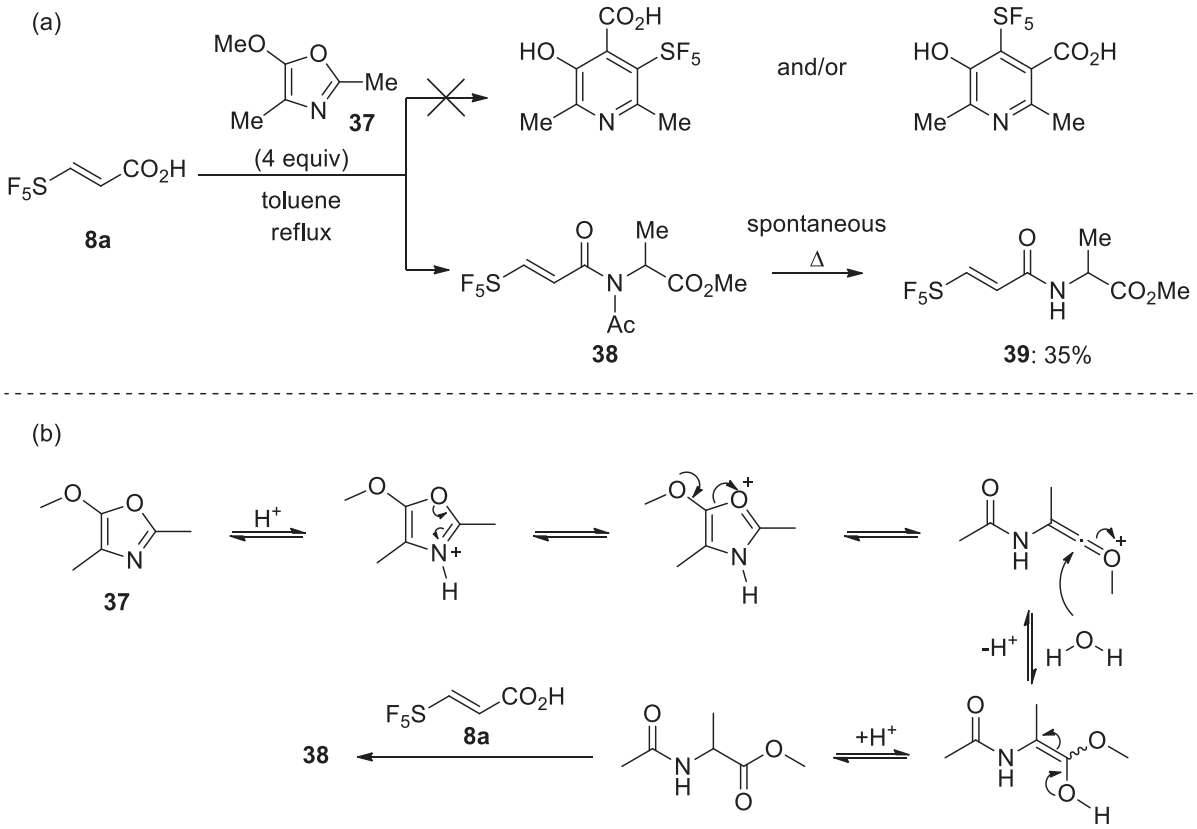
[94] Sandford, G.; Wilson, I.; Timperley, C. M. *J. Fluorine Chem.* **2004**, *125*, 1425.




**Scheme 69: Diels-Alder cycloadditions of $CF_3$- and $SF_5$-acrylic derivatives.**

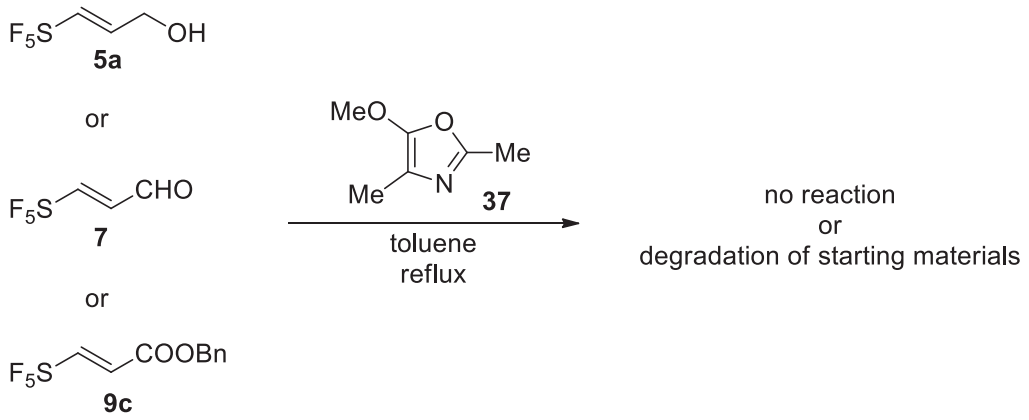
The cycloaddition partner, 2,4-dimethyl-5-methoxyoxazole **37**, was prepared from L-alanine methyl ester hydrochloride, via a two-step procedure, according to the literature.[95] Its reaction with $SF_5$-acrylic acid **8a** in refluxing toluene led to the formation of two pentafluorosulfanylated compounds (conversion ~90%). According to $^{19}F$ NMR, the ratio of these two products varied, depending on the reaction time. After the purification of the crude, we found out that instead of the pentafluorosulfanylated pyridines, the products **38** and **39** were formed (Scheme 70, (a)). This could be explained by the possible mechanism depicted on Scheme 70, (part (b)). The opening of the oxazole ring would lead to the formation of N-acetyl alanine, which could further react with $SF_5$-acide **8a**. The product **38** could then undergo a subsequent spontaneous deacetylation at high temperature, leading to the $SF_5$-amide **39** (Scheme 70, (a)).

[95] Griesback, A. G.; Bondock, S.; Lex, J. *J. Org. Chem.* **2003**, *68*, 9899.




**Scheme 70: Reaction of $SF_5$-acid 8a with oxazole 37 (a) and the proposed mechanism of oxazole-ring opening (b).**

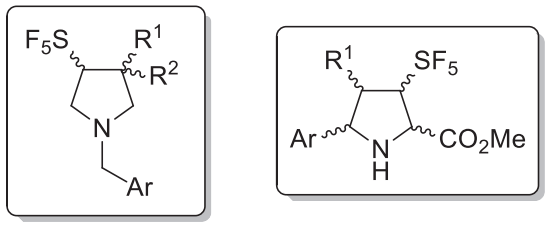
We have then tested Diels-Alder reactions of other $SF_5$-building blocks, such as alcohol **5a**, aldehyde **7**, or ester **9c**; nevertheless, none of them showed interesting reactivity toward oxazole **37** (Scheme 71). Either no reaction or degradation of starting materials was observed. Given these discouraging results, we turned our attention to the synthesis of other original non-aromatic $SF_5$-heterocycles.




**Scheme 71: Attempts of Diels-Alder cycloaddition of building-blocks 5a, 7 or 9c with oxazole 37.**

# 2. Synthesis of $SF_5$-pyrrolidines

Our next goal was to synthesize new pentafluorosulfanylated pyrrolidines (Figure 30), using our previously prepared $SF_5$-building blocks. In this section, we will briefly summarize general information about pyrrolidines and its mono-, and di-fluorinated, as well as trifluoromethylated derivatives. Few selected examples of the synthesis of such compounds will be also presented. We will next discuss 1,3-dipolar cycloadditions of our $SF_5$-unsaturated compounds with various dipoles, leading to the first pentafluorosulfanylated pyrrolidines. Finally, the last subsection will be devoted to the post-functionalisations of these novel non-aromatic heterocycles.




$R^1$ = $COOR^3$, $CONR^3R^4$ ; $R^2$ = Me, H

**Figure 30: Targeted pentafluorosulfanylated pyrrolidines.**

## 2.1. Pyrrolidines – a brief state of the art

### 2.1.1. Biological activities

Among five-membered heterocycles, pyrrolidines are widely encountered in natural products, pharmaceuticals or organocatalysts.[96] Several examples of pyrrolidine-containing active compounds are depicted on Figure 31. This five-membered heterocycle is present in natural products, such as L-proline, (-)-kainic acid or cocaine. Some common drugs, such as Captopril (for the treatment of hypertention), Sulpiride (for the treatmet of mental disorders) or Vildagliptin (for the treatment of type 2 diabetes), contain a pyrrolidine motif as well.

[96] (a) Michael, J.-P. *Nat. Prod. Rep.* **2008**, *25*, 139. (b) Han, M.-Y.; Jia, J.-Y.; Wang, W. *Tetrahedron Lett.* **2014**, *55*, 784. (c) Wurdemann, M.; Christoffers, J. *Tetrahedron* **2014**, *70*, 4640.

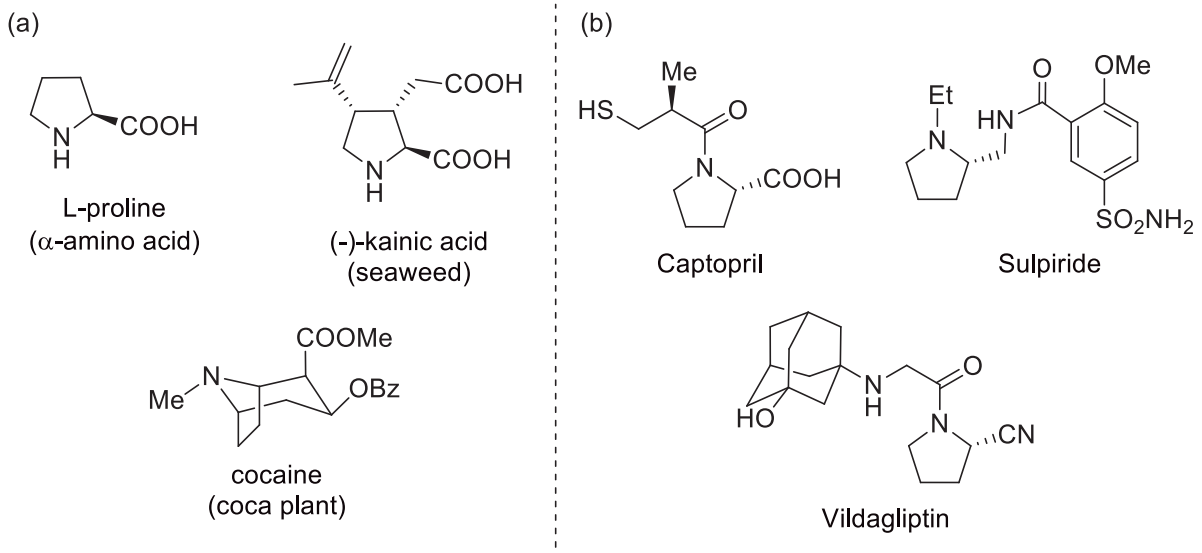



**Figure 31: Some examples of pyrrolidine-containing natural products and drugs on the market.**

In the literature, a particular attention has been given to the fluorine-containing pyrrolidines. It has been reported that the presence of one or more fluorine atoms on the pyrrolidine ring, could strongly affect the properties of those biologically active compounds.[97] For example, DNA gyrase inhibitors, containing fluorinated pyrrolidines (Figure 32), showed an enhanced antibacterial activity, improved pharmaco-kinetic properties and, in some cases, a lower genotoxicity, compared to the parent non-fluorinated analogues.[97a-c]

[97] (a) Li, Q.; Chu, D. T. W.; Claiborne, A.; Cooper, C. S.; Lee, K. M.; Raye, K.; Berst, K. B.; Donner, P.; Wang, W.; Hasvold, L.; Fung, A.; Ma, Z.; Tufano, M.; Flamm, R.; Shen, L. L.; Baranowski, J.; Nilius, A.; Alder, J.; Meulbroek, J.; Marsh, K.; Crowell, D.; Hui, Y.; Seif, L.; Melcher, L. M; Henry, R.; Spanton, S.; Faghih, R.; Klein, L. L.; Tanaka, S. K.; Plattner, J. J. *J. Med. Chem*. **1996**, *39*, 3070. (b) Li, Q.; Wang, W.; Berst, K. B.; Claiborne, A.; Hasvold, L.; Raye, K.; Tufano, M.; Nilius, A.; Shen, L. L.; Flamm, R.; Alder, J.; Marsh, K.; Crowell, D.; Chu, D. T. W.; Plattner, J. J. *Bioorg. Med. Chem. Lett.*. **1998**, *8*, 1953. (c) Asahina, Y.; Takei, M.; Kimura, T.; Fukuda, Y. *J. Med. Chem*. **2008**, *51*, 3238. (d) Edmondson, S. D.; Mastracchio, A.; Mathvink, R. J.; He, J.; Harper, B.; Park, Y.-J.; Beconi, M.; Di Salvo, J.; Eiermann, G. J.; He, H.; Leiting, B.; Leone, J. F.; Levorse, D. A.; Lyons, K.; Patel, R. A.; Patel, S. B.; Petrov, A.; Scapin, G.; Shang, J.; Roy, R. S.; Smith, A.; Wu, J. K.; Xu, S.; Zhu, B.; Thornberry, N. A.; Weber, A. E. *J. Med. Chem*. **2006**, *49*, 3614. (e) Ammirati, M. J.; Andrews, K. M.; Boyer, D. D.; Brodeur, A. M.; Danley, D. E.; Doran, S. D.; Hulin, B.; Liu, S.; McPherson, R. K.; Orena, S. J.; Parker, J. C.; Polivkova, J.; Qiu, X.; Soglia, C. B.; Treadway, J. L.; VanVolkenburg, M. A.; Wilder, D. C.; Piotrowski, D. W. *Bioorg. Med. Chem. Lett.* **2009**, *19,* 1991.

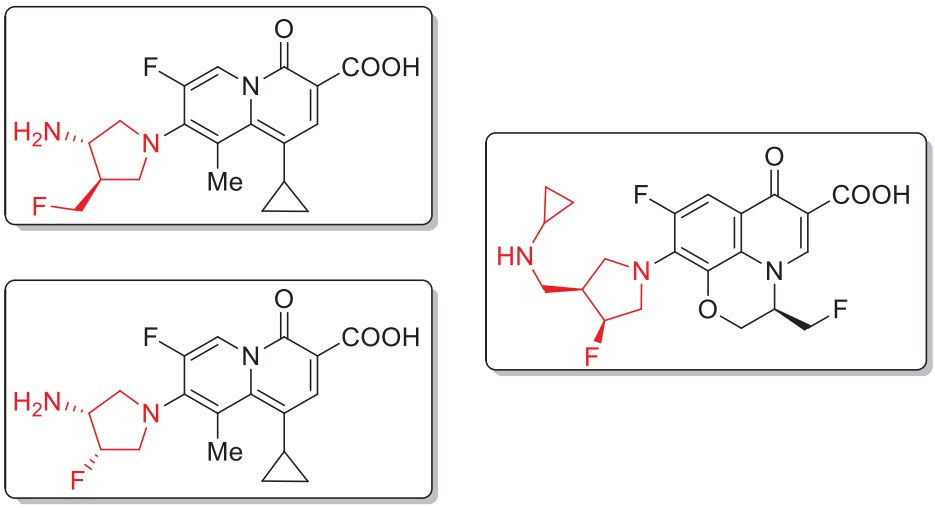



**Figure 32: DNA gyrase inhibitors, containing fluorinated pyrrolidines.**

Another significant example of difluoropyrrolidine-containing active compounds, are the dipeptidyl peptidase IV inhibitors, for the treatement of type 2 diabetes mellitus, depicted in Figure 33. An increased selectivity, an improvement of pharmaco-kinetic profile, as well as an excellent activity ($IC_{50}$= 6.3-12.9 nM), have been demonstrated for these derivatives.[97d,e]

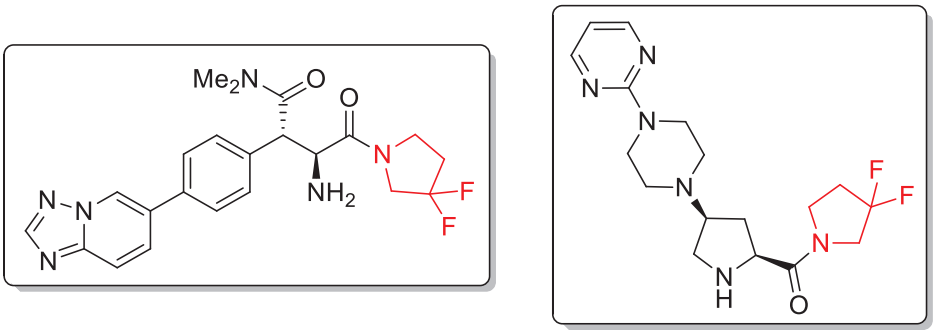


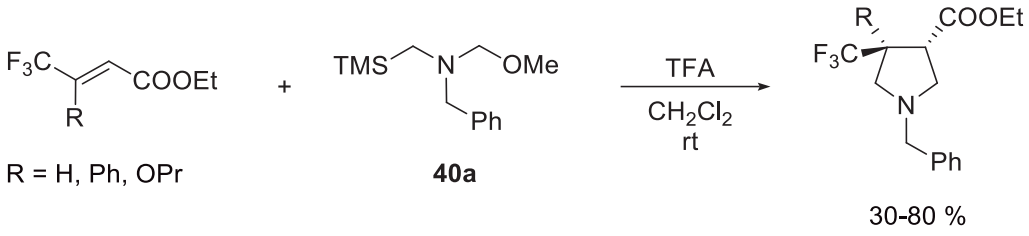

**Figure 33: Dipeptidyl peptidase IV inhibitors, containing difluorinated pyrrolidines.**

### 2.1.2. Selected syntheses of trifluoromethylated pyrrolidines

From the synthetic viewpoint one of the most commonly used methods for the construction of pyrrolidine ring, is the 1,3-dipolar cycloaddition of alkenes with azomethine ylides. Engaging mono- or di-fluoroolefins in such reactions led to the pyrrolidines, bearing one or two fluorine atoms in position 3, as in above presented active compounds. Reviewing

the literature, we were especially interested in the reactions, engaging trifluoromethylated acrylates, as the reactivity of those compounds could be quite close to the one of our pentafluorosulfanylated derivatives.

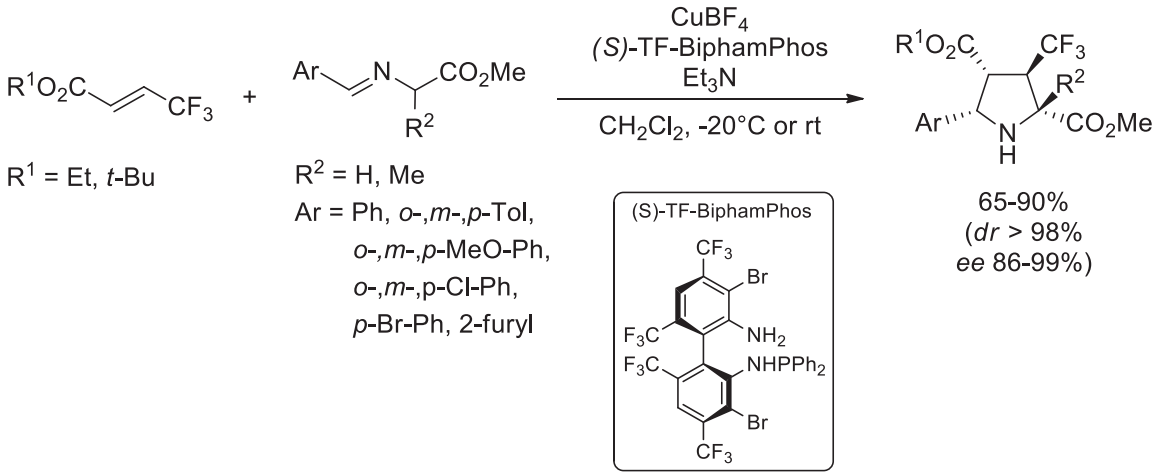
N-(Methoxymethyl)-N-[(trimethylsilyl)methyl]-N-benzylamine **40a**[98] has been used as azomethine ylide precursor in many 1,3-dipolar cycloadditions.[99] Such a reaction was successfully applied to 4,4,4-trifluorocrotonate derivatives, leading to racemic 3-$CF_3$-substituted pyrrolidines in good yields (70-80%), except for 3-propyloxy derivative (R = OPr), which was obtained in 30% yield (Scheme 72). The *E*-configuration of the starting $CF_3$-acrylates was conserved, leading diastereoselectively to the corresponding *trans*-pyrrolidines.[100]




**Scheme 72: 1,3-Dipolar cycloaddition of 4,4,4-trifluorocrotonates with azomethine ylide precursor 40a.**

Subsequently, a catalytic enantioselective approach for the synthesis of trifluoromethylated pyrrolidines, was developed.[101] The reactions of 4,4,4-trifluorocrotonates with imino ester derivatives, in the presence of $CuBF_4$/*(S)*-TF-BiphamPhos complex, were reported to afford trifluoromethylated pyrrolidines, in high yields and excellent stereoselectivities. It is worth noting that only one regioisomeric product was formed in such reactions (Scheme 73).

[98] (a) Kraus, G. A.; Nagy, O. J. *Tetrahedron* **1985**, *41*, 3537. (b) Padwa, A.; Haffmanns, G.; Tomas, M. *J. Org. Chem.* **1984**, *49*, 3314.
[99] Harwood, L. M.; Vickers, R. J. in *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A.; Pearson, W. H. (Eds.), Wiley, New York, 2003; p. 169.
[100] (a) Bégué, J.-P.; Bonnet-Delpon, D.; Lequeux, T. *Tetrahedron Lett.* **1993**, *34*, 3279. (b) Bégué, J.-P.; Bonnet-Delpon, Chennoufi, A.; Ourévitch, M.; Ravikumar, K. S.; Rock, A. H. *J. Fluorine Chem.* **2001**, *107*, 275.
[101] (a) Li, Q.-H.; Tong, M.-C.; Li, J.; Tao, H.-Y.; Wang, C.-J. *Chem. Commun.* **2011**, *47*, 11110. (b) Li, Q.-H.; Xue, Z.-Y.; Tao, H.-Y.; Wang, C.-J. *Tetrahedron Lett.* **2012**, *53*, 3650.

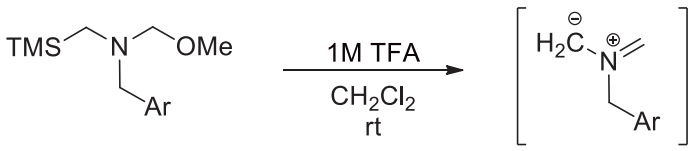



**Scheme 73: $CuBF_4$/*(S)*-TF-BiphamPhos-catalyzed 1,3-dipolar cycloadditions of 4,4,4-trifluorocrotonates with imino esters.**

Taking into account the attractiveness of fluorine-containing pyrrolidines, we decided to investigate 1,3-dipolar cycloaddition reactions of our new pentafluorosulfanylated building-blocks with azomethine ylides. As the properties of the $SF_5$-group are considered to be close to those of the trifluoromethyl one, we were expecting the formation of new $SF_5$-pyrrolidines, by applying conditions previously reported in $CF_3$-series.[100,101]

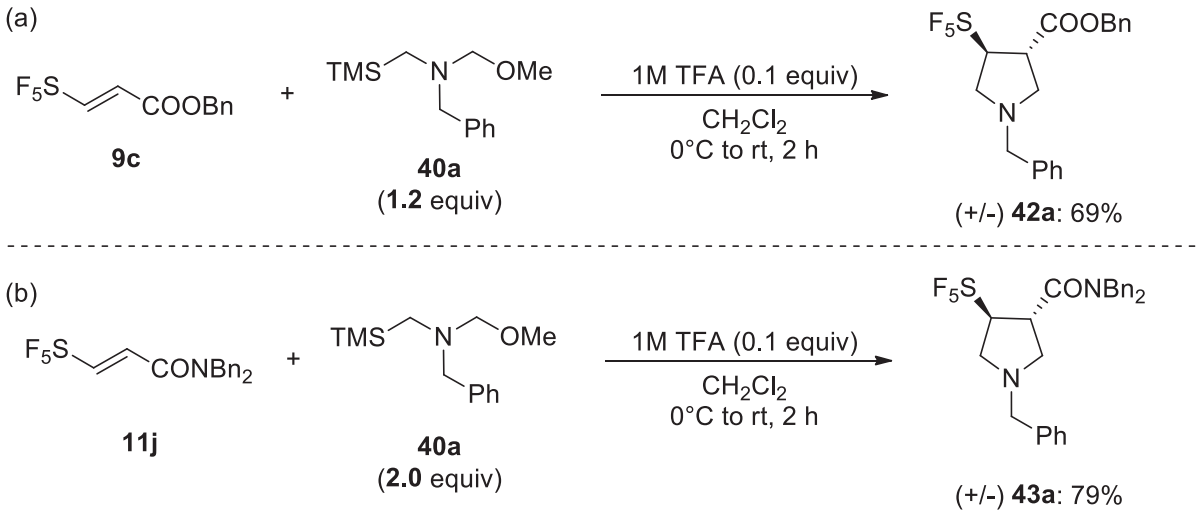
## 2.2. 1,3-Dipolar cycloadditions of $SF_5$-building blocks with azomethine ylide precursors 40a-b

For our initial studies, we selected dipole precursors **40a** and **40b**. These tertiary amines can easily generate the corresponding azomethine ylides **41a** and **41b**, in the presence of catalytic amount of trifluoroacetic acid (TFA), as depicted on Scheme 74.[100]




**Scheme 74: Generation of azomethine ylides 41a and 41b.**

To our delight, the reaction of pentafluorosulfanylated ester **9c** with compound **40a**, catalyzed by TFA in $CH_2Cl_2$, led to the formation of the expected pyrrolidine **42a** (Scheme 75, (a)). Product **42a** was isolated in 69% yield, as a racemic mixture. When the same conditions were applied to $SF_5$-amide **11j**, the corresponding cycloadduct **43a** was formed as well; nevertheless, the starting material was converted in only 46%. The use of 2 equivalents of dipole precursor **40a** resulted in almost total conversion (96%) of compound **11j**, leading to product **43a** in 79% isolated yield (Scheme 75, (b)).




**Scheme 75: Synthesis of pentafluorosulfanylated pyrrolidines 42a and 43a.**

We next engaged several pentafluorosulfanylated acrylic or allylic derivatives under the above conditions, in order to study the scope of this reaction (Figure 34).[102] We demonstrated that various $SF_5$-substituted unsaturated esters, secondary and tertiary amides, as well as chiral amide, reacted with dipole precursor **40a**, affording the pyrrolidines **42-43** in moderate to excellent yields. The $SF_5$-allylacetate **6** proved also to be a good dipolarophile, leading to the corresponding pyrrolidine **44** in 74% yield. When the PMB-substituted dipole precursor **40b** was reacted with esters **9c** or **9f**, the desired products **42e** and **42f** were isolated in 66% and 46% yield, respectively. It is worth noting that α-methylated ester **10a** and amide **12** reacted as well, to give the corresponding trisubstituted pyrrolidines **42d** and **43e**. Lower yields (36 and 46%, respectively) were obtained, which could be probably explained by the steric hindrance of the starting materials.

[102] Falkowska, E.; Tognetti, V.; Joubert, L.; Jubault, P.; Bouillon, J.-P.; Pannecoucke, X. *RSC Adv.* **2015**, *5*, 6864.

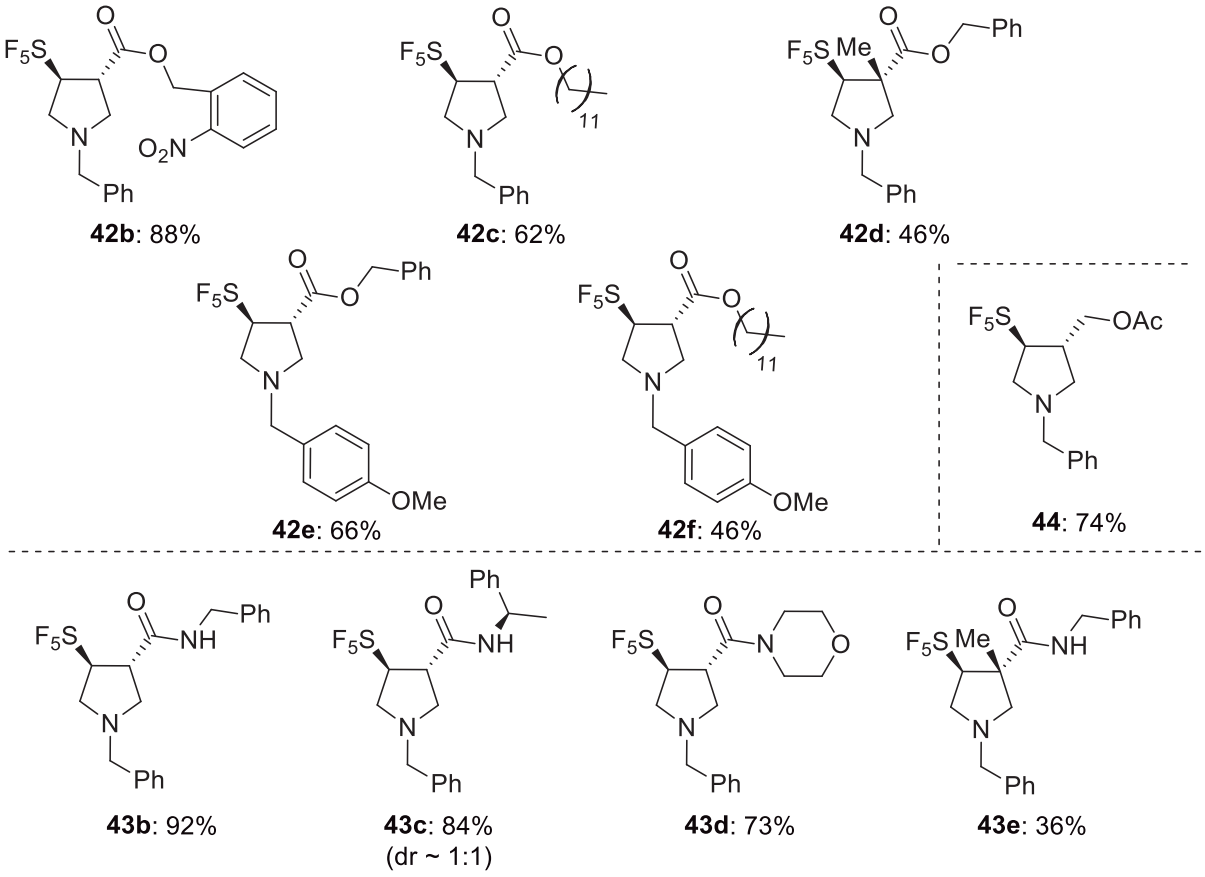



**Figure 34: Scope of the 1,3-dipolar cycloadditions with dipole precursors 40a and 40b.**

Concerning the stereoselectivity of the reaction, starting from *(E)*-acrylates **9-10**, *(E)*-acrylamides **11-12** or *(E)*-acetate **6**, only the *trans* pyrrolidines were formed, confirming thus the concerted mechanism of the 1,3-dipolar cycloaddition. All the pyrrolidines **42-44** were obtained as racemic mixtures, except for the product **43c**, which was obtained as a ~1:1 mixture of *trans* diastereoisomers. The latter two compounds were separated by silica gel column chromatography. *Trans* relationship between the $SF_5$- and amide-substituents was confirmed by X-ray diffraction analysis of the pyrrolidine **43b** (Figure 35).

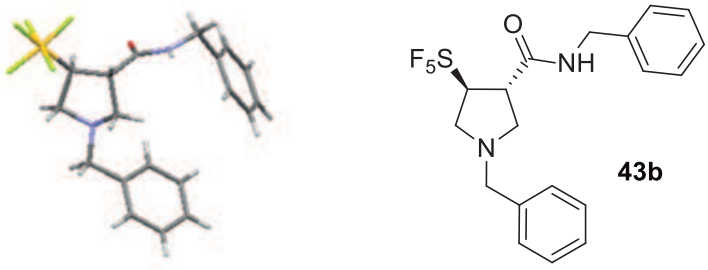
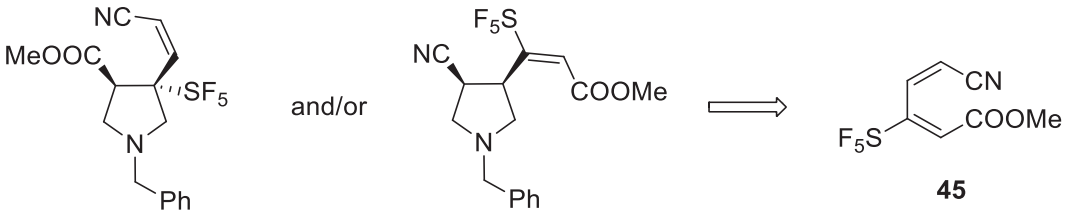


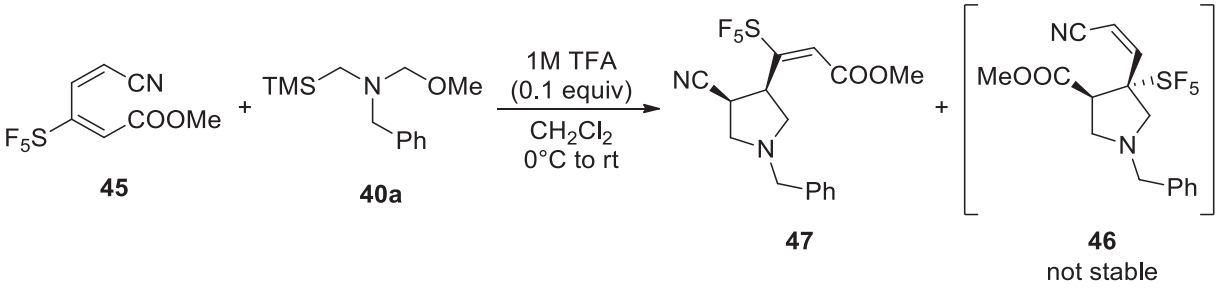

**Figure 35: X-ray diffraction analysis of $SF_5$-pyrrolidine 43b.**

It is worth noting that 1,3-dipolar cycloaddition of pentafluorosulfanylated diene **45** (Scheme 76),[65a] donated by Dr. Petr Beier from Academy of Sciences of Czech Republic, was attempted as well. Our aim was to synthesize a new pyrrolidine derivative **46**, bearing the $SF_5$-substituent directly attached to the heterocycle. Such compound could be formed from the reaction of the $SF_5$-substituted double bond of the diene **45** with dipole **41a**. From both double bonds present in compound **45**, the one bearing the $SF_5$-substituent, is the more electron-deficient one; however, it is also the more sterically hindered one. Thus, the formation of another cycloadduct **47** could be expected, as well.




**Scheme 76: Pyrrolidines 46 and 47 possibly obtained from diene 45.**

Indeed, in the reaction of diene **45** with dipole precursor **40a**, two major $SF_5$-products were detected by $^{19}F$ NMR of the reaction mixture, after 2.5 h. Nevertheless, after the "standard" quenching of the reaction mixture with the saturated aqueous solution of $NaHCO_3$, one of the pentafluorosulfanylated products disappeared (Table 12, entry 1). Purification by silica gel column chromatography led to the pyrrolidine **47** in 18% yield. The same phenomenon was observed, by prolonging the reaction time to 16 h (Table 12, entry 2). Assuming that the unstable product was the regioisomeric pyrrolidine **46**, such a behaviour could be explained by a possible elimination of $SF_4$ and HF from this cycloadduct, under basic condition, leading to the conjugated diene **48**, via the formation of carbanion-intermediate (Scheme 77). Such a hypothesis was confirmed by detecting the diene **48** by GC-MS analysis of the crude mixture. Thus, in order to avoid the base-induced elimination, we performed a modified slightly acidic work-up, using the aqueous solution of $NH_4Cl$ at the end of the reaction (Table 12, entry 3). Unfortunately, only the pyrrolidine **47** was obtained. Given these quite discouraging results, we did not continue further investigations of this reaction.



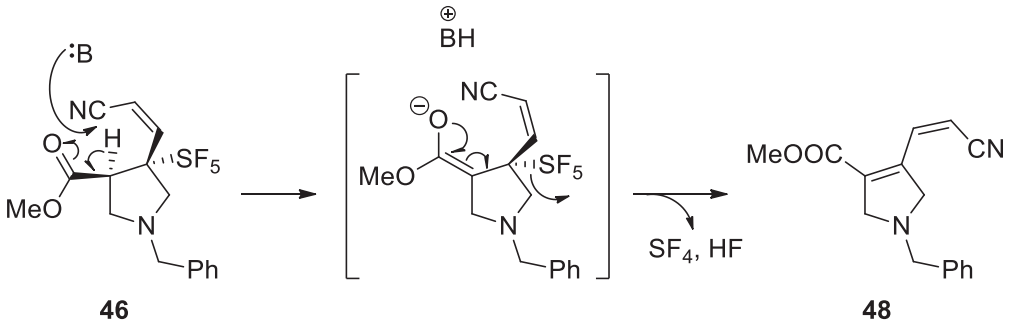

| Entry | Time (h) | Work-up | **47**:**46**[a] | | Conversion (%)[a] | Yield of **47** (%)[b] |
|---|---|---|---|---|---|---|
| | | | In the r. mix. | After the work-up | | |
| 1 | 2.5 | $NaHCO_{3(aq.)}$ | 1:1 | 1:0 | 90 | 18 |
| 2 | 16 | - | 1:0 | 1:0 | 90 | - [c] |
| 3 | 35 min | $NH_4Cl_{(aq.)}$ | 1:2 | 1:0 | 85 | - [c] |

[a] According to $^{19}F$ NMR of the crude mixture.

[b] Isolated yield.

[c] The crude mixture was not purified.

**Table 12: Attempts of 1,3-dipolar cycloaddition of diene 45 with azomethine ylide precursor 40a.**

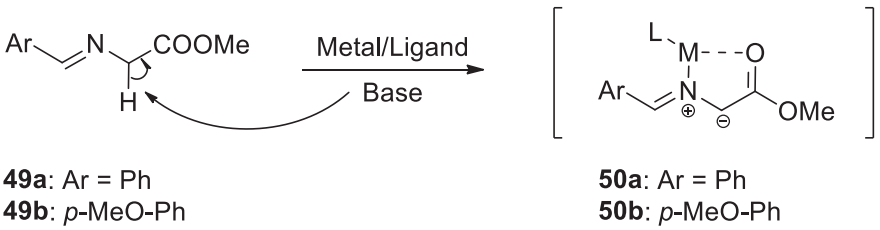



**Scheme 77: Possible elimination of $SF_4$ and HF from pyrrolidine 46.**

Having successfully developed the synthesis of new pentafluorosulfanylated pyrrolidines **42-44**, we then turned our attention to the use of other dipole precursors.

## 2.3. 1,3-Dipolar cycloadditions of $SF_5$-building blocks with imino esters 49a,b

After demonstrating that 1,3-dipolar cycloadditions occurred efficiently between $SF_5$-dipolarophiles and the precursors of azomethine ylide **40a** and **40b**, we were next investigating reactions with imino ester. The *in situ* metalation of compounds **49a,b** leads to the corresponding metalloazomethine dipoles **50a,b** (Scheme 78), which are known to react with electron-deficient alkenes. The attractiveness of the dipole precursors **49a,b** lies in the fact that by using a chiral ligand/metal complex, pyrrolidine derivatives with up to four different stereocontrolled chiral centers can be obtained.



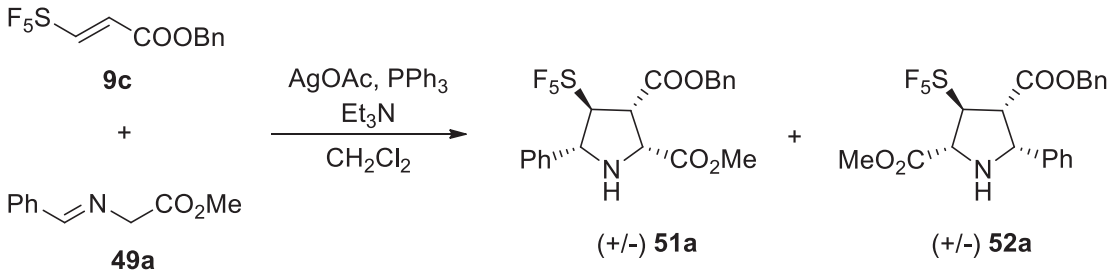

**49a**: Ar = Ph
**49b**: *p*-MeO-Ph

**50a**: Ar = Ph
**50b**: *p*-MeO-Ph

**Scheme 78: Generation of metalloazomethine dipoles 50a and 50b.**

### 2.3.1. Optimisation and scope of the reaction

Our study began with the reaction of $SF_5$-ester **9c** with compound **49a** (Table 13). Using glycine derivative **49a** (1.7 equiv), in the presence of 10 mol% $AgOAc/PPh_3$ and 15 mol% $Et_3N$,[101] at room temperature, two regioisomeric pyrrolidines **51a** and **52a** were obtained in a promising 40% yield (Entry 1). When the dipole precursor **49a** was used in a larger excess (3 equiv) and the quantities of $AgOAc/PPh_3$ and $Et_3N$ were increased to 20 mol% and 25 mol%, respectively, the pyrrolidines **51a** and **52a** were obtained in 75% yield; however, a long reaction time (90 h) was required (Entry 2). Finally, heating the reaction mixture at reflux resulted in the formation of products **51a** and **52a** in a good (73%) overall yield, within 21 h (Entry 3).




| Entry | Equivalents | | | | Temperature (°C) | Time (h) | Yield (%)[a] |
|---|---|---|---|---|---|---|---|
| | **49a** | AgOAc | $PPh_3$ | $Et_3N$ | | | |
| 1 | 1.7 | 0.1 | 0.1 | 0.15 | rt | 17 | 40 (1:1)[b] |
| 2 | 3 | 0.2 | 0.2 | 0.25 | rt | 90 | 75 (1:1)[b] |
| 3 | 3 | 0.2 | 0.2 | 0.25 | reflux | 21 | 73 (1:1)[b] |

[a] Global isolated yield of regioisomers.

[b] Ratio of regioisomers.

**Table 13: 1,3-Dipolar cycloadditions of $SF_5$-ester 9c with imino ester 49a.**

Having the optimal conditions in hand, we performed the reaction of ester **9c** with the *p*-methoxy-substituted dipole precursor **49b**. The latter one turned out to be less reactive, allowing the conversion of $SF_5$-derivative **9c** into the corresponding pyrrolidines **51b** and **52b** (ratio ~2:1) (Figure 36) in only 55%, after 21 h. Surprisingly, longer reaction time led to the degradation of expected products. When the $SF_5$-amide **11l** was engaged in the reaction with imino ester **49a**, lower conversion (55%) was observed as well, and the desired pyrrolidines **51c** and **52c** (ratio ~2:1) (Figure 36) were isolated in an overall 48% yield.

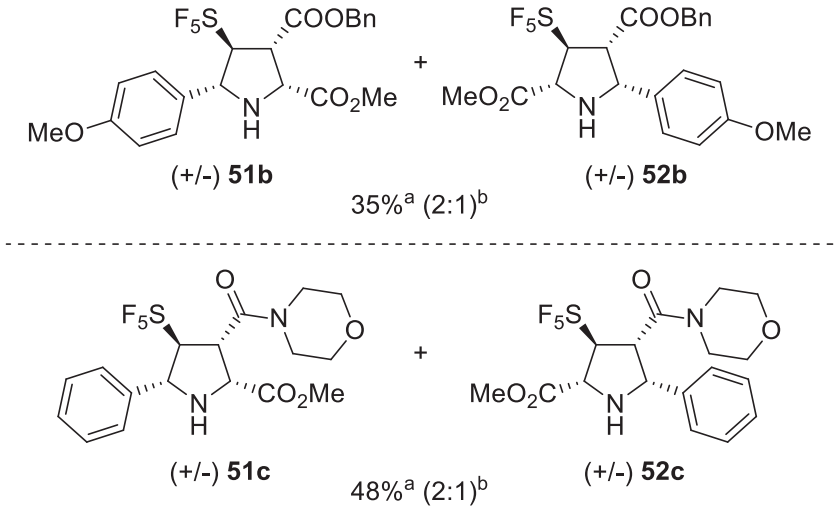



**Figure 36: Scope of the 1,3-dipolar cycloaddition with dipole precursors 49a-b.**
**[a] Isolated yield. [b] Ratio of regioisomers.**

### 2.3.2. Structure determination of pyrrolidines 51 and 52

In the above presented 1,3-dipolar cycloaddition reactions, the pyrrolidines **51**, **52** were generally obtained as mixtures of regioisomers. All of the products were formed as only one diastereoisomer. Their structures have been identified based on $^{1}H$, $^{13}C$, 2D NMR data and X-ray diffraction analysis. It is worth noting that in the previously reported reactions of trifluoromethylated analogues, the corresponding $CF_3$-pyrrolidines were obtained with a total regioselectivity and stereoselectivity, their structures being determined by X-ray diffraction analysis.[101]

The HMBC experiment of pyrrolidine **51a**, showed a strong $^{2}J$ correlation between the proton ($H^4$) adjacent to the $SF_5$ group and the carbon ($C^5$) bearing the phenyl substituent (Figure 37, (a)). The same relationship has been observed for all 4-$SF_5$-substituted pyrrolidines (**51a-c**). On the other hand, the carbon ($C^5$) of the pyrrolidine **52a** showed a $^{2}J$ correlation with the proton ($H^4$) adjacent to the benzyl ester group; confirming thus the presence of $SF_5$ group in the position 3 (Figure 37, (b)). Other 3-$SF_5$-substituted pyrrolidines (**52b**,**c**) exhibited similar correlations. Furthermore, the structure of compound **51a** was independently confirmed by the X-ray diffraction analysis (Figure 38).

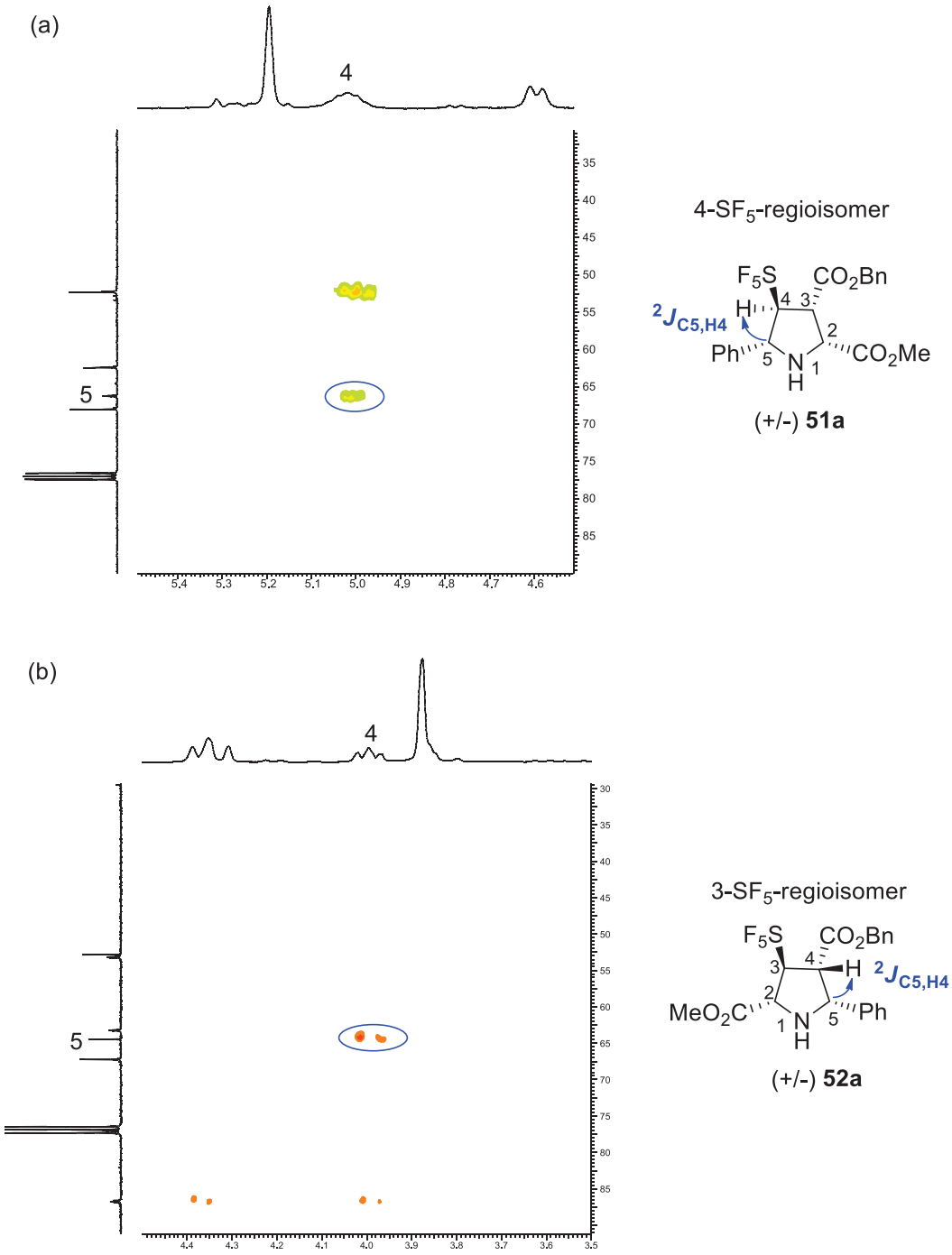



**Figure 37: Selected views of HMBC experiments of pyrrolidine 51a (a) and 52a (b).**

Concerning the stereochemical course of the reaction, all pentafluorosulfanylated pyrrolidines **51**, **52** were formed diastereoselectively. The stereochemistry of 4-$SF_5$-substituted pyrrolidine **51a** was confirmed by the previously mentioned X-ray analysis (Figure 38), whereas the NOESY experiment, was used to determine the configuration of the 3-$SF_5$-regioisomer **52a** (Figure 39). The latter one showed the correlation of the proton $H^2$

with both protons, $H^4$ and $H^5$, indicating their *syn*-configuration. On the other hand, the proton ($H^3$) adjacent to the $SF_5$-group was corelated with aromatic protons (Ph, Bn), indicating the location of the proton $H^3$ on the opposite side of the pyrrolidine ring, than the protons $H^2$, $H^4$ and $H^5$.

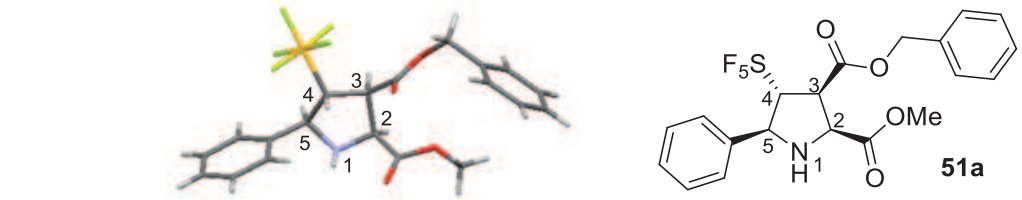



**Figure 38: Crystal structure of the 4-$SF_5$-pyrrolidine 51a.**

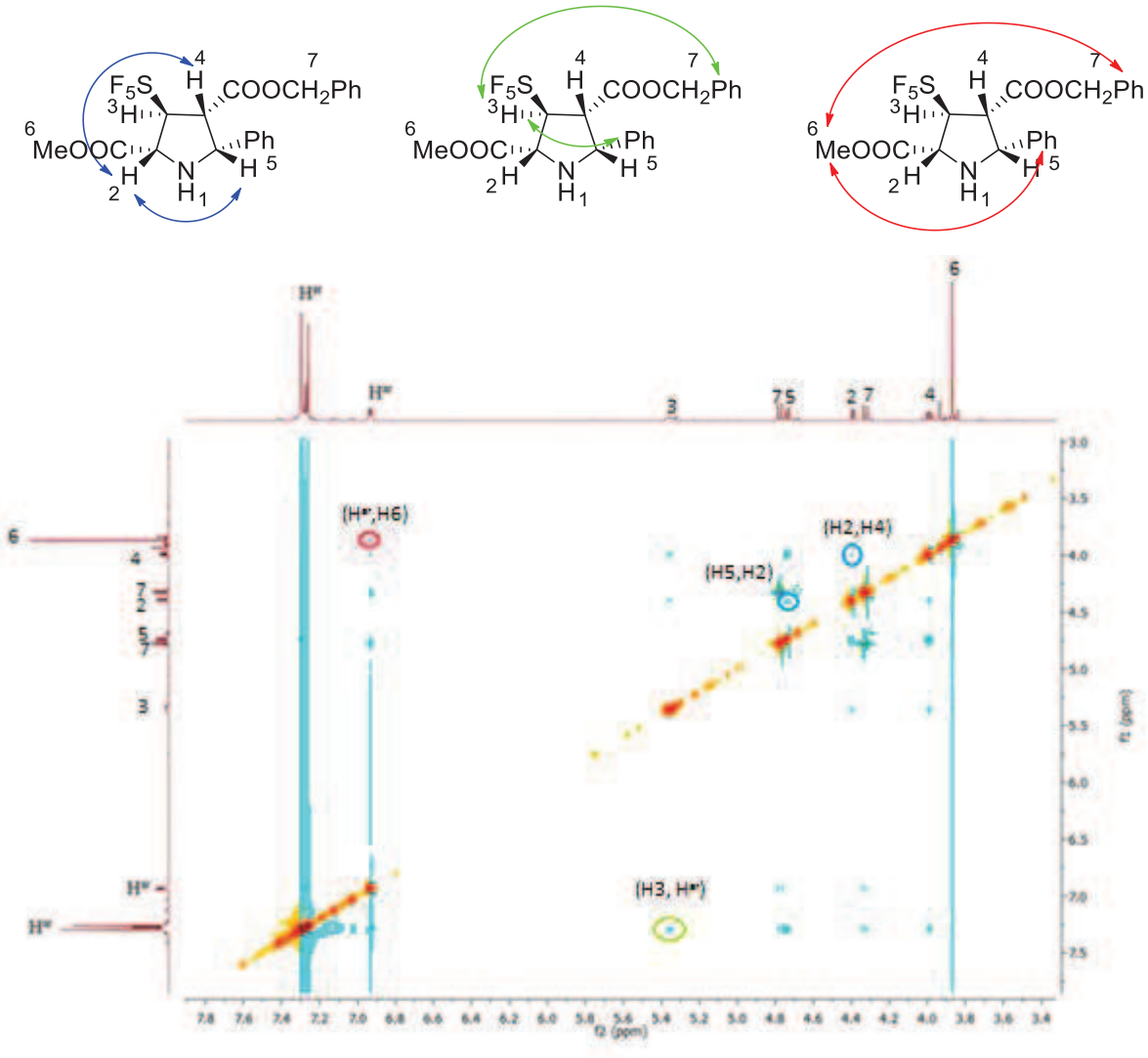
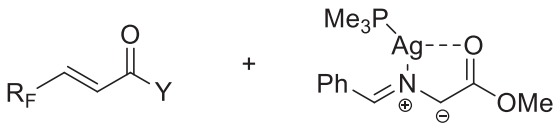



**Figure 39: NOESY experiment of 3-$SF_5$-pyrrolidine 52a.**

### 2.3.3. Comparison of the results in $SF_5$- and $CF_3$-series

In the 1,3-dipolar cycloaddition with imino ester **49a**, two major differences between the $SF_5$-series and the previously reported $CF_3$-one,[101] were observed. First, the rate of the reaction with pentafluorosulfanylated derivatives was much slower (21 h, at 40°C) than the one of trifluoromethylated analogues (5 h, at rt). Secondly, in the $CF_3$, series the reaction was almost totally regioselective, whereas in the case of $SF_5$-dipolarophiles, mixtures of 3- and 4-$SF_5$-substituted regioisomers were obtained.

For better understanting of different reactivity of $CF_3$- and $SF_5$-compounds, theoretical calculations have been carried out by Dr. V. Tognetti and Pr. L. Joubert from our research team.[102] Three model systems ($SF_5$-acrylic ester **9a**, $SF_5$-acrylamide **53** and $CF_3$-acrylic ester **54**) and imine complex with $[AgPMe_3]^+$ were investigated (Scheme 79). The first step of the reaction was the formation of a non-covalent adduct between the two reaction partners. This step was rationalized in the framework of conceptual DFT, showing the nucleophilic regions coming on top of the electrophilic areas. The subsequent formation of the C-C bonds was completed in one highly asynchronous step, or in two unconcerted steps.




**9a**: $R_F = SF_5$, Y = OMe
**53**: $R_F = SF_5$, Y = $NMe_2$
**54**: $R_F = CF_3$, Y = OMe

**Scheme 79: Model systems for the theoretical study.**

Relative energies of possible transition states and products, for the three model systems **9a**, **53** and **54** were then calculated, in order to discuss the competition between paths 1 and 2, leading to different regioisomeric products (Figure 40). According to the Gibbs activation barrier values, the pathway 1 was privileged for $CF_3$-ester **54**, whereas both pathways were possible for $SF_5$-ester **9a**. Concerning the $SF_5$-amide **53**, the pathway 2 was only slightly favoured. The $\Delta G°$ activation barriers values of the most favoured paths were as follows: 11 kcal/mol ($CF_3$-ester) < 12 kcal/mol ($SF_5$-ester) < 13 kcal/mol ($SF_5$-amide), confirming thus the slower rate of the reactions with $SF_5$-derivatives **9a** and **53**, relatively to the $CF_3$-one **54**.

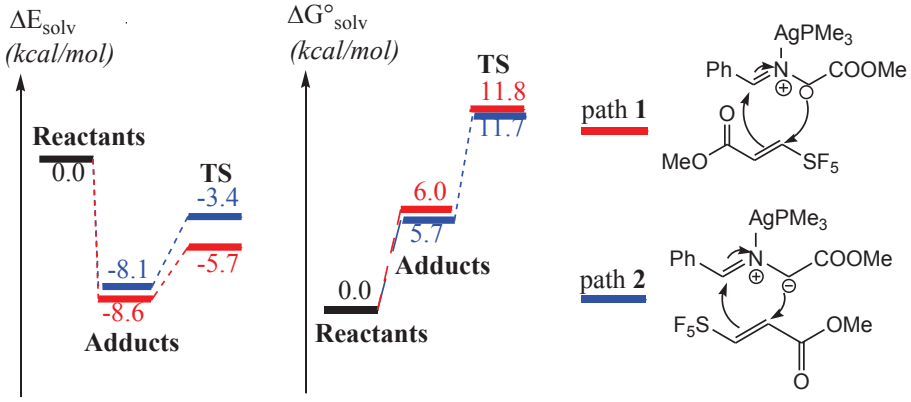
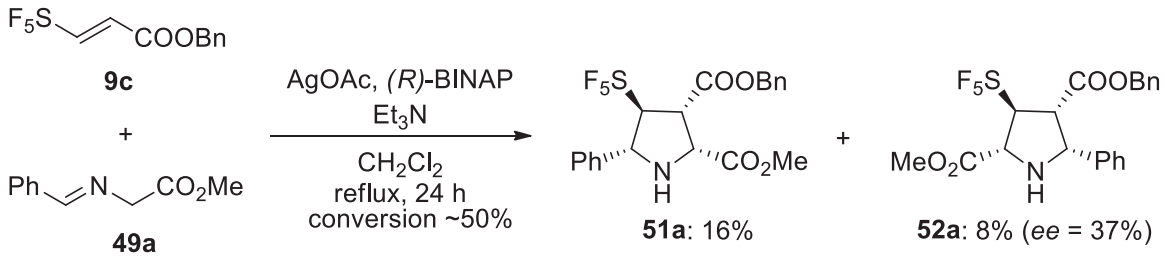



**Figure 40: Regiochemistry of 1,3-dipolar cycloaddition of $SF_5$-ester 9a according to $\Delta E_{Solv}$ and $\Delta G°_{Solv}$ viewpoints.**

The above theoretical study allowed us to rationalize the observed differences between the 1,3-dipolar cycloadditions of the $SF_5$- and $CF_3$-derivatives. Presented results of the theoretical calculations are in agreement with the experimentally observed ones.

### 2.3.4. Asymmetric version – preliminary results

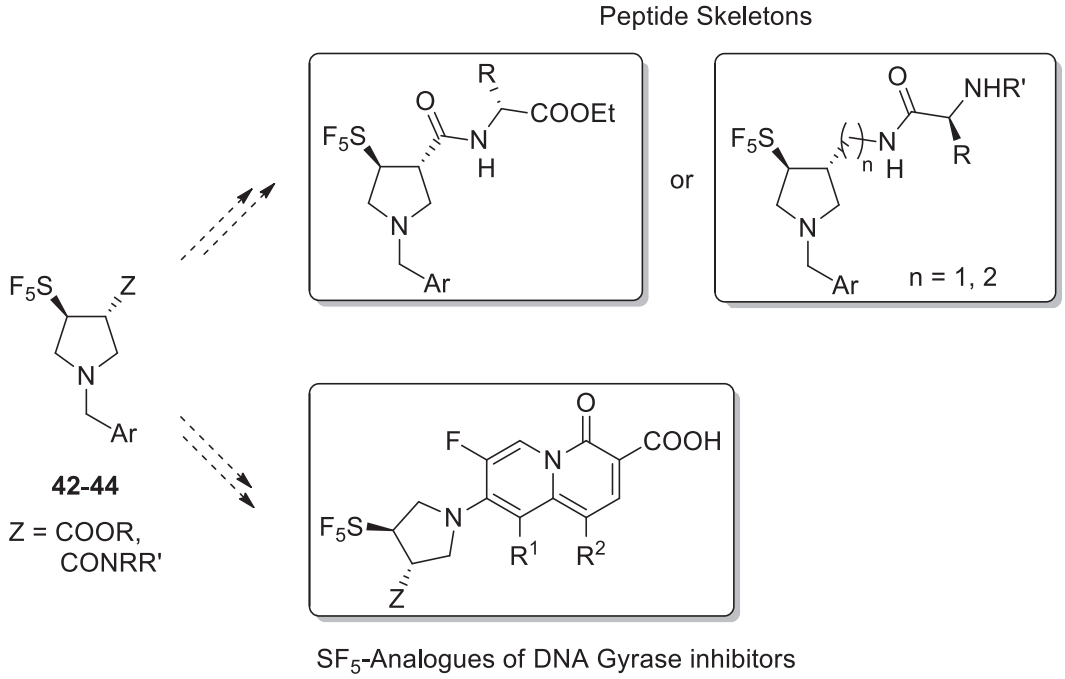
Encouraged by these results, we decided to investigate the enantioselective version of this reaction. For this purpose, we replaced the triphenylphoshine by the chiral *(R)*-BINAP ligand. After stirring the reaction mixture at reflux, for 24 h, the starting product **9c** was partially converted (50%) and, the corresponding pyrrolidines **51a** and **52a** were isolated in 8% and 16% yield, respectively (Scheme 80). Despite the low yield, the $SF_5$-pyrrolidine **52a** was obtained with a promising 37% enantiomeric excess (determined by chiral HPLC). Further screening of other chiral ligands and dipole precursors is currently under investigation in our laboratory.




**Scheme 80: Preliminary attempt for the asymmetric 1,3-dipolar cycloaddition of $SF_5$-ester 9c with dipole precursor 49a.**

## 2.4. Post-functionalizations of $SF_5$-containing pyrrolidines

Having developed an efficient synthesis of original pentafluorosulfanylated pyrrolidines **42-44** and **51**, **52**, we next investigated post-functionalization of these novel scaffolds, which could be further incorporated into more complex structures. This approach is especially attractive, from the point of view of the synthesis of the $SF_5$-containing peptides or potential biologically active compounds, such as $SF_5$-analogs of DNA Gyrase inhibitors (Scheme 81).[97a-c]




**Scheme 81: Possible synthesis of $SF_5$-pyrrolidine-containing peptides and analogues of DNA Gyrase inhibitors.**

In order to get the access to the above presented compounds of potential biological interest, we envisaged the synthesis of cyclic acid and amines, starting from disubstituted pentafluorosulfanylated pyrrolidines **42-44**. Acid and amines (Figure 41, (a)) could be further incorporated into peptide skeletons, via coupling reactions, whereas the debenzylated pyrrolidines (Figure 41, (b)) could be introduced into pyridone scaffolds, via $S_NAr$ type reactions, leading to the potential pentafluorosulfanylated antibacterial agents.

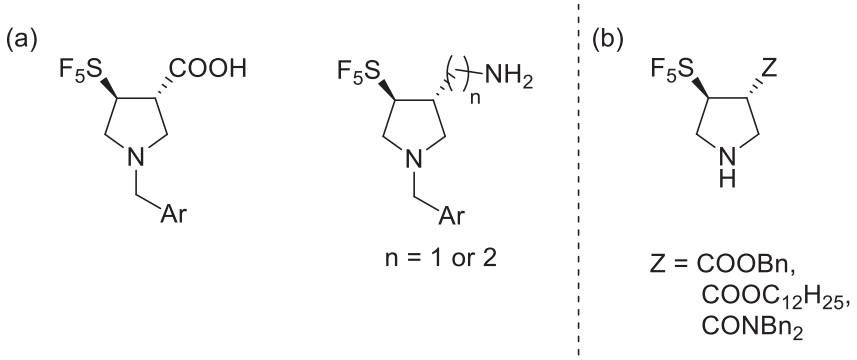


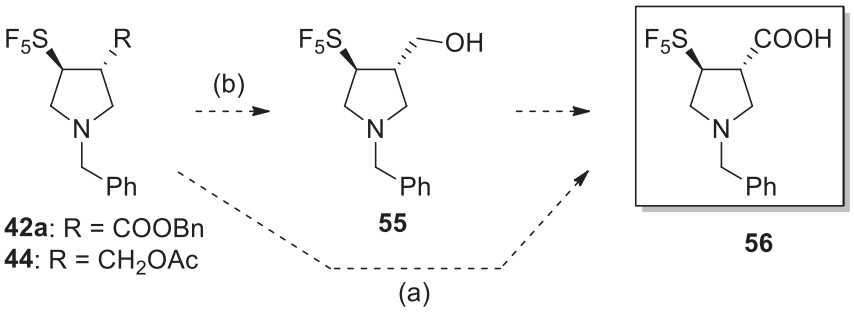

**Figure 41: Targeted pentafluorosulfanylated cyclic acid and amines**

In the following sections, the attempts for the synthesis of above acid and amines (Figure 41, (a)) will be first presented. The debenzylation reaction of disubstituted pyrrolidines **42-44** (Figure 41, (b)), will be further discussed.

### 2.4.1. Functionalizations toward peptide skeletons

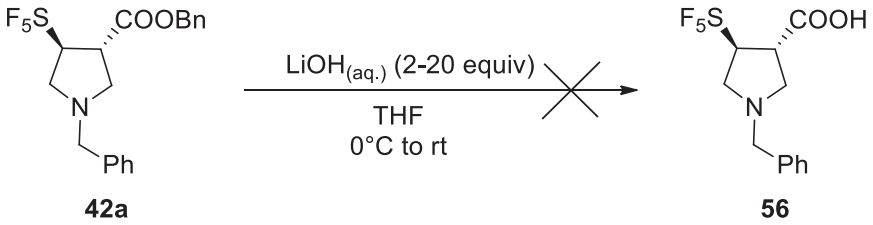
#### 2.4.1.1. Attempts for the synthesis of acid 56

In the context of pentafluorosulfanylated peptides preparation, we sought first to synthesize the acid **56**. This compound could be obtained either by the saponification of ester (Scheme 82, (a)), or by the oxidation of the corresponding alcohol **55** (Scheme 82, (b)).



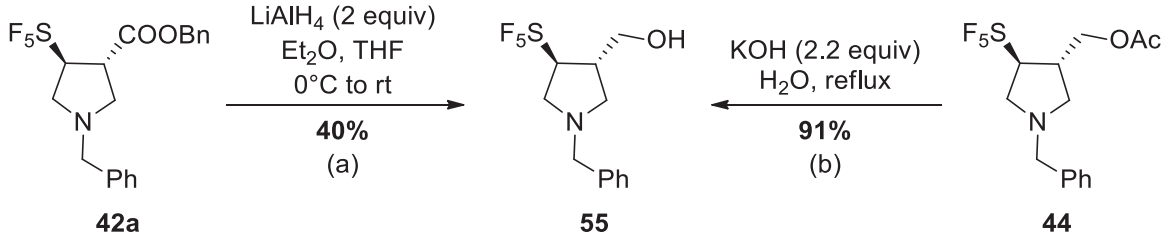

**Scheme 82: Possible syntheses of acid 56.**

Unfortunately, all attempts of the hydrolysis of the ester **42a** with an aqueous solution of LiOH, resulted only in the degradation of pentafluorosulfanylated material (Scheme 83), probably due to the elimination of $SF_4$ and HF as previously proposed. Therefore, we turned our attention to an alternative pathway via the alcohol **55** (Scheme 84).




**Scheme 83: Attempt for the synthesis of acid 56 from ester 42a.**

$SF_5$-Pyrrolidinyl alcohol **55** was first prepared by the reduction of the ester **42a**, using a suspension of $LiAlH_4$ in $Et_2O$ (Scheme 84, (a)). Despite the total conversion of the starting material, the final product **55** was isolated in only 40% yield. Alternatively, the alcohol **55** was synthesized by the deacetylation of pyrrolidine **44** (Scheme 84, (b)). Indeed, in the presence of refluxing aqueous solution of potassium hydroxide, the desired product **55** was obtained in 91% yield (Scheme 84, (b)).

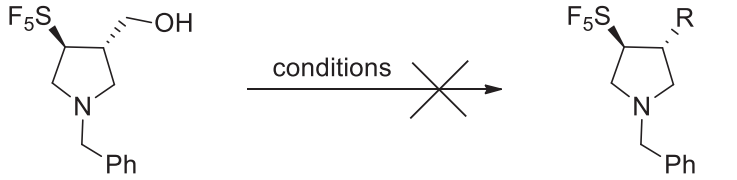



**Scheme 84: Synthesis of $SF_5$-pyrrolidinyl alcohol 55 starting from ester 42a or acetate 44.**

The oxidation of alcohol **55** to the corresponding acid **56** turned out to be more problematic (Table 14). When $CrO_3$ was used, as previously described for the synthesis of $SF_5$-acrylic acids **8**, we observed a total conversion of the starting material; however, the final product was lost during the work-up (Entry 1). Thus, we turned our attention to the preparation of aldehyde **57**, which could be further transformed into the desired carboxylic acid **56**.

When oxidants, such as pyridinium chlorochromate (PCC) or 2-iodoxybenzoic acid (IBX) were used, no expected aldehyde **57** was obtained. Despite testing different solvents and temperature, either no conversion, or degradation of starting material were observed (Entries 2-6). Swern oxidation also failed (Entry 7). Finally, using a catalytic amount of tetrapropylammonium perruthenate (TPAP) in the presence of N-methylmorpholine N-oxide (NMO) a partial conversion of the starting material was observed, according to $^{19}F$ NMR of

the reaction mixture (Entry 8). Nevertheless, the formation of expected aldehyde **57** could not be confirmed, probably due to its decomposition during the silica flash chromatography.




**55**

**56**: R = $CO_2H$
**57**: R = CHO

| Entry | Conditions | Product | Conversion[a] (%) |
|---|---|---|---|
| 1 | $CrO_3$ (4.0 equiv), AcOH (63.0 equiv), $H_2O$, 0°C to 8°C, 2h, then rt, overnight | **56** | 100 |
| 2 | PCC (2.0 equiv), $SiO_2$, $CH_2Cl_2$, rt, 3 h | **57** | 0 |
| 3 | IBX (1.2 equiv), ACN, rt, 18 h | **57** | 0 |
| 4 | IBX (3.0 equiv), AcOEt, rt, 2 h | **57** | 0 |
| 5 | IBX (3.0 equiv), AcOEt, 60°C, 2 h | **57** | degradation |
| 6 | IBX (3.0 equiv), DMSO, rt, 2 h | **57** | degradation |
| 7 | $(COCl)_2$ (1.4 equiv), DMSO (2.8 equiv), $Et_3N$ (6.0 equiv), $CH_2Cl_2$, -78°C to rt | **57** | degradation |
| 8 | TPAP (0.05 equiv), NMO (1.5 equiv), MS 3 Å, $CH_2Cl_2$, rt, overnight | **57** | 70 |

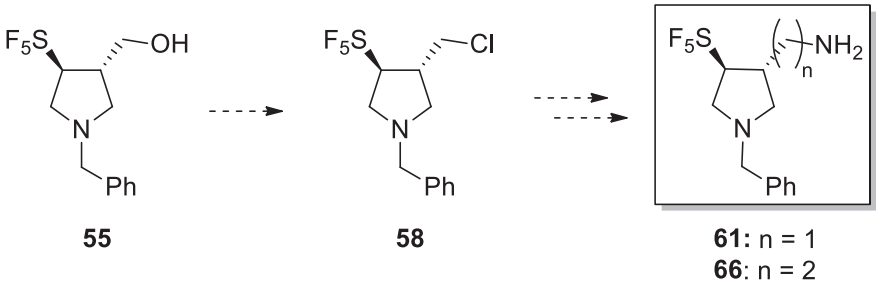
[a] According to $^{19}F$ NMR of the reaction mixture.

**Table 14: Attempts of the oxidation of alcohol 55 to acid 56 and aldehyde 57.**

Given the unsuccessful attempts of the synthesis of acid **56** and aldehyde **57**, we turned our attention to the preparation of $SF_5$-pyrrolidinyl amines **61** and **66**, which could give us the access to the pentafluorosulfanylated peptides.

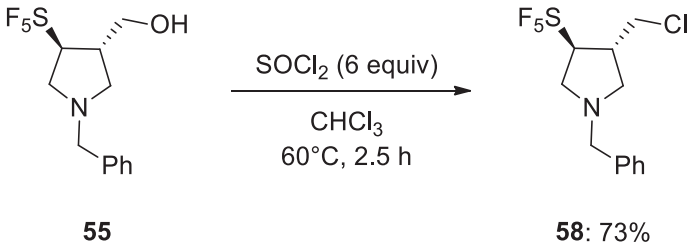
### 2.4.1.2. Attempts for the synthesis of amines 61 and 66

We were next interested in the preparation of amines **61** and **66**, which could be synthesized via nucleophilic substitution reactions of the corresponding 3-(chloromethyl)-substituted pyrrolidine **58** (Scheme 85).



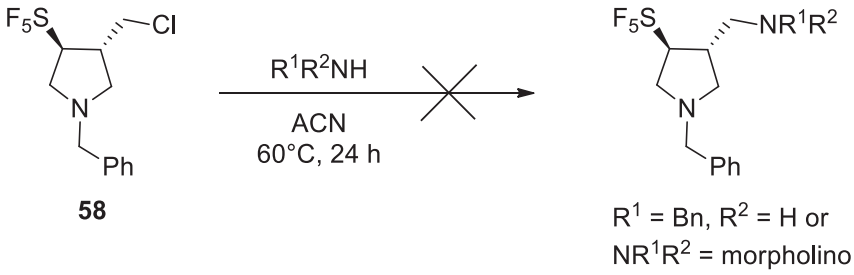

**Scheme 85: Possible synthesis of amines 61 and 66.**

The desired pyrrolidine **58** was synthesized by the chlorination reaction of alcohol **55**, using thionyl chloride, within 2.5 h, in a good 73% yield (Scheme 86). Having chloride **58** in hands, we were then investigating its reactivity toward several different nucleophiles.



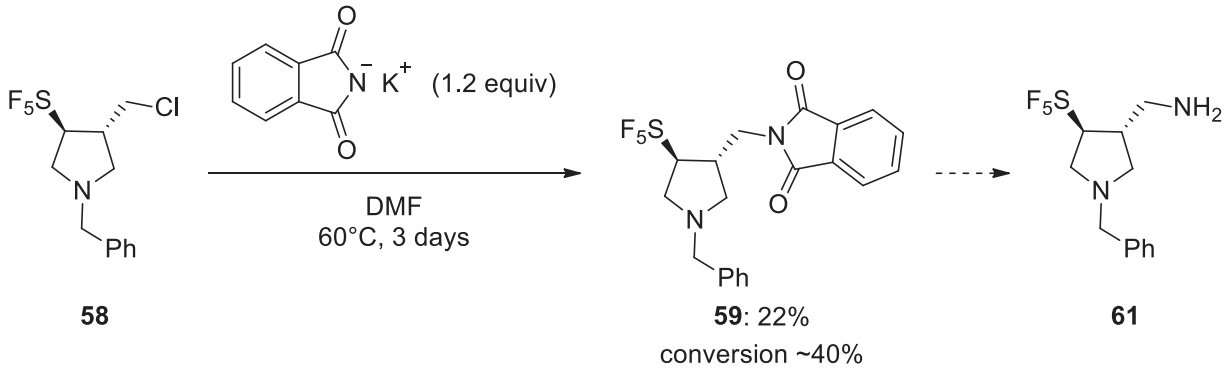

**Scheme 86: Synthesis of 3-(chloromethyl)pyrrolidine 58.**

We first desired to control the reactivity of compound **58** toward primary and secondary amines. The reactions with both benzylamine and morpholine were thus performed, but without any success. No conversion of the starting material was observed, even after heating the reaction mixture at 60°C for several hours (Scheme 87).




**Scheme 87: Attempts for the nucleophilic substitution of chloride 58 with benzylamine or morpholine.**

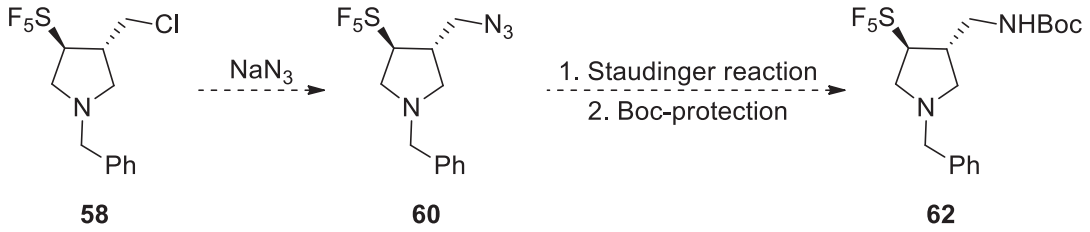
We have further performed the nucleophilic substitution of pyrrolidine **58** with phtalimide potassium salt, which behaves as a good and non-basic nucleophile. The deprotection of the resulting phtalimide **59** should liberate the corresponding primary amine **61** (Scheme 88), which could be further incorporated into a peptide skeleton. The reaction of chloride **58** with phtalimide potassium salt turned out to be slow: after heating at 60°C for 3 days, the starting product was converted in only 40%. Neither a large excess (3 equiv) of phtalimide potassium salt, nor a longer reaction time (5 days) improved the conversion. The expected product **59** was isolated in 22% yield.




**Scheme 88: Nucleophilic substitution of chloride 58 with phtalimide potassium salt.**

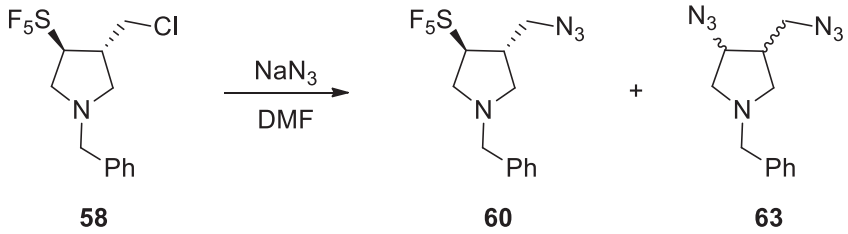
Given the very small quantity of the phtalimide **59** available, we chose to access to the primary amine **61** by an alternative pathway. Our idea was first to synthesize the azide **60**, via the nucleophilic substitution of the chloride **58** with sodium azide. We have further envisaged the Staudinger reaction[103] of azide **60**, followed by the subsequent *in situ* Boc-protection, which should lead to the desired N-Boc-protected amine **62** (Scheme 89).

[103] (a) Tian, W. Q.; Wang, Y. A. *J. Org. Chem.* **2004**, *69*, 4299. (b) Lin, F. L.; Hoyt, H. M.; Halbeek, H. V.; Bergman, R. G.; Bertozzi, C. R. *J. Am. Chem. Soc*. **2005**, *127*, 2686.




**Scheme 89: Alternative pathway to the amine 62.**

We were first investigating the reaction of pyrrolidine **58** with sodium azide (Table 15). When compound **58** was reacted with $NaN_3$ (2 equiv), in DMF at room temperature, no conversion of the starting material was observed (Entry 1). Heating the reaction mixture at 60°C led to the desired product **60** in 21% yield, within 20 h (Entry 2). Surprisingly, in addition to the expected azide **60** we observed also the formation of a non-fluorinated product **63**. In order to improve the conversion, a larger excess (4 equiv) of sodium azide was used; nevertheless, after 5 h, the product **60** was isolated in only 22% yield (Entry 3). Finally, increasing the reaction time to 20 h, led to 80% higher; however, the isolated yield of the desired pyrrolidine **60** was only slightly improved (28%) (Entry 4). It is worth noting that in almost all reactions the expected $SF_5$-pyrrolidine **60** was accompanied by a non-fluorinated diazide **63**, which was isolated by silica gel column chromatography, and identified by $^1H$ and $^{13}C$ NMR. Presence of the side product **63** could be explained by the ability of the $SF_5$-substituent to behave as a leaving group. Such a displacement of the $SF_5$-group by azido nucleophiles has been already reported in the literature.[104]




[104] Huang, Y.; Gard, G. L.; Shreeve, J. M. *Tetrahedron Lett.* **2010**, *51*, 6951.

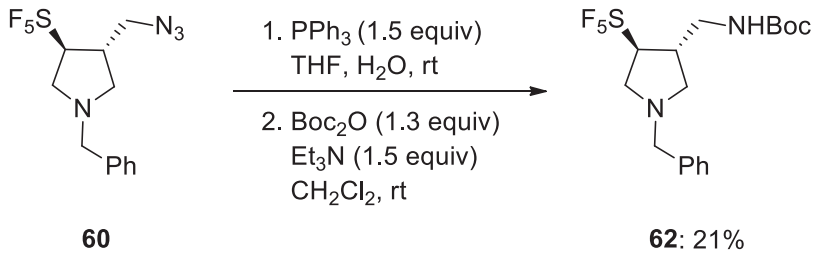
| Entry | $NaN_3$ (equiv) | Temperature (°C) | Time (h) | Conversion (%)[a] | Yield (%)[b] | |
|---|---|---|---|---|---|---|
| | | | | | **60** | **63** |
| 1 | 2 | rt | 4 | 0 | - | - |
| 2 | 2 | 60 | 20 | 60 | 21 | 40 |
| 3 | 4 | 60 | 5 | 60 | 22 | 34 |
| 4 | 4 | 60 | 20 | 80 | 28 | 50 |

[a] According to the quantity of the starting material **58** recovered after silica flash column chromatography.

[b] Isolated yield.

**Table 15: Nucleophilic substitution of chloride 58 with sodium azide.**

We have further performed the Staudinger reaction of azide **60**, followed by the subsequent Boc-protection. The desired amine **62** was obtained in a moderate 21% isolated yield, without further optimization (Scheme 90).



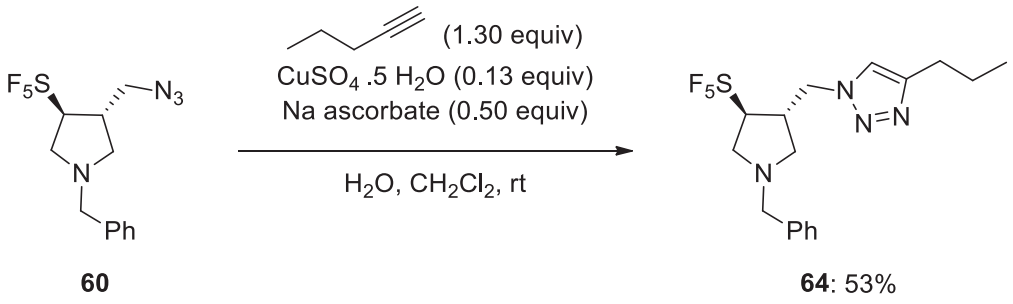

**60** **62**: 21%

**Scheme 90: Synthesis of N-Boc-protected amine 62.**

Having the pentafluorosulfanylated azide **60** in hand, we also desired to verify its reactivity under classical "click" chemistry conditions.[105] Such approach is especially attractive, as it could allow attaching the $SF_5$-pyrrolidine moiety into a selected scaffold.

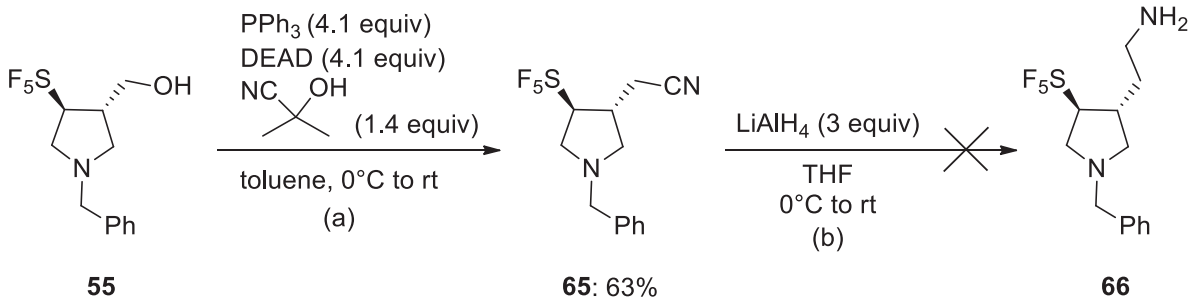
To our delight, the azide **60** reacted smoothly with pent-1-yne, in the presence of Cu(I), prepared *in situ* from $CuSO_4$/sodium ascorbate. The expected triazole **64** was obtained in non-optimized 53% yield, as only one regioisomer (Scheme 90).

[105] Thirumurugan, P.; Matosiuk, D.; Jozwiak, K. *Chem. Rev.* **2013**, *113*, 4905.




**Scheme 90: "Click" reaction of $SF_5$-azide 60.**

In the next step of our investigations on the functionalized $SF_5$-pyrrolidine scaffolds, we were interested in the preparation of amine **66**. This compound could be synthesized by the reduction of the corresponding nitrile **65**. In order to avoid the reaction of chloride **58** with the highly toxic potassium cyanide, we chose to synthesize the nitrile **65** via the Mitsunobu reaction[106] of the alcohol **55** (Scheme 91, (a)). The desired product **65** was obtained in 63% isolated yield. Unfortunately, the subsequent reduction using $LiAlH_4$ failed, leading to the complete degradation of the starting pyrrolidine **65** (Scheme 91, (b)).

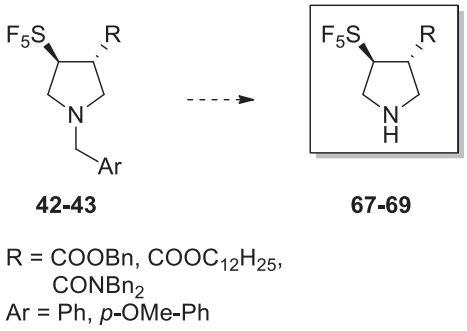



**Scheme 91: Synthesis of 3-(cyanomethyl)pyrrolidine 65 and the attempt of its reduction into amine 66.**

### 2.4.2. Functionalization toward $SF_5$-analogues of DNA Gyrase inhibitors

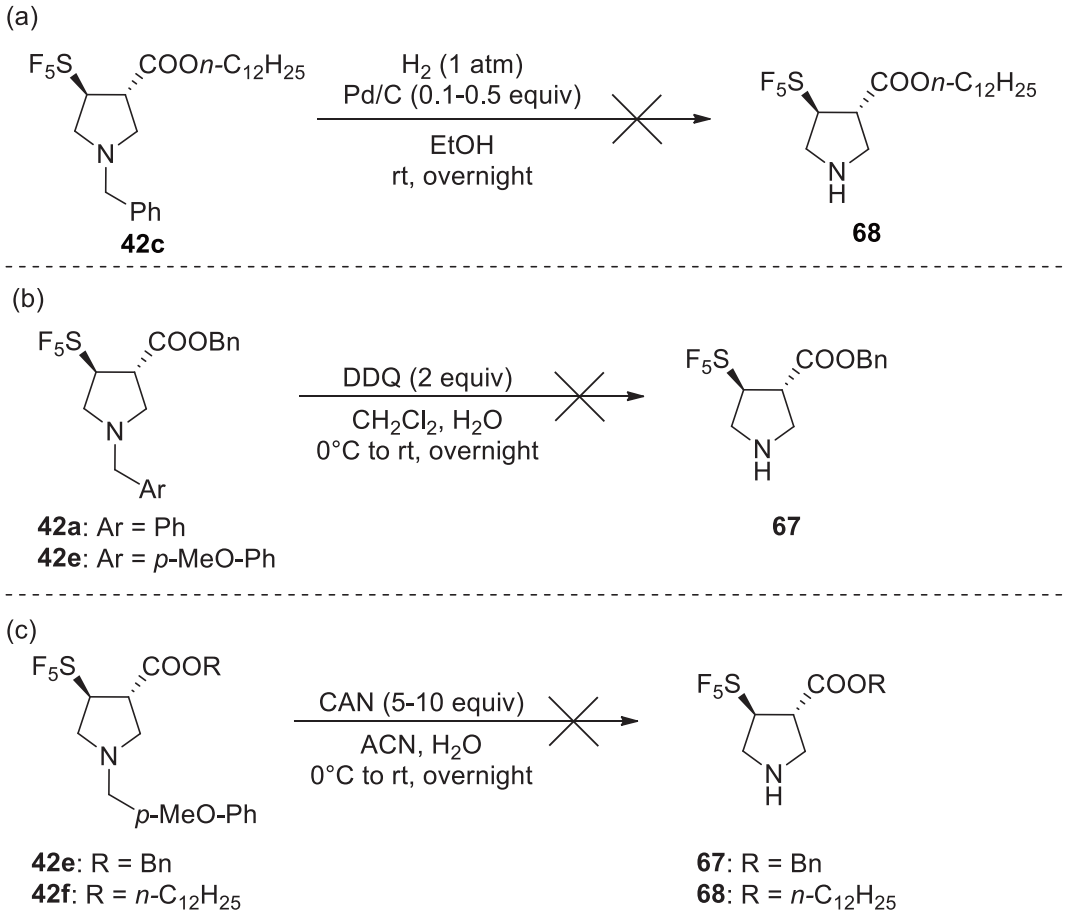
Continuing our post-functionalization studies, we desired to remove the benzyl group from the pentafluorosulfanylated pyrrolidines **42-43** (Scheme 92). This could allow the synthesis of compounds **67-69**, which could be further incorporated into potential active compounds (see Scheme 81).

[106] (a) Mitsunobu, O. in *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I. (Eds.), Pergamon Press, Oxford, 1991; p.1. (b) Mitsunobu, O. *Synthesis* **1981**, 1. (c) Hughes, D. L. *Org. React.* **1992**, *42*, 335. (d) Swamy, K. C. K.; Kumar, N. N. B.; Balaraman, E.; Kumar, K. *Chem. Rev.* **2009**, *109*, 2551.



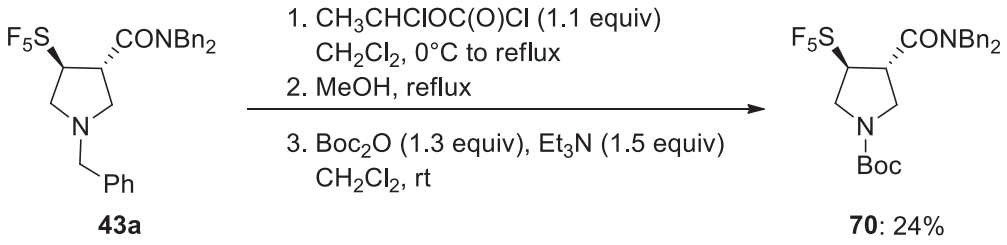

**Scheme 92: Synthesis of cyclic amines 67-69.**

Unfortunately, the usual catalytic hydrogenation of **42c**, in the presence of Pd/C, failed; the starting material was fully recovered (Scheme 93, (a)). The lack of the reactivity could be possibly due to the poisoning of the palladium catalyst by the sulfur atom. We thus tried to synthesize the deprotected pyrrolidines **67**, **68** by oxidative methods, using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (Scheme 93, (b)), or cerium (IV) ammonium nitrate (CAN) (Scheme 93, (c)). Nevertheless, all the attempts were unsuccessful.




**Scheme 93: Attempts of benzyl or *p*-methoxybenzyl deprotection of pyrrolidines 42.**

Finally, the deprotection of benzyl group was possible by treating the pyrrolidine **43a** with 1-chloroethylchloroformate followed by methanolysis.[107] The desired amine **69**·HCl was directly protected by a Boc-group, leading to the expected product **70**, in 24% overall isolated yield (Scheme 94).




**Scheme 94: Synthesis of N-Boc-protected pyrrolidine 70.**

Taking into account the successful synthesis of a variety of original functionalized pentafluorosulfanylated pyrrolidines, we desired to extend our strategy, based on the 1,3-dipolar cycloadditions, to other non-aromatic heterocycles. The synthesis of new pentafluorosulfanylated isoxazolidines, will be presented in the following section.

# 3. Synthesis of $SF_5$-isoxazolidines

In the next part of our project, we were investigating 1,3-dipolar cycloaddition reactions of $SF_5$-acrylic esters and amides with various substituted nitrones. The aim was to synthesize first $SF_5$-substituted isoxazolidines (Figure 42). Before describing our attempts in detail, we will shortly present the general information about 1,3-dipolar cycloaddition reactions of nitrones.

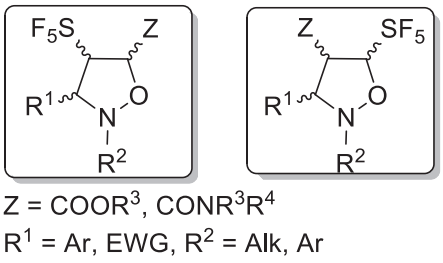


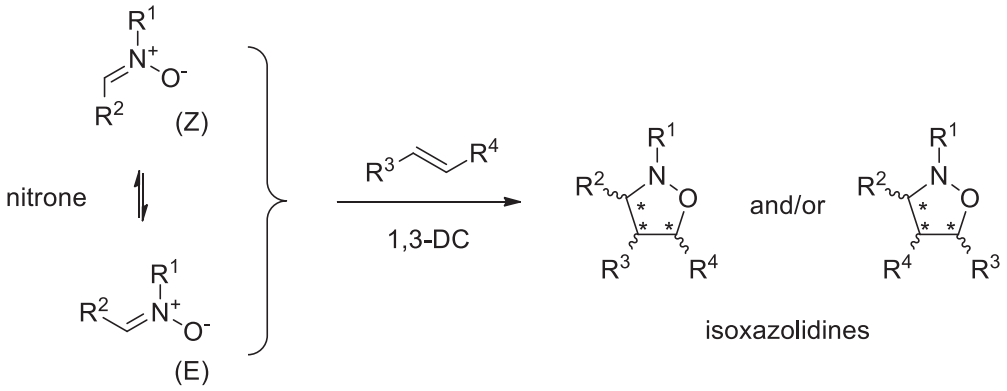

**Figure 42: Targeted $SF_5$-substituted isoxazolidines.**

[107] Yarmolchuk, V. S.; Shishkin, O. V.; Starova, V. S.; Zaporozhets, O. A.; Kravchuk, O.; Zozulya, S.; Komarov, I. V.; Mykhailiuk, P. K. *Eur. J. Org. Chem.* **2013**, 3086.

## 3.1. 1,3-Dipolar cycloadditions with nitrones

### 3.1.1. Generalities

Nitrones were synthesized for the first time in 1890 by Beckmann.[108] These compounds can be easily prepared from aldehydes, amines, imines or oximes.[109] Since they can react with a wide variety of unsaturated compounds (alkenes, alkynes, allenes, isocyanates, nitriles etc.), nitrones are attractive building-blocks. Among all these reactions, the most common one is the 1,3-dipolar cycloaddition with alkenes, leading to isoxazolidines (Scheme 95), which are an important class of heterocycles. These compounds can be submitted to further transformations: the opening of isoxazolidine ring by N–O bond cleavage via reduction, alkylation or oxidation to other nitrones could give rise to several new functional groups.[110] As a consequence, nitrones have been largely used for the synthesis of various natural products, especially sugars, nucleoside analogues, β-lactams or alkaloids.[111]




**Scheme 95: 1,3-Dipolar cycloaddition of nitrones with alkenes leading to substituted isoxazolidines.**

An important aspect of 1,3-dipolar cycloaddtion reactions of nitrones is the regioselectivity. In cycloadditions of non-polarized alkenes, steric factors play an important role. Generally, the most hindered extremity of the dipolarophile adds to the oxygen atom of the nitrone, leading to 5-substituted isoxazolidine (Scheme 96, (a)).[112]

[108] Beckmann, E. *Ber. Dtsch. Chem. Ges.* **1890**, *23*, 3331.
[109] (a) Grigor'ev, I. A. in *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis*; Feuer, H. (Ed.), John Wiley & Sons Inc., Hoboken, New Jersey, 2008; p. 129. (b) Tufariello, J. J. in *1,3-Dipolar Cycloaddition Chemistry*; Padwa., A. (Ed.), Wiley, New York, 1984; Vol. 1, p. 1.
[110] Nguyen, T. B.; Martel, A.; Dhal, R.; Dujardin, G. *Org. Lett.* **2008**, *20*, 4493.
[111] Jones, R. C. F.; Martin, J. N. in *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A.; Pearson, W. H. (Eds.), John Wiley & Sons Inc., New York, 2002; p. 1.
[112] Black, D. St. C.; Crozier, R. F.; Davis, V. C. *Synthesis* **1975**, 205.

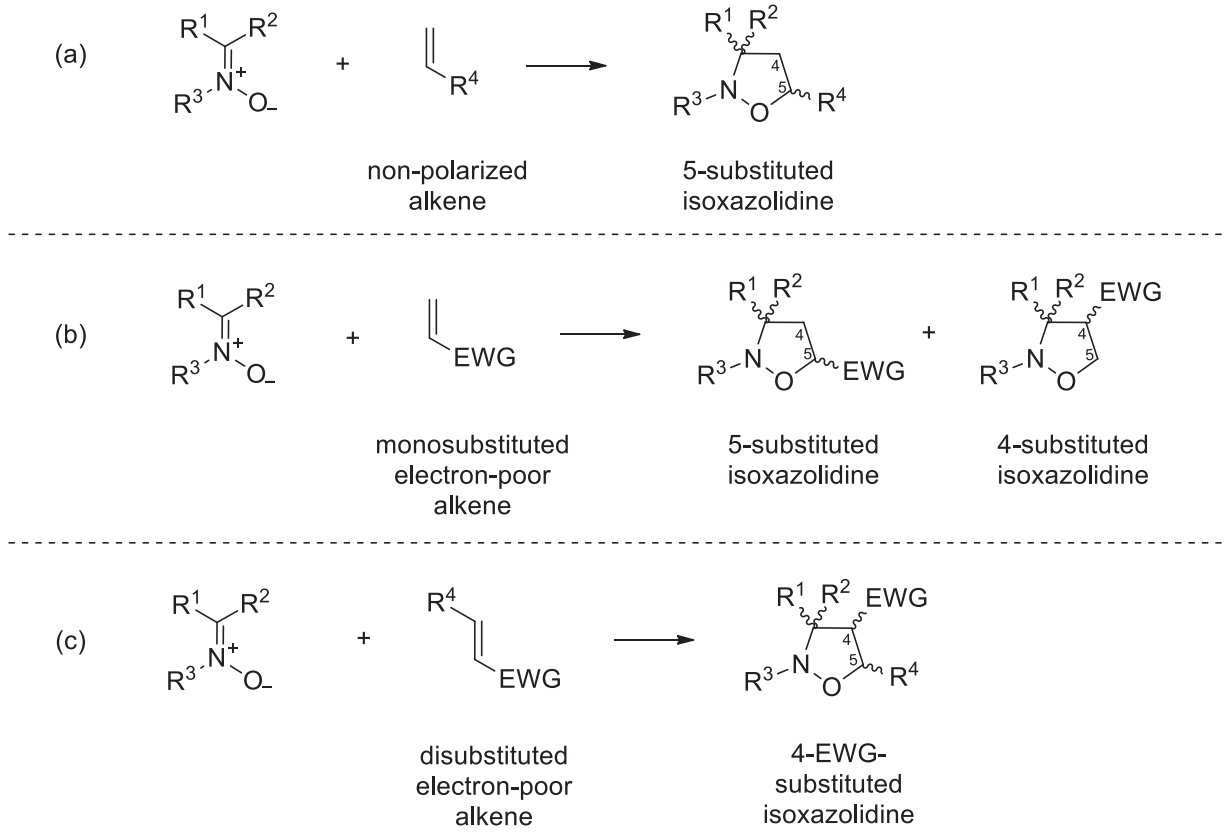
However, in the case of 1,3-dipolar cycloadditions of electron-poor alkenes, steric factors can be counterbalanced by electronic effects, and the "usual regioselectivity" can be reversed. This phenomenon can be explained by the fact that the transition state of the concerted 1,3-dipolar cycloaddition reaction is controlled by the frontier molecular orbitals (FMO) of the substrates. Three main cases of 1,3-dipolar cycloaddition reactions of nitrones are therefore observed, depending on the alkene substitution:

(a) 1,3-Dipolar cycloaddition of electron-rich or electron-neutral alkenes – the reaction is controlled by the $LUMO_{nitrone}$-$HOMO_{alkene}$ interaction. The $LUMO_{nitrone}$ has the largest coefficient at the carbon atom and the $HOMO_{alkene}$- at the terminal carbon. Therefore, 5-substituted isoxazolidines are obtained, which is also supported by the steric factors (Scheme 96, (a)).

(b) 1,3-Dipolar cycloaddition of monosubstituted alkenes with an EWG – the reaction is controlled by the $HOMO_{nitrone}$-$LUMO_{alkene}$ interaction. The $HOMO_{nitrone}$ has the largest coefficient at the oxygen atom and the $LUMO_{alkene}$- at the terminal carbon. In this case, the formation of 4-substituted isoxazolidines is favoured. However, mixture of 4- and 5-regioisomers is often obtained, as the steric factors are counterbalanced by the electronic effects (Scheme 96, (b)).

(c) 1,3-Dipolar cycloaddition of 1,2-disubstituted alkenes with an EWG – the reaction is controlled by the same FMO as in the case (b); however, the steric factor is eliminated and as the consequence the 4-EWG-substituted isoxasolidines are exclusively obtained (Scheme 96, (c)).[109b,113]

[113] Gothelf, K. V. in *Cycloaddition Reaction in Organic Synthesis*; Kobayashi, S.; Jorgensen, K. A. (Eds.), Wiley-VCH Verlag GmbH, Weinheim, 2002; p. 211.




**Scheme 96: (a) 1,3-Dipolar cycloadditions with non-polarized alkenes; (b) 1,3-dipolar cycloadditions with monosubstituted electron-poor alkenes; (c) 1,3-dipolar cycloadditions with disubstituted electron-poor alkenes.**

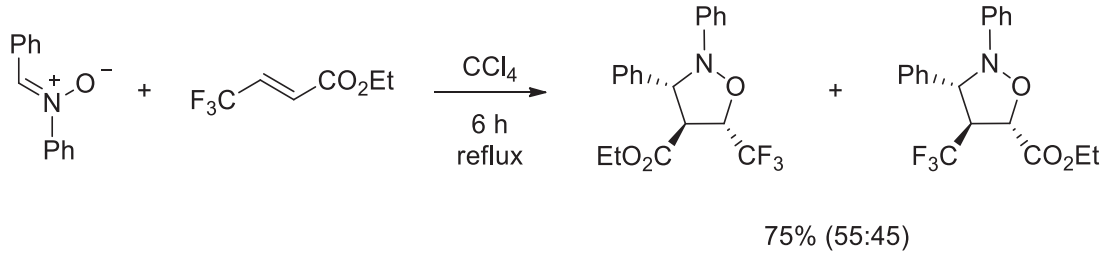
### 3.1.2. 1,3-Dipolar cycloaddition of nitrones with trifluoromethyl acrylates

In the literature, there are only few examples of 1,3-dipolar cycloadditions of nitrones with functionalized alkenes bearing the trifluoromethyl group. Reviewing the literature, we focused our attention on the reactions of $CF_3$-acrylates, as these compounds are structurally close to our pentafluorosulfanylated derivatives.

In 1991, Bravo *et al.* synthesized trifluoromethylated isoxazolidines from ethyl 4,4,4-trifluorocrotonate and *C,N*-diphenylnitrone (Scheme 97).[114] The cycloadducts were obtained in a good yield, as a mixture of two regioisomers (55:45). This lack of the regioselectivity

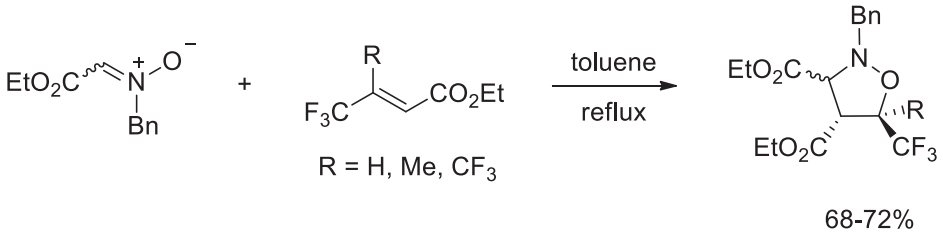
[114] Bravo, P.; Bruché, L.; Mele, A.; Zecchi, G. *J. Chem. Res.* **1991**, *81*, 719.

was assigned to the competitive influence of two EWG located on the C=C double bond of the dipolarophile.[114]




**Scheme 97: 1,3-Dipolar cycloadditions of ethyl 4,4,4-trifluorocrotonate with *C,N*-diphenylnitrone.**

One year later, 1,3-dipolar cycloaddition reactions using the same unsaturated ester and its substituted (R = Me, $CF_3$) derivatives with *N*-benzyl-*C*-ethoxycarbonylnitrone were described (Scheme 98).[115] These reactions were reported to be totally regioselective. The only obtained regioisomer was the one bearing the $CF_3$-group on the carbon C-5 of the isoxazolidine ring. The diastereoselectivity varied from 100:0 to 33:67, depending on the substitution of dipolarophiles.[115]




**Scheme 98: 1,3-Dipolar cycloadditions of ethyl 4,4,4-trifluorocrotonate derivatives with *N*-benzyl-*C*-ethoxycarbonylnitrone.**

To the best of our knowledge, no example of pentafluorosulfanylated isoxazolidines was reported up to date; therefore, we were interested in their synthesis.

[115] Bravo, P.; Bruché, L.; Fronza, G.; Zecchi, G. *Tetrahedron* **1992**, *44*, 9775.

## 3.2. 1,3-Dipolar cycloadditions of $SF_5$-acrylic derivatives with nitrones

### 3.2.1. Optimization and scope

In order to synthesize the new pentafluorosulfanylated isoxazolidines, we envisaged the use of some readily accessible nitrones, as depicted on Figure 43.

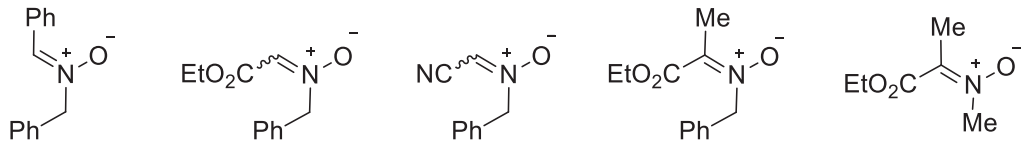
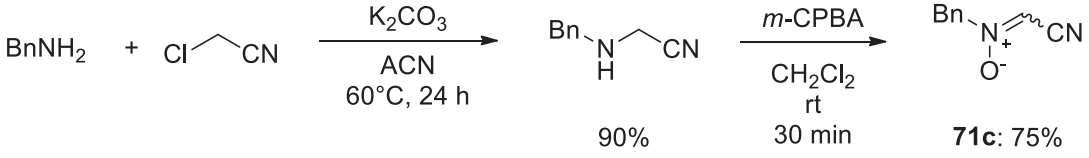



**Figure 43: Nitrones 71a-e used in this study.**

Compounds **71a, 71b, 71d** and **71e** were prepared by Dr. Mathieu Laurent (Université du Maine), as pure *E*- or *Z*-stereoisomers, except for the nitrone **71b**, which was obtained as a (2:1) mixture of *E/Z*-isomers.[116]

Nitrone **71c** was prepared by us in a two-step synthesis, according to the literature.[117] First, the monocyanomethylation of benzyl amine was performed, leading to *N*-benzyl-*N*-cyanomethylamine in 90% yield. The next step was the oxidation of the latter with *m*-CPBA, to give nitrone **71c** in 75% yield (Scheme 99). This compound, was obtained as a (7:3) mixture of *E*- and *Z*-stereoisomers. In the solid state, the *Z*-isomers of nitrones **71b**,**c** are predominant. However, in solution a rapid *E/Z*-equilibrium occurs at room temperature, as a result of the resonance effect between the nitrone moiety and the EWG.[118]

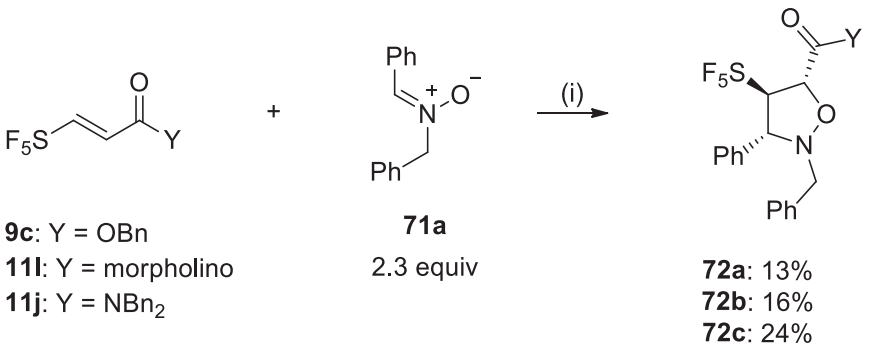



**Scheme 99: Two-step synthesis of nitrone 71c.**

[116] Nguyen, T. B.; Beauseigneur, A.; Martel, A.; Dhal, R.; Laurent, M. ; Dujardin, G. *J. Org. Chem.* **2010**, *75*, 611.
[117] Tokuyama, H.; Kuboyama, T.; Amano, A.; Yamashita, T.; Fukuyama, T. *Synthesis* **2000**, 1299.
[118] (a) Inouye, Y.; Hara, J.; Kakisawa, H. *Chem. Lett.* **1980**, 1407. (b) Inouye, Y.; Takaya, K.; Kakisawa, H. *Bull. Chem. Soc. Japan* **1983**, *56*, 3541. (c) Tamura, O.; Mita, N.; Imai, Y.; Nishimura, T.; Kiyotani, T.; Yamasaki, M.; Shiro, M.; Morita, N.; Okamoto, I.; Takeya, T.; Ishibashi, H.; Sakamoto, M. *Tetrahedron* **2006**, *62*, 12227.

Initially, we focused our attention on the reactions of our acrylic $SF_5$-building blocks with the usual nitrone **71a** (Scheme 100). The first attempt of cycloaddition of $SF_5$-benzylic ester **9c** with **71a** (1.3. equiv) in $CH_2Cl_2$ at room temperature for 12 h, or in refluxing DCE for 12 h, failed (conversion: ~0%). After stirring the ester **9c** and nitrone **71a** neat at 100°C for 20 h, we observed the formation of a new pentafluorosulfanylated product; however, the starting ester **9c** was still present in the reaction mixture (~55% according to $^{19}F$ NMR). Increasing the time of reaction did not improve the conversion. The final product **72a** was isolated in 13% yield. In order to improve the yield, we increased the temperature of the reaction up to 150°C, but after 3.5 h, we observed partial degradation of the final product. The same effect was observed when the reaction was performed at 150°C under microwave irradiation (200 W).

When changing the ester **9c** for the secondary amide **11l**, the corresponding isoxazolidine **72b** was obtained in 16% yield. Dibenzylamide **11j** was shown to be a little more reactive toward nitrone **71a**, as the corresponding cycloadduct **72c** was formed in a slightly better yield of 24%. Nevertheless, in all 1,3-dipolar cycloaddition reactions with nitrone **71a**, we observed low conversions (no more than ~50%) – the starting ester and amides were always recovered from the reaction mixtures, even after a long reaction time. It is worth noting that all cycloadducts **72a-c** were obtained as only one regio- and diastereoisomer. The regio- and diastereoselectivities of these reactions will be discussed in the Section 3.2.3.




**9c**: Y = OBn
**11l**: Y = morpholino
**11j**: Y = $NBn_2$

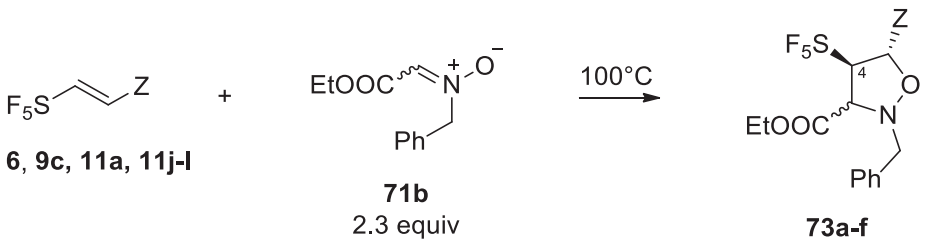
**71a**
2.3 equiv

**72a**: 13%
**72b**: 16%
**72c**: 24%

**Scheme 100: 1,3-Dipolar cycloadditions of $SF_5$-building blocks 9c, 11l and 11j with nitrone 71a. Reagents and conditions: (i) 100°C, neat, 20 h.**

We then turned our attention to the nitrone **71b** which is known to be more reactive.[118c] Cycloaddition reactions were performed under two sets of conditions: in nitromethane at 100°C (a polar solvent could enhance the dipole reactivity), or neat at 100°C. In both cases,

the reactions of ester **9c** with nitrone **71b** afforded the isoxazolidine **73a** in low yields (13-15%, Table 16, entries 1 and 2), as a mixture of two diastereoisomers. To our delight, reactions of dibenzylamide **11j** and morpholinoamide **11l** with nitrone **71b** (Table 16, entries 3-6) gave the corresponding cycloadducts **73b** and **73c** with significantly better yields (50% and 46% respectively), as mixtures of diastereoisomers. Long-chain tertiary amide **11k** reacted also with nitrone **71b** to give isoxazolidine **73d** with a moderate 31% yield (Table 16, entry 7). When the secondary amide **11a** was reacted with the nitrone **71b**, the corresponding isoxazolidine **73e** was diastereoselectively obtained in 17% yield (Table 16, entry 8). Finally, when we performed the reaction with the $SF_5$-allylic acetate **6**, the isoxazolidine **73f** was obtained in 23% yield as only one diastereoisomer (Table 16, entry 9). This last result showed that $SF_5$-derivative bearing an electron donating group on the double bond, led to similar yield and the same regioselectivity as the electron-poor $SF_5$-derivatives **6** or **8**. Conclusions of all attempts of cycloadditions with nitrone **37b** are as follows: firstly, the reactions in nitromethane required longer time, leading to lower conversions and yields, than those without solvent (Table 16, entries 2, 4, 6 vs 1, 3, 5). Secondly, increasing either the reaction time or heating at higher temperature did not improve the conversion of the reaction, because a partial degradation of the final product was observed. Thirdly, in all reactions we observed the total regioselectivity – only the cycloadducts bearing $SF_5$-group on carbon C-4 of isoxazolidine ring were obtained. Finally, since nitrone **71b** was used as a mixture of *E*- and *Z*-stereoisomers, most of the isoxazolidines in this series was obtained as mixtures of diastereoisomers, except for the derivatives **73e** and **73f**.

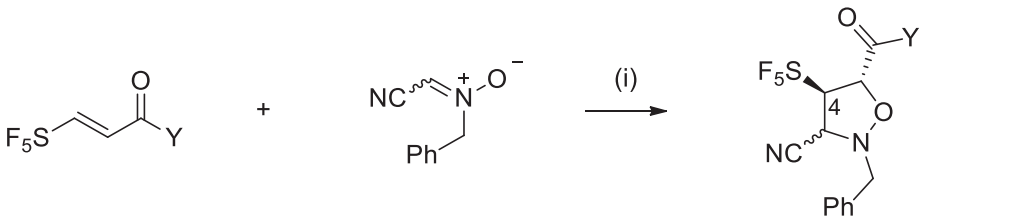


| Entry | $SF_5$-derivative | Z | Solvent | Time (min) | $SF_5$-derivative **6**, **9c**, **11a** or **11j-l** : isoxazolidine **73a-f**[a] | dr[b] | Yield (%)[c] |
|---|---|---|---|---|---|---|---|
| 1 | **9c** | COOBn | neat | 40 | 20:80 | 67:33 | **73a**: 15 |
| 2 | **9c** | COOBn | $CH_3NO_2$ | 90 | 35:65 | 86:14 | **73a**: 13 |
| 3 | **11j** | $CONBn_2$ | neat | 25 | 9:91 | 50:50 | **73b**: 50 |
| 4 | **11j** | $CONBn_2$ | $CH_3NO_2$ | 90 | 28:72 | 54:46 | **73b**: 30 |
| 5 | **11l** | CON-morpholino | neat | 40 | 14:86 | 55:45 | **73c**: 46 |
| 6 | **11l** | CON-morpholino | $CH_3NO_2$ | 90 | 29:71 | 58:42 | **73c**: 35 |
| 7 | **11k** | $CON(C_6H_{13})_2$ | neat | 60 | 20:80 | 50:50 | **73d**: 31 |
| 8 | **11a** | CONHBn | neat | 60 | 50:50 | 100:0 | **73e**: 17[d] |
| 9 | **6** | $CH_2OAc$ | neat | 300 | 50:50 | 100:0 | **73f**: 23 |

[a] According to $^{19}F$ NMR of reaction mixture.
[b] Calculated from $^{19}F$ NMR of crude product.
[c] Isolated yield.
[d] Isoxazolidine contaminated by **11a**, yield calculated from $^{1}H$ NMR.

**Table 16: 1,3-Dipolar cycloaddition of compounds 6, 9c, 11a and 11j-l with nitrone 71b.**

As the nitrone **71b** bearing an electron withdrawing group led to the isoxazolidines **73a-f** with better yields (up to 50%) than its phenyl analogue **71a**, we were expecting good results with the activated nitrone **71c**, as well. Unfortunately, the replacement of the ester group by the cyano one did not bring any improvement. Isoxazolidines **74a**,**b** were obtained with lower yields (13% and 20%, respectively) than the corresponding cycloadducts **73a-f** (Scheme 101). Moreover, longer reaction times were required (13-21 h instead of 40 minutes). Only 4-$SF_5$-regioisomers were formed in these reactions. All isoxazolidines in this series were also obtained as mixtures of diastereoisomers, which is in accordance with the stereochemistry of the starting nitrone **71c**.



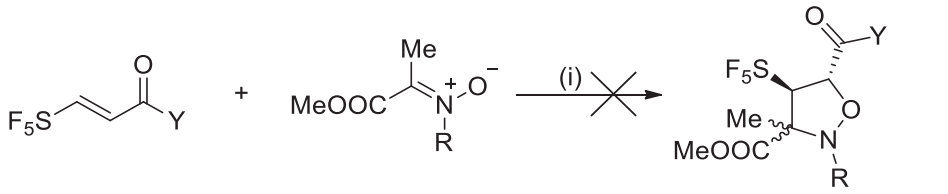

**9c**: Y = OBn
**11l**: Y = morpholino

**71c**
2.3 equiv

**74a**: 13% (dr = 77:23)
**74b**: 20% (dr = 75:25)[a]

**Scheme 101: 1,3-Dipolar cycloaddition of building blocks 9c, 11l and 11k with nitrone 71c. Reagents and conditions: (i) 100°C, neat, 13-21 h.**
**[a] Product 74b was contaminated by the starting amide 11l and nitrone 71c.**

Nitrones **71d** and **71e**, with an additional methyl substituent on the double bond, turned out to be bad partners in 1,3-dipolar cycloaddition reactions with our $SF_5$-building-blocks. We made several attempts of reactions of these dipoles with ester **9c** and amide **11j**, but even after long reaction times (14-20 h), neat, at 100°C, only traces of the expected isoxazolidines were observed (Table 17). This lack of reactivity could be probably explained by both the steric hindrance of nitrones **71d**,**e** and the bulkiness of the $SF_5$-group.




**9c**: Y = OBn
**11j**: Y = $NBn_2$

**71d**: R = Bn
**71e**: R = Me

**75:** Y = OBn, R = Bn
**76a**: Y = OBn, R = Me
**76b**: Y = $NBn_2$, R = Me

| Entry | $SF_5$-derivative | Nitrone | Z | Time (h) | $SF_5$-derivative **9c** or **11j** : isoxazolidine **75**, **76a-b**[a] |
|---|---|---|---|---|---|
| 1 | **9c** | **71d** | COOBn | 17 | 93:7 |
| 2 | **9c** | **71e** | COOBn | 14 | 96:4 |
| 3 | **11j** | **71e** | $CONBn_2$ | 19 | 96:4 |

[a] According to $^{19}F$ NMR of reaction mixture.

**Table 17: 1,3-Dipolar cycloadditions of building blocks 9c and 11j with nitrones 71d and 71e. Reagents and conditions: (i) 100°C, neat, 14-20 h.**

### 3.2.2. Structural determination of $SF_5$-isoxazolidines 72-74

In the reactions of $SF_5$-ester **9c**, amides **11** and acetate **6** with nitrones **71a-c**, all the cycloadducts were obtained as a unique regioisomer, bearing the $SF_5$-group on the position 4 of the isoxazolidine ring. Regarding the diastereoselectivity of these reactions, some heterocycles were obtained as diastereoisomeric mixtures, whereas others as only one diastereoisomer, depending on the configuration of nitrone and the substituents on the dipolarophile.

The regiochemistry of compounds **72-74** was determined from their $^{1}H$, $^{13}C$, 2D NMR data and X-ray diffraction analysis. In $^{13}C$ NMR spectra of all cycloadducts, we observed the presence of three different carbons coupled with fluorines: C-3 ($^{3}J_{C,F}$ = 3-4 Hz), C-4 ($^{2}J_{C,F}$ = 10-14 Hz) and C-5 ($^{3}J_{C,F}$ = 4-5 Hz) (Figure 44, (a)). In the case of the 5-$SF_5$-regioisomer, there would be no coupling between carbon C-3 and the fluorine atoms, because of the too long distance between these atoms. In consequence, we would observe only two coupled carbons (C-4 and C-5) on the $^{13}C$ NMR spectra (Figure 44, (b)).

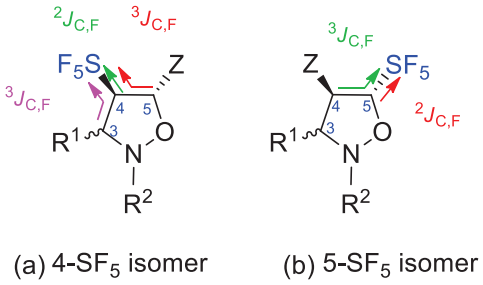



**Figure 44: Possible carbon-fluorine couplings in 4- and 5-$SF_5$-isoxazolidines.**

The second argument for the formation of 4-$SF_5$ substituted isoxazolidine, came from the COSY experiment. The proton ($H^A$) adjacent to the $SF_5$ group showed two strong $^{3}J$ correlations with both protons, $H^B$ and $H^C$. It means that the $SF_5$-group is located at the carbon C-4 (Figure 45, (a)). The other isomer would bear the pentafluorosulfanyl substituent at the carbon C-5, and in this case the proton $H^A$ would show only the $^{3}J$ correlation with the proton $H^B$. Moreover the $^{3}J$ correlations between protons $H^B$ and $H^C$ would be present, which is not the case in the COSY spectra (Figure 45, (b)).

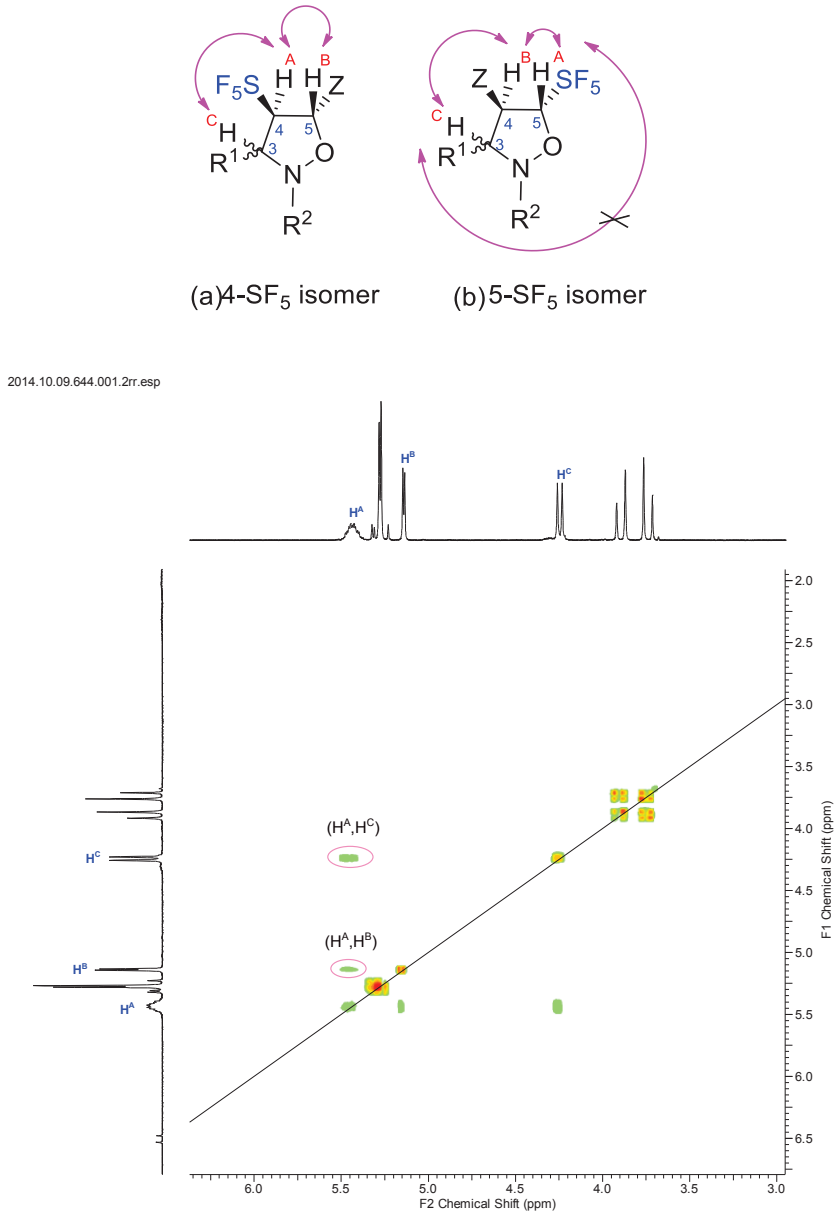


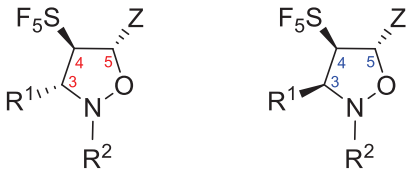

**Figure 45: $^{3}J_{H,H}$ correlations in 4- and 5-$SF_5$-isoxazolidines (COSY experiment of isoxazolidine 72a).**

Finally, the X-ray diffraction analysis of the isoxazolidine **73c** (Figure 46), confirmed the placement of the $SF_5$ group at the carbon C-4 of the ring. This analysis also proved the *trans*-relationship between the 4-$SF_5$-substituent and the 5-amide group, which is in accordance with the stereochemistry of the starting dipolarophile **11l**. The *trans*-configuration between the 4-$SF_5$-substituent and the 3-ester group was proved as well.


**73c**

**Figure 46: X-Ray structure of isoxazolidine 73c.**

A comparison of selected $^{19}F$ and $^{13}C$ NMR chemical shifts and some coupling constants was made, for the set of compounds **73a-f** (Table 18). The diastereoisomeric ratios varied from 50:50 (for compounds **73b,d**) to 100:0 (for compounds **73e**,**f**). The values of chemical shifts for the $SF_5$-group ($^{19}F$ NMR) as well as for the carbons C-3, C-4 and C-5 ($^{13}C$ NMR), were very similar for diastereoisomer n°1 of all isoxazolidines **73a-f** (red colour in Table 18). We observed the same regularity for the second diastereoisomers (blue colour in Table 18). These data clearly indicated a strong similarity of the chemical environments in both series of diastereoisomers. As the 3,4-*trans* and 4,5-*trans* configurations of the major diastereoisomer of compound **73c** were proved by X-ray diffraction analysis, we could reasonably assign the same configurations for all major diastereoisomers of isoxazolidines. The trend seems to be the same for heterocycles **72a-c** and **74a-c**; therefore, this proposal could be extended to other cycloadducts.




| | **73a** Dia 1 | **73a** Dia 2 | **73b** Dia 1 | **73b** Dia 2 | **73c** Dia 1 | **73c** Dia 2 | **73d** Dia 1 | **73d** Dia 2 | **73e** only 1 Dia | **73f** only 1 Dia |
|---|---|---|---|---|---|---|---|---|---|---|
| dr | 86:14 | | 50:50 | | 55:45 | | 50:50 | | 100:0 | 100:0 |
| $^{19}F$ | 61.4 (dd, $^2J_{F,F}$= 147.4 Hz, $^3J_{F,H}$ = 5.2 Hz, 4F) | 67.6 (dm, $^2J_{F,F}$ = 147.4 Hz, 4F) | 62.2 (dd, $^2J_{F,F}$ = 146.5 Hz, $^3J_{F,H}$ = 6.1 Hz, 4F) | 68.7 (dm, $^2J_{F,F}$ = 147.4 Hz, 4F) | 61.7 (dd, $^2J_{F,F}$ = 146.5 Hz, $^3J_{F,H}$ = 6.1 Hz, 4F) | 68.2 (dm, $^2J_{F,F}$ = 145.7 Hz, 4F) | 62.2 (dd, $^2J_{F,F}$ = 145.7 Hz, $^3J_{F,H}$ = 5.2 Hz, 4F) | 68.5 (dm, $^2J_{F,F}$ = 147.4 Hz, 4F), | 60.6 (dd, $^2J_{F,F}$ = 146.5 Hz, $^3J_{F,H}$ = 6.1 Hz, 4F) | 62.0 (dd, $^2J_{F,F}$ = 146.5 Hz, $^3J_{F,H}$ = 6.1 Hz, 4F) |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 71.0 ($q_t$, $^3J_{C,F}$ = 4.1 Hz) | 70.6 ($q_t$, $^3J_{C,F}$ = 3.5 Hz) | 68.1 ($q_t$, $^3J_{C,F}$ = 2.0 Hz) | 71.3 ($q_t$, $^3J_{C,F}$ = 3.9 Hz) | 67.9 (m) | 70.3 ($q_t$, $^3J_{C,F}$ = 3.3 Hz) | 67.6 ($q_t$, $^3J_{C,F}$ = 2.6 Hz) | 71.5 ($q_t$, $^3J_{C,F}$ = 4.0 Hz) | 70.4 ($q_t$, $^3J_{C,F}$ = 3.9 Hz) |
| $^{13}C$ | 77.6 ($q_t$, $^3J_{C,F}$ = 4.6 Hz) | 77.2 ($q_t$, $^3J_{C,F}$ = 4.6 Hz) | 75.6 (m) | 77.1 ($q_t$, $^3J_{C,F}$ = 4.4 Hz) | 75.4 (m) | 77.0 ($q_t$, $^3J_{C,F}$ = 4.6 Hz) | 75.4 (m) | 78.4 ($q_t$, $^3J_{C,F}$ = 4.0 Hz), | 76.7 ($q_t$, $^3J_{C,F}$ = 4.2 Hz) |
| | 89.3 ($q_t$, $^2J_{C,F}$ = 12.6 Hz) | 88.0 ($q_t$, $^2J_{C,F}$ = 24.0 Hz) | 85.6 ($q_t$, $^2J_{C,F}$ = 13.3 Hz) | 87.8 ($q_t$, $^2J_{C,F}$ = 11.8 Hz) | 85.3 ($q_t$, $^2J_{C,F}$ = 13.8 Hz) | 87.9 ($q_t$, $^2J_{C,F}$ = 11.1 Hz) | 85.8 ($q_t$, $^2J_{C,F}$ = 12.6 Hz) | 89.9 (m) | 88.7 ($q_t$, $^2J_{C,F}$ = 10.9 Hz) |

**Table 18: $^{19}F$ and $^{13}C$ NMR data for isoxazolidines 73a-f.**

### 3.2.3. Explanation of the regioselectivity and diastereoselectivity

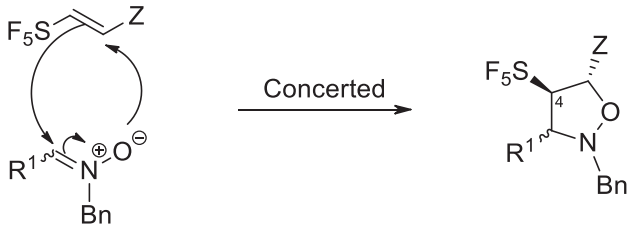
Having established the exact structure of our pentafluorosulfanylated isoxazolidines, we can conclude once again that there is a significant difference between the regioselectivity of 1,3-dipolar cycloadditions with the $SF_5$-dipolarophiles **6**, **9c** and **11**, and their $CF_3$-analogs. Indeed, in the reactions of $SF_5$-unsaturated compounds with nitrones **71a-c**, we observed exclusively the formation of 4-$SF_5$-isoxazolidines. This observation is different that the regioselectivity of the reactions of ethyl 4,4,4-trifluorocrotonate, in which the mixture of 4- and 5-regioisomers (Scheme 97) or only 5-$CF_3$-regioisomer (Scheme 98) were obtained.

Regarding previously described cycloadditions of nitrones with sulfur-substituted alkenes,[119] such reactions showed diverse regioselectivities. 1,3-Dipolar cycloadditions of sulfides led mainly to the regioisomer bearing the sulphur substituent on the carbon C-5 of the isoxazolidine ring. Reactions with sulfoxides gave the 4-substituted regioisomers, whereas sulfones generally led to the mixtures of both regioisomers.[119] Up to date nothing is known about the regioselectivity of the cycloadditions of nitrones with $SF_5$-substituted alkenes. However Dolbier *et al.*[69] recently reported the cycloadditions of $SF_5$-substituted acetylenes with *C,N*-arylnitrones. These reactions led exclusively to 4-$SF_5$-isoxazolines which is in accordance with our observations.

In order to explain the regioselectivity of 1,3-dipolar cycloadditions of our pentafluorosulfanylated compounds **9c**, **11** and **6** with nitrones, mechanistic investigations as

[119] Nguyen, T. B.; Martel, A.; Gaulon-Nourry, C.; Dhal, R.; Dujardin, G. *Org. Prep. Proc. Int.* **2012**, *44*, 1.

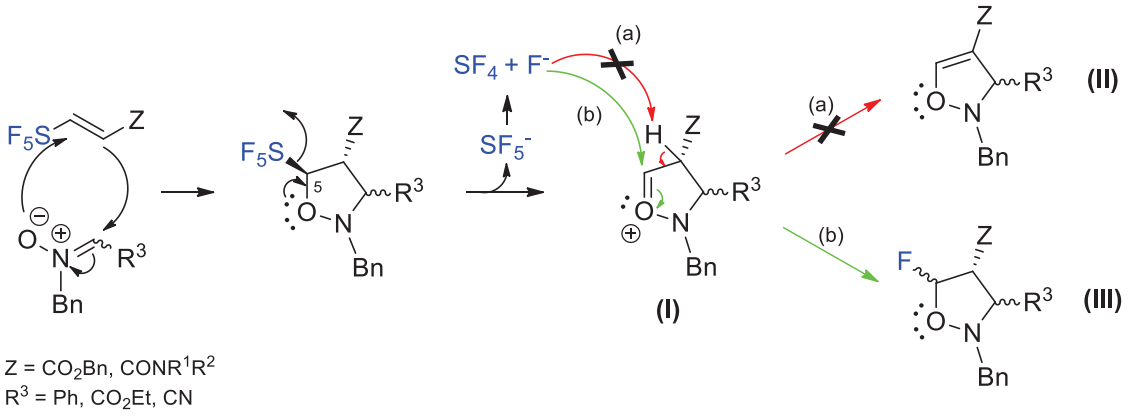
well as theoretical calculations were made (collaboration with Dr. V. Tognetti and Pr. L. Joubert). For 4-$SF_5$-regioisomers, we can easily explain its formation by a concerted 1,3-dipolar cycloaddition mechanism, in which both, O-C and C-C bonds, are formed simultaneously (Scheme 102).




**Scheme 102: Mechanism for the formation of 4-$SF_5$ regioisomers.**

Although no 5-$SF_5$-regioisomer was detected in the crude mixture, in most of the reactions we observed two singlets in $^{19}F$ NMR spectra (-153 ppm and +75 ppm respectively), which disappeared after the evaporation of the solvent. As an important part of the $SF_5$-material was lost in these cycloadditions (there were significant differences between the conversions and the isolated yields), we proposed a mechanism based on the elimination of pentafluorosulfanyl anion, as depicted in Scheme 103. First, the 5-$SF_5$-isoxazolidine could be formed via the 1,3-dipolar cycloaddition reaction. This cycloadduct would probably be unstable, due to the presence of the oxygen atom at the α-position of the $SF_5$-group, and an easy elimination of the pentafluorosulfanyl anion could occur. At this stage, the oxonium **(I)** and the pentafluorosulfanyl anion ($SF_5^-$) would be formed. The latter one could spontaneously decompose into $SF_4$, which is a gas, and the fluoride anion ($F^-$). Similar elimination of the $SF_5$-group was already described in the literature.[77] In the next part of these transformations, two pathways are possible: (a) the fluoride anion could behave as a base allowing the deprotonation of the oxonium **(I)** and leading to the corresponding non-fluorinated isoxazoline **(II)**; (b) the fluoride anion could behave as a nucleophile and attack the electrophilic carbon, leading to 5-fluoroisoxazolidine **(III)**. According to the experimental data, the compound **(II)** was not detected in the crude, whereas one of the observed $^{19}F$ NMR singlets (-153 ppm) could fit with monofluorinated derivatives **(III)**. Therefore, we selected the pathway (b) as more probable. Unfortunately, we have never recovered the 3-fluoro

isoxazolidine **(III)** after the silica gel chromatography. The proposed pathway (b) was also confirmed by a convergent DFT-CDFT-QTAIM theoretical study.[120]

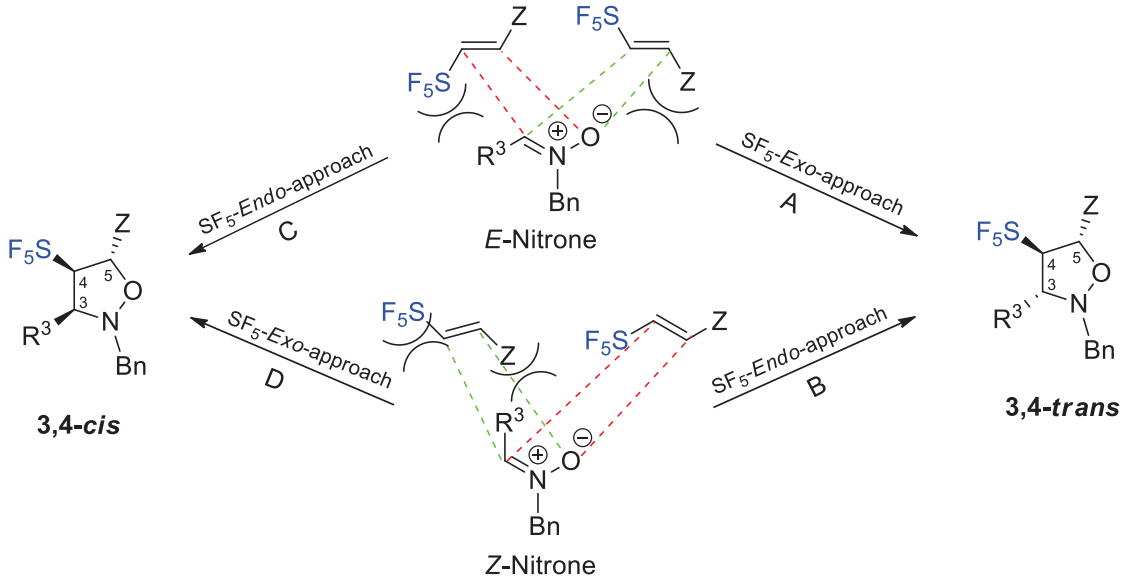



**Scheme 103: Proposed mechanism for the formation of 5-$SF_5$-regioisomer and its possible subsequent transformations.**

The second important issue to discuss is the diastereoselectivity of these cycloaddition reactions, which generally depends on the configuration of the starting nitrone, and on the substituents at the double C=C bond of dipolarophile. Only one diastereoisomer was detected in our reactions with nitrones possessing a fixed *E*- or *Z*-configuration, while either a sole diastereoisomer, or both diastereoisomeric isoxazolidines were obtained in the reactions with nitrones showing mixtures *E*/*Z*-configurations. To explain that, we depicted in Scheme 104 all possible *endo*- and *exo*- approaches of the $SF_5$-dipolarophile on the *E*- and *Z*-nitrones. In the cycloaddition reactions of nitrone **71a** having a pure *Z*-geometry, only the 3,4-*trans* diastereoisomers were obtained. Such configuration is probably the result of the *endo*-approach of the dipolarophile (approach B), which minimizes the steric interactions between the bulky $SF_5$-group and the phenyl substituent (on carbons C-4 and C-3, respectively). In the case of nitrones **71b** and **71c**, existing as mixtures of *E*- and *Z*-isomers, the 3,4-*trans*-isoxazolidines could be formed, as previously, by the *endo*-approach on the *Z*-nitrones (approach B), but also by the *exo*-approach on the *E*-nitrone (approach A). Both approaches minimize steric interactions between the $SF_5$- and the $R^3$-substituents; however, the approach A suffers simultaneously from the steric interactions between the Z-moiety and the nitrone. As a consequence, the approach A is possible only with less sterically demanding Z-groups, such as for example CONHBn (**73e**) or $CH_2OAc$ (**73f**), leading exclusively to 3,4-*trans*-

[120] Falkowska, E.; Laurent, M. Y.; Tognetti, V.; Joubert, L.; Jubault, P.; Bouillon, J.-P.; Pannecoucke, X. *Tetrahedron* **2015**, *71*, 8067.

diastereoisomer. For the alkenes with more bulky Z-group, $SF_5$-*endo*-approaches (B and C) are more favoured, thus the diastereoisomeric mixtures are obtained.



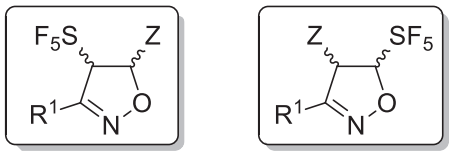

Z = $CO_2Bn$, $CONR^1R^2$, $CH_2OAc$; $R^3$ = Ph, $CO_2Et$, CN

**Scheme 104: Possible explanation of the favoured 3,4-*trans* relative configuration of isoxazolidines 73a-f.**

The stereoselectivity is therefore the resultant of the balance between two different steric interactions. If the $SF_5$-dipolarophile bears a bulky Z-substituent, then the $SF_5$-*endo*-approaches (B and C) will be favoured and a mixture of diastereoisomers will be obtained. In the opposite case, minimizing the steric interactions with $SF_5$-group will lead only to 3,4-*trans*-diastereoisomer (approaches A and B).

## 4. Attempts for the synthesis of $SF_5$-isoxazolines

Having successfully developped the synthesis of pentafluorosulfanylated pyrrolidines and isoxazolidines, we continued to explore the preparation of other $SF_5$-substituted five-membered heterocycles. Our next goal was to get the access to pentafluorosulfanylated isoxazolines (Figure 47), starting from $SF_5$-acrylic building-blocks.



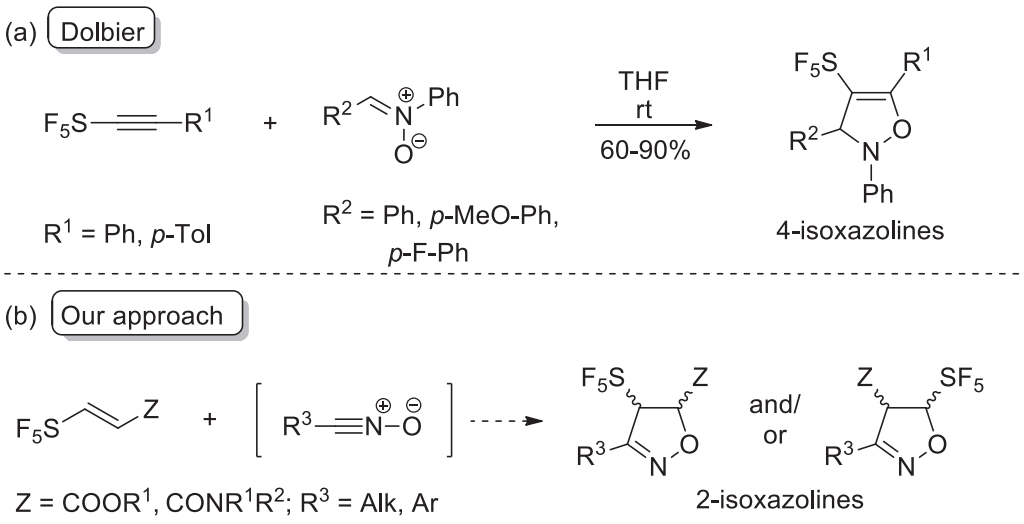

Z = $COOR^2$, $CONR^2R^3$
$R^1$ = Alk, Ar

**Figure 47: Targeted pentafluorosulfanylated isoxazolines.**

## 4.1. A brief state of the art

Similarly as other nitrogen-containing heterocycles, isoxazolines are present in many biologically active compounds and natural products.[121] Concerning their preparation, 1,3-dipolar cycloaddition reactions of alkenes or alkynes, with nitrile oxides or nitrones, respectively, are commonly used.

The synthesis of $SF_5$-substituted 4-isoxazolines, based on the 1,3-dipolar cycloaddition of $SF_5$-acetylenes with nitrones, was very recently reported (Scheme 105, (a)).[69] We decided to develop an alternative methodology, leading to pentafluorosulfanylated 2-isoxasolines, by the reaction of $SF_5$-acrylic derivatives with nitrile oxides (Scheme 105, (b)).

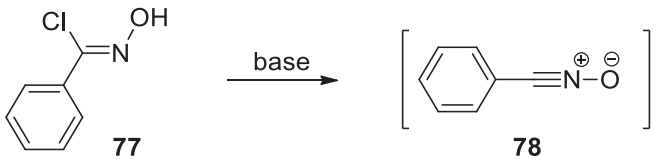



**Scheme 105: Synthesis of pentafluorosulfanylated isoxazolines.**

[121] (a) Zhang, P.; Wei, C.; Wang, E.; Wang, W.; Liu, M.; Yin, Q.; Chen, H.; Wang, Y.L.; Zhang, J. *Carbohydr. Res.* **2012**, *351*, 7. (b) Wang, Y.; Shao, Y.; Wang, L.; Fang, X.; Yu, X.; Zhi, C.; Yang, H.; Qu, X.; Yao, H.; Xu, J. *Agric. Food Chem.* **2012**, *60*, 8435.

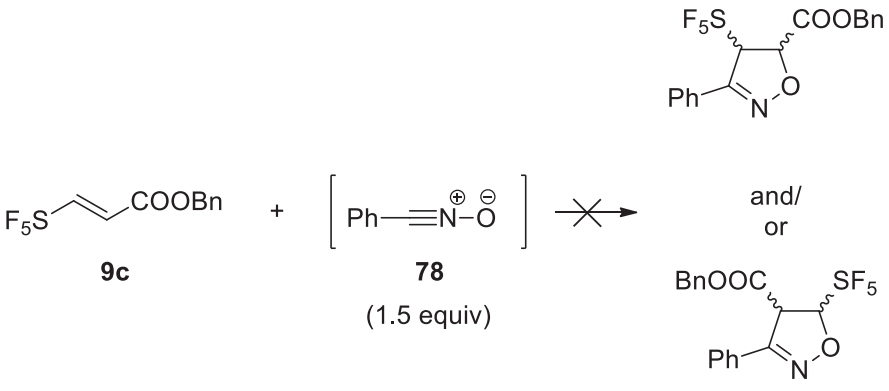
## 4.2. Attempts for 1,3-dipolar cycloadditions of $SF_5$-acrylic esters 9 and amides 11 with nitrile oxides 78, 81 and 83

We were first interested in the reactions of $SF_5$-acrylic ester **9c** with the common phenylnitrile oxide **78**, which could be generated from the corresponding benzohydroxyiminoyl chloride **77**, in the presence of a base (such as triethylamine), as depicted on Scheme 106.




**Scheme 106: Generation of phenylnitrile oxide 78.**

1,3-Dipolar cycloaddition of $SF_5$-derivative **9c** with *in situ* generated nitrile oxide **78** was first investigated (Table 19). No formation of the expected isoxazolines was observed either at room temperature, or in refluxing dichloromethane, even after 64 hours (Entries 1, 2). We have than performed a reaction in refluxing dichloroethane, but without any success (Entry 3). After the evaporation of the solvent and heating the residue at 110°C for 16 h, no conversion of the starting material was observed, as well (Entry 4). We have finaly performed the reaction in two-steps: first, the nitrile oxide **78** was prepared in the presence of NaOH in $Et_2O$ and isolated; then, it was reacted with the $SF_5$-ester **9c**, neat, at 140°C. Unfortunately we did not observe the formation of the desired $SF_5$-isoxazolines (Entry 5).



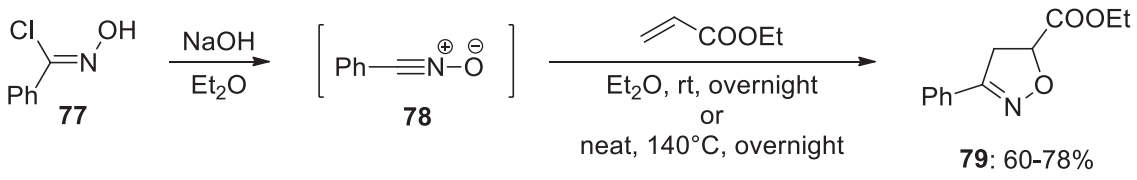
| Entry | Solvent | Temperature (°C) | Time (h) | Conversion (%)[a] |
|---|---|---|---|---|
| 1 | $CH_2Cl_2$ | rt | 12 | 0 |
| 2 | $CH_2Cl_2$ | 40 | 64 | 0 |
| 3 | DCE | 90 | 17 | 0 |
| 4 | neat | 110 | 17 | 0 |
| 5[b] | neat | 140 | 24 | 0 |

[a] According to $^{19}F$ NMR of the crude mixture.

[b] The reaction was performed in two steps.

**Table 19: Attempts for the 1,3-dipolar cycloaddition of $SF_5$-ester 9c with nitrile oxide 78.**

Taking into consideration a possible competitive dimerization of nitrile oxide **78**,[122] we performed a test reaction with non-fluorinated acrylate, with the objective to confirm the ability of nitrile oxide **78** to undergo 1,3-dipolar cycloaddition. By reacting nitrile oxide **78** with ethyl acrylate, the expected isoxazoline **79** was obtained in good yield (Scheme 107). Therefore, one may deduce that the lack of the reactivity in 1,3-dipolar cycloaddition of nitrile oxide **78** with ester **9c**, came from the $SF_5$-derivative, and not from the dipole. Such observation could be probably due to a high steric hindrance of the $SF_5$-substituent, as well as the competing electronic effects of the $SF_5$- and ester-group in compound **9c**.

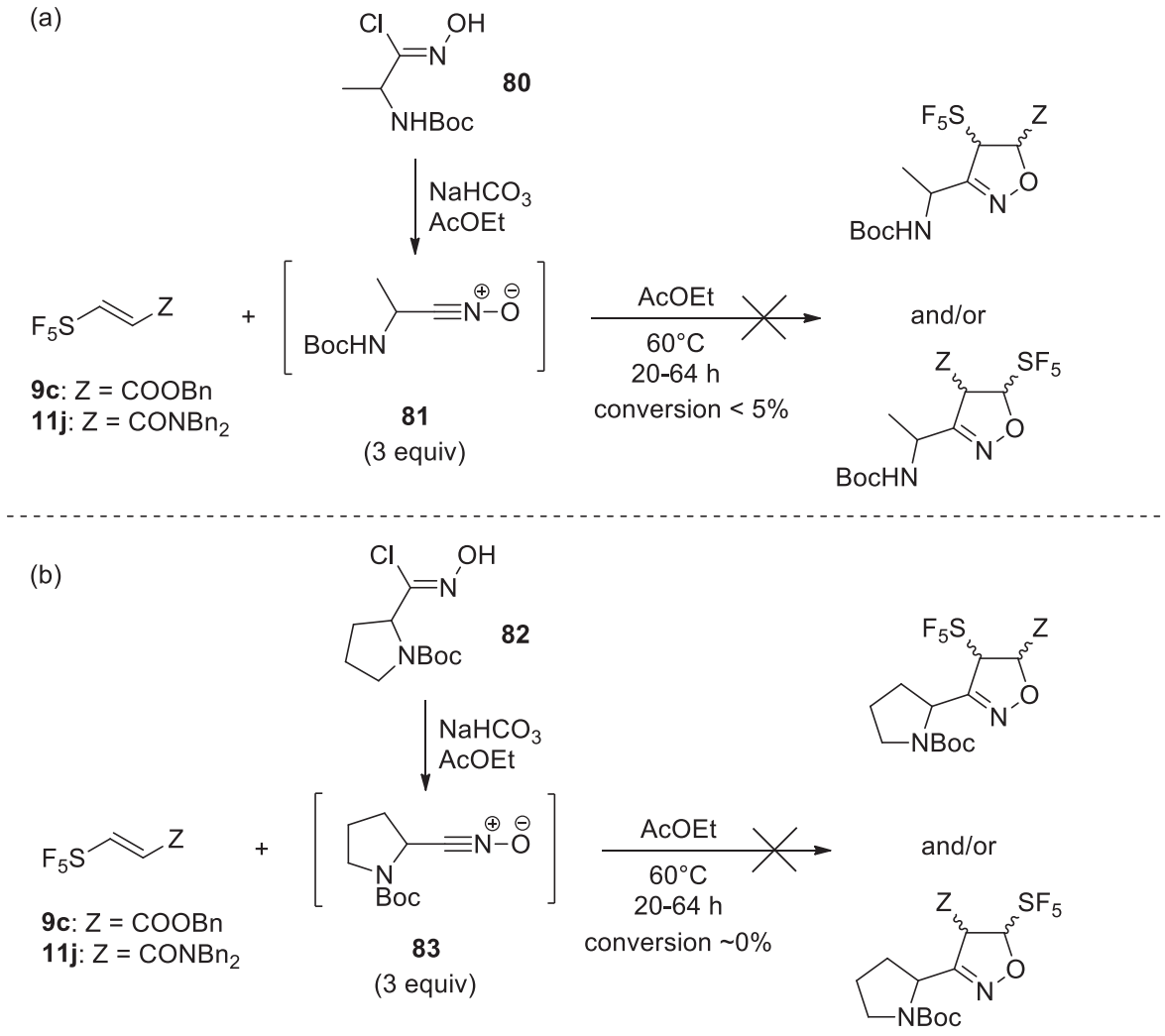



**Scheme 107: 1,3-Dipolar cycloaddition of acrylate n° with nitril oxide 78.**

We then turned our attention to the use of more reactive aliphatic nitrile oxide precursors **80** (Scheme 108, (a)) and **82** (Scheme 108, (b)), furnished by Dr. Pavel Mykhailiuk from Enamine Company, Ukraine. Unfortunately, neither the reactions with benzylic ester **9c**, nor those with dibenzylamide **11j** led to the formation of the expected

[122] Dubrovskiy, A.V.; Larock, R. C. *Org. Lett.* **2010**, *12*, 1180.

cycloadducts (Scheme 108). The $SF_5$-derivatives were completely recovered even at high temperature and after long reaction time.

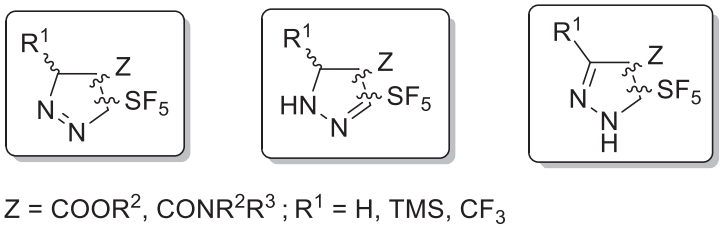



**Scheme 108: Attempts for 1,3-dipolar cycloadditions of $SF_5$-derivatives 9c and 11j with nitrile oxides 81 and 83.**

Discouraged by the lack of the reactivity of the pentafluorosulfanylated alkenes in all above described reactions, we abandoned this approach, and turned our attention to 1,3-dipolar reactions with other dipoles.

# 5. Attempts for the synthesis of $SF_5$-pyrazolines

As part of our research program for new pentafluorosulfanylated heterocycles, we were next interested in 1,3-dipolar cycloadditions of $SF_5$-esters **9** and amides **11** with diazomethane derivatives, which can potentially lead to new pentafluorosulfanylated pyrazolines (Figure 48).




$Z = COOR^2, CONR^2R^3$ ; $R^1 = H, TMS, CF_3$

**Figure 48: Targeted pentafluorosulfanylated pyrazolines.**

## 5.1. State of the art

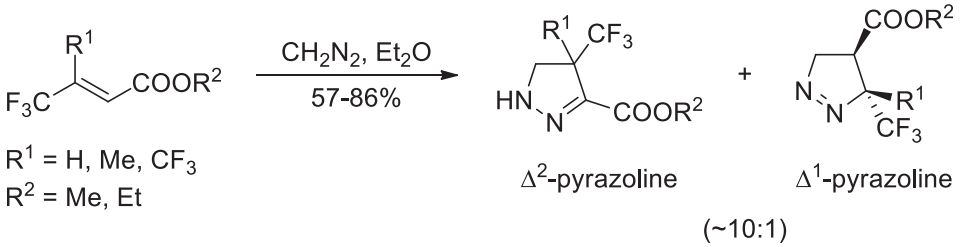
Pyrazolines do not only play an important role in drug discovery, displaying a broad spectrum of biological activities,[123] but they can also serve as precursors for the synthesis of other scaffolds, such as cyclopropanes, pyrazoles, or diamines.[124] Among all diazomethane derivatives which could be used in 1,3-dipolar cycloadditions, we were especially attracted by the easily available trimethylsilyldiazomethane and trifluoromethyldiazomethane.

Concerning the previously reported examples of 1,3-dipolar cycloaddition of electron-deficient alkenes with diazomethane and its derivatives, we first focused our attention on the reactions with trifluoromethylated acrylates. It has been reported that 1,3-dipolar cycloadditions of the $CF_3$-substituted acrylic derivatives with diazomethane proceeded

[123] (a) Kumar, S.; Bawa, S.; Drabu, S.; Kumar, R.; Gupta, H. *Recent Pat. Antiinfect. Drug Discov.* **2009**, *4*, 154. (b) Liu, X.-H.; Ruan, B.-F.; Li, J.; Chen, F.-H.; Song, B.-A.; Zhu, H.-L.; Bhadury, P.-S.; Zhao, J. *Mini-Rev. Med. Chem.* **2011**, *11*, 771. (c) Marella, A.; Ali, M.R.; Alam, M.T.; Saha, R.; Tanwar, O.; Akhter, M.; Shaquiquzzaman, M.; Mumtaz Alam, M. *Mini-Rev. Med. Chem.* **2013**, *13*, 921.

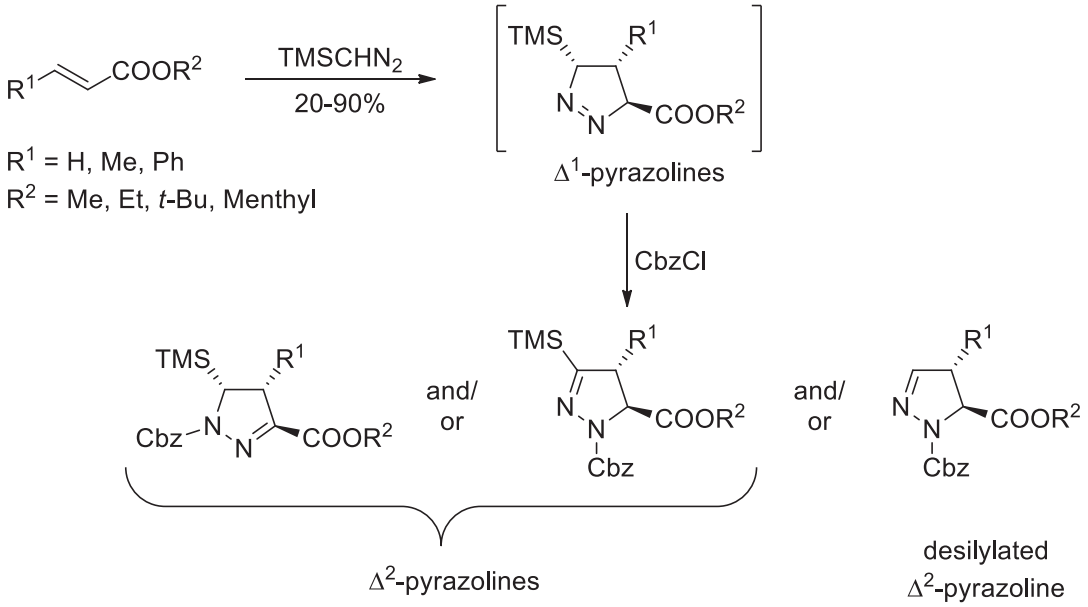
[124] (a) Padmavathi, V.; Kumari, C.P.; Venkatesh, B.C.; Padmaja, A. *Eur. J. Med. Chem.* **2011**, *46*, 5317. (b) Muralikrishna, A.; Venkatesh, B.C.; Padmavathi, V.; Padmaja, A.; Kondaiah, P.; Krishna, N.S. *Eur. J. Med. Chem.* **2012**, *54*, 605. (c) Chenevert, R.; Jacques, F. *Tetrahedron: Asymmetry* **2006**, *11*, 1017.

smoothly, leading to the corresponding cycloadducts in good yields (Scheme 109).[125] In most of cases, $\Delta^2$-pyrazoline was obtained as the sole, or largely predominant, product.




**Scheme 109: 1,3-Dipolar cycloadditions of diazomethane with $CF_3$-acrylates.**

Because of its commercial availability, TMS-diazomethane constitutes a good alternative to a highly explosive and toxic diazomethane. In previously reported 1,3-dipolar cycloadditions with α,β-unsaturated esters, TMS-diazomethane led to unstable $\Delta^1$-pyrazolines, which after further isomerization or desilylation, and quenching with benzyl chloroformate, afforded the corresponding $\Delta^2$-pyrazolines (Scheme 110).[126]

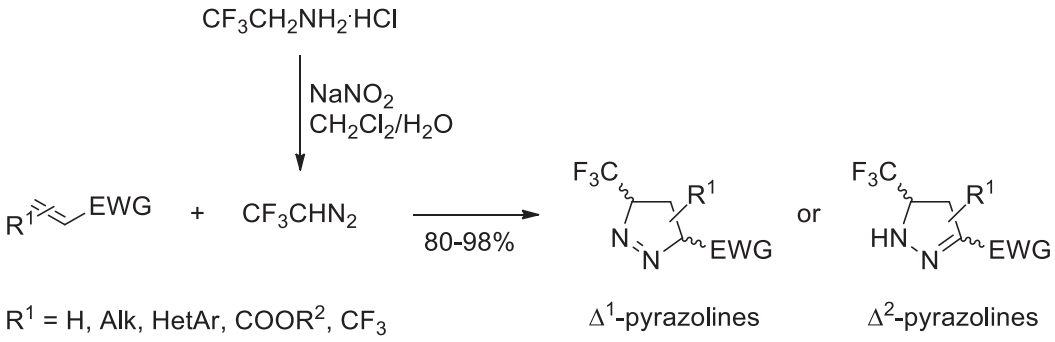



**Scheme 110: 1,3-Dipolar cycloadditions of TMS-diazomethane with α,β-unsaturated esters.**

Concerning the trifluoromethyldiazomethane, 1,3-dipolar cycloadditions engaging this reagent could offer an entry to the pyrazolines containing $CF_3$-substituent. Trifluoromethyldiazomethane was easily generated *in situ* from the commercially available

[125] Bravo, P.; Bruché, L.; Diliddo, D.; Fronza, G. *J. Chem. Res.* **1992**, 40.
[126] Simovic, D.; Di, M.; Marks, V.; Chatfield, D.C.; Rein, K.S. *J. Org. Chem.* **2007**, *72*, 650.

2,2,2-trifluoroethylamine, according to Dr. Mykhailiuk's procedure.[127] The 1,3-dipolar cycloadditions of $CF_3$-diazomethane with electron-deficient alkenes were reported to afford trifluoromethylated $\Delta^1$- or $\Delta^2$-pyrrazolines in excellent yields (Scheme 111). Therefore, applying these conditions to our $SF_5$-electron-deficient alkenes, appeared especially attractive.

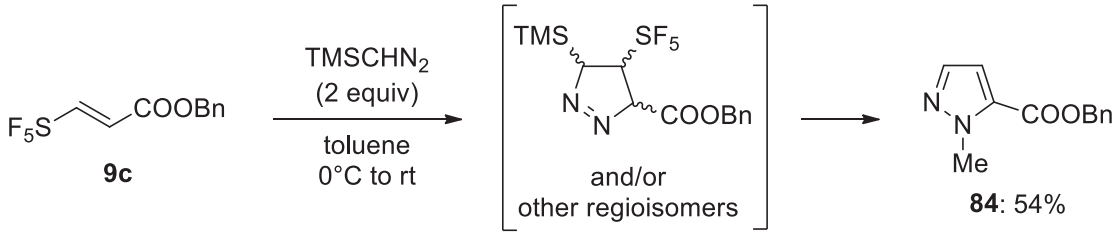



**Scheme 111: 1,3-Dipolar cycloadditions of $CF_3$-diazomethane with electron-deficient alkenes.**

## 5.2. Attempts for 1,3-dipolar cycloadditions of esters 9 and amides 11 with diazomethane derivatives

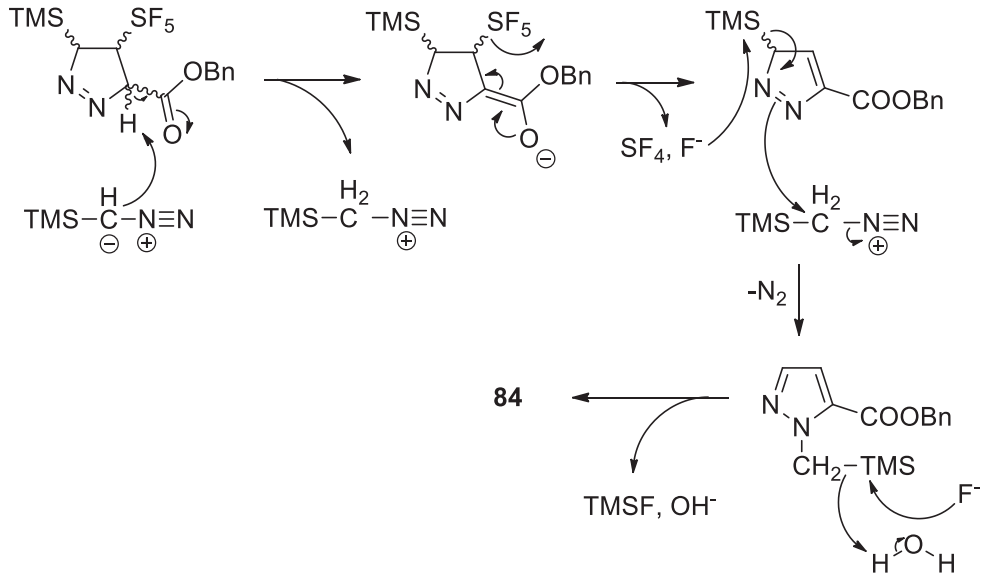
We started our investigation of 1,3-dipolar cycloadditions with diazomethane derivatives, by the reaction of $SF_5$-acrylic ester **9c** with trimethylsilyldiazomethane (Scheme 112). After 5 hours at room temperature, in toluene, the $^{19}F$ NMR of the reaction mixture showed a complete conversion of the starting material, and the presence of one $SF_5$-product was detected. Unfortunately, after purifying the crude product by column chromatography on the silica gel, the non-fluorinated pyrazole **84** was exclusively obtained in good yield (confirmed by 2D NMR, and GC-MS analysis).

[127] Slobodyanyuk, E. Y.; Artamonov, O. S.; Shishkin, O. V.; Mykhailiuk, P. K. *Eur. J. Org. Chem.* **2014**, 2487.



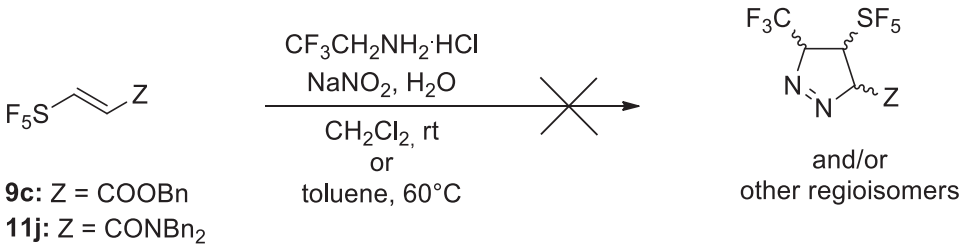

**Scheme 112: 1,3-Dipolar cycloaddition of $SF_5$-ester 9c with TMS-diazomethane.**

This observation might indicate that once again, we were faced with an elimination of $SF_4$ and HF, from the pentafluorosulfanylated heterocycle. A possible mechanism for the formation of pyrazole **84** is depicted on Scheme 113. We suppose that the trimethylsilyldiazomethane used in excess could act as a base, inducing the elimination of the pentafluorosulfanyl anion ($SF_5^-$) from the $SF_5$-pyrazoline. Further deprotection of the trimethylsilyl group by the fluoride anion (coming from the decomposition of previously released $SF_5^-$), and the subsequent N-methylation by TMS-diazomethane should lead to the pyrazole **84** (Scheme 113).




**Scheme 113: Proposed mechanism for the formation of pyrazole 84.**

We further performed several attempts for the 1,3-dipolar cycloaddition of $SF_5$-ester **9c** and amide **11j** with $CF_3$-diazomethane (Scheme 114). No conversion was observed when the reaction was performed in dichloromethane at room temperature. Heating the reaction mixture at 60°C, in toluene, afforded exclusively degradation products.




**Scheme 114: 1,3-Dipolar cycloadditions of $SF_5$-ester 9c and amide 11j with $CF_3$-diazomethane.**

Despite our efforts, we did not succeed to synthesize the targeted pentafluorosulfanylated pyrazolines. Given the elimination of the $SF_5$-group in the reactions with TMS-diazomethane, as well as the lack of the reactivity in the reactions with $CF_3$-diazomethane, this approach was abandoned.

# 6. Conclusion

We have successfully developed the synthesis of original pentafluorosulfanylated five-membered heterocycles. Our strategy, based on 1,3-dipolar cycloaddition reactions of $SF_5$-acrylic derivatives, turned out to be applicable to various dipoles; nevertheless, some limitations have been found.

First, a straightforward single step procedure for the preparation of $SF_5$-subtituted pyrrolidines **42-44** and **51**,**52**, using pentafluorosulfanyl-substituted acrylic esters **9**,**10**, amides **11**,**12** and allylic acetate **6** was developed. 1,3-Dipolar cycloaddition reactions of these building-blocks with two different types of azomethine ylide precursors (**40a**,**b** and **49a**,**b**) led to various $SF_5$-pyrrolidines in good yields. Moreover, the main factors accounting for the regiochemistry of these reactions were rationalized by a convergent DFT-Conceptual DFT-QTAIM theoretical study. Preliminary attempt of the synthesis of enantiopure $SF_5$-pyrrolidines **51a**,**52a** has been performed as well, leading to a promising ~37% enantiomeric excess. We have also subjected some of pyrrolidines **42-44** to a series of chemical transformations, affording various functionalized derivatives **60**, **62** and **70**, which could be further incorporated into more complex structures of biological interest.

We have also performed 1,3-dipolar cycloaddition reactions of $SF_5$-acrylic building-blocks **6** and **9-11** with nitrones **71a-e** leading to the original 4-$SF_5$-isoxazolidines **72-76**,

with a total regioselectivity. The diastereoselectivity of these reactions depended on the nature of the nitrone and the dipolarophile, and was explained by *endo*- and *exo*-approaches of the $SF_5$-dipolarophiles on the nitrones. Structures of 4-$SF_5$-regioisomers were assigned by NMR experiments and by X-ray diffraction analysis. Although these pentafluorosulfanylated isoxazolidines were obtained in low to moderate yields, we proposed two mechanistic pathways (based on the elimination of $SF_5^-$ anion) which could reasonably explain the loss of $SF_5$-materials, as well as the observed regioselectivity. Our mechanistic considerations were supported by the theoretical calculations.

Several attempts for the synthesis of other nitrogen-containing pentafluorosulfanylated heterocycles, such as $SF_5$-pyridines, $SF_5$-isoxazolines, or $SF_5$-pyrazolines, have been performed as well; nevertheless, all of them failed. The main limitation of the preparation of pentafluorosulfanylated pyridines via the Umemoto's procedure was the low stability of the $SF_4Cl$-intermediates. The cycloaddition reactions of $SF_5$-derivatives with oxazole, nitrile oxides or diazomethane derivatives were unsuccesfull, due to the lack of reactivity of the $SF_5$-building-blocks, on the one hand, or to a spontanous β-elimination of the $SF_5^-$ anion, on the other hand.

# General Conclusion

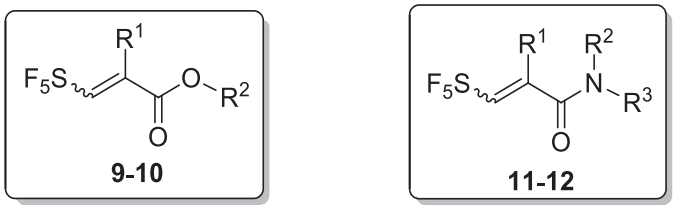
# and

# Perspectives

# 1. Conclusion

New pentafluorosulfanylated building-blocks, such as α,β-unsaturated $SF_5$-containing esters and amides, $SF_5$-allylsilanes or $SF_5$-homoallylic alcohols, have been prepared. Their reactivity was then investigated, some of them being successfully applied in 1,3-dipolar cycloaddition reactions leading to the original five-membered nitrogen-containing heterocycles, such as pentaflurosulfanylated pyrrolidines or isoxazolidines.

Our attention was first turned to pentafluorosulfanylated allylic and acrylic derivatives. We have elaborated an efficient and straightforward synthesis of $SF_5$-substituted acrylic esters **9-10** and amides **11-12** (Figure 48). Our four-step sequence started from the radical addition of $SF_5Cl$ to the commercially available allylic acetate derivatives. The key-step of this strategy was the coupling reactions of $SF_5$-acrylic acids with alcohols or amines. Esterification reactions were catalyzed by DCC/DMAP/HOBt system, whereas amidifications were efficient in the presence of both, DCC/HOBt or $T_3P/Et_3N$ systems. Our new method turned out to be compatible with a variety of substrates, constituting a good alternative for the previously described syntheses of $SF_5$-acrylic esters. These new pentafluorosulfanylated derivatives constitute a class of versatile building-blocks, which are especially interesting for cycloaddtion reactions.




$R^1$ = H, Me
$R^2$ = Alk, Ar, Cycle

$R^1$ = H, Me
$R^2$, $R^3$ = Alk, Ar

**Figure 48: New $SF_5$-acrylic esters 9-10 and amides 11-12.**

We have also succeeded to synthesize new pentafluorosulfanylated allylsilanes **21a-c** (Figure 49), using the same type of strategy, based on the radical addition of $SF_5Cl$ to allylsilanes. Unfortunately, despite our efforts, all attempts of allylation reactions of aldehydes, using our new $SF_5$-allylsilanes, failed. Nevertheless, we were able to access to the desired pentafluorosulfanylated homoallylic alcohols **22a-c** and **23a-c** (Figure 49), by another method. They were obtained as regioisomeric γ- and α-products, by the In-mediated reactions

of $SF_5$-allylbromide with different aldehydes. The low yields of these reactions could be explained by a possible formation of an allylindium intermediate, in which fluorine atoms of the $SF_5$-group could probably coordinate to the metal, making the further reaction impossible. Despite the quite disappointing yields, this allylation remains the first example of In-mediated reaction, using a pentafluorosulfanylated coumpound.

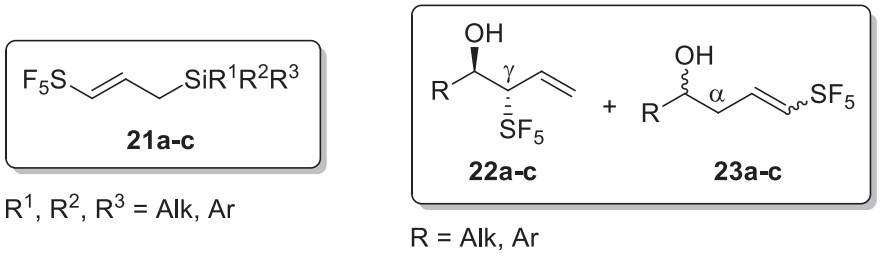



**Figure 49: New $SF_5$-allylsilanes 21a-c and $SF_5$-homoallylic alcohols 22a-c and 23a-c.**

Unfortunately, the introduction of the $SF_5$-group into other unsaturated derivatives turned out to be more problematic. Our attempts of the $SF_5Cl$ addition to allyl sulfide, allyl stannane or allyl phosphine failed. The analogous reaction with propargyl acetate and $SF_5Cl$ led also to a complex mixture of pentafluorosulfanylated products.

Having the new pentafluorosulfanylated building-blocks in hand, we have developed an efficient synthesis of original $SF_5$-containing pyrrolidines (Figure 50). Disubstituted and tetrasubstituted pyrrolidines were obtained by 1,3-dipolar cycloadditions of $SF_5$-acrylic derivatives with two different types of azomethine ylides (**41a,b** and **50a,b**). A comparative study between $CF_3$- and $SF_5$-acrylic derivatives was performed for these 1,3-dipolar cycloadditions. In the tetrasubstituted series (pyrrolidines **51**, **52**), significant differences were observed, compared to the previously reported reactions of trifluoromethyl analogues. The first one concerned the rate of the reaction, which was much slower in the case of $SF_5$-derivatives; the second one was the regioselectivity. Both of these differences were explained by a convergent DFT-conceptual DFT-QTAIM theoretical study. We have further performed an attempt of the enantioselective 1,3-dipolar cycloaddition with azomethine ylide **50a**. Although, we have not yet obtained a satisfactory enantiomeric excess (ee ~37%) at this stage, the result is promising, and further investigation should give us the access to the first enantiopure $SF_5$-pyrrolidines. Finally, a series of chemical transformations of the disubstituted $SF_5$-pyrrolidines **42-44** was performed. Using classical conditions of post-functionalization, we succeeded the synthesis of original pentafluorosulfanylated pyrrolidines

(**60**, **62**, **70**), which could be further introduced into peptides or potential biologically active compounds, such as for example DNA-gyrase inhibitors.

The first synthesis of pentafluorosulfanylated isoxazolidines was developed as well. 1,3-Dipolar cycloadditions of our $SF_5$-acrylic esters and amides with various nitrones led to these original heterocycles in moderate yields. Once again, the regioselectivity of these reactions was compared to the one observed in $CF_3$-series. In order to explain the observed regioselectivity and the low yields of the reaction, we proposed two pathways, including the loss of $SF_4$ and HF from one of the regioisomeric isoxazolidines. Our mechanistic considerations were again confirmed by convergent DFT-CDFT-QTAIM theoretical study.

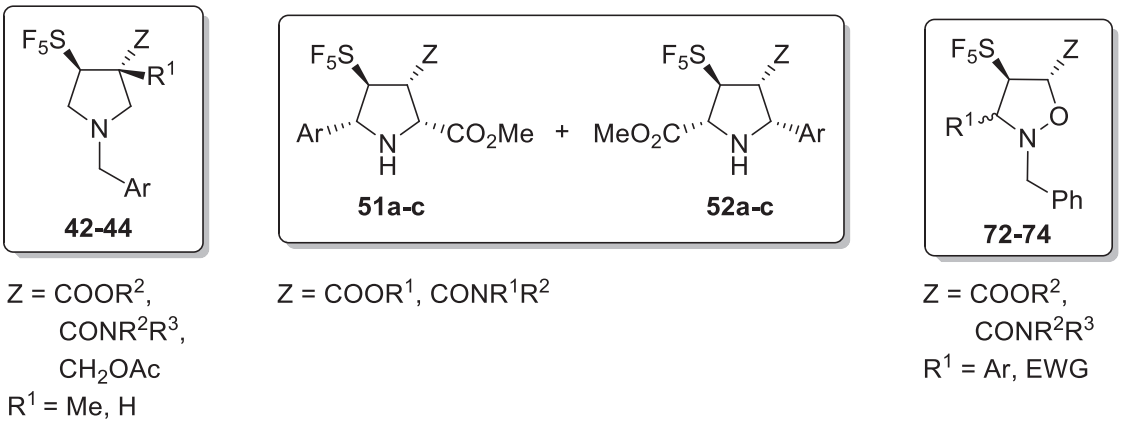



**Figure 50: New $SF_5$-pyrrolidines (42-44 and 51,52) and $SF_5$-isoxazolidines (72-76).**

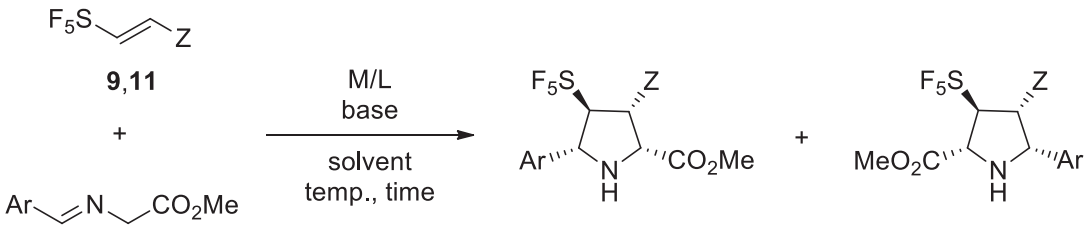
Despite all our efforts, the attempts for the synthesis of other pentafluorosulfanylated heterocycles, such as $SF_5$-pyridines, $SF_5$-isoxazolines, or $SF_5$-pyrazolines, failed. Our first approach using the Umemoto's methodology for the preparation of pentafluorosulfanylated pyridines was promising. Nevertheless, during our investigations, Dolbier's group has reported the synthesis of 2-pyridylsulfur pentafluorides using the same approach; thus, we turned our attention to another strategy. Attempts of Diels-Alder reaction of $SF_5$-acrylic acid with oxazoles were unsuccessful, leading exclusively to the opening of the oxazole ring, whereas other $SF_5$-building blocks turned out to be unreactive under these conditions. The lack of the reactivity of pentafluorosulfanylated acrylic derivatives was also observed in the reactions with nitrile oxides, making impossible the synthesis of $SF_5$-substituted isoxazolines. Finally, in the reactions of $SF_5$-acrylic compounds with diazomethane derivatives, either the lack of the reactivity, or the elimination of $SF_5$-group was observed.

In conclusion, we have demonstrated that in many reactions, the behaviour of the pentafluorosulfanylated derivatives is quite different than the one of trifluoromethylated compounds. The main drawback in the reactions of $SF_5$-derivatives (especially the cycloadducts) is their tendency to undergo a spontanous β-elimination of $SF_4$ and HF in basic medium, leading to non-fluorinated products. Despite this obstacle, we succeeded to synthesize a variety of new pentafluorosulfanylated building-blocks and few five-membered nitrogen-containing heterocycles.

# 2. Perspectives

Two main objectives for a future work on pentafluorosulfanylated derivatives are envisaged in our laboratory. The first one is the synthesis of first enantiopure tetrasubstituted $SF_5$-pyrrolidines, and the second one is the introduction of a functionalized $SF_5$-pyrrolidine motif into peptides or potential biologically active compounds.

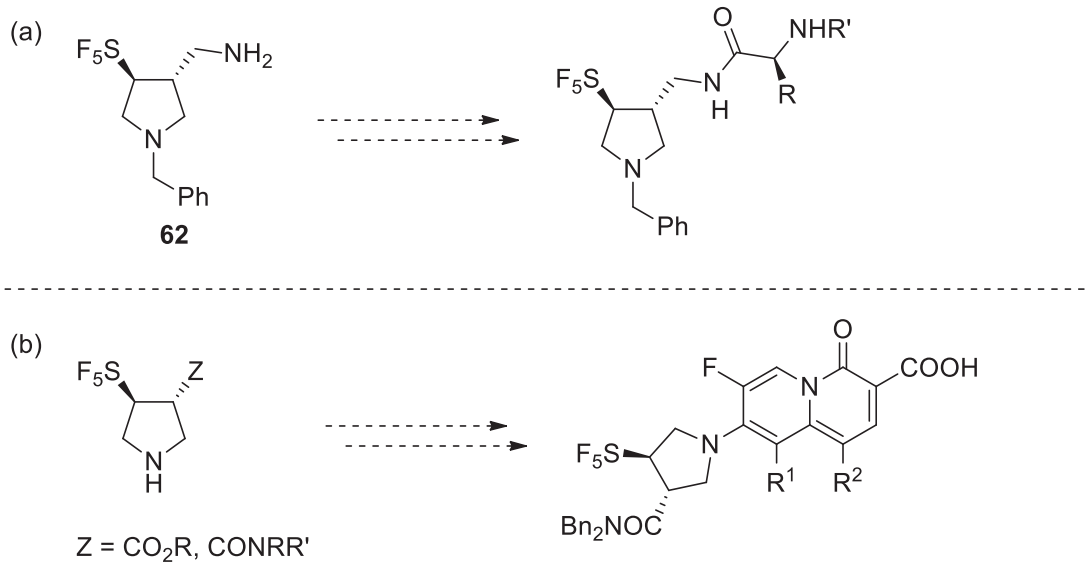
We have already performed first attempts of asymetric 1,3-dipolar cycloaddition of our $SF_5$-acrylic derivative **9c** with azomethine ylide **50a**, leading to the corresponding $SF_5$-pyrrolidines **51a** and **52a** with a promising 37% enantiomeric excess. The screening of other metal/chiral ligand complexes is currently under investigation in our laboratory. The influence of other parameters, such as temperature and time of the reaction, the type of dipole, dipolarophile, or base, on the enantiomeric excess will be investigated as well (Scheme 115).




Z = $COOR^1$, $CONR^1R^2$; M = AgOAc, $Cu(CH_3CN)_4BF_4$
L = *(R)*-BINAP, TF-BiphamPhos; Ar = Ph, MeO-Ph, Cl-Ph, Tol, Napht

**Scheme 115: Asymmetric 1,3-dipolar cycloaddition of $SF_5$-acrylic derivatives 9 and 11 with azomethine ylides.**

Concerning the synthesis of pentafluorosulfanylated compounds of biological interest, we have already demonstrated that the $SF_5$-pyrrolidines (motif found in natural or active products) are able to undergo various chemical transformations, leading to the cyclic amines (**60**, **62**, **70**), which could be further introduced into more complex structures. We envisage the optimisation of some steps: especially the nucleophilic substitution of pyrrolidine **58** with phtalimide potassium salt, followed by the deprotection, or the cleavage of benzyl group from the pyrrolidines **42-44**, in order to improve the overall yields of funtionalized pyrrolidines. Coupling reactions of derivative **62** could be further performed in order to obtain pentafluorosulfanylated peptides (Scheme 116, (a)). The incorporation of the heterocycle **70** into pyridone scaffolds (via $S_NAr$ type reaction), leading to the potential pentafluorosulfanylated antibacterial agents, could be also attempted (Scheme 116, (b)).




**Scheme 116: Incorporation of $SF_5$-pyrrolidine motive into compounds of biological interest.**

# Experimental Part

# 1. General remarks

All reactions were carried out in dried glassware under argon, unless otherwise noted. Dry THF and $CH_2Cl_2$ were obtained by drying over Na / benzophenone and $CaH_2$ respectively, followed by distillation. Reaction temperatures are reported as the temperature of the bath surrounding the vessel. Commercially available chemicals were obtained from Acros Organics, Aldrich Chemical Co., ABCR ($SF_5Cl$), Alfa Aesar, Fischer Scientific and were used without further purification. Dipoles precursors **40a,b**[128] and **49a**,**b**[129], nitrone **71c**[117] and nitrile oxide precursor **77**[130] were prepared from commercially available compounds, in one or two-step synthesis, according to the literature. Diene **45** was given by Dr. Petr Beier (Academy of Sciences of Czech Republic). Nitrones **71a, 71b, 71d** and **71e** were prepared by Dr. Mathieu Laurent (Université du Maine). Nitrile oxide procursors **80** and **82** were given by Dr. Pavel Mykhailiuk (Enamine Company, Ukraine).

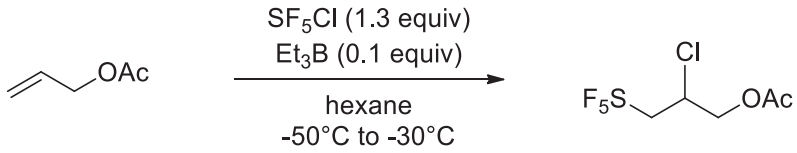
$^1H$ NMR (300 MHZ), $^{13}C$ NMR (75 MHz) and $^{19}F$ NMR (282 MHz) spectra were recorded on a Bruker DXP 300. Chemical shifts (δ) are quoted in ppm relative to TMS ($^1H$), $CDCl_3$ ($^{13}C$) and $CFCl_3$ ($^{19}F$) as external references. Coupling constants (J) are quoted in Hz. The following abbreviations were used for the multiplicities: s singlet, d doublet, t triplet, q quartet, $q_t$ quintuplet, dd doublet of doublet, dm doublet of multiplet, m multiplet. The residual solvent signal was also used as internal reference ($CDCl_3$: $\delta_H$ = 7.26 ppm, $\delta_C$ = 77.00 ppm). High-Resolution Mass Spectra (HRMS) were recorded on Waters LCT Premier. Infrared spectra were recorded on a Perkin Elmer FT-IR spectrometer Paragon 100 (ATR); the wave lengths (ν) of recorded IR-signals are quoted in $cm^{-1}$. Melting points were measured on a Kofler melting point apparatus. Analytical Thin Layer Chromatography (TLC) was performed on precoated 200 μm layer thickness silica gel 60 Alugram® Xtra SIL G/$UV_{254}$. Revelation was accomplished with short wave UV light (λ= 254 nm), potassium permanganate staining solution or phosphomolybdenic acid followed by heating. Flash chromatography was performed on Merck silica gel (40-63 mesh).

[128] Padwa, A.; Dent, W. *J. Org. Chem.* **1987**, *52*, 235.
[129] Lopez-Perez, A.; Segler, M.; Adrio, J.; Carretero, J. C. *J. Org. Chem.* **2011**, *76*, 1945.
[130] Vo, Q. V.; Trenerry, C.; Rochfort, S.; Wadeson, J.; Leyton, C.; Hughes, A. B. *Bioorg. Med. Chem.* **2013**, *21*, 5945.

# 2. Synthesis of $SF_5$-building blocks

## 2.1. Pentafluorosulfanylated allylic alcohols 5a-c, allylic acetate 6, acrylic aldehyde 7 and acrylic acids 8a,b

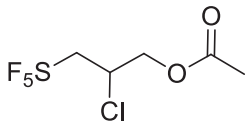
### 2.1.1. Typical procedure for the radical addition of $SF_5Cl$ to allylic acetates 1a-c




**1a** **3a**

In a 100 mL three-neck flask, equipped with an inlet and outlet of gas, distilled hexane (30 mL) was introduced. The reaction mixture was cooled to -50°C, and $SF_5Cl$ (15.2 g, 1.3 equiv, 93.5 mmol) was condensed into the flask (the trap filled with $NaOH_{aq}$ solution was installed after the gas outlet tube). Prop-2-enyl acetate **1a** (7.8 mL, 1.0 equiv, 71.9 mmol) and $Et_3B$ (7.0 mL, 0.1 equiv, 7.2 mmol, 1 M in hexane) were added dropwise and the reaction mixture was allowed to reach -30°C. The reaction mixture was stirred at this temperature for 1 h and then it was left at room temperature overnight. The resulting mixture was passed through a short silica gel plug and the latter was washed with *n*-pentane (2 x 50 mL) and $CH_2Cl_2$ (3 x 50 mL). The filtrate was concentrated under reduced pressure to give the desired product **3a** as a colourless liquid (18.4 g, 97%).

**2-Chloro-3-pentafluorosulfanylpropyl acetate 3a**[77]



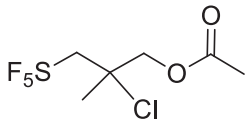

**$C_5H_8ClF_5O_2S$**
**M = 262.63 g/mol**

**$^{19}F$ NMR ($CDCl_3/CFCl_3$, 282 MHz)**: δ 66.2 (dm, 4F, $^2J_{F,F}$ = 149.1 Hz), 81.8 (m, 1F).

**$^1H$ NMR ($CDCl_3$, 300 MHz)**: δ 2.16 (s, 3H, C$\underline{H}_3$), 3.90-4.16 (m, 2H, C$\underline{H}_2SF_5$), 4.28-4.41 (m, 2H, C$\underline{H}_2$OAc), 4.57 (m, 1H, C$\underline{H}$(Cl)$CH_2SF_5$).

**$^{13}$C NMR ($CDCl_3$, 75 MHz)**: δ 20.5 (s, $\underline{C}H_3$) 51.9 (q$_t$, $^3J_{C,F}$ = 4.4 Hz, $\underline{C}H(Cl)CH_2SF_5$), 65.5 (s, $\underline{C}H_2OAc$), 73.1 (q$_t$, $^2J_{C,F}$ = 14.9 Hz, $\underline{C}H_2SF_5$), 170.1 (s, $\underline{C}$=O).

**2-Chloro-2-methyl-3-pentafluorosulfanylpropyl acetate 3b**




**$C_6H_{10}ClF_5O_2S$**
**M = 276.65 g/mol**

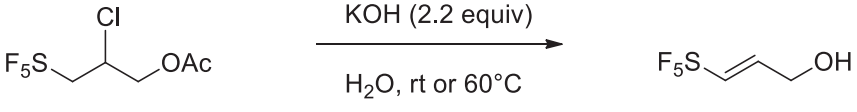
The title compound was synthesised from acetate **1b** (2.0 mL, 1.0 equiv, 16.3 mmol), $SF_5Cl$ (3.5 g, 1.3 equiv, 21.2 mmol) and $Et_3B$ (1.6 mL, 0.1 equiv, 1.6 mmol, 1 M in hexane) according to the typical procedure. The desired product **3b** was obtained after work-up as a colourless liquid (3.7 g, 83%).

**$^{19}$F NMR ($CDCl_3$/$CFCl_3$, 282 MHz)**: δ 69.0 (dm, 4F, $^2J_{F,F}$ = 145.7 Hz), 82.8 (m, 1F).

**$^1$H NMR ($CDCl_3$, 300 MHz)**: δ 1.82 (s, 3H, C$\underline{H}_3$), 2.15 (s, 3H, C$\underline{H}_3$COO), 3.92-4.25 (m, 2H, C$\underline{H}_2SF_5$), 4.31 (d, 1H, $^2J_{H,H}$ = 12.2 Hz, C$\underline{H}_A$H$_B$OAc), 4.38 (d, 1H, $^2J_{H,H}$ = 12.2 Hz, CH$_A\underline{H}_B$OAc).

**$^{13}$C NMR ($CDCl_3$, 75 MHz)**: δ 20.6 (s, $\underline{C}H_3$), 30.6 (s, $\underline{C}H_3$(C)Cl), 43.2 (q$_t$, $^3J_{C,F}$ = 5.1 Hz, $CH_3\underline{C}(Cl)CH_2SF_5$), 63.5 (s, $\underline{C}H_2OAc$), 68.3 (q$_t$, $^2J_{C,F}$ = 15.0 Hz, $\underline{C}H_2SF_5$), 168.1 (s, $\underline{C}$=O).

### 2.1.2. Typical procedure for the elimination-hydrolysis reaction

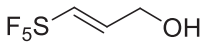



**3a** **5a**

Solution of KOH (7.76 g, 2.2 equiv, 0.138 mol) in water (40 mL) was added to compound **3a** (16.57 g, 1.0 equiv, 0.063 mol). The reaction mixture was stirred vigorously at room temperature for 18 h. After the completion of the reaction, $CH_2Cl_2$ (30 mL) was

added to the reaction mixture and it was stirred vigorously for 5 minutes. The phases were separated and the aqueous phase was washed with $CH_2Cl_2$ (2 x 30 mL). Combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure to give the desired product **5a** as a colourless liquid (10.89 g, 94%).

***(E)*-3-Pentafluorosulfanylprop-2-en-1-ol 5a**[42,77]



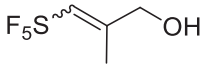

**$C_3H_5F_5OS$**
**M = 184.13 g/mol**

**IR ($cm^{-1}$)**: 3332, 1448, 1371, 1095.

**$^{19}F$ NMR ($CDCl_3/CFCl_3$, 282 MHz)**: δ 62.9 (dd, 4F, $^2J_{F,F}$ = 150.9 Hz, $^3J_{F,H}$ = 3.5 Hz), 83.1 (m, 1F).

**$^1H$ NMR ($CDCl_3$, 300 MHz)**: δ 1.70 (t, 1H, $^3J_{H,H}$ = 5.6 Hz, O<u>H</u>), 4.39 (m, 2H, C<u>H</u>$_2$OH), 6.61 (dm, 1H, $^3J_{H,H}$ = 14.6 Hz, C<u>H</u>=CHSF$_5$), 6.68-6.81 (m, 1H, CH=C<u>H</u>SF$_5$).

***(E/Z)*-2-Methyl-3-pentafluorosulfanylprop-2-en-1-ol 5b**




**$C_4H_7F_5OS$**
**M = 198.15 g/mol**

The title compound was synthesised from acetate **3b** (3.70 g, 1.0 equiv, 13.4 mmol) and KOH (1.65 g, 2.2 equiv, 29.4 mol) in water (4.5 mL) at 60°C according to the typical procedure. The desired product **5b** (*E/Z* mixture ~3:1) was obtained after work-up as a colourless liquid (1.87 g, 71%).

**IR ($cm^{-1}$)**: 3390, 2963, 2928, 2854, 1694, 1087.

**HRMS ($ESI^-$)**: calcd for $C_4H_6F_5OS$ (*m/z*) 197.0060 $[M - H]^-$, found 197.0055.

*Diastereoisomer E:*

**$^{19}$F NMR ($CDCl_3/CFCl_3$, 282 MHz)**: δ 65.8 (dd, 4F, $^2J_{F,F}$ = 149.1 Hz, $^3J_{F,H}$ = 8.7 Hz), 85.3 (m, 1F).

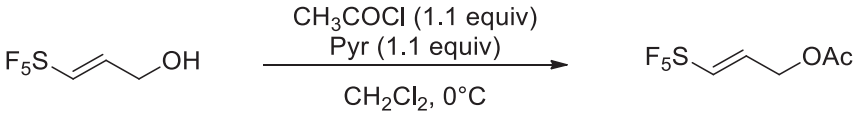
**$^1$H NMR ($CDCl_3$, 300 MHz)**: δ 1.75 (m, 1H, O<u>H</u>), 1.94 (s, 3H, C<u>H</u>$_3$), 4.18 (m, 2H, C<u>H</u>$_2$OH), 6.58 ($q_t$, 1H, $^3J_{H,F}$ = 8.7 Hz, C=C<u>H</u>$SF_5$).

*Diastereoisomer Z:*

**$^{19}$F NMR ($CDCl_3/CFCl_3$, 282 MHz)**: δ 65.7 (dd, 4F, $^2J_{F,F}$ = 149.1 Hz, $^3J_{F,H}$ = 8.7 Hz), 84.8 (m, 1F).

**$^1$H NMR ($CDCl_3$, 300 MHz)**: δ 1.55 (m, 1H, O<u>H</u>), 2.00 (s, 3H, C<u>H</u>$_3$), 4.47 (m, 2H, C<u>H</u>$_2$OH), 6.24 ($q_t$, 1H, $^3J_{H,F}$ = 8.7 Hz, C=C<u>H</u>$SF_5$).

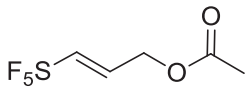
### 2.1.3. Acetylation of $SF_5$-allylic alcohol 5a




**5a** **6**

Alcohol **5a** (1.0 g, 1.0 equiv, 5.43 mmol) was dissolved in dry $CH_2Cl_2$ (13 mL) and it was cooled to 0°C. Acetyl chloride (0.42 mL, 1.1. equiv, 5.92 mmol) and distilled pyridine (0.47 mL, 1.1 equiv, 5.92 mmol) were added dropwise to this solution and the reaction mixture was stirred at 0°C for 6 h. Water (6 mL) was then added to the reaction mixture and the phases were separated. The organic phase was washed with brine (6 mL), water (6 mL), dried over $MgSO_4$ and concentrated under reduced pressure to afford the desired product **6** as a colourless oil (1.2 g, 94%).

***(E)*-3-Pentafluorosulfanylprop-2-en-1-yl acetate 6**[46]

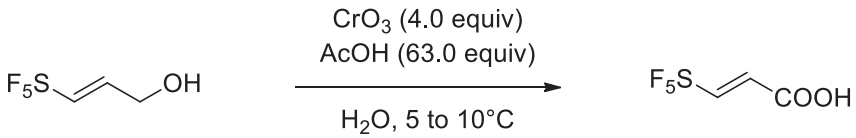


**$C_5H_7F_5O_2S$**
**M = 226.16 g/mol**

**$^{19}$F NMR ($CDCl_3/CFCl_3$, 282 MHz)**: δ 62.4 (dm, 4F, $^2J_{F,F}$ = 149.2 Hz), 82.0 (m, 1F).

**$^1$H NMR ($CDCl_3$, 300 MHz)**: δ 2.15 (s, 3H, C$\underline{H}_3$), 4.74 (m, 2H, C$\underline{H}_2$OAc), 6.56 (dm, 1H, $^3J_{H,H}$ = 14.9 Hz, C$\underline{H}$=CHSF$_5$), 6.62-6.71 (m, 1H, CH=C$\underline{H}$SF$_5$).

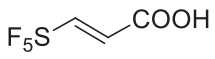
### 2.1.4. Typical procedure for the oxidation of $SF_5$-allylic alcohols 5a,b to acids 8a,b




**5a** **8a**

$CrO_3$ (46.2 g, 4 equiv, 0.46 mol) was dissolved in glacial acetic acid (417.0 mL, 63 equiv, 7.27 mol) and water (47 mL) and it was cooled to 5°C. Allylic alcohol **5a** (21.3 g, equiv, 0.12 mol) was added dropwise to this solution (temperature during the addition: 5-9°C). The reaction mixture was stirred at 5-9°C for 2 h and then it was left at room temperature overnight. The reaction mixture was then diluted with water (400 mL) and extracted with $Et_2O$ (5 x 200 mL). The combined organic phase was washed with brine (50 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by Kugelrohr distillation (65-70°C, 2 mbar) to afford the desired product **8a** as a colourless solid with a low melting point (25-27°C) (14.86 g, 65%).

***(E)*-3-Pentafluorosulfanylprop-2-enoic acid 8a**[42b]



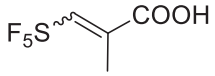

**$C_3H_3F_5O_2S$**
**M = 198.11 g/mol**

**IR ($cm^{-1}$)**: 3101, 1717, 1263.

**$^{19}F$ NMR ($CDCl_3/CFCl_3$, 282 MHz)**: δ 62.3 (dm, 4F, $^2J_{F,F}$ = 150.9 Hz), 78.0 (m, 1F).

**$^1H$ NMR ($CDCl_3$, 300 MHz)**: δ 6.61 (d, 1H, $^3J_{H,H}$ = 14.7 Hz, C<u>H</u>=CHSF$_5$), 7.53 (dm, 1H, $^3J_{H,H}$ = 14.7 Hz, CH=C<u>H</u>SF$_5$), 10.61 (br s, 1H, COO<u>H</u>).

***(E/Z)*-2-Methyl-3-pentafluorosulfanylprop-2-enoic acid 8b**




**$C_4H_5F_5O_2S$**
**M = 212.14 g/mol**

The title compound was synthesized from alcohol **5b** (1.5 g, 1 equiv, 7.6 mmol), $CrO_3$ (3.0 g, 4 equiv, 30.4 mmol) in acetic acid/water (27:3 mL) mixture, according to the typical procedure. The desired product **8b** (*E/Z* mixture ~3:1) was obtained after Kugelrohr distillation (65-80°C, 2 mbar) as a colourless oil (1.1 g, 70%).

**IR ($cm^{-1}$)**: 3079, 1715, 1263.

**HRMS ($ESI^-$)**: calcd for $C_4H_4F_5O_2S$ (*m/z*) 210.9852 $[M - H]^-$, found 210.9848.

*Diastereoisomer E:*

**$^{19}F$ NMR ($CDCl_3/CFCl_3$, 282 MHz)**: δ 64.1 (dd, 4F, $^2J_{F,F}$ = 150.9 Hz, $^3J_{F,H}$ = 8.7 Hz), 80.4 (m, 1F).

**$^1H$ NMR ($CDCl_3$, 300 MHz)**: δ 2.23 (m, 3H, C<u>H</u>$_3$), 7.46 (m, 1H, C=C<u>H</u>SF$_5$), 10.13 (br s, 1H, COO<u>H</u>).

**$^{13}$C NMR ($CDCl_3$, 75 MHz)**: δ 14.3 ($q_t$, $^4J_{C,F}$ = 2.2 Hz, $\underline{C}H_3$), 134.0 ($q_t$, $^3J_{C,F}$ = 5.3 Hz, $\underline{C}$=CHSF$_5$), 148.5 ($q_t$, $^2J_{C,H}$ = 22.5 Hz, C=$\underline{C}$HSF$_5$), 171.3 (s, $\underline{C}$=O)

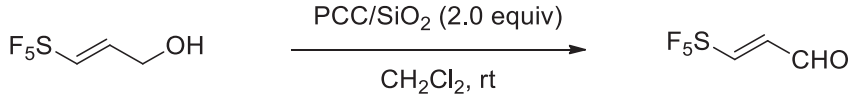
*Diastereoisomer Z:*

**$^{19}$F NMR ($CDCl_3$/$CFCl_3$, 282 MHz)**: δ 65.0 (dm, 4F, $^2J_{F,F}$ = 150.9 Hz), 80.0 (m, 1F).

**$^1$H NMR ($CDCl_3$, 300 MHz)**: δ 2.16 (m, 3H, C$\underline{H}_3$), 6.37 (m, 1H, C=C$\underline{H}$SF$_5$), 10.13 (br s, 1H, COO$\underline{H}$).

**$^{13}$C NMR ($CDCl_3$, 75 MHz)**: δ 20.3 (s, $\underline{C}H_3$), 135.4 (m, $\underline{C}$=CHSF$_5$), 137.1 ($q_t$, $^2J_{C,H}$ = 22.6 Hz, C=$\underline{C}$HSF$_5$), 172.5 (s, $\underline{C}$=O)

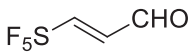
### 2.1.5. Oxidation of $SF_5$-allylic alcohol 5a to aldehyde 7




**5a** **7**

PCC (3.0 g, 2 equiv, 13.8 mmol) was finely crushed in a mortar with an equal quantity of silica gel and it was suspended in $CH_2Cl_2$ (35 mL). To this suspension was added dropwise a solution of alcohol **5a** (1.3 g, 1 equiv, 6.9 mmol) in $CH_2Cl_2$ (7 mL) and the reaction mixture was stirred at room temperature for 2.5 h. $Et_2O$ (40 mL) was added to precipitate chromium salts which were removed by filtration trough a plug of silica gel (2 cm on the bottom) and celite (1 cm on the top). The solvents were removed by distillation under atmospheric pressure to give the desired product **7** (556 mg, 44 %).

***(E)*-3-Pentafluorosulfanylprop-2-enal 5**[42c,d]



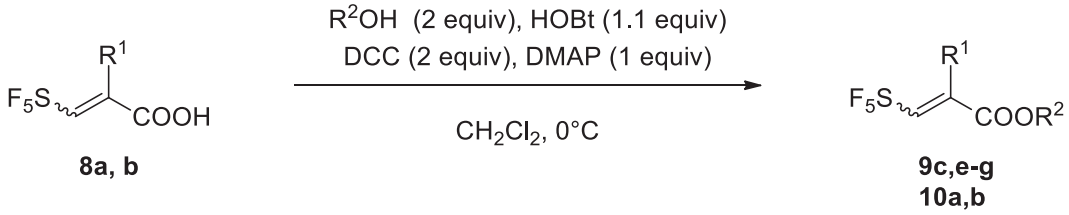

**$C_3H_3F_5OS$**
**M = 182.11 g/mol**

**$^{19}$F NMR ($CDCl_3$/$CFCl_3$, 282 MHz)**: δ 62.3 (dm, 4F, $^2J_{F,F}$ = 152.6 Hz), 77.5 (m, 1F).

**$^1$H NMR ($CDCl_3$, 300 MHz)**: δ 6.74 (dd, 1H, $^3J_{H,H}$ = 15.1 Hz, $^3J_{H,H}$ = 6.8 Hz, C<u>H</u>CHO), 7.3-7.4 (m, 1H, C<u>H</u>$SF_5$), 9.70 (d, 1H, $^3J_{H,H}$ = 6.8 Hz, C<u>H</u>O).

## 2.2. Pentafluorosulfanylated α,β-unsaturated esters 9,10 and amides 11,12

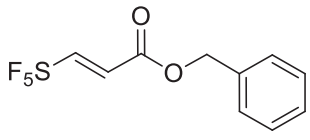
### 2.2.1. General procedure for the preparation of esters 9 and 10




**8a, b** → **9c,e-g**, **10a,b**

To a stirred solution of acid **8** (1 equiv, 2.7 mmol) in dry $CH_2Cl_2$ (13 mL) under argon, at 0°C, was added HOBt (1.1 equiv, 2.9 mmol), DCC (2.0 equiv, 5.4 mmol), alcohol (2.0 equiv, 5.4 mmol) and DMAP (1.0 equiv, 2.7 mmol). The reaction mixture was stirred at this temperature for 1.5 h. The resulting mixture was then filtered and the precipitate was washed with $CH_2Cl_2$ (40 mL). The filtrate was washed with water (3 x 15 mL), 2 M $HCl_{aq}$ solution (3 x 15 mL) and brine (15 mL). The organic layer was dried over $MgSO_4$. After removal of solvent under reduced pressure, the crude product was purified by silica gel column chromatography leading to ester **9** or **10**.

***(E)*-Benzyl 3-(pentafluorosulfanyl)prop-2-enoate 9c**




**$C_{10}H_9F_5O_2S$**
**M = 288.23 g/mol**

The title compound was prepared according to the general procedure. The resulting crude product was purified by silica gel column chromatography (cyclohexane/AcOEt = 98:2) to afford **9c** in 64% yield as a colourless oil.

**Rf** = 0.53 (cyclohexane/AcOEt = 92:8)

**IR ($cm^{-1}$)**: 3092, 2934, 1731, 1456, 1245.

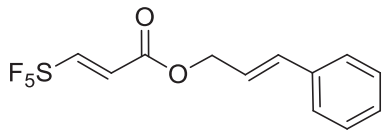
**HRMS ($ESI^+$)**: calcd for $C_{10}H_{10}F_5O_2S$ (*m/z*) 289.2243 $[M + H]^+$, found 289.2241.

**$^{19}F$ NMR ($CDCl_3/CFCl_3$, 282 MHz)**: δ 62.4 (dd, 4F, $^2J_{F,F}$ = 150.9 Hz, $^3J_{F,H}$ = 6.1 Hz), 78.6 (m, 1F).

**$^1H$ NMR ($CDCl_3$, 300 MHz)**: δ 5.28 (s, 2H, C<u>H</u>$_2$), 6.64 (d, 1H, $^3J_{H,H}$ = 14.8 Hz, C<u>H</u>=CH-$SF_5$), 7.41 (m, 5H, Ph), 7.4-7.5 (m, 1H, CH=C<u>H</u>-$SF_5$).

**$^{13}C$ NMR ($CDCl_3$, 75 MHz)**: δ 67.8 (s, <u>C</u>H$_2$), 127.2 ($q_t$, $^3J_{C,F}$ = 7.2 Hz, <u>C</u>H=CH-$SF_5$), 128.6 (s, 2x <u>C</u>H Ph), 128.7 (s, 2x <u>C</u>H Ph), 128.8 (s, <u>C</u>H Ph), 134.6 (s, <u>C</u>$_q$ Ph), 152.5 ($q_t$, $^2J_{C,F}$ = 22.6 Hz, CH=<u>C</u>H-$SF_5$), 162.9 (s, <u>C</u>=O).

***(E)*-Cinnamyl 3-(pentafluorosulfanyl)prop-2-enoate 9e**




**$C_{12}H_{11}F_5O_2S$**
**M = 314.27 g/mol**

The title compound was prepared according to the general procedure. The resulting crude product was purified by silica gel column chromatography (cyclohexane/AcOEt = 90:10) to afford **9e** in 46% yield as a colourless oil.

**Rf** = 0.40 (cyclohexane/AcOEt = 90:10)

**IR ($cm^{-1}$)**: 3085, 3030, 1732, 1498.

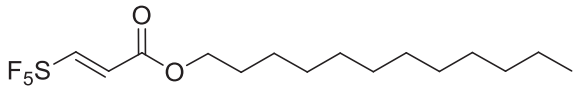
**MS ($ESI^+$)**: 298, 289, 219, 130.

**$^{19}$F NMR ($CDCl_3/CFCl_3$, 282 MHz)**: δ 62.4 (dd, 4F, $^2J_{F,F}$ = 150.9 Hz, $^3J_{F,H}$ = 5.2 Hz), 78.6 (m, 1F).

**$^1$H NMR ($CDCl_3$, 300 MHz)**: δ 4.91 (d, 2H, $^3J_{H,H}$ = 6.6 Hz, OC<u>H</u>$_2$), 6.33 (dt, 1H, $^3J_{H,H}$ = 15.9 Hz, $^3J_{H,H}$ = 6.6 Hz, C<u>H</u>=CHPh), 6.64 (d, 1H, $^3J_{H,H}$ = 14.7 Hz, C<u>H</u>=CHSF$_5$), 6.74 (d, 1H, $^3J_{H,H}$ = 15.9 Hz, CH=C<u>H</u>Ph), 7.31-7.45 (m, 5H, Ph), 7.46-7.56 (m, 1H, CH=C<u>H</u>SF$_5$).

**$^{13}$C NMR ($CDCl_3$, 75 MHz)**: δ 66.6 (s, O<u>C</u>H$_2$), 121.7 (s, <u>C</u>H=CHPh), 126.7 (s, 2x <u>C</u>H Ph), 127.2 ($q_t$, $^3J_{C,F}$ = 7.2 Hz, <u>C</u>H=CHSF$_5$), 128.4 (s, <u>C</u>H Ph), 128.7 (s, 2x <u>C</u>H Ph), 135.8 (m, 2C, CH=<u>C</u>HPh + <u>C</u>$_q$ Ph), 152.4 ($q_t$, $^2J_{C,F}$ = 22.6 Hz, CH=<u>C</u>HSF$_5$), 162.9 (s, <u>C</u>=O).

***(E)*-Dodecyl 3-(pentafluorosulfanyl)prop-2-enoate 9f**




**$C_{15}H_{27}F_5O_2S$**
**M = 352.40 g/mol**

The title compound was prepared according to the general procedure. The resulting crude product was purified by silica gel column chromatography (cyclohexane/AcOEt = 99:1) to afford **9f** in 44% yield as a colourless oil.

**Rf** = 0.70 (cyclohexane/AcOEt = 98:2)

**IR (cm$^{-1}$)**: 2925, 2856, 1734, 1310.

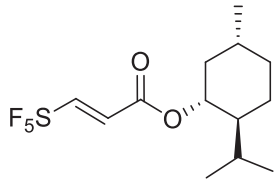
**MS (ESI$^+$)**: 333, 318, 298, 225.

**$^{19}$F NMR ($CDCl_3/CFCl_3$, 282 MHz)**: δ 62.4 (dd, 4F, $^2J_{F,F}$ = 150.9 Hz, $^3J_{F,H}$ = 5.2 Hz), 78.8 (m, 1F).

**$^1$H NMR ($CDCl_3$, 300 MHz)**: δ 0.89 (t, 3H, $^3J_{H,H}$ = 6.6 Hz, C<u>H</u>$_3$), 1.27 (m, 18H, 9 x C<u>H</u>$_2$), 1.70 (m, 2H, C<u>H</u>$_2$CH$_2$O), 4.23 (t, 2H, $^3J_{H,H}$ = 6.7 Hz, OC<u>H</u>$_2$), 6.59 (d, 1H, $^3J_{H,H}$ = 14.8 Hz, C<u>H</u>=CHSF$_5$), 7.42 (m, 1H, CH=C<u>H</u>SF$_5$).

**$^{13}$C NMR ($CDCl_3$, 75 MHz)**: δ 14.1 (s, $\underline{C}H_3$), 22.7 (s, $\underline{C}H_2$), 25.8 (s, $\underline{C}H_2$), 28.4 (s, $\underline{C}H_2$), 29.2 (s, $\underline{C}H_2$), 29.3 (s, $\underline{C}H_2$), 29.46 (s, $\underline{C}H_2$), 29.55 (s, $\underline{C}H_2$), 29.62 (s, 2 x $\underline{C}H_2$), 31.9 (s, $\underline{C}H_2$), 66.3 (s, O$\underline{C}H_2$), 127.5 ($q_t$, $^3J_{C,F}$ = 7.2 Hz, $\underline{C}H$=CHSF$_5$), 152.1 ($q_t$, $^2J_{C,F}$ = 22.0 Hz, CH=$\underline{C}$HSF$_5$), 163.2 (s, $\underline{C}$=O).

***(E)*-(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 3-(pentafluorosulfanyl)prop-2-enoate 9g**




**$C_{13}H_{21}F_5O_2S$**
**M = 314.27 g/mol**

The title compound was prepared according to the general procedure. The resulting crude product was purified by silica gel column chromatography (cyclohexane/AcOEt = 99:1) to afford **9g** in 27% yield as a colourless oil.

**Rf** = 0.70 (cyclohexane/AcOEt = 99:1)

**IR (cm$^{-1}$)**: 2957, 2926, 2871, 1726, 1456, 1247.

**MS (ESI$^+$)**: 315 $[M+H]^+$, 306, 225.

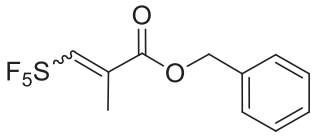
**$^{19}$F NMR ($CDCl_3$/$CFCl_3$, 282 MHz)**: δ 62.5 (dd, 4F, $^2J_{F,F}$ = 150.9 Hz, $^3J_{F,H}$ = 5.2 Hz), 79.0 (m, 1F).

**$^1$H NMR ($CDCl_3$, 300 MHz)**: δ 0.77 (d, 3H, $^2J_{H,H}$ = 6.9 Hz, C$\underline{H}_3$), 0.87-0.89 (m, 1H, C$\underline{H}$), 0.90-0.94 (m, 6H, 2 x C$\underline{H}_3$), 1.07 (m, 2H, C$\underline{H}_2$), 1.41-1.53 (m, 2H, C$\underline{H}_2$), 1.72 (m, 2H, C$\underline{H}_2$), 1.85 (m, 1H, C$\underline{H}$), 2.03 (m, 1H, C$\underline{H}$), 4.83 (td, 1H, $^3J_{H,H}$ = 10.9 Hz, $^3J_{H,H}$ = 4.4 Hz, OC$\underline{H}$), 6.57 (d, 1H, $^3J_{H,H}$ = 14.7 Hz, C$\underline{H}$=CHSF$_5$), 7.41 (m, 1H, CH=C$\underline{H}$SF$_5$).

**$^{13}$C NMR ($CDCl_3$, 75 MHz)**: δ 16.2 (s, $\underline{C}H_3$CH(CH$_2$)$_2$), 20.7 (s, $\underline{C}H_3$CHCH$_3$), 21.9 (s, CH$_3$CH$\underline{C}$H$_3$), 23.4 (s, $\underline{C}H_2$), 26.3 (s, $\underline{C}$H), 31.4 (s, $\underline{C}$H), 34.1 (s, $\underline{C}H_2$), 40.6 (s, $\underline{C}H_2$), 46.9 (s,

CH), 76.5 (s, OCH), 127.8 ($q_t$, $^3J_{C,F}$ = 7.2 Hz, CH=$CHSF_5$), 152.0 ($q_t$, $^2J_{C,F}$ = 22.0 Hz, CH=$CHSF_5$), 162.7 (s, C=O).

**_(E/Z)_-Benzyl 2-methyl-3-(pentafluorosulfanyl)prop-2-enoate 10a**




**$C_{11}H_{11}F_5O_2S$**
**M = 302.26 g/mol**

The title compound was obtained as a mixture of diastereoisomers (*E*/*Z* ~3:1) according to the general procedure. Only *E*-isomer was isolated by silica gel column chromatography (cyclohexane/AcOEt = 98:2) in 71% yield as a colourless oil.

*Diastereoisomer E:*

**Rf** = 0.63 (cyclohexane/AcOEt = 92:8)

**IR ($cm^{-1}$)**: 3100, 3025, 1727, 1455, 1378, 1328, 1241.

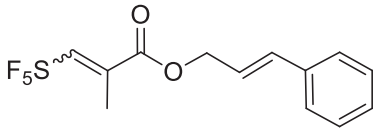
**MS ($ESI^+$)**: 285, 269, 225, 221.

**$^{19}F$ NMR ($CDCl_3/CFCl_3$, 282 MHz)**: δ 62.9 (dd, 4F, $^2J_{F,F}$ = 150.9 Hz, $^3J_{F,H}$ = 8.7 Hz), 81.2 (m, 1F).

**$^1H$ NMR ($CDCl_3$, 300 MHz)**: δ 2.23 (m, 3H, $CH_3$), 5.28 (s, 2H, $CH_2$), 7.3-7.5 (m, 6H, CH=$CHSF_5$ + Ph).

**$^{13}C$ NMR ($CDCl_3$, 75 MHz)**: δ 14.7 (s, $CH_3$), 68.1 (s, $CH_2$), 128.5 (s, 2 x CH Ph), 128.7 (s, 3 x CH Ph), 134.7 ($q_t$, $^3J_{C,F}$ = 5.2 Hz, C=$CHSF_5$), 134.8 (s, $C_q$ Ph), 147.0 ($q_t$, $^2J_{C,F}$ = 20.9 Hz, C=$CHSF_5$), 165.4 (s, C=O).

***(E/Z)*-Cinnamyl 2-methyl-3-(pentafluorosulfanyl)prop-2-enoate 10b**



**$C_{13}H_{13}F_5O_2S$**
**M = 328.30 g/mol**

The title compound was prepared as a mixture of diastereoisomers (*E*/*Z* ~ 3:1) according to the general procedure. The resulting crude product was purified by silica gel column chromatography (cyclohexane/AcOEt = 90:10) to afford two separated diastereoisomers **10b** in 55% overall yield as colourless oils.

*Diastereoisomer E:*

**Rf** = 0.19 (cyclohexane/AcOEt = 90:10)

**IR ($cm^{-1}$)**: 3000, 2930, 1726, 1496, 1451, 1328, 1243.

**$^{19}F$ NMR ($CDCl_3/CFCl_3$, 282 MHz)**: δ 64.4 (dd, 4F, $^2J_{F,F}$ = 150.9 Hz, $^3J_{F,H}$ = 8.7 Hz), 81.3 (m, 1F).

**$^1H$ NMR ($CDCl_3$, 300 MHz)**: δ 2.23 (m, 3H, C<u>H</u>$_3$), 4.89 (d, 2H, $^3J_{H,H}$ = 6.7 Hz, OC<u>H</u>$_2$), 6.33 (dt, 1H, $^3J_{H,H}$ = 15.9 Hz, $^3J_{H,H}$ = 6.7 Hz, C<u>H</u>=CHPh), 6.73 (d, 1H, $^3J_{H,H}$ = 15.9 Hz, CH=C<u>H</u>Ph), 7.3-7.5 (m, 6H, CH=C<u>H</u>$SF_5$ + Ph).

*Diastereoisomer Z:*

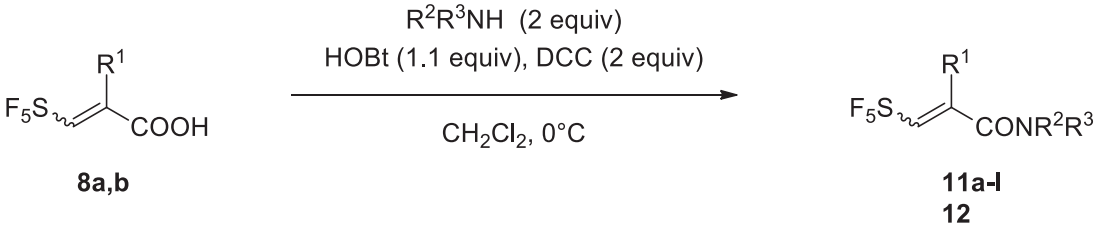
**Rf** = 0.17 (cyclohexane/AcOEt = 90:10)

**IR ($cm^{-1}$)**: 3026, 2980, 1726, 1445, 1334, 1243.

**$^{19}F$ NMR ($CDCl_3/CFCl_3$, 282 MHz)**: δ 65.0 (dd, 4F, $^2J_{F,F}$ = 150.9 Hz, $^3J_{F,H}$ = 8.7 Hz), 80.8 (m, 1F).

**$^1H$ NMR ($CDCl_3$, 300 MHz)**: δ 2.11 (m, 3H, C<u>H</u>$_3$), 4.89 (d, 2H, $^3J_{H,H}$ = 6.6 Hz, OC<u>H</u>$_2$), 6.30 (dt, 1H, $^3J_{H,H}$ = 15.9 Hz, $^3J_{H,H}$ = 6.6 Hz, C<u>H</u>=CHPh), 6.73 (d, 1H, $^3J_{H,H}$ = 15.9 Hz, CH=C<u>H</u>Ph), 7.3-7.5 (m, 6H, CH=C<u>H</u>$SF_5$ + Ph).

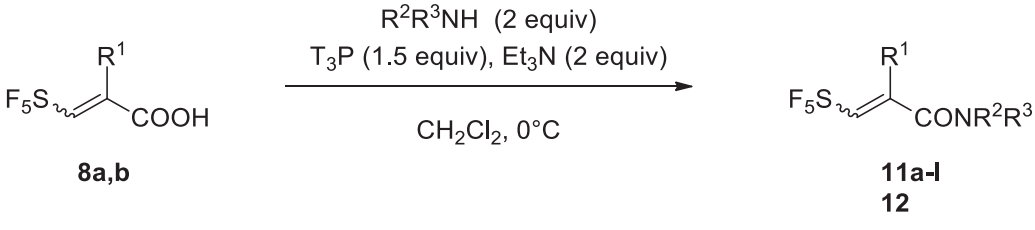
### 2.2.2. General procedure for the preparation of amides 11 and 12 – Procedure A




**8a,b** **11a-l** **12**

To a stirred solution of acid **8** (1 equiv, 1.87 mmol) in dry $CH_2Cl_2$ (8 mL) under argon, at 0°C, was added HOBt (1.1 equiv, 2.05 mmol), DCC (2 equiv, 3.74 mmol) and amine (2 equiv, 3.74 mmol). The reaction mixture was stirred at this temperature for 1.5 h. The resulting mixture was then filtered and the precipitate was washed with $CH_2Cl_2$ (40 mL). The filtrate was washed with water (3 x 15 mL), 2 M $HCl_{aq.}$ solution (3 x 15 mL) and brine (3 x 15 mL). The organic layer was dried over $MgSO_4$. After removal of solvent under reduced pressure, the crude product was purified by silica gel column chromatography leading to amide **11** or **12**.

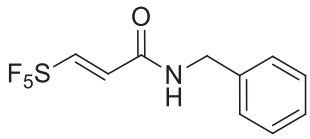
### 2.2.3. General procedure for the preparation of amides 11 and 12 – Procedure B




**8a,b** **11a-l** **12**

To a stirred solution of acid **8** (1 equiv, 1.57 mmol) in dry $CH_2Cl_2$ (7 mL) under argon, at 0°C, was added $Et_3N$ (2 equiv, 3.14 mmol), $T_3P$ (1.5 equiv, 2.36 mmol) and amine (2 equiv, 3.14 mmol). The reaction mixture was stirred at this temperature for 1 h. The resulting mixture was then diluted with $CH_2Cl_2$ (20 mL) and washed with water (2 x 10 mL). The organic layer was dried over $MgSO_4$. After removal of solvent under reduced pressure, the crude product was purified by silica gel column chromatography leading to amide **11** or **12**.

***(E)*-*N*-Benzyl-3-(pentafluorosulfanyl)prop-2-enamide 11a**



**$C_{10}H_{10}F_5NOS$**
**M = 287.25 g/mol**

The title compound was prepared according to the procedure B. Resulting crude product was purified by silica gel column chromatography (cyclohexane/AcOEt = 90:10) to afford **11a** in 93% yield as a white solid.

**M.p.**: 127-128°C

**Rf** = 0.30 (cyclohexane/AcOEt = 80:20)

**IR ($cm^{-1}$)**: 3304, 3073, 2920, 1666, 1629.

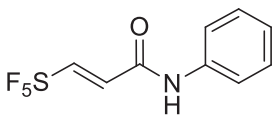
**HRMS ($ESI^-$)**: calcd for $C_{10}H_9F_5NOS$ (*m/z*) 286.0325 $[M - H]^-$, found 286.0315.

**$^{19}F$ NMR ($CDCl_3/CFCl_3$, 282 MHz)**: δ 63.0 (dd, 4F, $^2J_{F,F}$ = 150.9 Hz, $^3J_{F,H}$ = 5.2 Hz), 79.8 (m, 1F).

**$^1H$ NMR ($CDCl_3$, 300 MHz)**: δ 4.55 (d, 2H, $^3J_{H,H}$ = 5.7 Hz, C$\underline{H}_2$), 6.02 (br s, 1H, N$\underline{H}$), 6.57 (d, 1H, $^3J_{H,H}$ = 14.2 Hz, C$\underline{H}$=CHSF$_5$), 7.3-7.4 (m, 5H, Ph), 7.4-7.5 (m, 1H, CH=C$\underline{H}$SF$_5$).

**$^{13}C$ NMR ($CDCl_3$, 75 MHz)**: δ 44.2 (s, $\underline{C}H_2$), 127.9 (s, 2 x $\underline{C}$H Ph), 128.0 (s, $\underline{C}$H Ph), 128.9 (s, 2 x $\underline{C}$H Ph), 129.1 ($q_t$, $^3J_{C,F}$ = 6.6 Hz, $\underline{C}$H=CHSF$_5$), 136.7 (s, $\underline{C}_q$ Ph), 150.1 ($q_t$, $^2J_{C,F}$ = 22.2 Hz, CH=$\underline{C}$HSF$_5$), 161.6 (s, $\underline{C}$=O).

***(E)*-3-(Pentafluorosulfanyl)-*N*-phenylprop-2-enamide 11b**



**$C_9H_8F_5NOS$**
**M = 273.22 g/mol**

The title compound was prepared according to the procedure A. Resulting crude product was purified by silica gel column chromatography (cyclohexane/AcOEt = 90:10) to afford **11b** in 98% yield as a white solid.

**M.p.**: 171-172°C

**Rf** = 0.36 (cyclohexane/AcOEt = 90:10)

**IR ($cm^{-1}$)**: 3268, 3091, 1669.

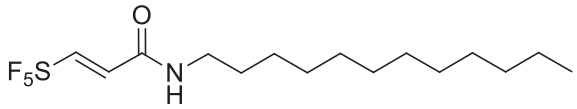
**HRMS ($ESI^+$)**: calcd for $C_9H_8F_5NOSNa$ (*m/z*) 296.0144 $[M + Na]^+$, found 296.0136.

**$^{19}F$ NMR ($CDCl_3/CFCl_3$, 282 MHz)**: δ 62.6 (dd, 4F, $^2J_{F,F}$ = 150.9 Hz, $^3J_{F,H}$ = 5.2 Hz), 79.5 (m, 1F).

**$^1H$ NMR ($CDCl_3$, 300 MHz)**: δ 6.76 (d, 1H, $^3J_{H,H}$ = 14.3 Hz, C<u>H</u>=CHSF$_5$), 7.20 (m, 1H, Ph) 7.37 (m, 2H, Ph), 7.4-7.6 (m, 3H, CH=C<u>H</u>SF$_5$ + Ph), 7.67 (br s, 1H, N<u>H</u>).

**$^{13}C$ NMR ($CDCl_3$, 75 MHz)**: δ 120.4 (s, 2 x <u>C</u>H Ph), 125.7 (s, <u>C</u>H Ph), 129.3 (s, 2 x <u>C</u>H Ph), 129.6 ($q_t$, $^3J_{C,F}$ = 7.0 Hz, <u>C</u>H=CHSF$_5$), 136.7 (s, <u>C</u>$_q$ Ph), 150.9 ($q_t$, $^2J_{C,F}$ = 22.3 Hz, CH=<u>C</u>HSF$_5$), 159.6 (s, <u>C</u>=O).

***(E)-N*-Dodecyl-3-(pentafluorosulfanyl)prop-2-enamide 11c**




**$C_{15}H_{28}F_5NOS$**
**M = 365.45 g/mol**

The title compound was prepared according to the procedure A. Resulting crude product was purified by silica gel column chromatography (cyclohexane/AcOEt = 96:4) to afford **11c** in 72% yield as a white solid.

**M.p.**: 72-73°C

**Rf** = 0.38 (cyclohexane/AcOEt = 90:10)

**IR ($cm^{-1}$)**: 3311, 2916, 2853, 1667.

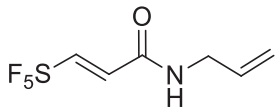
**HRMS ($ESI^+$)**: calcd for $C_{15}H_{28}F_5NOSNa$ (*m/z*) 388.1709 $[M + Na]^+$, found 388.1702.

**$^{19}F$ NMR ($CDCl_3/CFCl_3$, 282 MHz)**: δ 63.0 (dd, 4F, $^2J_{F,F}$ = 151.7 Hz, $^3J_{F,H}$ = 6.1 Hz), 80.0 (m, 1F).

**$^1H$ NMR ($CDCl_3$, 300 MHz)**: δ 0.89 (t, 3H, $^3J_{H,H}$ = 6.6 Hz, C<u>H</u>$_3$), 1.2-1.4 (m, 18H, 9 x C<u>H</u>$_2$), 1.5-1.6 (m, 2H, C<u>H</u>$_2$CH$_2$NH), 3.34 (m, 2H, C<u>H</u>$_2$NH), 6.40 (m, 1H, N<u>H</u>), 6.63 (d, 1H, $^3J_{H,H}$ = 14.4 Hz, C<u>H</u>=CHSF$_5$), 7.38 (m, 1H, CH=C<u>H</u>SF$_5$).

***Selected* $^{13}C$ NMR ($CDCl_3$, 75 MHz)**: δ 14.1 (s, <u>C</u>H$_3$), 22.7 (s, <u>C</u>H$_2$), 26.9 (s, <u>C</u>H$_2$), 29.20 (s, <u>C</u>H$_2$), 29.25 (s, <u>C</u>H$_2$), 29.31 (s, <u>C</u>H$_2$), 29.47 (s, <u>C</u>H$_2$), 29.54 (s, <u>C</u>H$_2$), 29.59 (s, 2 x <u>C</u>H$_2$), 31.9 (s, <u>C</u>H$_2$), 129.4 (q$_t$, $^3J_{C,F}$ = 6.6 Hz, <u>C</u>H=CHSF$_5$), 149.8 (q$_t$, $^2J_{C,F}$ = 22.0 Hz, CH=<u>C</u>HSF$_5$), 161.7 (s, <u>C</u>=O).

## ***(E)-N*-Allyl-3-(pentafluorosulfanyl)prop-2-enamide 11d**




**$C_6H_8F_5NOS$**
**M = 237.19 g/mol**

The title compound was prepared according to the procedure A. Resulting crude product was purified by silica gel column chromatography (cyclohexane/AcOEt = 80:20) to afford **11d** in 60% yield as a white solid.

**M.p.**: 53-54°C

**Rf** = 0.24 (cyclohexane/AcOEt = 80:20)

**IR ($cm^{-1}$)**: 3290, 3085, 2932, 1666, 1627, 1550.

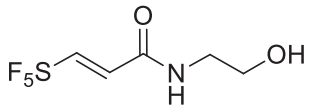
**HRMS ($ESI^+$)**: calcd for $C_6H_9F_5NOS$ (*m/z*) 238.0325 $[M + H]^+$, found 238.0321.

**$^{19}$F NMR ($CDCl_3/CFCl_3$, 282 MHz)**: δ 63.0 (dd, 4F, $^2J_{F,F}$ = 150.9 Hz, $^3J_{F,H}$ = 5.2 Hz), 79.8 (m, 1F).

**$^1$H NMR ($CDCl_3$, 300 MHz)**: δ 3.97 (m, 2H, C<u>H</u>$_2$NH), 5.18-5.27 (m, 2H, C<u>H</u>$_2$=CH), 5.84 (m, 1H, CH$_2$=C<u>H</u>), 6.71 (d, 1H, $^3J_{H,H}$ = 14.5 Hz, C<u>H</u>=CHSF$_5$), 6.77 (m, 1H, N<u>H</u>), 7.39 (m, 1H, CH=C<u>H</u>SF$_5$).

**$^{13}$C NMR ($CDCl_3$, 75 MHz)**: δ 42.5 (s, <u>C</u>H$_2$NH), 117.7 (s, <u>C</u>H$_2$=CH), 128.9 (q$_t$, $^3J_{C,F}$ = 6.6 Hz, <u>C</u>H=CHSF$_5$), 132.8 (s, CH$_2$=<u>C</u>H), 150.3 (q$_t$, $^2J_{C,F}$ = 22.6 Hz, CH=<u>C</u>HSF$_5$), 161.4 (s, <u>C</u>=O).

***(E)-N*-(2-Hydroxyethyl)-3-pentafluorosulfanylprop-2-enamide 11e**




**$C_5H_8F_5NO_2S$**
**M =241.18 g/mol**

The title compound was prepared according to the procedure B. Resulting crude product was purified by silica gel column chromatography (cyclohexane/AcOEt = 40:60) to afford **11e** in 32% yield as a colourless oil.

**Rf** = 0.15 (cyclohexane/AcOEt = 50:50)

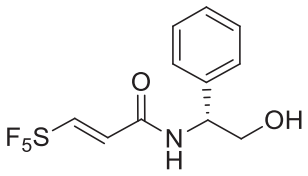
**IR (cm$^{-1}$)**: 3312, 1667, 1632, 1557, 1434, 1339, 1244.

**HRMS (ESI$^+$)**: calcd for $C_5H_9F_5NO_2S$ (*m/z*) 242.0274 $[M + H]^+$, found 242.0273.

**$^{19}$F NMR ($CDCl_3/CFCl_3$, 282 MHz)**: δ 62.9 (dd, 4F, $^2J_{F,F}$ = 150.9 Hz, $^3J_{F,H}$ = 5.2 Hz), 79.7 (m, 1F).

**$^1$H NMR ($CDCl_3$, 300 MHz)**: δ 2.11 (m, 1H, O<u>H</u>), 3.57 (m, 2H, C<u>H</u>$_2$), 3.81 (m, 2H, C<u>H</u>$_2$), 6.39 (br s, 1H, N<u>H</u>), 6.61 (d, 1H, $^3J_{H,H}$ = 14.4 Hz, C<u>H</u>=CHSF$_5$), 7.45 (m, 1H, CH=C<u>H</u>SF$_5$).

***(R,E)-N*-(2-Hydroxy-1-phenylethyl)-3-pentafluorosulfanylprop-2-enamide 11f**




**$C_{11}H_{12}F_5NO_2S$**
**M = 317.28 g/mol**

The title compound was prepared according to the procedure B. Resulting crude product was purified by silica gel column chromatography (cyclohexane/AcOEt = 60:40) to afford **11f** in 60% yield as a colourless oil.

**Rf** = 0.14 (cyclohexane/AcOEt = 7:3)

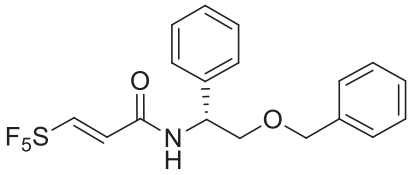
**IR ($cm^{-1}$)**: 3307, 1668, 1635, 1558, 1356, 1255.

**HRMS ($ESI^+$)**: calcd for $C_{11}H_{13}F_5NO_2S$ (*m/z*) 318.0587 $[M + H]^+$, found 318.0592.

**$^{19}F$ NMR ($CDCl_3/CFCl_3$, 282 MHz)**: δ 63.0 (dd, 4F, $^2J_{F,F}$ = 150.9 Hz, $^3J_{F,H}$ = 5.2 Hz), 79.6 (m, 1F).

**$^1H$ NMR ($CDCl_3$, 300 MHz)**: δ 3.0-3.2 (m, 1H, OH), 3.74 (m, 2H, $CH_2OH$), 5.01 (m, 1H, CH Ph), 6.93 (d, 1H, $^3J_{H,H}$ = 14.3 Hz, CH=$CHSF_5$), 7.3-7.5 (m, 7H, Ph + CH=CH$SF_5$ + NH).

***(R,E)-N*-[2-(Benzyloxy)-1-phenylethyl]-3-pentafluorosulfanylprop-2-enamide 11g**




**$C_{18}H_{18}F_5NO_2S$**
**M = 407.40 g/mol**

The title compound was prepared according to the procedure A. Resulting crude product was purified by silica gel column chromatography (cyclohexane/AcOEt = 85:15) to afford **11g** in 59% yield as a white solid.

**M.p.**: 175-176°C

**Rf** = 0.35 (cyclohexane/AcOEt = 85:15)

**IR ($cm^{-1}$)**: 3290, 3072, 2921, 1663, 1624, 1552, 1451, 1350, 1250.

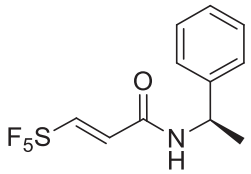
**HRMS ($ESI^+$)**: calcd for $C_{18}H_{19}F_5NO_2S$ (*m/z*) 408.1057 $[M + H]^+$, found 408.1043.

**$^{19}F$ NMR ($CDCl_3/CFCl_3$, 282 MHz)**: δ 63.1 (dd, 4F, $^2J_{F,F}$ = 150.9 Hz, $^3J_{F,H}$ = 5.2 Hz), 79.9 (m, 1F).

**$^1H$ NMR ($CDCl_3$, 300 MHz)**: δ 3.79 (m, 2H, C$\underline{H}_2$CHPh), 4.54 (s, 2H, C$\underline{H}_2$Ph), 5.23 (m, 1H, $CH_2C\underline{H}$Ph), 6.52 (br s, 1H, N$\underline{H}$), 6.57 (d, 1H, $^3J_{H,H}$ = 14.5 Hz, C$\underline{H}$=CHSF$_5$), 7.30-7.40 (m, 10H, 2 x Ph), 7.40-7.47 (m, 1H, CH=C$\underline{H}$SF$_5$).

**$^{13}C$ NMR ($CDCl_3$, 75 MHz)**: δ 53.5 (s, $\underline{C}$H Ph), 71.9 (s, $\underline{C}H_2$), 73.3 (s, $\underline{C}H_2$), 126.8 (s, 2 x $\underline{C}$H Ph), 127.8 (s, 2 x $\underline{C}$H Ph), 127.9 (s, $\underline{C}$H Ph), 128.0 (s, $\underline{C}$H Ph), 128.5 (s, 2 x $\underline{C}$H Ph), 128.6 (s, 2 x $\underline{C}$H Ph), 129.1 ($q_t$, $^3J_{C,F}$ = 6.7 Hz, $\underline{C}$H=CHSF$_5$), 137.3 (s, $\underline{C}_q$ Ph), 138.7 (s, $\underline{C}_q$ Ph), 150.2 ($q_t$, $^2J_{C,F}$ = 22.2 Hz, CH=$\underline{C}$HSF$_5$), 161.0 (s, $\underline{C}$=O).

## ***(R,E)*-3-(Pentafluorosulfanyl)-*N*-(1-phenylethyl)prop-2-enamide 11h**




**$C_{11}H_{12}F_5NOS$**
**M = 301.28 g/mol**

The title compound was prepared according to the procedure A. Resulting crude product was purified by silica gel column chromatography (cyclohexane/AcOEt = 90:10) to afford **11h** in 67% yield as a white solid.

**M.p.**: 142°C

**Rf** = 0.35 (cyclohexane/AcOEt = 90:10)

**IR ($cm^{-1}$)**: 3311, 3073, 1669, 1450.

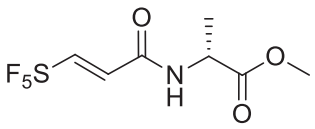
**HRMS ($ESI^+$)**: calcd for $C_{11}H_{13}F_5NOS$ (*m/z*) 302.0638 $[M + H]^+$, found 302.0642.

**$^{19}F$ NMR ($CDCl_3/CFCl_3$, 282 MHz)**: δ 63.0 (dd, 4F, $^2J_{F,F}$ = 150.9 Hz, $^3J_{F,H}$ = 5.2 Hz), 79.9 (m, 1F).

**$^1H$ NMR ($CDCl_3$, 300 MHz)**: δ 1.54 (d, 3H, $^3J_{H,H}$ = 6.9 Hz, C<u>H</u>$_3$), 5.16 (m, 1H, C<u>H</u>NH), 6.34 (m, 1H, N<u>H</u>), 6.58 (d, 1H, $^3J_{H,H}$ = 14.4 Hz, C<u>H</u>=CHSF$_5$), 7.2-7.4 (m, 5H, Ph), 7.3-7.5 (m, 1H, CH=C<u>H</u>SF$_5$).

**$^{13}C$ NMR ($CDCl_3$, 75 MHz)**: δ 21.3 (s, <u>C</u>H$_3$), 49.8 (s, <u>C</u>HNH), 126.2 (s, 2 x <u>C</u>H Ph), 127.9 (s, <u>C</u>H Ph), 128.9 (s, 2 x <u>C</u>H Ph), 129.2 (q$_t$, $^3J_{C,F}$ = 6.6 Hz, <u>C</u>H=CHSF$_5$), 141.8 (s, <u>C</u>$_q$ Ph), 150.2 (q$_t$, $^2J_{C,F}$ = 22.3 Hz, CH=<u>C</u>HSF$_5$), 160.6 (s, <u>C</u>=O).

## *(R,E)*-Methyl 2-(3-pentafluorosulfanylprop-2-enylamido)propanoate 11i




**$C_7H_{10}F_5NO_3S$**
**M = 283.22 g/mol**

The title compound was prepared according to the procedure A. Resulting crude product was purified by silica gel column chromatography (cyclohexane/AcOEt = 80:20) to afford **11i** in 60% yield as a white solid.

**M.p.**: 90-91°C

**Rf** = 0.18 (cyclohexane/AcOEt = 80:20)

**IR ($cm^{-1}$)**: 3310, 3080, 2925, 1743, 1671, 1634, 1544, 1217.

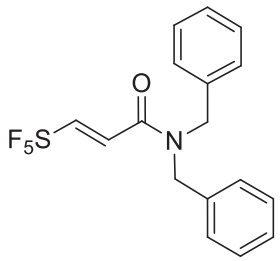
**HRMS ($ESI^+$)**: calcd for $C_7H_{11}F_5NO_3S$ (*m/z*) 284.0380 $[M + H]^+$, found 284.0386.

**$^{19}F$ NMR ($CDCl_3/CFCl_3$, 282 MHz)**: δ 62.9 (dd, 4F, $^2J_{F,F}$ = 150.9 Hz, $^3J_{F,H}$ = 5.2 Hz), 79.6 (m, 1F).

**$^{1}$H NMR ($CDCl_3$, 300 MHz)**: δ 1.49 (d, 3H, $^{3}J_{H,H}$ = 7.2 Hz, CHC<u>H</u>$_3$), 3.80 (s, 3H, OC<u>H</u>$_3$), 4.69 (m, 1H, C<u>H</u>NH), 6.51 (br s, 1H, N<u>H</u>), 6.63 (d, 1H, $^{3}J_{H,H}$ = 14.4 Hz, C<u>H</u>=CHSF$_5$), 7.43 (m, 1H, CH=C<u>H</u>SF$_5$).

**$^{13}$C NMR ($CDCl_3$, 75 MHz)**: δ 18.3 (s, <u>C</u>H$_3$CH), 48.6 (s, CH$_3$<u>C</u>H), 52.9 (s, O<u>C</u>H$_3$), 128.8 (q$_t$, $^{3}J_{C,F}$ = 6.6 Hz, <u>C</u>H=CHSF$_5$), 150.5 (q$_t$, $^{2}J_{C,F}$ = 22.3 Hz, CH=<u>C</u>HSF$_5$), 161.0 (s, <u>C</u>(O)NH), 173.1 (s, <u>C</u>(O)OCH$_3$).

***(E)*-*N*,*N*-Dibenzyl-3-pentafluorosulfanylprop-2-enamide 11j**




**$C_{17}H_{16}F_5NOS$**
**M =377.37 g/mol**

The title compound was prepared according to the procedure A. Resulting crude product was purified by silica gel column chromatography (cyclohexane/AcOEt = 98:2) to afford **11j** in 57% yield as a yellow oil.

**Rf** = 0.38 (cyclohexane/AcOEt = 90:10)

**IR (cm$^{-1}$)**: 3067, 2928, 1658, 1429.

**HRMS (ESI$^+$)**: calcd for $C_{17}H_{17}F_5NOS$ (*m/z*) 378.0951 $[M + H]^+$, found 378.0948.

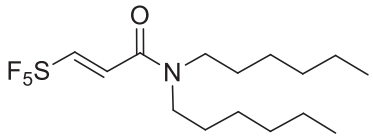
**$^{19}$F NMR ($CDCl_3$/$CFCl_3$, 282 MHz)**: δ 62.7 (dd, 4F, $^{2}J_{F,F}$ = 150.9 Hz, $^{3}J_{F,H}$ = 6.9 Hz), 80.0 (m, 1F).

**$^{1}$H NMR ($CDCl_3$, 300 MHz)**: δ 4.50 (s, 2H, C<u>H</u>$_2$), 4.67 (s, 2H, C<u>H</u>$_2$), 7.05 (d, 1H, $^{3}J_{H,H}$ = 14.3 Hz, C<u>H</u>=CHSF$_5$), 7.0-7.4 (m, 10H, 2 x Ph), 7.50 (m, 1H, CH=C<u>H</u>SF$_5$).

**$^{13}$C NMR ($CDCl_3$, 75 MHz)**: δ 49.0 (s, <u>C</u>H$_2$), 50.4 (s, <u>C</u>H$_2$), 126.5 (s, 2 x <u>C</u>H Ph), 126.9 (q$_t$, $^{3}J_{C,F}$ = 6.9 Hz, <u>C</u>H=CHSF$_5$), 127.9 (s, <u>C</u>H Ph), 128.2 (s, <u>C</u>H Ph), 128.5 (s, 2 x <u>C</u>H Ph), 128.8

(s, 2 x CH Ph), 129.2 (2 x CH Ph), 135.4 (s, $C_q$ Ph), 136.1 (s, $C_q$ Ph), 151.4 ($q_t$, $^2J_{C,F}$ = 21.9 Hz, CH=CHSF$_5$), 163.1 (s, C=O).

***(E)*-*N*,*N*-Di(*n*-hexyl-3-pentafluorosulfanylprop-2-enamide 11k**



**$C_{15}H_{28}F_5NOS$**
**M = 365,45 g/mol**

The title compound was prepared according to the procedure A. Resulting crude product was purified by silica gel column chromatography (cyclohexane/AcOEt = 90:10) to afford **11k** in 60% yield as a yellow oil.

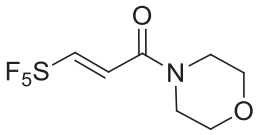
**Rf** = 0.22 (cyclohexane/AcOEt = 96:4)

**IR ($cm^{-1}$)**: 2928, 2862, 1668.

**$^{19}$F NMR ($CDCl_3$/$CFCl_3$, 282 MHz)**: δ 62.7 (dd, 4F, $^2J_{F,F}$ = 150.9 Hz, $^3J_{F,H}$ = 5.2 Hz), 80.5 (m, 1F).

**$^1$H NMR ($CDCl_3$, 300 MHz)**: δ 0.9-1.0 (m, 6H, 2 x $CH_3$), 1.2-1.4 (m, 12H, 5 x $CH_2$), 1.5-1.7 (m, 4H, 2 x $NCH_2CH_2$), 3.31 (m, 2H, $NCH_2CH_2$), 3.40 (m, 2H, $NCH_2CH_2$), 7.00 (d, 1H, $^3J_{H,H}$ = 14.2 Hz, CH=CHSF$_5$), 7.40 (m, 1H, CH=CHSF$_5$).

***(E)*-*N*-Morpholino-3-pentafluorosulfanylprop-2-enamide 11l**



**$C_7H_{10}F_5NO_2S$**
**M = 267.22 g/mol**

The title compound was prepared according to the procedure A. Resulting crude product was purified by silica gel column chromatography (cyclohexane/AcOEt = 70:30) to afford **11l** in 86% yield as a white solid.

**M.p.**: 114-115°C

**Rf** = 0.13 (cyclohexane/AcOEt = 80:20)

**IR ($cm^{-1}$)**: 3041, 2997, 2927, 1663, 1605, 1442, 1306, 1271, 1254.

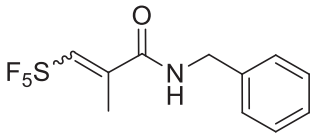
**HRMS ($ESI^+$)**: calcd for $C_7H_{11}F_5NO_2S$ (*m/z*) 267.9761, $[M + H]^+$, found 267.9758.

**$^{19}F$ NMR ($CDCl_3/CFCl_3$, 282 MHz)**: δ 62.7 (dd, 4F, $^2J_{F,F}$ = 150.9 Hz, $^3J_{F,H}$ = 6.9 Hz), 80.0 (m, 1F).

**$^1H$ NMR ($CDCl_3$, 300 MHz)**: δ 3.5-3.6 (m, 2H, C$\underline{H}_2$), 3.6-3.8 (m, 6H, 3 x C$\underline{H}_2$), 7.00 (d, 1H, $^3J_{H,H}$ = 14.3 Hz, C$\underline{H}$=CHSF$_5$), 7.36 (m, 1H, CH=C$\underline{H}$SF$_5$).

**$^{13}C$ NMR ($CDCl_3$, 75 MHz)**: δ 42.6 (s, N$\underline{C}H_2$), 46.4 (s, N$\underline{C}H_2$), 66.5 (s, 2 x O$\underline{C}H_2$), 126.0 ($q_t$, $^3J_{C,F}$ = 7.0 Hz, $\underline{C}$H=CHSF$_5$), 150.9 ($q_t$, $^2J_{C,F}$ = 22.0 Hz, CH=$\underline{C}$HSF$_5$), 161.1 (s, $\underline{C}$=O).

**(*E*,*Z*)-*N*-Benzyl-2-methyl-3-(pentafluorosulfanyl)prop-2-enamide 12**




**$C_{11}H_{12}F_5NOS$**
**M = 301.28 g/mol**

The title compound was prepared as a mixture of diastereoisomers (E/Z ~ 3:1) according to the procedure A. Only *E*-isomer was isolated by silica gel column chromatography (cyclohexane/AcOEt = 90:10) in 72% yield as a white solid.

*Diastereoisomer E*:

**M.p.**: 134-135°C

**Rf** = 0.38 (cyclohexane/AcOEt = 80/20)

**HRMS (ESI$^+$)**: calcd for $C_{11}H_{13}F_5NOS$ (*m/z*) 302.0638 $[M + H]^+$, found 302.0634.

**$^{19}$F NMR ($CDCl_3/CFCl_3$, 282 MHz)**: δ 65.0 (dd, 4F, $^2J_{F,F}$ = 150.0 Hz, $^3J_{F,H}$ = 6.9 Hz), 82.0 (m, 1F).

**$^1$H NMR ($CDCl_3$, 300 MHz)**: δ 2.21 (s, 3H, C<u>H</u>$_3$), 4.50 (d, 2H, $^3J_{H,H}$ = 5.7 Hz, C<u>H</u>$_2$), 6.24 (br s, 1H, N<u>H</u>), 6.92 ($q_t$, 1H, $^3J_{F,H}$ = 6.9 Hz, CH=C<u>H</u>$SF_5$), 7.28-7.40 (m, 5H, Ph).

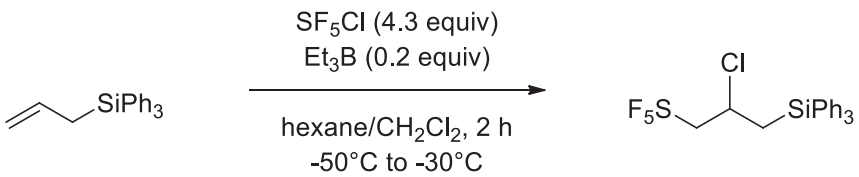
**$^{13}$C NMR ($CDCl_3$, 75 MHz)**: δ 15.4 (s, <u>C</u>$H_3$), 44.2 (s, <u>C</u>$H_2$), 127.87 (s, 2 x <u>C</u>H Ph), 127.92 (s, <u>C</u>H Ph), 128.9 (s, 2 x <u>C</u>H Ph), 137.0 (s, <u>C</u>$_q$ Ph), 138.9 ($q_t$, $^3J_{C,F}$ = 5.0 Hz, <u>C</u>=CH$SF_5$), 142.1 ($q_t$, $^2J_{C,F}$ = 19.8 Hz, C=<u>C</u>H$SF_5$), 166.4 (s, <u>C</u>=O).

*Diastereoisomer Z (in the crude mixture)*:

**$^{19}$F NMR ($CDCl_3/CFCl_3$, 282 MHz)**: δ 65.6 (dd, 4F, $^2J_{F,F}$ = 147.4 Hz, $^3J_{F,H}$ = 6.9 Hz), 81.7 (m, 1F).

## 2.3. Pentafluorosulfanylated allylsilanes 21a-c

### 2.3.1. Typical procedure for the radical addition of $SF_5Cl$ to allylsilanes 19a-d

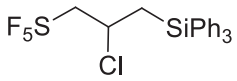



**19b** **20b**

In a 50 mL three-neck flask, equipped with an inlet and outlet of gas, allyltriphenylsilane **19b** (2.44 g, 1.0 equiv, 8.1 mmol) in $CH_2Cl_2$/hexane (8:5 mL) was introduced. The solution was cooled to -50°C and $SF_5Cl$ (3.35 g, 4.3 equiv, 33.5 mmol) was condensed into it. The mixture was warmed to -30°C and $Et_3B$ (1.60 mL, 0.2 equiv, 1.6 mmol, 1M in hexane) was added dropwise. The reaction mixture was stirred at this temperature for 2 h and then it was left at room temperature overnight. The resulting mixture was passed through a short silica plug and it was washed with cyclohexane (2 x 20 mL)

and $CH_2Cl_2$ (2 x 20 mL). The filtrate was concentrated under reduced pressure to give desired compound **20b** as a yellow oil (3.64 g, 97%).

**(2-Chloro-3-pentafluorosulfanylpropyl)triphenylsilane 20b**

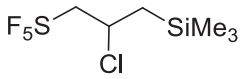



**$C_{21}H_{20}ClF_5SSi$**
**M = 462.98 g/mol**

**$^{19}$F NMR ($CDCl_3/CFCl_3$, 282 MHz)** : δ 65.5 (dm, 4F, $^2J_{F,F}$ = 147.4 Hz), 82.9 (m, 1F).

**$^1$H NMR ($CDCl_3$, 300 MHz)**: δ 2.13 (dd, 1H, $^2J_{H,H}$ = 15.3 Hz, $^3J_{H,H}$ = 6.8 Hz, C$\underline{H}_A$H$_B$SiPh$_3$), 2.23 (dd, 1H, $^2J_{H,H}$ = 15.3 Hz, $^3J_{H,H}$ = 6.8 Hz, CH$_A$$\underline{H}_B$SiPh$_3$), 3.87 (m, 2H, C$\underline{H}_2$SF$_5$), 4.54 (m, 1H, C$\underline{H}$Cl), 7.4-7.7 (m, 15H, 3 x Ph).

**(2-Chloro-3-pentafluorosulfanylpropyl)trimethylsilane 20a**



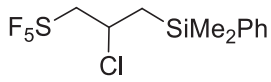

**$C_6H_{14}ClF_5SSi$**
**M = 276.77 g/mol**

The title compound was synthesised from allyltrimethylsilane **19a** (5.95 g, 1.0 equiv, 52.1 mmol), $SF_5Cl$ (8.35 g, 1.6 equiv, 83.4 mol) and $Et_3B$ (5.20 mL, 0.1 equiv, 5.2 mmol, 1 M in hexane) in hexane (45 mL) according to the typical procedure. The desired product **20a** was obtained after work-up as yellow oil (1.96 g, 14%). The low yield of the reaction was due to the low boiling point of the final product.

**$^{19}$F NMR ($CDCl_3/CFCl_3$, 282 MHz)**: δ 65.3 (dm, 4F, $^2J_{F,F}$ = 147.4 Hz), 83.1 (m, 1F).

**$^1$H NMR ($CDCl_3$, 300 MHz)**: δ 0.13 (m, 9H, Si(C$\underline{H}_3$)$_3$), 1.29 (m, 2H, C$\underline{H}_2$Si(CH$_3$)$_3$), 3.97 (m, 2H, C$\underline{H}_2$SF$_5$), 4.50 (m, 1H, C$\underline{H}$Cl).

**(2-Chloro-3-pentafluorosulfanylpropyl)dimethylphenylsilane 20c**



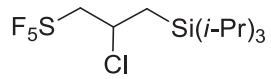

**$C_{11}H_{16}ClF_5SSi$**
**M = 338.84 g/mol**

The title compound was synthesised from allyldimethylphenylsilane **19c** (0.75 g, 1.0 equiv, 4.2 mmol), $SF_5Cl$ (2.94 g, 7.0 equiv, 29.4 mmol) and $Et_3B$ (0.80 mL, 0.2 equiv, 0.8 mmol, 1 M in hexane) in hexane (7 mL), according to the typical procedure. The desired product **20c** was obtained after work-up as a yellow oil (1.13 g, 79%).

**$^{19}$F NMR ($CDCl_3$/$CFCl_3$, 282 MHz)**: δ 65.4 (dm, 4F, $^2J_{F,F}$ = 147.4 Hz), 83.0 (m, 1F).

**$^1$H NMR ($CDCl_3$, 300 MHz)**: δ 0.41 (s, 3H, SiC$\underline{H}_3$), 0.44 (s, 3H, SiC$\underline{H}_3$), 1.4-1.6 (m, 2H, C$\underline{H}_2$Si$(CH_3)_2$Ph), 3.89 (m, 2H, C$\underline{H}_2SF_5$), 4.44 (m, 1H, C$\underline{H}$Cl), 7.4-7.5 (m, 3H, Ph), 7.5-7.6 (m, 2H, Ph).

**(2-Chloro-3-pentafluorosulfanylpropyl)tri(isopropyl)silane 20d**



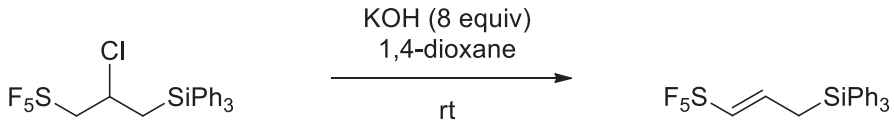

**$C_{12}H_{26}ClF_5SSi$**
**M = 360.93 g/mol**

The title compound was synthesised from allyltri(isopropyl)silane **19d** (2.7 g, 1.0 equiv, 13.6 mmol), $SF_5Cl$ (5.8 g, 4.3 equiv, 57.8 mmol) and $Et_3B$ (2.7 mL, 0.2 equiv, 2.7 mmol, 1 M in hexane) in hexane (24 mL) according to the typical procedure. The desired product **20d** was obtained after work-up as a yellow oil (1.13 g, 84%).

**$^{19}$F NMR ($CDCl_3$/$CFCl_3$, 282 MHz)**: δ 65.3 (dm, 4F, $^2J_{F,F}$ = 147.4 Hz), 83.1 (m, 1F).

**$^1$H NMR ($CDCl_3$, 300 MHz)**: δ 1.0-1.1 (m, 21H, Si(*i*-P$\underline{r}$)$_3$), 1.37 (d, 2H, $^3J_{H,H}$ = 7.2 Hz, C$\underline{H}_2$Si(*i*-Pr)$_3$), 4.01 (m, 2H, C$\underline{H}_2SF_5$), 4.57 (m, 1H, C$\underline{H}$Cl).

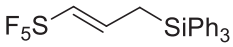
### 2.3.2. Typical procedure for the elimination reaction of compounds 20b-d




**20b** **21a**

Triphenylsilane **20b** (460 mg, 1 equiv, 0.99 mmol) was treated with KOH (525 mg, 8 equiv, 7.95 mmol) in 1,4-dioxane (1.3 mL). The reaction mixture was stirred at room temperature for 25 minutes. The resulting mixture was then filtered and the precipitate was washed with $CH_2Cl_2$. The filtrate was concentrated under reduced pressure to give crude product; the latter was purified by Kugelrohr distillation (80-140°C, 0.2 mbar) to give compound **21a** as a yellow oil (367 mg, 87%).

**(*E*)-(3-Pentafluorosulfanylallyl)triphenylsilane 21a**

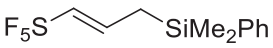



**$C_{21}H_{19}F_5SSi$**
**M = 426.52 g/mol**

**$^{19}$F NMR ($CDCl_3/CFCl_3$, 282 MHz** : δ 63.0 (dd, 4F, $^2J_{F,F}$ = 150.9 Hz, $^3J_{F,H}$ = 5.2 Hz), 84.8 (m, 1F).

**$^1$H NMR ($CDCl_3$, 300 MHz)**: δ 2.44 (dm, 2H, $^3J_{H,H}$ = 8.7 Hz, $C\underline{H}_2SiPh_3$), 6.16-6.25 (m, 1H, $CH{=}C\underline{H}SF_5$), 6.49 (m, 1H, $C\underline{H}{=}CHSF_5$), 7.2-7.6 (m, 15H, 3 x Ph).

**(*E*)-(3-Pentafluorosulfanylallyl)dimethylphenylsilane 21b**




**$C_{11}H_{15}F_5SSi$**
**M = 302.38 g/mol**

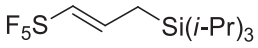
The title compound was synthesised from dimethylphenylsilane **20c** (0.51 g, 1 equiv, 1.50 mmol) and KOH (1.30 g, 15 equiv, 23.07 mmol), according to the typical procedure.

The desired product **21b** was obtained after Kugelrohr distillation (80-140°C, 0.2 mbar), as a yellow oil (95 mg, 21%).

**$^{19}$F NMR ($CDCl_3/CFCl_3$, 282 MHz)**: δ 63.2 (dd, 4F, $^2J_{F,F}$ = 150.9 Hz, $^3J_{F,H}$ = 5.2 Hz), 85.2 (m, 1F).

**$^1$H NMR ($CDCl_3$, 300 MHz)**: δ 0.34 (s, 3H, C$\underline{H}_3$), 0.37 (s, 3H, C$\underline{H}_3$), 1.82 (dm, 2H, $^3J_{H,H}$ = 8.9 Hz, C$\underline{H}_2$Si$(CH_3)_2$Ph), 6.17-6.25 (m, 1H, CH=C$\underline{H}$S$F_5$), 6.49 (m, 1H, C$\underline{H}$=CHS$F_5$), 7.2-7.6 (m, 5H, Ph).

**(*E*)-(3-Pentafluorosulfanylallyl)tri(isopropyl)silane 21c**




**$C_{12}H_{25}F_5SSi$**
**M = 324.47 g/mol**

The title compound was synthesised from tri(isopropyl)silane **20d** (0.72 g, 1 equiv, 2.0 mmol) and KOH (0.90 g, 8 equiv, 16.1 mmol), according to the typical procedure. The desired product **21c** was obtained after the work-up, without further purification, as a yellow oil (0.49 g, 76%).

**IR ($cm^{-1}$)**: 2944, 2867, 1462, 1144.

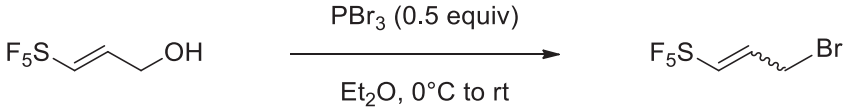
**MS (EI)**: *m/z* 281 $[M-(i\text{-Pr})]^+$, 185, 157 $[(i\text{-Pr})_3Si]^+$, 149, 115, 97.

**$^{19}$F NMR ($CDCl_3/CFCl_3$, 282 MHz)**: δ 63.0 (dd, 4F, $^2J_{F,F}$ = 149.1 Hz, $^3J_{F,H}$ = 5.2 Hz), 85.5 (m, 1F).

**$^1$H NMR ($CDCl_3$, 300 MHz)**: δ 1.08 (m, 21H, Si(*i*-P$\underline{r}$)$_3$), 1.71 (dm, 2H, $^3J_{H,H}$ = 9.2 Hz, C$\underline{H}_2$Si(*i*-Pr)$_3$), 6.28-6.37 (m, 1H, CH=C$\underline{H}$S$F_5$), 6.61 (m, 1H, C$\underline{H}$=CHS$F_5$).

## 2.4. Pentafluorosulfanylted homoallylic alcohols 22a-c and 23a-c

### 2.4.1. Preparation of starting bromide 24




**5a** **24**

Solution of allyl alcohol **5a** (0.83 g, 1.0 equiv, 4.5 mmol) in $Et_2O$ (13 mL) was cooled to 0°C and $PBr_3$ (0.21 mL, 0.5 equiv, 2.3 mmol) was added dropwise. The reaction mixture was allowed to reach room temperature and it was stirred for 3 h. The reaction mixture was poured into ice-cold water (8 mL). The phases were separated and the organic phase was washed with 5% $NaHCO_{3aq.}$ solution (5 x 4 mL), brine (4 mL) and it was dried over $MgSO_4$. The solvent was partially removed by distillation under atmospheric pressure to give desired product **24** (0.72 g, 65%) as a mixture of diastereoisomers (*E/Z* ~1.5:1) in solution in $Et_2O$.

**(*E/Z*)-3-Bromo-1-pentafluorosulfanylprop-1-en 24**


**$C_3H_4BrF_5S$**
**M = 247.02 g/mol**

**HRMS (ESI$^+$)**: calcd for $C_3H_4BrF_5NaS$ (*m/z*) 268.9035 $[M+Na]^+$, found 268.9037.

*Diastereoisomer E:*

**$^{19}$F NMR ($CDCl_3/CFCl_3$, 282 MHz)**: δ 62.6 (dm, 4F, $^2J_{F,F}$ = 149.1 Hz), 81.3 (m, 1F).

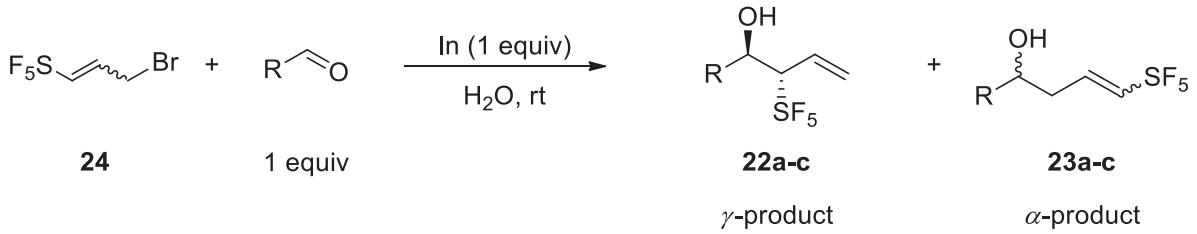
**$^1$H NMR ($CDCl_3$, 300 MHz)**: δ 3.9-4.0 (m, 2H, C$\underline{H}_2$Br), 6.5-6.8 (m, 2H).

*Diastereoisomer Z:*

**$^{19}$F NMR ($CDCl_3/CFCl_3$, 282 MHz)**: δ 62.6 (dd, 4F, $^2J_{F,F}$ = 149.1 Hz), 81.2 (m, 1F).

**$^1$H NMR ($CDCl_3$, 300 MHz)**: δ 4.7-4.9 (m, 2H, C$\underline{H}_2$Br), 6.5-6.8 (m, 2H).

### 2.4.2. General procedure for the In-mediated allylation



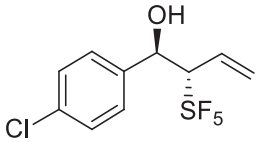

**24** 1 equiv **22a-c** **23a-c**

$\gamma$-product $\alpha$-product

Bromide **24** (1 equiv, 0.4 mmol), aldehyde (1 equiv, 0.4 mmol) and indium (1 equiv, 0.4 mmol) in water (0.5 mL) were stirred in a sealed tube at room temperature. After 18 h the reaction mixture was poured into 1M $HCl_{aq.}$ solution (1 mL) and it was extracted with $CH_2Cl_2$ (5 x 2 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography leading to separated $\gamma$-products **22a-c** (only *anti* diastereoisomer) and $\alpha$-products **23a-c** (mixtures of *E/Z* isomers).

**2.4.2.1.** The reaction of bromide **24** with *p*-chlorobenzaldehyde was carried out according to the general procedure and led to a mixture of $\gamma$- and $\alpha$-products **22a** and **23a** (~0.4:0.6). The resulting crude was purified by silica gel column chromatography (EP/AcOEt = from 98:2 to 84:16) to afford two separated regioisomers: $\gamma$-product **22a** as only *anti* diastereoisomer in 19% yield (colorless oil) and $\alpha$-product **23a** as a mixture of *E/Z* isomers (~1:1) in 12% yield (colorless oil).

***Anti* 1-(4-chlorophenyl)-2-pentafluorosulfanylbut-3-en-1-ol 22a**




**$C_{10}H_{10}ClF_5OS$**
**M = 308.70 g/mol**

**Rf** = 0.60 (EP/AcOEt = 84:16)

**IR ($cm^{-1}$)**: 3426, 2925, 1686, 1593, 1492.

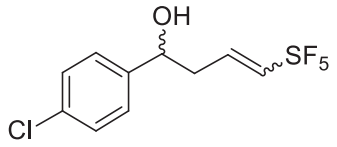
**HRMS (ESI$^+$)**: calcd for $C_{10}H_{11}ClF_5OS$ (*m/z*) 309.5814 $[M+H]^+$, found 309.5809.

**$^{19}$F NMR ($CDCl_3/CFCl_3$, 282 MHz)**: δ 56.3 (dd, 4F, $^2J_{F,F}$ = 142.2 Hz, $^3J_{F,H}$ = 6.9 Hz), 84.1 (m, 1F).

**$^1$H NMR ($CDCl_3$, 300 MHz)**: δ 2.44 (br s, 1H, O<u>H</u>), 4.33 (m, 1H, C<u>H</u>$SF_5$), 5.06 (d, 1H, $^3J_{H,H}$ = 17.3 Hz, CH=C<u>H</u>$_A$H$_B$), 5.43 (d, 1H, $^3J_{H,H}$ = 10.2 Hz, CH=CH$_A$<u>H</u>$_B$), 5.65 (d, 1H, $^3J_{H,H}$ = 4.0 Hz, C<u>H</u>OH), 6.26 (m, 1H, C<u>H</u>=$CH_2$), 7.3-7.5 (m, 4H, Ar).

**$^{13}$C NMR ($CDCl_3$, 75 MHz)**: δ 72.3 ($q_t$, $^3J_{C,F}$ = 3.3 Hz, <u>C</u>HOH), 95.4 ($q_t$, $^2J_{C,F}$ = 7.2 Hz, <u>C</u>H$SF_5$), 126.2 (s, CH=<u>C</u>$H_2$), 126.6 ($q_t$, $^3J_{C,F}$ = 3.3 Hz, <u>C</u>H=$CH_2$), 127.6 (s, 2 x <u>C</u>H Ar), 128.6 (s, 2 x <u>C</u>H Ar), 134.0 (s, <u>C</u>$_q$ Ar), 138.1 (s, <u>C</u>$_q$ Ar).

**<u>*(E/Z)*-1-(4-Chlorophenyl)-4-pentafluorosulfanylbut-3-en-1-ol 23a</u>**




**$C_{10}H_{10}ClF_5OS$**
**M = 308.70 g/mol**

**Rf** = 0.20 (EP/AcOEt = 84:16)

**IR (cm$^{-1}$)**: 3380, 2929, 1661, 1598, 1492, 1411.

**HRMS (ESI$^+$)**: calcd for $C_{10}H_{11}ClF_5OS$ (*m/z*) 309.5814 $[M+H]^+$, found 309.5810.

*Diastereoisomer n°1:*

**$^{19}$F NMR ($CDCl_3/CFCl_3$, 282 MHz)**: δ 62.1 (dd, 4F, $^2J_{F,F}$ = 152.6 Hz, $^3J_{F,H}$ = 5.2 Hz), 83.1 (m, 1F).

**$^1$H NMR ($CDCl_3$, 300 MHz)**: δ 2.02 (br s, 1H, O<u>H</u>), 2.5-2.6 (m, 1H, C<u>H</u>$_A$H$_B$CH=CH), 2.8-2.9 (m, 1H, CH$_A$<u>H</u>$_B$CH=CH), 4.84 (m, 1H, C<u>H</u>OH), 6.0-6.1 (m, 1H, C<u>H</u>=CH$SF_5$), 6.3-6.6 (m, 1H, CH=C<u>H</u>$SF_5$), 7.3-7.4 (m, 4H, Ar).

**$^{13}$C NMR ($CDCl_3$, 75 MHz)**: δ 39.9 (s, $\underline{C}H_2CH=CH$), 72.2 (s, $\underline{C}HOH$), 127.0 (s, 2 x $\underline{C}H$ Ar), 128.9 (s, 2 x $\underline{C}H$ Ar), 132.3 ($q_t$, $^3J_{C,F}$ = 5.2 Hz, $\underline{C}H=CHSF_5$), 133.9 (s, $\underline{C}_q$ Ar), 140.7 ($q_t$, $^2J_{C,F}$ = 17.9 Hz, $CH=\underline{C}HSF_5$), 141.3 (s, $\underline{C}_q$ Ar).

*Diastereoisomer n°2:*

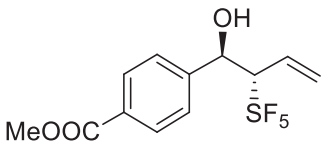
**$^{19}$F NMR ($CDCl_3/CFCl_3$, 282 MHz)**: δ 64.3 (dd, 4F, $^2J_{F,F}$ = 148.3 Hz, $^3J_{F,H}$ = 7.8 Hz), 83.4 (m, 1F).

**$^1$H NMR ($CDCl_3$, 300 MHz)**: δ 2.02 (br s, 1H, O$\underline{H}$), 2.5-2.6 (m, 1H, $C\underline{H}_AH_BCH=CH$), 2.8-2.9 (m, 1H, $CH_A\underline{H}_BCH=CH$), 4.84 (m, 1H, C$\underline{H}$OH), 6.3-6.6 (m, 2H, C$\underline{H}$=$CHSF_5$ + $CH=C\underline{H}SF_5$), 7.3-7.4 (m, 4H, Ar).

**$^{13}$C NMR ($CDCl_3$, 75 MHz)**: δ 37.9 (s, $\underline{C}H_2CH=CH$), 72.3 (s, $\underline{C}HOH$), 127.1 (s, 2 x $\underline{C}H$ Ar), 128.9 (s, 2 x $\underline{C}H$ Ar), 133.9 (s, $\underline{C}_q$ Ar), 134.6 ($q_t$, $^3J_{C,F}$ = 6.9 Hz, $\underline{C}H=CHSF_5$), 141.5 (s, $\underline{C}_q$ Ar), 142.7 ($q_t$, $^2J_{C,F}$ = 18.2 Hz, $CH=\underline{C}HSF_5$).

**2.4.2.2.** The reaction of bromide **24** with methyl 4-formylbenzoate was carried out according to the general procedure and led to a mixture of *γ*- and *α*-products **22b** and **23b** (~0.3:0.7). The resulting crude was purified by silica gel column chromatography (EP/$Et_2O$ = from 70:30 to 50:50) to afford two separated regioisomers: *γ*-product **22b** as only *anti* diastereoisomer in 27% yield (colourless oil) and *α*- product **23b** as a mixture of *E/Z* isomers (~1:1) in 11% yield (colourless oil).

***Anti* Methyl 4-(1-hydroxy-2-pentafluorosulfanylbut-3-en-1-yl)benzoate 22b**




**$C_{12}H_{13}F_5O_3S$**
**M = 332.29 g/mol**

**Rf** = 0.35 (EP/$Et_2O$ = 50:50)

**IR (cm$^{-1}$)**: 3393, 2950, 1718, 1468, 1429.

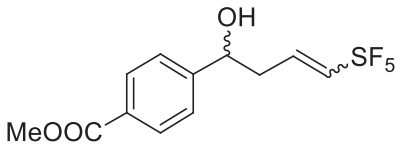
**HRMS (ESI$^+$)**: calcd for $C_{12}H_{14}F_5O_3S$ (*m/z*) 333.0231 $[M+H]^+$, found 333.0226.

**$^{19}$F NMR ($CDCl_3/CFCl_3$, 282 MHz)**: δ 56.4 (dd, 4F, $^2J_{F,F}$ = 142.2 Hz, $^3J_{F,H}$ = 6.9 Hz), 84.0 (m, 1F).

**$^1$H NMR ($CDCl_3$, 300 MHz)**: δ 2.80 (br s, 1H, O<u>H</u>), 3.90 (s, 3H, COOC<u>H</u>$_3$), 4.36 (m, 1H, C<u>H</u>$SF_5$), 5.00 (d, 1H, $^3J_{H,H}$ = 17.1 Hz, CH=C<u>H</u>$_A$H$_B$), 5.38 (d, 1H, $^3J_{H,H}$ = 10.1 Hz, CH=CH$_A$<u>H</u>$_B$), 5.70 (m, 1H, C<u>H</u>OH), 6.24 (m, 1H, C<u>H</u>=CH$_2$), 7.39 (d, 2H, $^3J_{H,H}$ = 7.5 Hz, Ar), 7.99 (d, 2H, $^3J_{H,H}$ = 7.5 Hz, Ar).

**$^{13}$C NMR ($CDCl_3$, 75 MHz)**: δ 52.2 (s, COO<u>C</u>H$_3$), 72.5 (q$_t$, $^3J_{C,F}$ = 3.3 Hz, <u>C</u>HOH), 95.2 (q$_t$, $^2J_{C,F}$ = 7.2 Hz, <u>C</u>H$SF_5$), 126.0 (s, CH=<u>C</u>H$_2$), 126.2 (s, 2 x <u>C</u>H Ar), 126.7 (q$_t$, $^3J_{C,F}$ = 3.3 Hz, <u>C</u>H=CH$_2$), 129.6 (s, 2 x <u>C</u>H Ar), 129.9 (s, <u>C</u>$_q$ Ar), 144.8 (s, <u>C</u>$_q$ Ar), 166.7 (<u>C</u>=O).

**<u>*(E/Z)*-Methyl 4-(1-hydroxy-4-pentafluorosulfanylbut-3-en-1-yl)benzoate 23b</u>**




**$C_{12}H_{13}F_5O_3S$**
**M = 332.29 g/mol**

**Rf** = 0.31 (EP/$Et_2O$ = 70:30)

**IR (cm$^{-1}$)**: 3443, 2957, 1703, 1438, 1417.

**HRMS (ESI$^+$)**: calcd for $C_{12}H_{14}F_5O_3S$ (*m/z*) 333.0231 $[M+H]^+$, found 333.0228.

*Diastereoisomer n°1:*

**$^{19}$F NMR ($CDCl_3/CFCl_3$, 282 MHz)**: δ 62.1 (dm, 4F, $^2J_{F,F}$ = 150.1 Hz), 83.0 (m, 1F).

**$^1$H NMR ($CDCl_3$, 300 MHz)**: δ 2.26 (br s, 1H, O<u>H</u>), 2.58 (m, 2H, C<u>H</u>$_2$CH=CH), 3.92 (s, 3H, COOC<u>H</u>$_3$), 4.92 (m, 1H, C<u>H</u>OH), 5.9-6.2 (m, 1H, C<u>H</u>=CH$SF_5$), 6.3-6.6 (m, 1H, CH=C<u>H</u>$SF_5$), 7.44 (d, 2H, $^3J_{H,H}$ = 8.2 Hz, Ar), 8.04 (d, 2H, $^3J_{H,H}$ = 8.2 Hz, Ar).

**$^{13}$C NMR ($CDCl_3$, 75 MHz)**: δ 39.8 (s, $\underline{C}H_2CH=CH$), 52.2 (s, $COO\underline{C}H_3$), 72.4 (s, $\underline{C}HOH$), 125.6 (s, 2 x $\underline{C}H$ Ar), 129.9 (s, $\underline{C}_q$, Ar), 130.0 (s, 2 x $\underline{C}H$ Ar), 134.5 ($q_t$, $^3J_{C,F}$ = 6.9 Hz, $\underline{C}H=CHSF_5$), 142.8 (m, $CH=\underline{C}HSF_5$), 147.9 (s, $\underline{C}_q$ Ar), 166.8 (s, $\underline{C}=O$).

*Diastereoisomer n°2:*

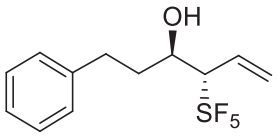
**$^{19}$F NMR ($CDCl_3$/$CFCl_3$, 282 MHz)**: δ 64.3 (dm, 4F, $^2J_{F,F}$ = 149.1 Hz), 83.3 (m, 1F).

**$^1$H NMR ($CDCl_3$, 300 MHz)**: δ 2.22 (br s, 1H, O$\underline{H}$), 2.87 (m, 2H, $C\underline{H}_2CH=CH$), 3.92 (s, 3H, $COOC\underline{H}_3$), 4.92 (m, 1H, C$\underline{H}$OH), 6.3-6.6 (m, 2H, C$\underline{H}$=CHSF$_5$ + CH=C$\underline{H}$SF$_5$), 7.44 (d, 2H, $^3J_{H,H}$ = 8.2 Hz, Ar), 8.04 (d, 2H, $^3J_{H,H}$ = 8.2 Hz, Ar).

**$^{13}$C NMR ($CDCl_3$, 75 MHz)**: δ 37.9 (s, $\underline{C}H_2CH=CH$), 52.2 (s, $COO\underline{C}H_3$), 72.5 (s, $\underline{C}HOH$), 125.6 (s, 2 x $\underline{C}H$ Ar), 129.9 (s, $\underline{C}_q$ Ar), 133.0 (s, 2 x $\underline{C}H$ Ar), 132.2 ($q_t$, $^3J_{C,F}$ = 5.2 Hz, $\underline{C}H=CHSF_5$), 140.8 ($q_t$, $^2J_{C,F}$ = 18.2 Hz, $CH=\underline{C}HSF_5$), 148.0 (s, $\underline{C}_q$ Ar), 166.8 (s, $\underline{C}=O$).

**2.4.2.3.** The reaction of bromide **24** with 3-phenylpropanal was carried out according to the general procedure and led to a mixture of *γ*- and *α*-products **22c** and **23c** (~0.4:0.6). The resulting crude was purified by silica gel column chromatography (EP/$Et_2O$ = from 95:5 to 80:20) to afford only *γ*-product **22c** as *anti* diastereoisomer in 8% yield (colourless oil).

***Anti* 1-Phenyl-4-pentafluorosulfanylhex-5-en-3-ol 22c**




**$C_{12}H_{15}F_5OS$**
**M = 302.30 g/mol**

**Rf** = 0.28 (EP/$Et_2O$ = 90:10)

**IR (cm$^{-1}$)**: 3469, 3028, 2925, 2858, 1604, 1497, 1455, 1257.

**HRMS (ESI$^+$)**: calcd for $C_{12}H_{16}F_5OS$ (*m/z*) 303.1130 $[M+H]^+$, found 303.1129.

**$^{19}$F NMR ($CDCl_3/CFCl_3$, 282 MHz)**: δ 56.3 (dd, 4F, $^2J_{F,F}$ = 142.2 Hz, $^3J_{F,H}$ = 6.9 Hz), 84.5 (m, 1F).

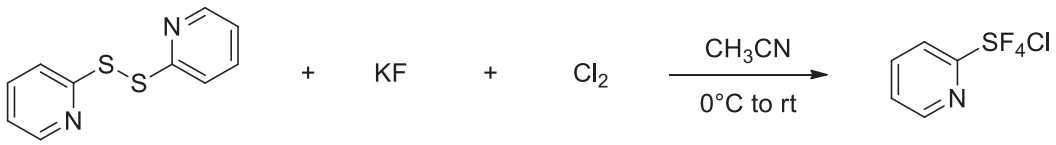
***Selected* $^1$H NMR ($CDCl_3$, 300 MHz)**: δ 4.2-4.4 (m, 1H, C<u>H</u>$SF_5$), 4.4-4.6 (m, 1H, C<u>H</u>OH), 5.48 (d, 1H, $^3J_{H,H}$ = 17.2 Hz, CH=C<u>H</u>$_A$H$_B$), 5.64 (d, 1H, $^3J_{H,H}$ = 10.1 Hz, CH=CH$_A$<u>H</u>$_B$), 6.28 (m, 1H, C<u>H</u>=$CH_2$), 7.3-7.6 (m, 5H, Ph).

***Selected* $^{13}$C NMR ($CDCl_3$, 75 MHz)**: δ 70.1 ($q_t$, $^3J_{C,F}$ = 2.8 Hz, <u>C</u>HOH), 94.7 ($q_t$, $^2J_{C,F}$ = 7.2 Hz, <u>C</u>H$SF_5$), 125.4 (m, <u>C</u>H=$CH_2$) 126.2 (s, CH=<u>C</u>$H_2$), 128.4 (s, 2 x <u>C</u>H Ph), 128.5 (s, <u>C</u>H Ph), 128.6 (s, 2 x <u>C</u>H Ph), 140.9 (s, <u>C</u>$_q$ Ph).

# 3. Synthesis of $SF_5$-heterocycles

## 3.1. Pentafluorosulfanylated pyridines – direct approach

**Procedure for the chlorination-fluorine substitution step**

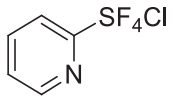



**34**

16 equiv 8.8 equiv

A 250 mL round bottom flask equipped with gas inlet-outlet tubes was charged with spray dried KF (5.1 g, 16.0 equiv, 87.1 mmol) and dry acetonitrile (30 mL). The solution was cooled to 0°C and $Cl_2$ (3.4 g, 8.8 equiv, 48.0 mmol) was bubbled into the stirred reaction mixture for 15 minutes (a trap filled with $H_2SO_4$ was installed between $Cl_2$ cylinder and reactor, and a trap filled with $NaOH_{aq}$ solution was installed after gas outlet tube). The 2,2'-dithiodipyridine (1.2 g, 1.0 equiv, 5.4 mmol) was added and the reaction mixture was stirred for 15 minutes at room temperature and then it was left without stirring for 24 h. The reaction mixture was filtered under argon atmosphere and the precipitate was washed with acetonitrile (20 mL). The filtrate was concentrated under reduced pressure to give the desired product **34** (1.6 g, 67%). The product was kept in a Teflon vessel in order to avoid its decomposition.

**2-Pyridylsulfur chlorotetrafluoride 34**[70]



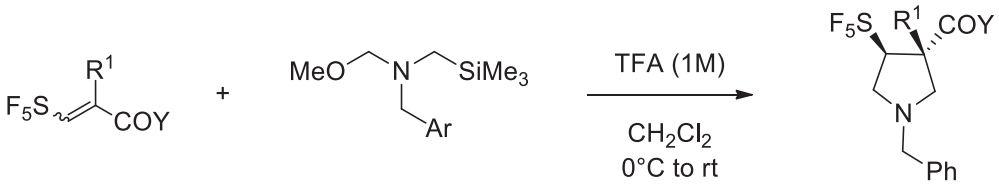

**$C_5H_4ClF_4NS$**
**M = 221.60 g/mol**

**$^{19}$F NMR ($CDCl_3/CFCl_3$, 282 MHz)**: δ 129.0 (s, 4F)

**$^1$H NMR ($CDCl_3$, 300 MHz)**: δ 7.4-7.6 (m, 1H), 7.6-7.8 (m, 1H), 7.8-8.0 (m, 1H), 8.0-8.2 (m, 1H).

## 3.2. Pentafluorosulfanylated pyrrolidines

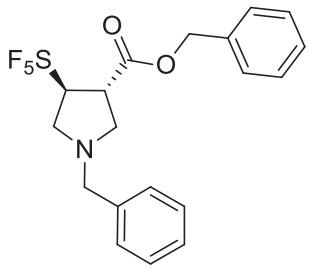
### 3.2.1. General procedure for the synthesis of di- and tri-substituted $SF_5$-pyrrolidines 42-44




**6 or 9-12** **40** 1.2-2 equiv (+/-)-**40-42**

To a stirred solution of allylic acetate **6**, ester **9**,**10** or amide **11**,**12** (1.0 equiv, 10 mmol) in dry $CH_2Cl_2$ (56 mL) under argon, was added the dipole precursor **40** (1.2 equiv, 12 mmol or 2.0 equiv, 20 mmol, depending on the substrate). The mixture was cooled to 0°C and 1 M TFA solution (0.1 equiv, 1 mmol) in $CH_2Cl_2$ (1 mL) was added at this temperature. After 2 h of stirring at room temperature, $NaHCO_{3sat.}$ solution (~10 mL) was added to the reaction mixture until pH = 7. The organic phase was separated, washed with brine (10 mL) and dried over $MgSO_4$. After removal of solvent under reduced pressure, the crude product was purified by silica gel column chromatography leading to pyrrolidines **40-42**.

**(±)-*N*-Benzyl-3-(benzyloxycarbonyl)-4-pentafluorosulfanylpyrrolidine 42a**




**$C_{19}H_{20}F_5NO_2S$**
**M = 421.42 g/mol**

The title compound was prepared according to the general procedure. The resulting crude product was purified by silica gel column chromatography (PE/AcOEt = 92:8) to afford **42a** in 69% yield as a colourless oil.

**Rf** = 0.27 (PE/AcOEt = 94:6)

**IR ($cm^{-1}$)**: 3033, 2807, 1738, 1173.

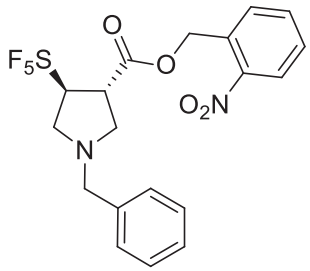
**HRMS ($ESI^+$)**: calcd for $C_{19}H_{21}F_5NO_2S$ (*m/z*) 422.1213 $[M+H]^+$, found 422.1197.

**$^{19}F$ NMR ($CDCl_3/CFCl_3$, 282 MHz)**: δ 59.2 (dd, 4F, $^2J_{F,F}$ = 143.9 Hz, $^3J_{F,H}$ = 5.2 Hz), 84.7 (m, 1F).

**$^1H$ NMR ($CDCl_3$, 300 MHz)**: δ 2.9-3.0 (m, 3H, C$\underline{H}_2$CHCOOBn + C$\underline{H}_A\underline{H}_B$CHSF$_5$), 3.23 (m, 1H, CH$_A\underline{H}_B$CHSF$_5$), 3.6-3.7 (m, 3H, NC$\underline{H}_2$Ph + C$\underline{H}$COOBn), 5.03 (m, 1H, C$\underline{H}$SF$_5$), 5.20 (s, 2H, COOC$\underline{H}_2$Ph), 7.3-7.4 (m, 10H, 2 x Ph).

**$^{13}C$ NMR ($CDCl_3$, 75 MHz)**: δ 46.7 ($q_t$, $^3J_{C,F}$ = 3.6 Hz, $\underline{C}$HCHSF$_5$), 55.8 (s, $\underline{C}$H$_2$CHCOOBn), 56.4 ($q_t$, $^3J_{C,F}$ = 4.7 Hz, $\underline{C}$H$_2$CHSF$_5$), 58.9 (N$\underline{C}$H$_2$Ph), 67.3 (s, COO$\underline{C}$H$_2$), 83.3 ($q_t$, $^2J_{C,F}$ = 11.1 Hz, $\underline{C}$HSF$_5$), 127.3 (s, $\underline{C}$H Ph), 128.0 (s, 2 x $\underline{C}$H Ph), 128.3 (s, $\underline{C}$H Ph), 128.37 (s, 2 x $\underline{C}$H Ph), 128.38 (s, 2 x $\underline{C}$H Ph), 128.5 (s, 2 x $\underline{C}$H Ph), 135.3 (s, $\underline{C}_q$ Ph ), 137.4 (s, $\underline{C}_q$ Ph), 171.6 (s, $\underline{C}$=O).

**(±)-*N*-Benzyl-3-[(2'-nitro)benzyloxycarbonyl)]-4-pentafluorosulfanylpyrrolidine 42b**



**$C_{19}H_{19}F_5N_2O_4S$**
**M = 466.42 g/mol**

The title compound was prepared according to the general procedure. The resulting crude product was purified by silica gel column chromatography (PE/AcOEt = 86:14) to afford **42b** in 88% yield as a yellow oil.

**Rf** = 0.29 (PE/AcOEt = 86:14)

**IR ($cm^{-1}$)**: 2919, 1705, 1522, 1342.

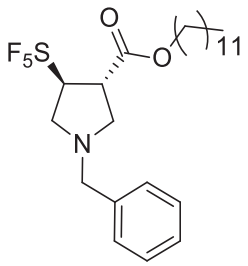
**HRMS ($ESI^+$)**: calcd for $C_{19}H_{20}F_5N_2O_4S$ (*m/z*) 467.1064 $[M+H]^+$, found 467.1064.

**$^{19}F$ NMR ($CDCl_3/CFCl_3$, 282 MHz)**: δ 59.2 (dd, 4F, $^2J_{F,F}$ = 143.9 Hz, $^3J_{F,H}$ = 5.2 Hz), 84.6 (m, 1F).

**$^1H$ NMR ($CDCl_3$, 300 MHz)**: δ 2.9-3.0 (m, 3H, $C\underline{H}_AH_BCHSF_5$ + $C\underline{H}_2CHCOO$), 3.25 (m, 1H, $CH_A\underline{H}_BCHSF_5$), 3.63 (d, 1H, $^2J_{H,H}$ = 13.2 Hz, 1H, $NC\underline{H}_AH_BPh$), 3.69 (d, 1H, $^2J_{H,H}$ = 13.2 Hz, $NCH_A\underline{H}_BPh$), 3.71-3.78 (m, 1H, $C\underline{H}COO$), 5.03 (m, 1H, $C\underline{H}SF_5$), 5.61 (s, 2H, $COOC\underline{H}_2PhNO_2$), 7.3-7.4 (m, 5H, Ph), 7.5-7.6 (m, 2H, $PhNO_2$), 7.67 (dd, 1H, $^3J_{H,H}$ = 7.4 Hz, $^3J_{H,H}$ = 7.4 Hz, $PhNO_2$), 8.15 (d, 1H, $^3J_{H,H}$ = 8.2 Hz, $PhNO_2$).

**$^{13}C$ NMR ($CDCl_3$, 75 MHz)**: δ 46.7 ($q_t$, $^3J_{C,F}$ = 3.5 Hz, $\underline{C}HCOO$), 55.8 (s, $\underline{C}H_2CHCOO$), 56.4 ($q_t$, $^3J_{C,F}$ = 4.7 Hz, $\underline{C}H_2CHSF_5$), 58.9 (s, $N\underline{C}H_2Ph$), 64.0 (s, $COO\underline{C}H_2PhNO_2$), 83.2 ($q_t$, $^2J_{C,F}$ = 11.6 Hz, $\underline{C}HSF_5$), 125.1 (s, $\underline{C}H$ Ar), 127.4 (s, $\underline{C}H$ Ar), 128.41 (s, 2 x $\underline{C}H$ Ar), 128.44 (s, 2 x $\underline{C}H$ Ar), 128.9 (s, $\underline{C}H$ Ar), 129.0 (s, $\underline{C}H$ Ar), 131.3 (s, $\underline{C}H$ Ar), 133.8 (s, $\underline{C}_q$ Ar), 137.4 (s, $\underline{C}_q$ Ar), 147.4 (s, $\underline{C}_q$ Ar), 171.3 (s, $\underline{C}$=O).

**(±)-*N*-Benzyl-3-(dodecyloxycarbonyl)-4-pentafluorosulfanylpyrrolidine 42c**




**$C_{24}H_{38}F_5NO_2S$**
**M = 499,62 g/mol**

The title compound was prepared according to the general procedure. The resulting crude product was purified by silica gel column chromatography (PE/AcOEt = 96:4) to afford **42c** in 62% yield as a colourless oil.

**Rf** = 0.26 (PE/AcOEt = 96:4)

**IR ($cm^{-1}$)**: 2924, 2854, 1740, 1457, 1189.

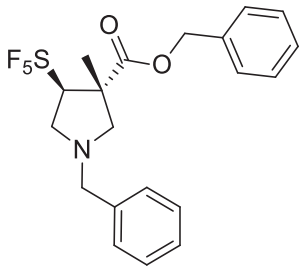
**HRMS ($ESI^+$)**: calcd for $C_{24}H_{39}F_5NO_2S$ (*m/z*) 500.2622 $[M+H]^+$, found 500.2621.

**$^{19}F$ NMR ($CDCl_3/CFCl_3$, 282 MHz)**: δ 59.1 (dd, 4F, $^2J_{F,F}$ = 143.9 Hz, $^3J_{F,H}$ = 5.2 Hz), 84.8 (m, 1F).

**$^1H$ NMR ($CDCl_3$, 300 MHz)**: δ 0.89 (m, 3H, $C\underline{H}_3$), 1.2-1.4 (m, 18H, 9 x $C\underline{H}_2$), 1.5-1.6 (m, 2H, $COOCH_2C\underline{H}_2$), 2.89 (d, 2H, $^3J_{H,H}$ = 6.8 Hz, $C\underline{H}_2CHCOO$), 2.98 (m, 1H, $C\underline{H}_AH_BCHSF_5$), 3.21 (m, 1H, $CH_A\underline{H}_BCHSF_5$), 3.6-3.7 (m, 3H, $C\underline{H}COO$ + $NC\underline{H}_2Ph$), 4.15 (t, 2H, $^3J_{H,H}$ = 6.6 Hz, $COOC\underline{H}_2CH_2$), 5.00 (m, 1H, $C\underline{H}SF_5$), 7.3-7.4 (m, 5H, Ph).

**$^{13}C$ NMR ($CDCl_3$, 75 MHz)**: δ 14.1 (s, $\underline{C}H_3$), 22.7 (s, $\underline{C}H_2$), 25.7 (s, $\underline{C}H_2$), 28.5 (s, $\underline{C}H_2$), 29.2 (s, $\underline{C}H_2$), 29.3 (s, $\underline{C}H_2$), 29.45 (s, $\underline{C}H_2$), 29.52 (s, $\underline{C}H_2$), 29.6 (s, 2 x $\underline{C}H_2$), 31.9 (s, $\underline{C}H_2$), 46.8 ($q_t$, $^3J_{C,F}$ = 3.7 Hz, $\underline{C}HCOO$), 56.0 (s, $\underline{C}H_2CHCOO$), 56.5 ($q_t$, $^3J_{C,F}$ = 4.4 Hz, $\underline{C}H_2CHSF_5$), 59.1 (s, $N\underline{C}H_2Ph$), 65.8 (s, $COO\underline{C}H_2$), 83.4 ($q_t$, $^2J_{C,F}$ = 11.6 Hz, $\underline{C}HSF_5$), 127.4 (s, $\underline{C}H$ Ph), 128.41 (s, 2 x $\underline{C}H$ Ph), 128.45 (s, 2 x $\underline{C}H$ Ph), 137.5 (s, $\underline{C}_q$ Ph), 171.9 (s, $\underline{C}$=O).

**(±)-*N*-Benzyl-3-(benzyloxycarbonyl)-3-methyl-4-pentafluorosulfanylpyrrolidine 42d**



**$C_{20}H_{22}F_5NO_2S$**
**M = 435.45 g/mol**

The title compound was prepared according to the general procedure. The resulting crude product was purified by silica gel column chromatography (PE/AcOEt = 98:2) to afford **42d** in 46% yield as a colourless oil.

**Rf** = 0.28 (PE/AcOEt = 96:4)

**IR ($cm^{-1}$)**: 1734, 1455, 1263, 1212, 1107.

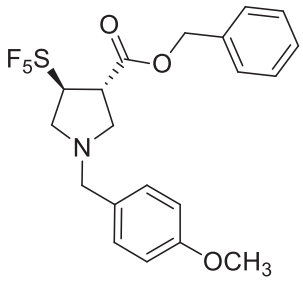
**HRMS ($ESI^+$)**: calcd for $C_{20}H_{23}F_5NO_2S$ (*m/z*) 436.1370 $[M+H]^+$, found 436.1367.

**$^{19}F$ NMR ($CDCl_3/CFCl_3$, 282 MHz)**: δ 65.7 (dm, 4F, $^2J_{F,F}$ = 143.9 Hz), 85.0 (m, 1F).

**$^1H$ NMR ($CDCl_3$, 300 MHz)**: δ 1.69 (s, 3H, C$\underline{H}_3$), 2.83 (d, 1H, $^2J_{H,H}$ = 8.8 Hz, C$\underline{H}_A$H$_B$C(CH$_3$)COOBn), 2.95 (d, 1H, $^2J_{H,H}$ = 8.8 Hz, CH$_A\underline{H}_B$C(CH$_3$)COOBn), 3.21 (m, 1H, C$\underline{H}_A$H$_B$CHSF$_5$), 3.47 (m, 1H, CH$_A\underline{H}_B$CHSF$_5$), 3.74 (m, 2H, NC$\underline{H}_2$Ph), 5.20 (s, 2H, COOC$\underline{H}_2$Ph), 5.2-5.3 (m, 1H, C$\underline{H}$SF$_5$), 7.3-7.4 (m, 10H, 2 x Ph).

**$^{13}C$ NMR ($CDCl_3$, 75 MHz)**: δ 19.5 (m, $\underline{C}H_3$), 52.9 (s, $\underline{C}$(CH$_3$)COOBn), 53.3 (q$_t$, $^3J_{C,F}$ = 5.0 Hz, $\underline{C}H_2$CHSF$_5$), 60.0 (s, $\underline{C}H_2$C(CH$_3$)COOBn), 64.4 (s, N$\underline{C}H_2$Ph), 67.6 (s, COO$\underline{C}H_2$Ph), 86.1 (q$_t$, $^2J_{C,F}$ = 10.5 Hz, $\underline{C}$HSF$_5$), 127.4 (s, $\underline{C}$H Ph), 128.2 (s, 2 x $\underline{C}$H Ph), 128.4 (s, 2 x $\underline{C}$H Ph), 128.45 (s, $\underline{C}$H Ph), 128.51 (s, 2 x $\underline{C}$H Ph), 128.6 (s, 2 x $\underline{C}$H Ph), 135.4 (s, $\underline{C}_q$ Ph), 137.9 (s, $\underline{C}_q$ Ph), 172.9 (s, $\underline{C}$=O).

**(±)-*N*-(*p*-Methoxybenzyl)-3-(benzyloxycarbonyl)-4-pentafluorosulfanylpyrrolidine 42e**




**$C_{20}H_{22}F_5NO_3S$**
**M = 451.45 g/mol**

The title compound was prepared according to the general. The resulting crude product was purified by silica gel column chromatography (PE/AcOEt = 92/8) to afford **42e** in 66% yield as a colourless oil.

**Rf** = 0.27 (PE/AcOEt = 94:6)

**IR ($cm^{-1}$)**: 2835, 1743, 1615, 1515.

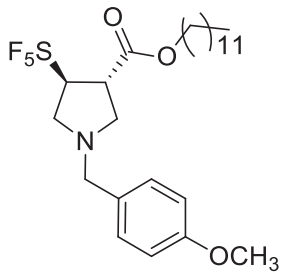
**HRMS ($ESI^+$)**: calcd for $C_{20}H_{23}F_5NO_3S$ (*m/z*) 452.1319 $[M+H]^+$, found 452.1320.

**$^{19}F$ NMR ($CDCl_3/CFCl_3$, 282 MHz)**: δ 59.2 (dd, 4F, $^2J_{F,F}$ = 144.8 Hz, $^3J_{F,H}$ = 6.1 Hz), 84.7 (m, 1F).

**$^1H$ NMR ($CDCl_3$, 300 MHz)**: δ 2.8-3.0 (m, 3H, C$\underline{H}_2$CHCOOBn + C$\underline{H}_A$H$_B$CHSF$_5$), 3.22 (m, 1H, CH$_A\underline{H}_B$CHSF$_5$), 3.52 (d, 1H, $^2J_{H,H}$ = 12.8 Hz, NC$\underline{H}_A$H$_B$), 3.60 (d, 1H, $^2J_{H,H}$ = 12.8 Hz, NCH$_A\underline{H}_B$), 3.6-3.7 (m, 1H, C$\underline{H}$COOBn), 3.81 (s, 3H, C$\underline{H}_3$), 5.02 (m, 1H, C$\underline{H}$SF$_5$), 5.19 (s, 2H, C$\underline{H}_2$Bn), 6.86 (d, 2H, $^3J_{H,H}$ = 8.6 Hz, PhOMe), 7.19 (d, 2H, $^3J_{H,H}$ = 8.6 Hz, PhOMe), 7.3-7.4 (m, 5H, Ph).

**$^{13}C$ NMR ($CDCl_3$, 75 MHz)**: δ 46.7 ($q_t$, $^3J_{C,F}$ = 3.3 Hz, $\underline{C}$HCHSF$_5$), 55.3 (s, $\underline{C}$H$_3$), 55.8 (s, $\underline{C}$H$_2$CHCOOBn), 56.4 ($q_t$, $^3J_{C,F}$ = 4.7 Hz, $\underline{C}$H$_2$CHSF$_5$), 58.4 (N$\underline{C}$H$_2$), 67.4 (s, COO$\underline{C}$H$_2$Ph), 83.3 ($q_t$, $^2J_{C,F}$ = 11.1 Hz, $\underline{C}$HSF$_5$), 113.8 (s, 2 x $\underline{C}$H Ar), 128.1 (s, 2 x $\underline{C}$H Ar), 128.4 (s, $\underline{C}$H Ar), 128.6 (s, 2 x $\underline{C}$H Ar), 129.4 (s, $\underline{C}_q$ PhOMe), 129.7 (s, 2 x $\underline{C}$H Ar), 135.3 (s, $\underline{C}_q$ Ph), 159.0 (s, $C_q$ PhOMe), 171.7 ($\underline{C}$=O).

**(±)-*N*-(*p*-Methoxybenzyl)-3-(dodecyloxycarbonyl)-4-pentafluorosulfanylpyrrolidine 42f**




**$C_{25}H_{40}F_5NO_3S$**
**M = 529.65 g/mol**

The title compound was prepared according to the general procedure. The resulting crude product was purified by silica gel column chromatography (PE/AcOEt = 94:6) to afford **42f** in 46% yield as a colourless oil.

**Rf** = 0.44 (PE/AcOEt = 90:10)

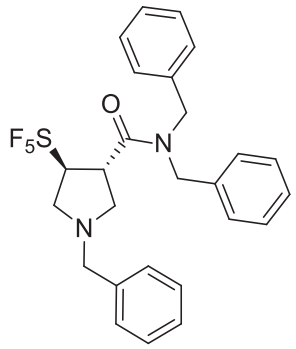
**IR ($cm^{-1}$)**: 2924, 2854, 1739, 1514, 1462, 1248, 1180.

**$^{19}F$ NMR ($CDCl_3/CFCl_3$, 282 MHz)**: δ 59.1 (dd, 4F, $^2J_{F,F}$ = 145.7 Hz, $^3J_{F,H}$ = 5.2 Hz), 84.9 (m, 1F).

**$^1H$ NMR ($CDCl_3$, 300 MHz)**: δ 0.89 (t, 3H, $^3J_{H,H}$ = 6.6 Hz, C$\underline{H}_3$CH$_2$), 1.2-1.4 (m, 18H, 9 x C$\underline{H}_2$), 1.63 (m, 2H, COOCH$_2$C$\underline{H}_2$), 2.87 (d, 2H, $^3J_{H,H}$ = 7.0 Hz, C$\underline{H}_2$CHCOO), 2.95 (dd, 1H, $^2J_{H,H}$ = 10.2 Hz, $^3J_{H,H}$ = 8.3 Hz, C$\underline{H}_A$H$_B$CHSF$_5$), 3.19 (m, 1H, CH$_A\underline{H}_B$CHSF$_5$), 3.5-3.6 (m, 3H, C$\underline{H}$COO + NC$\underline{H}_2$Ph), 3.81 (s, 3H, C$\underline{H}_3$O), 4.15 (t, 2H, $^3J_{H,H}$ = 6.7 Hz, COOC$\underline{H}_2$CH$_2$), 4.98 (m, 1H, C$\underline{H}$SF$_5$), 6.87 (d, 2H, $^3J_{H,H}$ = 8.6 Hz, PhOMe), 7.21 (d, 2H, $^3J_{H,H}$ = 8.6 Hz, PhOMe).

**$^{13}C$ NMR ($CDCl_3$, 75 MHz)**: δ 14.1 (s, C$\underline{H}_3$CH$_2$), 22.7 (s, C$\underline{H}_2$), 25.7 (s, C$\underline{H}_2$), 28.5 (s, C$\underline{H}_2$), 29.2 (s, C$\underline{H}_2$), 29.3 (s, C$\underline{H}_2$), 29.46 (s, C$\underline{H}_2$), 29.54 (s, C$\underline{H}_2$), 29.6 (s, 2 x C$\underline{H}_2$), 31.9 (s, C$\underline{H}_2$), 46.8 ($q_t$, $^3J_{C,F}$ = 3.6 Hz, C$\underline{H}$COO), 55.2 (s, C$\underline{H}_3$O), 55.9 (s, C$\underline{H}_2$CHCOO), 56.4 ($q_t$, $^3J_{C,F}$ = 4.4 Hz, C$\underline{H}_2$CHSF$_5$), 58.5 (s, NC$\underline{H}_2$Ph), 65.8 (s, COOC$\underline{H}_2$), 83.5 ($q_t$, $^2J_{C,F}$ = 11.6 Hz, C$\underline{H}$SF$_5$), 113.8 (s, 2 x C$\underline{H}$ Ph), 129.6 (s, C$\underline{H}$ PhOMe), 129.7 (s, 2 x C$\underline{H}$ PhOMe), 159 (s, C$\underline{_q}$ PhOMe), 171.9 (s, C$\underline{=}$O).

**(±)-*N*,*N*-Dibenzyl-1-benzyl- 4-pentafluorosulfanylpyrrolidin-3-ylcarboxamide 43a**




**$C_{26}H_{27}F_5N_2OS$**
**M = 510.56 g/mol**

The title compound was prepared according to the general procedure. The resulting crude product was purified by silica gel column chromatography (PE/AcOEt = 88:12) to afford **43a** in 79% yield as a white solide.

**M.p.**: 80°C

**Rf** = 0.16 (PE/AcOEt = 90:10)

**IR ($cm^{-1}$)**: 3030, 2807, 1648.

**HRMS ($ESI^+$)**: calcd for $C_{26}H_{28}F_5N_2OS$ (*m/z*) 511.1843 $[M+H]^+$, found 511.1837.

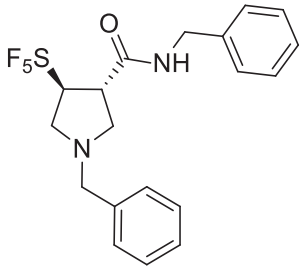
**$^{19}F$ NMR ($CDCl_3/CFCl_3$, 282 MHz)**: δ 59.6 (dd, 4F, $^2J_{F,F}$ = 145.7 Hz, $^3J_{F,H}$ = 5.2 Hz), 85.6 (m, 1F).

**$^1H$ NMR ($CDCl_3$, 300 MHz)**: δ 2.64 (m, 1H, $C\underline{H}_AH_BCHCONBn_2$), 2.80 (m, 1H, $CH_A\underline{H}_BCHCONBn_2$), 3.17 (m, 2H, $C\underline{H}_2CHSF_5$), 3.53 (d, 1H, $^2J_{H,H}$ = 13.3 Hz, $NC\underline{H}_AH_BPh$), 3.71 (d, 1H, $^2J_{H,H}$ = 13.3 Hz, $NCH_A\underline{H}_BPh$), 3.88 (m, 1H, $C\underline{H}CONBn_2$), 4.30-4.50 (m, 3H, $NC\underline{H}_2Ph$ + $NC\underline{H}_AH_BPh$), 4.89 (d, 1H, $^2J_{H,H}$ = 14.7 Hz, $NCH_A\underline{H}_BPh$), 5.48 (m, 1H, $C\underline{H}SF_5$), 7.1-7.2 (m, 5H, Ph), 7.3-7.4 (m, 10H, 2 x Ph).

**$^{13}C$ NMR ($CDCl_3$, 75 MHz)**: δ 44.7 ($q_t$, $^3J_{C,F}$ = 3.3 Hz, $\underline{C}HCONBn_2$), 48.7 (s, $CON\underline{C}H_2Ph$), 49.7 (s, $CON\underline{C}H_2Ph$), 56.2 ($q_t$, $^3J_{C,F}$ = 5.0 Hz, $\underline{C}H_2CHSF_5$), 56.4 (s, $\underline{C}H_2CHCONBn_2$), 59.0 (s, $N\underline{C}H_2Ph$), 84.3 ($q_t$, $^2J_{C,F}$ = 10.3 Hz, $\underline{C}HSF_5$), 126.4 (s, 2 x $\underline{C}$H Ph), 127.3 (s, $\underline{C}$H Ph), 127.5

(s, CH Ph), 127.9 (s, CH Ph), 128.0 (s, 2 x CH Ph), 128.4 (s, 4 x CH Ph), 128.7 (s, 2 x CH Ph), 129.0 (s, 2 x CH Ph), 135.7 (s, $C_q$ Ph), 136.8 (s, $C_q$ Ph), 137.5 (s, $C_q$ Ph), 171.4 (s, C=O).

**(±)-*N*-Benzyl-1-benzyl-4-pentafluorosulfanylpyrrolidin-3-ylcarboxamide 43b**




**$C_{19}H_{21}F_5N_2OS$**
**M = 420.44 g/mol**

The title compound was prepared according to the general procedure. The resulting crude product was purified by silica gel column chromatography (cyclohexane/AcOEt = 82:18) to afford **43b** in 92% yield as a white solid.

**M.p.**: 126-128°C

**Rf** = 0.12 (cyclohexane/AcOEt = 82:18)

**IR ($cm^{-1}$)**: 3269, 2796, 1639, 1557, 1431.

**HRMS ($ESI^+$)**: calcd for $C_{19}H_{22}F_5N_2OS$ (*m/z*) 421.1373 $[M+H]^+$, found 421.1366.

**$^{19}F$ NMR ($CDCl_3/CFCl_3$, 282 MHz)**: δ 59.3 (dd, 4F, $^2J_{F,F}$ = 145.7 Hz, $^3J_{F,H}$ = 5.2 Hz), 85.0 (m, 1F).

**$^1H$ NMR ($CDCl_3$, 300 MHz)**: δ 2.8-2.9 (m, 2H, $CH_2CHCONHBn$), 3.1-3.2 (m, 2H, $CH_2CHSF_5$), 3.43 (m, 1H, CHCONHBn), 3.6-3.7 (m, 2H, $NCH_2Ph$), 4.36 (dd, 1H, $^2J_{H,H}$ = 14.5 Hz, $^3J_{H,H}$ = 5.1 Hz, $NHCH_AH_BPh$), 4.46 (dd, 1H, $^2J_{H,H}$ = 14.5 Hz, $^3J_{H,H}$ = 5.1 Hz, $NHCH_AH_BPh$), 5.00 (m, 1H, $CHSF_5$), 6.07 (br s, 1H, NH), 7.2-7.3 (m, 10H, 2 x Ph).

**$^{13}C$ NMR ($CDCl_3$, 75 MHz)**: δ 43.9 (s, $CONHCH_2Ph$), 48.7 ($q_t$, $^3J_{C,F}$ = 3.6 Hz, $CHCHSF_5$), 56.5 (m, $CH_2CHSF_5$), 56.6 (s, $CH_2CHCONHBn$), 59.1 (s, $NCH_2Ph$), 84.6 ($q_t$, $^2J_{C,F}$ = 11.0 Hz,

$\underline{C}HSF_5$), 126.7 (s, $\underline{C}H$ Ph), 127.4 (s, 2 x $\underline{C}H$ Ph), 127.7 (s, 2 x $\underline{C}H$ Ph), 128.1 (s, $\underline{C}H$ Ph), 128.5 (s, 2 x CH Ph), 128.8 (s, 2 x $\underline{C}H$ Ph), 137.6 (s, $\underline{C}_q$ Ph), 137.7 (s, $\underline{C}_q$ Ph), 171.0 (s, $\underline{C}$=O).

## Crystallographic data

The crystal data are collected in Table 20. The full crystallographic parameters (atomic coordinates, bond length, angles and anisotropic displacements) are deposit to the Cambridge Crystallographic Data Centre (Nr CCDC1024823).

| | |
|---|---|
| Chemical Formula | $C_{19}H_{21}F_5N_2OS$ |
| Molecular Weight / $g.mol^{-1}$ | 420.44 |
| Crystal System | Orthorhombic |
| Space Group | *P*na$2_1$ (33) |
| Z , Z' (asymmetric units per unit cell) | 4, 1 |
| a / *Å* | 9.2994(9) |
| b / *Å* | 12.5496(1) |
| c / *Å* | 17.0351(2) |
| V / $Å^3$ | 1988.1(3) |
| $d_{calc}$ / $g.cm^{-3}$ | 1.405 |
| F(000) / $e^-$ | 872 |
| Absolute structure parameter | 0.10(11) |
| Absorption coefficient μ (MoK$\alpha_1$) / $mm^{-1}$ | 0.220 |

**Table 20: Crystal data**

## Structural description

The asymmetric unit is composed of one molecule of $C_{19}H_{21}F_5N_2OS$ (Figures 52 and 53). The carbon atoms C9 and C 10 exhibit an absolute configuration S and S. Some Hydrogen interactions are established between two consecutive molecules along *a* axis (Figures 54 and 55), Table 21. These interactions lead to the formation of periodic bond chains spreading along *a* direction.

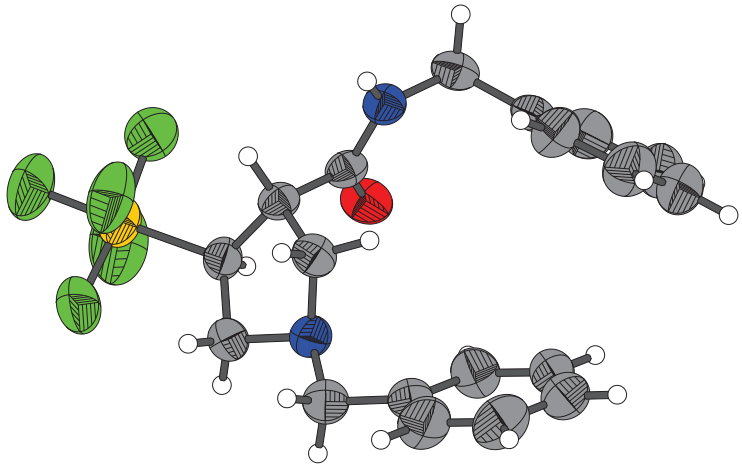


**Figure 52: Asymmetric unit in thermal ellipsoidal representation.**

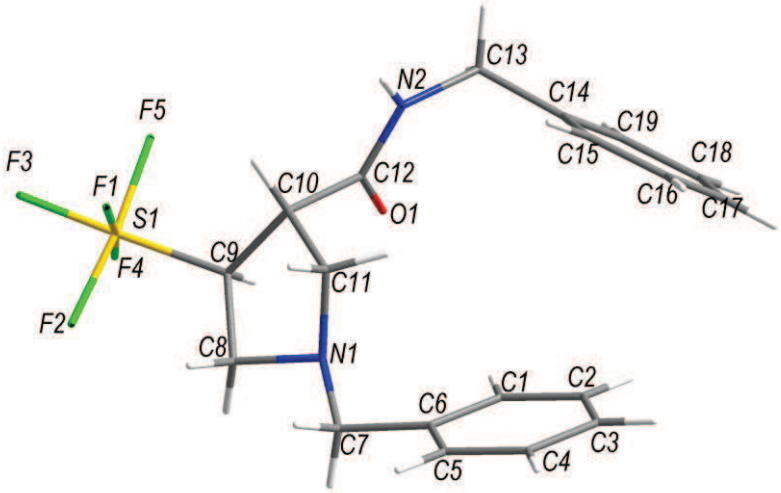



**Figure 53: Asymmetric unit with atoms labels.**

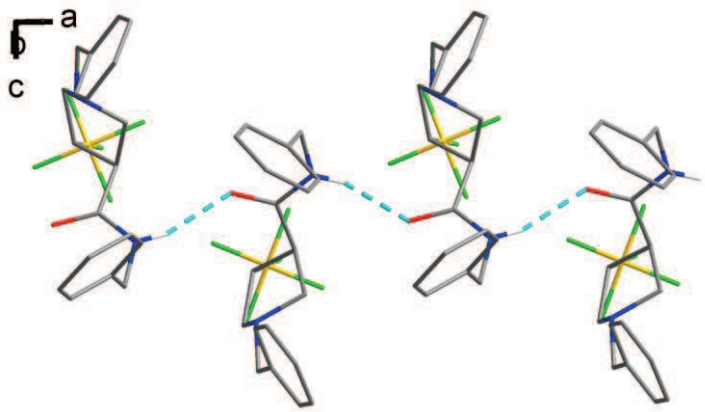



**Figure 54: Hydrogen bond between adjacent molecules along a axis (dashed blue lines).**

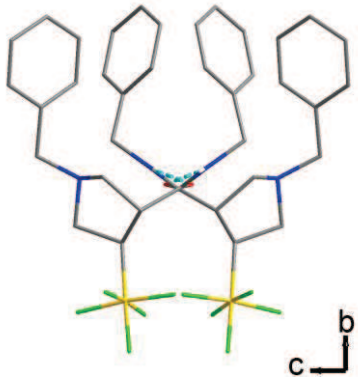



**Figure 55: Projection along a of one molecular chain built from the hydrogen bonds.**

| D-H...A | d(D-H) | d(H...A) | d(D...A) | <(DHA) |
|---|---|---|---|---|
| N(2)-H(2A)...O(1)#1 | 0.86 | 2.04 | 2.866(4) | 162.1 |

Symmetry transformations used to generate equivalent atoms: #1 x-1/2,y,-z+3/2

**Table 21: Hydrogen bond table.**

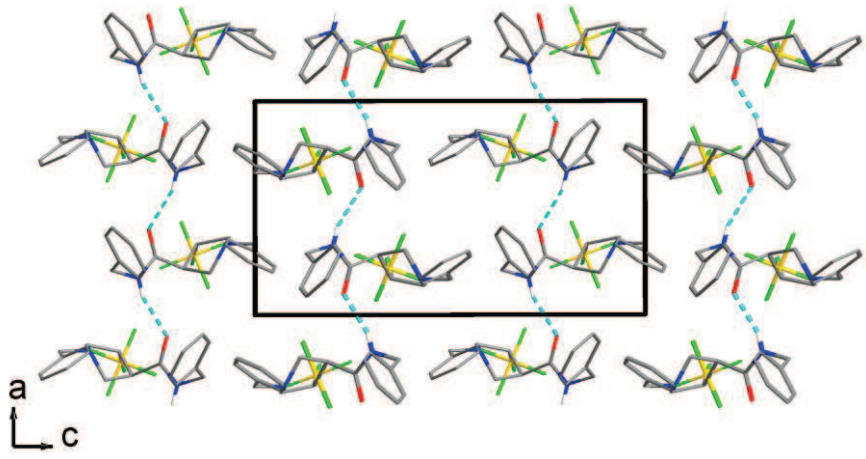



**Figure 56: Projection along b axis, the periodic bond chains are stacked along c.**

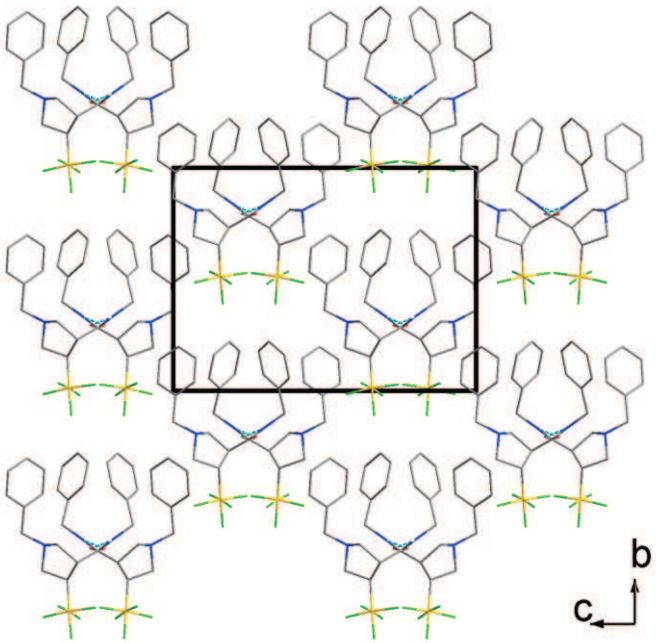
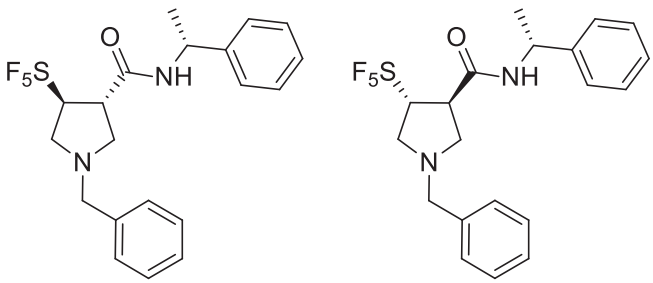



**Figure 57: Projection along a axis, the periodic bond chains are organised in conjunction**

## *N*-[(1R)-1-Phenylethyl]-1-benzyl-4-pentafluorosulfanylpyrrolidin-3-ylcarboxamide 43c




**$C_{20}H_{23}F_5N_2OS$**
**M = 434.47 g/mol**

The title compound was prepared according to the general procedure. The resulting crude product was purified by silica gel column chromatography (cyclohexane/AcOEt = 82:18) to afford two diastereoisomers **43c** as white solids in 44% and 40% yield, respectively.

*Diastereoisomer n°1:*

**M.p.**: 120-121°C

**Rf** = 0.18 (cyclohexane/AcOEt = 82:18)

**IR ($cm^{-1}$)**: 3305, 2806, 1641, 1545, 1453.

**HRMS ($ESI^+$)**: calcd for $C_{20}H_{24}F_5N_2OS$ (*m/z*) 435.1530 $[M+H]^+$, found 435.1524.

**$^{19}F$ NMR ($CDCl_3/CFCl_3$, 282 MHz)**: δ 59.3 (dd, 4F, $^2J_{F,F}$ = 143.9 Hz, $^3J_{F,H}$ = 5.2 Hz), 85.1 (m, 1F).

**$^1H$ NMR ($CDCl_3$, 300 MHz)**: δ 1.47 (d, 3H, $^3J_{H,H}$ = 6.5 Hz, 3H, C<u>H</u>$_3$), 2.7-2.8 (m, 2H, C<u>H</u>$_2$CHCONH), 3.13 (m, 2H, C<u>H</u>$_2$CHSF$_5$), 3.39 (m, 1H, C<u>H</u>CONH), 3.5-3.7 (m, 2H, C<u>H</u>$_2$Ph), 4.93 (m, 1H, C<u>H</u>SF$_5$), 5.10 (m, 1H, CH$_3$C<u>H</u>Ph), 6.07 (d, 1H, $^3J_{H,H}$ = 7.1 Hz, N<u>H</u>), 7.2-7.5 (m, 10H, 2 x Ph).

**$^{13}C$ NMR ($CDCl_3$, 75 MHz)**: δ 21.6 (s, <u>C</u>H$_3$), 48.4 ($q_t$, $^3J_{C,F}$ = 3.3 Hz, <u>C</u>HCHSF$_5$), 49.1 (s, NH<u>C</u>H(CH$_3$)Ph), 56.3 (m, <u>C</u>H$_2$CHSF$_5$), 56.4 (s, <u>C</u>H$_2$CHCONH), 59.0 (s, N<u>C</u>H$_2$Ph), 84.6 ($q_t$, $^2J_{C,F}$ = 11.0 Hz, <u>C</u>HSF$_5$), 126.0 (s, 2 x <u>C</u>H Ph), 127.4 (s, <u>C</u>H Ph), 127.5 (s, <u>C</u>H Ph), 128.43 (s, 2 x <u>C</u>H Ph), 128.45 (s, 2 x <u>C</u>H Ph), 128.7 (s, 2 x <u>C</u>H Ph), 137.6 (s, <u>C</u>$_q$ Ph), 142.7 (s, <u>C</u>$_q$ Ph), 170.1 (s, <u>C</u>=O).

*Diastereoisomer n°2:*

**M.p.**: 116-118°C

**Rf** = 0.07 (cyclohexane/AcOEt = 82:18)

**IR ($cm^{-1}$)**: 3326, 2804, 1650, 1549, 1451.

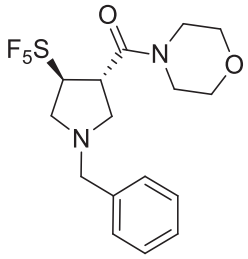
**HRMS ($ESI^+$)**: calcd for $C_{20}H_{24}F_5N_2OS$ (*m/z*) 435.1530 $[M+H]^+$, found 435.1541.

**$^{19}F$ NMR ($CDCl_3/CFCl_3$, 282 MHz)**: δ 59.3 (dd, 4F, $^2J_{F,F}$ = 145.7 Hz, $^3J_{F,H}$ = 5.2 Hz), 85.2 (m, 1F).

**$^1H$ NMR ($CDCl_3$, 300 MHz)**: δ 1.52 (d, 3H, $^3J_{H,H}$ = 6.8 Hz, C<u>H</u>$_3$), 2.8-2.9 (m, 2H, C<u>H</u>$_2$CHCONH), 3.1-3.3 (m, 2H, C<u>H</u>$_2$CHSF$_5$), 3.44 (m, 1H, C<u>H</u>CONH), 3.63 (d, 1H, $^2J_{H,H}$ = 12.7 Hz, NC<u>H</u>$_A$H$_B$Ph), 3.75 (d, 1H, $^2J_{H,H}$ = 12.7 Hz, NCH$_A$<u>H</u>$_B$Ph), 4.95 (m, 1H, C<u>H</u>SF$_5$), 5.14 (m, 1H, CH$_3$C<u>H</u>Ph), 6.17 (br s, 1H, N<u>H</u>), 7.3-7.5 (m, 10H, 2 x Ph).

**$^{13}$C NMR ($CDCl_3$, 75 MHz)**: δ 21.6 (s, $\underline{C}H_3$), 48.3 (q$_t$, $^3J_{C,F}$ = 3.3 Hz, $\underline{C}HCHSF_5$), 49.0 (s, NH$\underline{C}$H($CH_3$)Ph), 56.5 (m, $\underline{C}H_2CHSF_5$), 56.6 (s, $\underline{C}H_2CHCONH$), 59.0 (s, N$\underline{C}H_2$Ph), 84.6 (q$_t$, $^2J_{C,F}$ = 10.7 Hz, $\underline{C}HSF_5$), 125.9 (s, 2 x $\underline{C}$H Ph), 127.3 (s, $\underline{C}$H Ph), 127.4 (s, $\underline{C}$H Ph), 128.43 (s, 2 x $\underline{C}$H Ph), 128.47 (s, 2 x $\underline{C}$H Ph), 128.6 (s, 2 x $\underline{C}$H Ph), 137.6 (s, $\underline{C}_q$ Ph), 142.7 (s, $\underline{C}_q$ Ph), 170.3 (s, $\underline{C}$=O).

**(±)-*N*-Morpholino-1-benzyl-4-pentafluorosulfanylpyrrolidin-3-ylcarboxamide 43d**




**$C_{16}H_{21}F_5N_2O_2S$**
**M = 400.41 g/mol**

The title compound was prepared according to the general procedure. The resulting crude product was purified by silica gel column chromatography (PE/AcOEt = 7:3) to afford **43d** in 73% yield as a white solid.

**M.p.**: 96°C

**Rf** = 0.25 (cyclohexane/AcOEt = 70:30)

**IR (cm$^{-1}$)**: 2925, 2852, 1644, 1437, 1230.

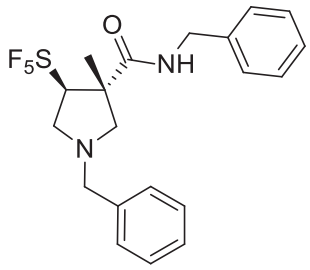
**HRMS (ESI$^+$)**: calcd for $C_{16}H_{22}F_5N_2O_2S$ (*m/z*) 401.1322 $[M+H]^+$, found 401.1310.

**$^{19}$F NMR ($CDCl_3$/$CFCl_3$, 282 MHz)**: δ 59.0 (dd, 4F, $^2J_{F,F}$ = 145.7 Hz, $^3J_{F,H}$ = 5.2 Hz), 85.5 (m, 1F).

**$^1$H NMR ($CDCl_3$, 300 MHz)**: δ 2.58 (m, 1H, C$\underline{H}_A$H$_B$CHCON), 2.98 (m, 1H, CH$_A\underline{H}_B$CHCON), 3.1-3.3 (m, 2H, $\underline{C}H_2CHSF_5$), 3.4-39 (m, 11H, $\underline{C}$HCON + NC$\underline{H}_2$Ph, 4 x C$\underline{H}_{2morpolino}$), 5.33 (m, 1H, $\underline{C}$HSF$_5$), 7.3-7.4 (m, 5H, Ph).

**$^{13}$C NMR ($CDCl_3$, 75 MHz)**: δ 42.7 (s, N<u>C</u>$H_{2morpholino}$), 44.0 ($q_t$, $^3J_{C,F}$ = 3.6 Hz, <u>C</u>HCON), 46.0 (s, N<u>C</u>$H_{2morpholino}$), 56.0 ($q_t$, $^3J_{C,F}$ = 5.0 Hz, <u>C</u>$H_2CHSF_5$), 56.1 (m, <u>C</u>$H_2SF_5$), 59.0 (s, N<u>C</u>$H_2$Ph), 66.5 (s, O<u>C</u>$H_{2morpholino}$), 66.7 (s, O<u>C</u>$H_{2morpholino}$), 84.1 ($q_t$, $^2J_{C,F}$ = 10.5 Hz, <u>C</u>$HSF_5$), 127.3 (s, <u>C</u>H Ph), 128.36 (s, 2 x <u>C</u>H Ph), 128.43 (s, 2 x <u>C</u>H Ph), 137.4 (s, <u>C</u>$_q$ Ph), 170.0 (s, <u>C</u>=O).

**(±)-*N*-Benzyl-1-benzyl-3-methyl-4-pentafluorosulfanylpyrrolidin-3-ylcarboxamide 43e**




**$C_{20}H_{23}F_5N_2OS$**
**M = 434.47 g/mol**

The title compound was prepared according to the general procedure. The resulting crude product was purified by silica gel column chromatography (EP/AcOEt = 85:15) to afford **43e** in 36% yield as a colorless liquid.

**Rf** = 0.24 (EP/AcOEt = 80:20)

**IR (cm$^{-1}$)**: 3346, 3027, 1642, 1532, 1453.

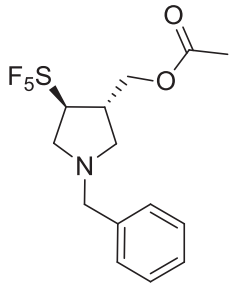
**HRMS (ESI$^+$)**: calcd for $C_{20}H_{24}F_5N_2OS$ (*m/z*) 435.1530 $[M+H]^+$, found 435.1519.

**$^{19}$F NMR ($CDCl_3$/$CFCl_3$, 282 MHz)**: δ 65.6 (dd, 4F, $^2J_{F,F}$ = 143.9 Hz, $^3J_{F,H}$ = 3.5 Hz), 85.4 (m, 1F).

**$^1$H NMR ($CDCl_3$, 300 MHz)**: δ 1.68 (s, 3H, C<u>H</u>$_3$), 2.75 (d, 1H, $^2J_{H,H}$ = 8.8 Hz, C<u>H</u>$_A$H$_B$C(CH$_3$)CONH), 2.98 (d, 1H, $^2J_{H,H}$ = 8.8 Hz, CH$_A$<u>H</u>$_B$C(CH$_3$)CONH), 3.22 (m, 1H, C<u>H</u>$_A$H$_B$CHSF$_5$), 3.51 (m, 1H, CH$_A$<u>H</u>$_B$CHSF$_5$), 3.75 (s, 2H, NC<u>H</u>$_2$Ph), 4.45 (dd, 1H, $^2J_{H,H}$ = 14.6 Hz, $^3J_{H,H}$ = 5.0 Hz, NHC<u>H</u>$_A$H$_B$Ph), 4.60 (dd, 1H, $^2J_{H,H}$ = 14.6 Hz, $^3J_{H,H}$ = 5.0 Hz, NHCH$_A$<u>H</u>$_B$Ph), 5.42 (m, 1H, C<u>H</u>SF$_5$), 6.27 (br s, 1H, N<u>H</u>), 7.3-7.4 (m, 10H, 2 x Ph).

**$^{13}$C NMR ($CDCl_3$, 75 MHz)**: δ 18.9 (m, $\underline{C}H_3$), 44.1 (s, NH$\underline{C}H_2$Ph), 53.3 (q$_t$, $^3J_{C,F}$ = 5.0 Hz, $\underline{C}H_2CHSF_5$), 52.9 (s, $C_q$, CH$\underline{C}$($CH_3$)CONH), 59.8 (s, $\underline{C}H_2C(CH_3)CONH$), 65.1 (s, N$\underline{C}H_2$Ph), 86.7 (q$_t$, $^2J_{C,F}$ = 9.9 Hz, $\underline{C}HSF_5$), 127.3 (s, $\underline{C}$H Ph), 127.7 (s, 2 x $\underline{C}$H Ph), 128.1 (s, $\underline{C}$H Ph), 128.3 (s, 2 x $\underline{C}$H Ph), 128.4 (s, 2 x $\underline{C}$H Ph), 128.8 (s, 2 x $\underline{C}$H Ph), 137.8 (s, $\underline{C}_q$ Ph), 138.1 (s, $\underline{C}_q$ Ph), 172.3 (s, $\underline{C}$=O).

**(±)-(1-Benzyl-4-pentafluorosulfanylpyrrolidin-3-yl)methyl acetate 44**




**$C_{14}H_{18}F_5NO_2S$**
**M = 359.36 g/mol**

The title compound was prepared according to the general procedure (2 equiv of dipole precursor **40a**, 40°C, 2.5 h). The resulting crude product was purified by silica gel column chromatography (cyclohexane/AcOEt = 85:15) to afford **44** in 74% yield as a colourless oil.

**Rf** = 0.18 (cyclohexane/AcOEt = 92:8)

**IR (cm$^{-1}$)**: 2809, 1743, 1226, 1043.

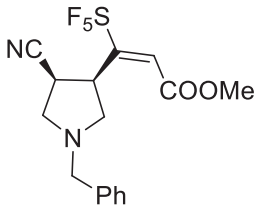
**HRMS (ESI$^+$)**: calcd for $C_{14}H_{19}F_5NO_2S$ (*m/z*) 360.1057 $[M+H]^+$, found 360.1053.

**$^{19}$F NMR ($CDCl_3$/$CFCl_3$, 282 MHz)**: δ 59.2 (dd, 4F, $^2J_{F,F}$ = 144.8 Hz, $^3J_{F,H}$ = 6.1 Hz), 85.6 (m, 1F).

**$^1$H NMR ($CDCl_3$, 300 MHz)**: δ 2.07 (s, 3H, C$\underline{H}_3$), 2.62 (d, 2H, $^3J_{H,H}$ = 5.6 Hz, C$\underline{H}_2$CHC$H_2$OAc), 2.89 (m, 1H, C$\underline{H}_A$H$_B$CHSF$_5$), 3.1-3.2 (m, 2H, CH$_A\underline{H}_B$CHSF$_5$ + C$\underline{H}$C$H_2$OAc), 3.57 (d, 1H, $^2J_{H,H}$ = 12.8 Hz, NC$\underline{H}_A$H$_B$Ph), 3.65 (d, 1H, $^2J_{H,H}$ = 12.8 Hz, NCH$_A\underline{H}_B$Ph), 4.1-4.2 (m, 3H, C$\underline{H}_2$OAc + C$\underline{H}$SF$_5$), 7.3-7.5 (m, 5H, Ph).

**$^{13}$C NMR ($CDCl_3$, 75 MHz)**: δ 20.7 (s, $\underline{C}H_3$), 41.1 ($q_t$, $^3J_{C,F}$ = 3.0 Hz, $\underline{C}HCH_2OAc$), 55.6 (s, $\underline{C}H_2CHCH_2OAc$), 57.1 ($q_t$, $^3J_{C,F}$ = 5.0 Hz, $\underline{C}H_2CHSF_5$), 59.3 (s, $N\underline{C}H_2Ph$), 65.2 (s, $\underline{C}H_2OAc$), 84.8 ($q_t$, $^2J_{C,F}$ = 10.6 Hz, $\underline{C}HSF_5$), 127.3 (s, $\underline{C}H$ Ph), 128.4 (m, 4 x $\underline{C}H$ Ph), 137.8 (s, $\underline{C}_q$ Ph), 170.8 (s, $\underline{C}$=O).

**(±)-Methyl 3-(1-benzyl-4-cyanopyrrolidin-3-yl)-3-pentafluorosulfanylprop-2-enoate 47**




**$C_{16}H_{17}F_5N_2O_2S$**
**M = 396.38 g/mol**

The title compound was prepared according to the general procedure (2 equiv of dipole precursor **40a**). The resulting crude product was purified by silica gel column chromatography (cyclohexane/AcOEt = 85:15) to afford **47** in 18% yield as a colourless oil.

**Rf** = 0.27 (EP/AcOEt = 80:20)

**IR (cm$^{-1}$)**: 3031, 2951, 2210, 1705, 1667, 1496, 1454.

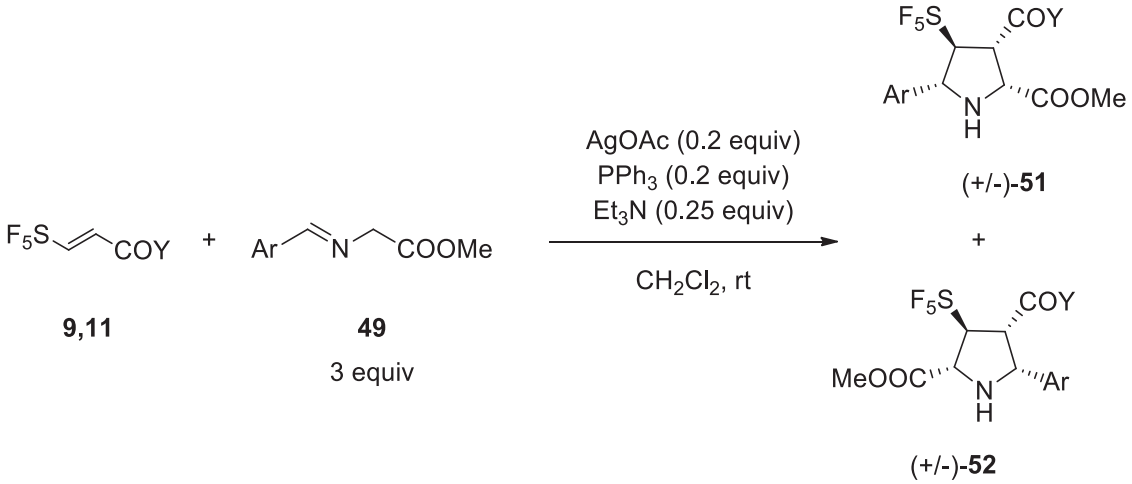
**HRMS (ESI$^+$)**: calcd for $C_{16}H_{18}F_5N_2O_2S$ (*m/z*) 397.1009 $[M+H]^+$, found 397.1018.

**$^{19}$F NMR ($CDCl_3$/$CFCl_3$, 282 MHz)**: δ 57.4 (dm, 4F, $^2J_{F,F}$ = 147.4 Hz), 81.5 (m, 1F).

**$^1$H NMR ($CDCl_3$, 300 MHz)**: δ 2.95-3.03 (m, 2H, $C\underline{H}_2$), 3.13 (m, 1H, $C\underline{H}_AH_B$), 3.33 (m, 1H, $CH_A\underline{H}_B$), 3.57-3.67 (m, 1H, $C\underline{H}CN$), 3.72 (s, 2H, $NCH_2Ph$), 3.83 (s, 3H, $COOC\underline{H}_3$), 4.07-4.16 (m, 1H, $C\underline{H}CSF_5$), 6.88 (s, 1H, C=$C\underline{H}COOCH_3$), 7.3-7.4 (m, 5H, Ph).

***Selected* $^{13}$C NMR ($CDCl_3$, 75 MHz)**: δ 32.7 (s, $\underline{C}HCN$), 41.3 (m, $\underline{C}HCSF_5$), 52.9 (s, $COO\underline{C}H_3$), 56.5 (m, 2 x $\underline{C}H_2$), 58.8 (s, $N\underline{C}H_2Ph$), 118.3 (s, $\underline{C}N$), 127.5 (s, $\underline{C}H$ Ph), 128.0 ($q_t$, $^3J_{C,F}$ = 5.8 Hz, $\underline{C}H$=$CSF_5$), 128.5 (s, 2 x $\underline{C}H$ Ph), 128.7 (s, 2 x $\underline{C}H$ Ph), 137.6 (s, $\underline{C}_q$ Ph), 163.9 (s, $\underline{C}$=O).

### 3.2.2. General procedure for the synthesis of tetrasubstituted $SF_5$-pyrrolidines 51,52

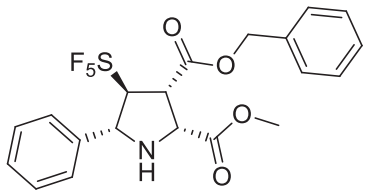



$PPh_3$ (0.20 equiv, 0.8 mmol) and AgOAc (0.20 equiv, 0.8 mmol) were dissolved in dry $CH_2Cl_2$ (37 mL) under argon, and stirred at room temperature for 1 h. Then, the dipole precursor **49** (3.00 equiv, 12.3 mmol), $Et_3N$ (0.25 equiv, 1.0 mmol) and ester **9** or amide **11** (1.00 equiv, 4.1 mmol) were added successively. After stirring at room temperature or at reflux, the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography leading to pyrrolidines **51** and **52**.

**3.2.2.1.** The reaction of ester **9c** with imino ester **49a** was carried out according to the general procedure and led to a 1:1 mixture of regioisomers **51a** and **52a**. The resulting crude product was purified by silica gel column chromatography (EP/AcOEt = 84:16) to afford **51a** and **52a** in 37% and 36% yield, respectively.

**3.2.2.2.** The reaction of ester **9c** with imino ester **49a** was carried out according to the general procedure (*(R)*-BINAP instead of $PPh_3$) and led to a 2:1 mixture of regioisomers **51a** and **52a**. The resulting crude product was purified by silica gel column chromatography (EP/AcOEt = 84:16) to afford **51a** and **52a** in 16% and 8% yield, respectively. The product **52a** was analyzed by chiral HPLC to determine the enantiomeric excess 37% (heptane/isopropanol = 80:20, flow rate 1.0mL/min, $\lambda$ = 230 nm, $t_r$ = 6.95 min and 7.17 min).

**(±)-3-Benzyl-2-methyl-4-pentafluorosulfanyl-5-phenylpyrrolidine-2,3-dicarboxylate 51a**



**$C_{20}H_{20}F_5NO_4S$**
**M = 465.43 g/mol**

**M.p.**: 118-120°C

**Rf** = 0.18 (EP/AcOEt = 80:20)

**IR ($cm^{-1}$)**: 2966, 1746, 1727, 1456, 1338, 1277, 1222, 1201.

**HRMS ($ESI^+$)**: calcd for $C_{20}H_{21}F_5NO_4S$ (*m/z*) 466.1111 $[M+H]^+$, found 466.1129.

**$^{19}F$ NMR ($CDCl_3/CFCl_3$, 282 MHz)**: δ 63.1 (dm, 4F, $^2J_{F,F}$ = 145.7 Hz), 84.7 (m, 1F).

**$^1H$ NMR ($CDCl_3$, 300 MHz)**: δ 2.63 (br s, 1H, NH), 3.51 (s, 3H, $CH_3$), 4.1-4.2 (m, 1H, CHCOOBn), 4.2-4.3 (m, 1H, $CHCOOCH_3$), 4.60 (d, 1H, $^3J_{H,H}$ = 7.6 Hz, CHPh), 5.02 (m, 1H, $CHSF_5$), 5.19 (s, 2H, $CH_2Ph$), 7.3-7.7 (m, 10H, 2 x Ph).

**$^{13}C$ NMR ($CDCl_3$, 75 MHz)**: δ 52.3 (m, CHCOOBn), 52.4 (s, $CH_3$), 62.5 (s, $CHCOOCH_3$), 66.3 (m, CHPh), 68.0 (s, $CH_2Ph$), 91.9 ($q_t$, $^2J_{C,F}$ = 7.4 Hz, $CHSF_5$), 127.4 (s, 2 x CH Ph), 128.6 (s, 5 x CH Ph), 128.7 (s, CH Ph), 129.0 (s, 2 x CH Ph), 134.7 (s, $C_q$ Ph), 137.6 (s, $C_q$ Ph), 170.0 (s, C=O), 170.9 (s, C=O).

**Crystallographic data**

The crystal data are collected in Table 22. The full crystallographic parameters (atomic coordinates, bond length, angles and anisotropic displacements) are deposit to the Cambridge Crystallographic Data Centre (Nr CCDC1024824).

| | |
|---|---|
| Chemical Formula | $C_{20}H_{20}F_5NO_4S$ |
| Molecular Weight / $g.mol^{-1}$ | 465.4 |
| Crystal System | Monoclinic |
| Space Group | $P2_1$ |
| Z , Z' (asymmetric units per unit cell) | 2,1 |
| a / $Å$ | 5.7359(6) |
| b / $Å$ | 14.0228(15) |
| c / $Å$ | 12.8595(14) |
| β / ° | 97.839(2) |
| V / $Å^3$ | 1024.67(19) |
| $d_{calc}$ / $g.cm^{-3}$ | 1.509 |
| F(000) / $e^-$ | 480 |
| Absolute structure parameter | 0.02(7) |
| Absorption coefficient μ (MoKα$_1$) / $mm^{-1}$ | 0.231 |

**Table 22: Crystal data.**

## Structural description

The asymmetric unit is composed of one molecule of $C_{20}H_{20}F_5NO_4S$ (Figures 58 and 59). Four (F1 to F4) of the five fluorine atoms are statistically disordered. The statistical occupancy is shared between two crystallographic sites for the fluorine atoms F1 to F4. This distribution is 57 /43 %. The packing is represented on figures 60 to 62, the cohesion between molecules is ensured by Van der Waals interactions.

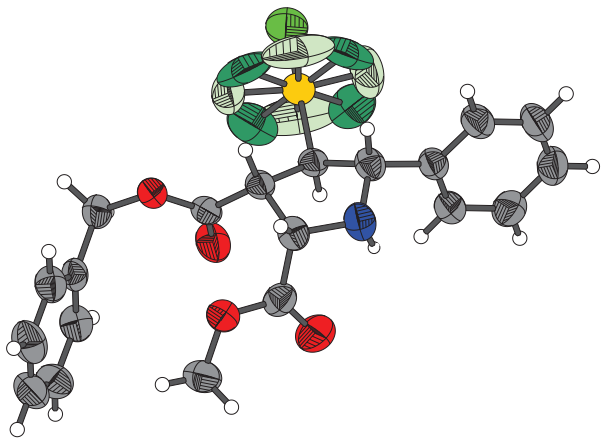


**Figure 58: Asymmetric unit in thermal ellipsoidal representation. In light green the fluorine atoms with a statistical occupancy of 43%, in darker green the fluorine atoms with a statistical occupancy of 57%.**

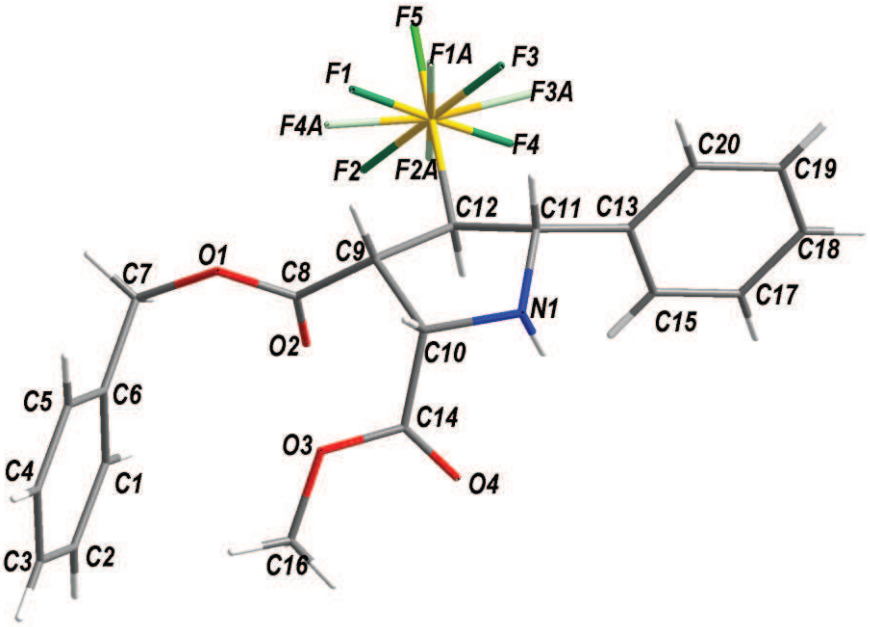



**Figure 59: Asymmetric unit with atoms labels. In light green the fluorine atoms with a statistical occupancy of 43%, in darker green the fluorine atoms with a sof of 57%.**

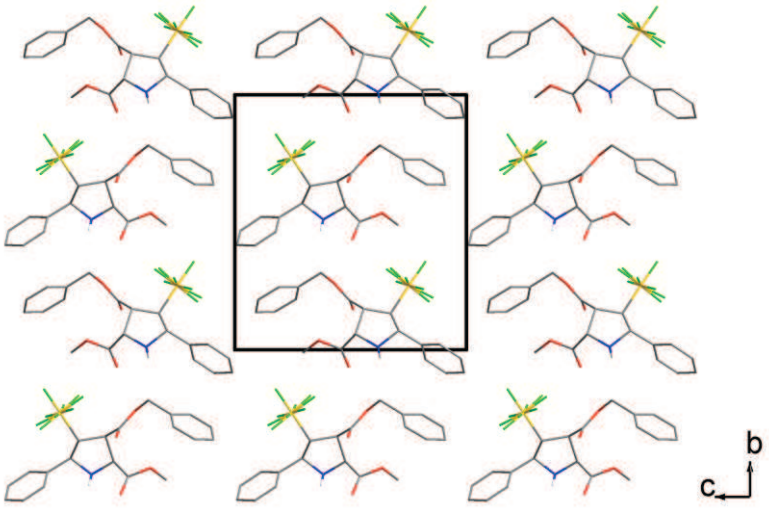



**Figure 60: Projection along a axis.**

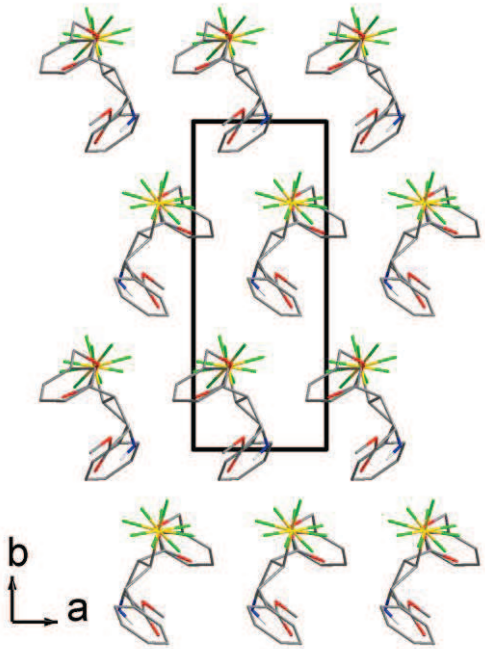



**Figure 61: Projection along c axis.**

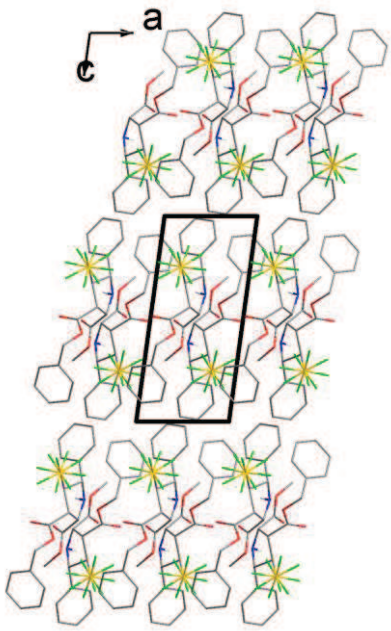
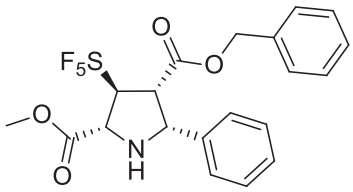



**Figure 62: Projection along b axis.**

**(±)-4-Benzyl-2-methyl-3-pentafluorosulfanyl-5-phenylpyrrolidine-2,4-dicarboxylate 52a**



**$C_{20}H_{20}F_5NO_4S$**
**M = 465.43 g/mol**

**M.p.**: 98-99°C

**Rf** = 0.25 (EP/AcOEt = 80:20)

**IR ($cm^{-1}$)**: 2960, 1734, 1716, 1440, 1392, 1261, 1240, 1177.

**HRMS ($ESI^+$)**: calcd for $C_{20}H_{21}F_5NO_4S$ (*m/z*) 466.1111 $[M+H]^+$, found 466.1118.

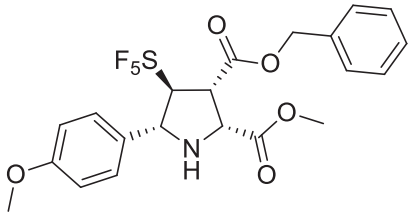
**$^{19}F$ NMR ($CDCl_3/CFCl_3$, 282 MHz)**: δ 61.4 (dd, 4F, $^2J_{F,F}$ = 145.7 Hz, $^3J_{F,H}$ = 5.2 Hz), 83.9 (m, 1F).

**$^1H$ NMR ($CDCl_3$, 300 MHz)**: δ 2.66 (br s, 1H, NH), 3.88 (s, 3H, $CH_3$), 3.99 (m, 1H, CHCOOBn), 4.3-4.4 (m, 2H, $COOCH_AH_BPh$ + $CHCOOCH_3$), 4.7-4.8 (m, 2H, CHPh), 5.3-5.5 (m, 1H, $COOCH_AH_BPh$), 6.9-7.0 (m, 2H, Ph), 7.3-7.6 (m, 8H, Ph).

**$^{13}C$ NMR ($CDCl_3$, 75 MHz)**: δ 53.0 (s, $CH_3$), 53.4 (s, CHCOOBn), 63.4 ($q_t$, $^3J_{C,F}$ = 3.9 Hz, $CHCOOCH_3$), 64.6 (s, CHPh), 67.4 (s, $COOCH_2Ph$), 86.9 ($q_t$, $^2J_{C,F}$ = 10.9 Hz, $CHSF_5$), 127.2 (s, 2 x CH Ph), 128.33 (s, 3 x CH Ph), 128.38 (s, 2 x CH Ph), 128.44 (s, 2 x CH Ph), 128.48 (s, CH Ph), 134.6 (s, $C_q$ Ph), 136.8 (s, $C_q$ Ph), 170.1 (s, C=O), 170.2 (s, C=O).

**3.2.2.3.** The reaction of ester **9c** with imino ester **49b** was carried out according to the general procedure as described above and led to a 2:1 mixture of regioisomers **51b** and **52b**. The resulting crude product was purified by silica gel column chromatography (EP/AcOEt = 84:16) to afford the mixture of **51b** and **52b** in 35% overall yield.

**(±)-3-Benzyl-2-methyl-4-pentafluorosulfanyl-5-(*p*-methoxyphenyl)pyrrolidine-2,3-dicarboxylate 51b**



**$C_{21}H_{22}F_5NO_5S$**
**M = 495.46 g/mol**

**M.p.**: 118-119°C

**Rf** = 0.14 (EP/AcOEt = 84:16)

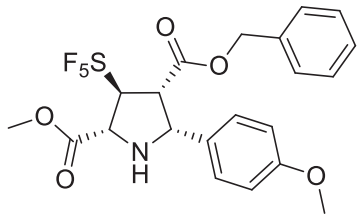
**IR ($cm^{-1}$)**: 2958, 2841, 1743, 1609, 1520, 1459, 1437.

**HRMS ($ESI^+$)**: calcd for $C_{21}H_{23}F_5NO_5S$ (*m/z*) 496.1217 $[M+H]^+$, found 496.1219.

**$^{19}F$ NMR ($CDCl_3/CFCl_3$, 282 MHz)**: δ 63.0 (dd, 4F, $^2J_{F,F}$ = 145.7 Hz, $^3J_{F,H}$ = 5.2 Hz), 84.9 (m, 1F).

***Selected* $^1H$ NMR ($CDCl_3$, 300 MHz)**: δ 3.51 (s, 3H, $COOCH_3$), 3.83 (s, 3H, $PhOCH_3$), 4.10-4.14 (m, 1H, CHCOOBn), 4.20 (d, 1H, $^3J_{H,H}$ = 8.2 Hz, $CHCOOCH_3$), 4.56 (d, 1H, $^3J_{H,H}$ = 8.4 Hz, CHPh), 4.96 (m, 1H, $CHSF_5$), 5.19 (s, 2H, $COOCH_2Ph$), 6.91 (d, 2H, $^3J_{H,H}$ = 7.8 Hz, Ar), 7.3-7.5 (m, 7H, Ar).

**(±)-4-Benzyl-2-methyl-3-pentafluorosulfanyl-5-(*p*-methoxyphenyl)pyrrolidine-2,4-dicarboxylate 52b**



**$C_{21}H_{22}F_5NO_5S$**
**M = 495.46 g/mol**

**M.p.**: 103-104°C

**Rf** = 0.19 (EP/AcOEt = 84:16)

**IR ($cm^{-1}$)**: 2958, 2835, 1750, 1609, 1515.

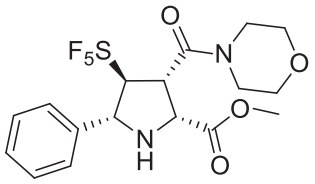
**HRMS ($ESI^+$)**: calcd for $C_{21}H_{23}F_5NO_5S$ (*m/z*) 496.1217 $[M+H]^+$, found 496.1217.

**$^{19}F$ NMR ($CDCl_3/CFCl_3$, 282 MHz)**: δ 61.3 (dd, 4F, $^2J_{F,F}$ = 145.7 Hz, $^3J_{F,H}$ = 5.2 Hz), 84.0 (m, 1F).

**$^1H$ NMR ($CDCl_3$, 300 MHz)**: δ 3.79 (s, 3H, OC$\underline{H}_3$), 3.87 (s, 3H, COOC$\underline{H}_3$), 3.8-3.9 (m, 1H, C$\underline{H}$COOBn), 4.36 (d, 1H, $^3J_{H,H}$ = 9.0 Hz, C$\underline{H}$COOCH$_3$), 4.46 (d, 1H, $^2J_{H,H}$ = 12.1 Hz, C$\underline{H}_A$H$_B$Ph), 4.69 (d, 1H, $^3J_{H,H}$ = 9.0 Hz, C$\underline{H}$Ar), 4.80 (d, 1H, $^2J_{H,H}$ = 12.1 Hz, CH$_A\underline{H}_B$Ph), 5.37 (m, 1H, C$\underline{H}$SF$_5$), 6.80 (d, 2H, $^3J_{H,H}$ = 8.1 Hz, Ar), 6.9-7.1 (m, 2H, Ar), 7.21 (d, 2H, $^3J_{H,H}$ = 7.7 Hz, Ar), 7.3-7.4 (m, 1H, Ar), 7.86 (d, 2H, $^3J_{H,H}$ = 7.7 Hz, Ar).

**3.2.2.4.** The reaction of amide **11l** with imino ester **49a** was carried out according to the general procedure as described above and led to a 2:1 mixture of regioisomers **51c** and **52c**. The resulting crude product was purified by silica gel column chromatography (EP/AcOEt = 68:32) to afford **51c** and **52c** in 30% and 18% yield, respectively.

**(±)-2-Methyl-3-morpholinocarbonyl-4-pentafluorosulfanyl-5-phenylpyrrolidine-2-carboxylate 51c**




**$C_{17}H_{21}F_5N_2O_4S$**
**M = 444.42 g/mol**

**M.p.**: 103-105°C

**Rf** = 0.24 (EP/AcOEt = 68:32)

**IR (cm$^{-1}$)**: 3303, 2919, 2858, 1738, 1632, 1459.

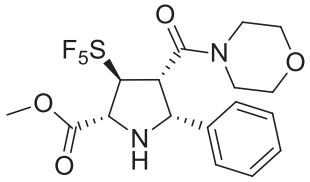
**HRMS (ESI$^+$)**: calcd for $C_{17}H_{22}F_5N_2O_4S$ (*m/z*) 445.1220 $[M+H]^+$, found 445.1225.

**$^{19}$F NMR ($CDCl_3/CFCl_3$, 282 MHz)**: δ 63.2 (dd, 4F, $^2J_{F,F}$ = 145.7 Hz, $^3J_{F,H}$ = 5.2 Hz), 85.7 (m, 1F).

**$^1$H NMR ($CDCl_3$, 300 MHz)**: δ 3.00 (br s, 1H, NH), 3.6-3.9 (m, 11H, 4 x $CH_{2morpholino}$ + $COOCH_3$), 4.22 (m, 1H, CHCON), 4.36 (m, 1H, $CHCOOCH_3$), 4.57 (d, 1H, $^3J_{H,H}$ = 8.3 Hz, CHPh), 5.06 (m, 1H, $CHSF_5$), 7.3-7.5 (m, 3H, Ph), 7.5-7.6 (d, 2H, $^3J_{H,H}$ = 6.8 Hz, Ph).

**$^{13}$C NMR ($CDCl_3$, 75 MHz)**: δ 42.6 (s, $CH_{2morpholino}$), 46.9 (s, $CH_{2morpholino}$), 52.7 (s, $COOCH_3$), 64.0 (s, $CHCOOCH_3$), 66.4 (s, $CH_{2morpholino}$), 66.7 (s, $CH_{2morpholino}$), 66.8 (m, CHCON), 70.5 (m, CHPh), 94.0 ($q_t$, $^2J_{C,F}$ = 6.3 Hz, $CHSF_5$), 127.5 (s, 2 x CH Ph), 128.7 (s, CH Ph), 129.0 (s, 2 x CH Ph), 137.5 (s, $C_q$ Ph), 169.7 (s, C=O), 170.8 (s, C=O).

**(±)-2-Methyl-4-morpholinocarbonyl-3-pentafluorosulfanyl-5-phenylpyrrolidine-2-carboxylate 52c**




**$C_{17}H_{21}F_5N_2O_4S$**
**M = 444.42 g/mol**

**M.p.**: 93-94°C

**Rf** = 0.32 (EP/AcOEt = 68:32)

**IR (cm$^{-1}$)**: 3291, 2927, 2857, 1748, 1650, 1441.

**$^{19}$F NMR ($CDCl_3/CFCl_3$, 282 MHz)**: δ 61.4 (dd, 4F, $^2J_{F,F}$ = 145.7 Hz, $^3J_{F,H}$ = 6.9 Hz), 85.3 (m, 1F).

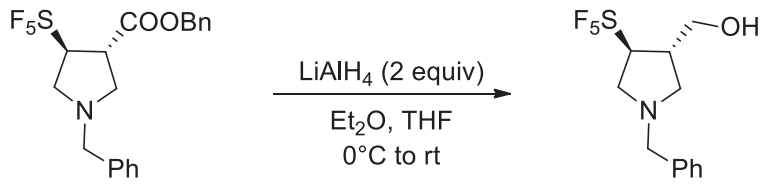
***Selected* $^1$H NMR ($CDCl_3$, 300 MHz)**: δ 2.6-2.7 (m, 1H, $CH_{2morpholino}$), 2.8-2.9 (m, 1H, $CH_{2morpholino}$), 3.0-3.5 (m, 6H, $CH_{2morpholino}$), 3.88 (s, 3H, $COOCH_3$), 4.10 (dd, 1H, $^3J_{H,H}$ =

7.9 Hz, $^{3}J_{H,H}$ = 4.5 Hz, C<u>H</u>CON), 4.40 (d, 1H, $^{3}J_{H,H}$ = 7.8 Hz, C<u>H</u>COOCH$_3$), 4.54 (d, 1H, $^{3}J_{H,H}$ = 7.9 Hz, C<u>H</u>Ph), 5.53 (m, 1H, C<u>H</u>SF$_5$), 7.3-7.4 (m, 5H, Ph).

**$^{13}$C NMR (CDCl$_3$, 75 MHz)**: δ 42.0 (s, <u>C</u>H$_{2morpholino}$), 45.9 (s, <u>C</u>H$_{2morpholino}$), 49.4 (m, <u>C</u>HCON), 53.0 (s, COO<u>C</u>H$_3$), 53.4 (s, <u>C</u>H$_{2morpholino}$), 64.1 (q$_t$, $^{3}J_{C,F}$ = 4.4 Hz, <u>C</u>HCOOCH$_3$), 65.7 (s, <u>C</u>H$_{2morpholino}$), 66.1 (s, <u>C</u>H Ph), 89.5 (q$_t$, $^{2}J_{C,F}$ = 8.8 Hz, <u>C</u>HSF$_5$), 127.6 (s, 2 x <u>C</u>H Ph), 128.7 (s, 2 x <u>C</u>H Ph), 129.0 (s, <u>C</u>H Ph), 136.0 (s, <u>C</u>$_q$ Ph), 168.4 (s, <u>C</u>=O), 170.0 (s, <u>C</u>=O).

### 3.2.3. Post-functionalisations of $SF_5$-pyrrolidines

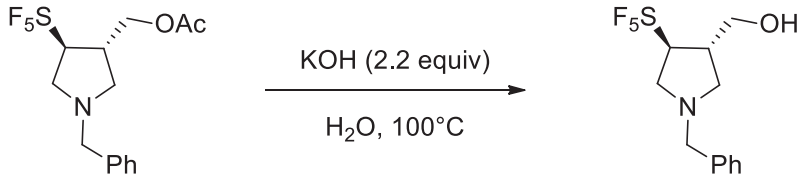
#### 3.2.3.1. Synthesis of $SF_5$-pyrrolidinyl alcohol 55 - <u>Procedure A</u>




**42a** **55**

Pyrrolidine **42a** (180 mg, 1 equiv, 0.43 mmol) in Et$_2$O/THF (1:1 mL) was added to a suspention of LiAlH$_4$ in Et$_2$O (0.85 mL, 2 equiv, 0.86 mmol, 1 M in Et$_2$O) at 0°C. The reaction mixture was allowed to reach room temperature and it was stirred overnight. The reaction mixture was then cooled to 0°C, water (4 mL) was added carefully and the crude was filtred on the celite. The precipitate was washed with AcOEt (4 mL). Organic phase was washed with water (2 mL) and with 5% NaHCO$_{3aq.}$ solution (2 mL), dried over MgSO$_4$ and concentrated under reduced pressure. Crude product was purified by silica gel column chromatography (EP/AcOEt = 7:3) giving the desired product **55** (53 mg, 40%) as a yellow solid.

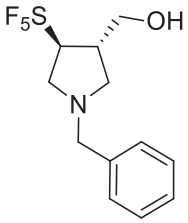
### 3.2.3.2. Synthesis of $SF_5$-pyrrolidinyl alcohol 55 - Procedure B




**44** **55**

KOH (51 mg, 2.2 equiv, 0.91 mmol) in water (0.3 mL) was added to pyrrolidine **44** (149 mg, 1.0 equiv, 0.41 mmol) and the reaction mixture was stirred at 100°C for 23 h. After cooling to room temperature, $CH_2Cl_2$ (1 mL) was added to the reaction mixture and the latter was stirred vigorously for 10 minutes. Organic phase was separated, dried over $MgSO_4$ and concentrated under the reduced pressure to give the desired product **55** (119 mg, 91%) as a yellow solid.

**(±)-(1-Benzyl-4-pentafluorosulfanylpyrrolidin-3-yl)methanol 55**




**$C_{12}H_{16}F_5NOS$**
**M = 317.32 g/mol**

**Rf** = 0.12 (EP/AcOEt = 90:10)

**IR ($cm^{-1}$)**: 3334, 3036, 2806, 1659, 1496, 1455, 1249.

**HRMS ($ESI^+$)**: calcd for $C_{12}H_{17}F_5NOS$ (*m/z*) 318.0951 $[M+H]^+$, found 318.0955.

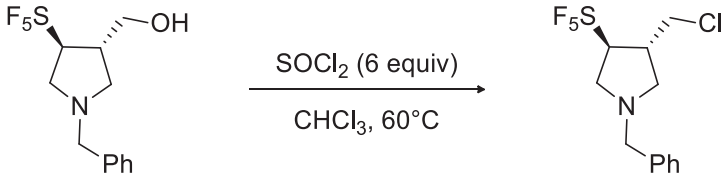
**$^{19}F$ NMR ($CDCl_3/CFCl_3$, 282 MHz)**: δ 59.3 (dd, 4F, $^2J_{F,F}$ = 143.9 Hz, $^3J_{F,H}$ = 6.9 Hz), 85.8 (m, 1F).

**$^1H$ NMR ($CDCl_3$, 300 MHz)**: δ 2.66 (m, 1H, $C\underline{H}_AH_BCHCH_2OH$), 2.81-2.90 (m, 2H, $C\underline{H}_AH_BCHSF_5$ + $CH_A\underline{H}_BCHCH_2OH$), 2.97 (m, 1H, $C\underline{H}CH_2OH$), 3.07 (m, 1H, $O\underline{H}$), 3.33

(m, 1H, $CH_A\underline{H}_BCHSF_5$), 3.6-3.7 (m, 2H, $NC\underline{H}_2Ph$), 3.7-3.8 (m, 1H, $C\underline{H}_AH_BOH$), 3.76-3.80 (m, 1H, $CH_A\underline{H}_BOH$), 4.45 (m, 1H, $C\underline{H}SF_5$), 7.3-7.4 (m, 5H, Ph).

**$^{13}$C NMR ($CDCl_3$, 75 MHz)**: δ 43.5 ($q_t$, $^3J_{C,F}$ = 3.0 Hz, $\underline{C}HCH_2OH$), 56.3 (s, $\underline{C}H_2CHCH_2OH$), 57.1 ($q_t$, $^3J_{C,F}$ = 5.0 Hz, $\underline{C}H_2CHSF_5$), 59.6 (s, $N\underline{C}H_2Ph$), 64.8 (s, $\underline{C}H_2OH$), 84.1 ($q_t$, $^2J_{C,F}$ = 10.5 Hz, $\underline{C}HSF_5$), 127.7 (s, $\underline{C}H$ Ph), 128.6 (s, 2 x $\underline{C}H$ Ph), 128.7 (s, 2 x $\underline{C}H$ Ph), 137.1 (s, $\underline{C}_q$ Ph).

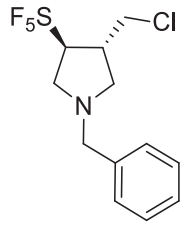
### 3.2.3.3. Synthesis of $SF_5$-pyrrolidinyl chloride 58




**55** **58**

Alcohol **55** (444 mg, 1 equiv, 1.4 mmol) was dissolved in $CHCl_3$ (4 mL) and $SOCl_2$ (0.6 mL, 6 equiv, 8.4 mmol) was added dropwise. The reaction mixture was stirred at 60°C for 2.5 h. After cooling the reaction mixture to room temperature, 5% $NaHCO_{3aq.}$ solution was added until pH = 7-8. The mixture was then extracted with AcOEt (2 x 4 mL) and combined organic phases were washed with brine (3 mL) dried over $MgSO_4$ and concentrated under reduced pressure. Crude product was purified by silica gel column chromatography (EP/AcOEt = 9:1) giving the desired product **58** (343 mg, 73%) as a yellow oil.

**(±)-1-Benzyl-3-chloromethyl-4-pentafluorosulfanylpyrrolidine 58**




**$C_{12}H_{15}ClF_5NS$**
**M = 335.76 g/mol**

**Rf** = 0.45 (EP/$Et_2O$ = 90:10)

**IR ($cm^{-1}$)**: 2924, 2854, 1496, 1455, 1294.

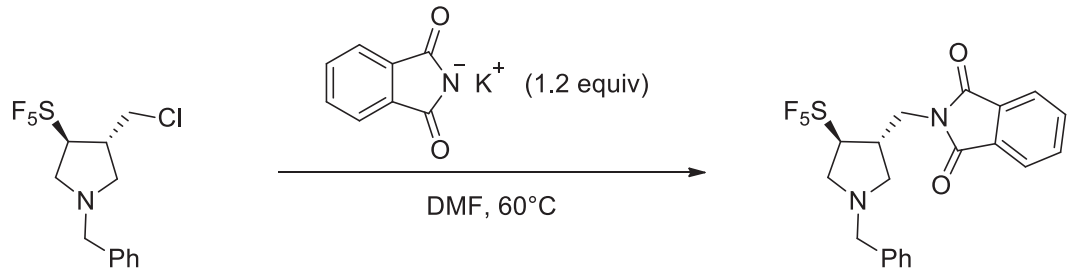
**HRMS ($ESI^+$)**: calcd for $C_{12}H_{16}ClF_5NS$ (*m/z*) 336.0612 $[M+H]^+$, found 366.0609.

**$^{19}F$ NMR ($CDCl_3/CFCl_3$, 282 MHz)**: δ 59.4 (dd, 4F, $^2J_{F,F}$ = 144.8 Hz, $^3J_{F,H}$ = 6.1 Hz), 85.3 (m, 1F).

**$^1H$ NMR ($CDCl_3$, 300 MHz)**: δ 2.68-2.74 (m, 1H, $C\underline{H}_AH_BCHCH_2Cl$), 2.80 (dd, 1H, $^2J_{H,H}$ = 9.5 Hz, $^3J_{H,H}$ = 3.8 Hz, $CH_A\underline{H}_BCHCH_2Cl$), 2.97 (dd, 1H, $^2J_{H,H}$ = 10.2 Hz, $^3J_{H,H}$ = 7.9 Hz, $C\underline{H}_AH_BCHSF_5$), 3.1-3.2 (m, 2H, $CH_A\underline{H}_BCHSF_5$ + $C\underline{H}CH_2Cl$), 3.58-3.74 (m, 4H, $CHC\underline{H}_2Cl$ + $NC\underline{H}_2Ph$), 4.24 (m, 1H, $C\underline{H}SF_5$), 7.3-7.4 (m, 5H, Ph).

**$^{13}C$ NMR ($CDCl_3$, 75 MHz)**: δ 44.0 ($q_t$, $^3J_{C,F}$ = 3.3 Hz, $\underline{C}HCH_2Cl$), 45.9 (s, $CH\underline{C}H_2Cl$), 56.1 (s, $\underline{C}H_2CHCH_2Cl$), 57.2 ($q_t$, $^3J_{C,F}$ = 4.4 Hz, $\underline{C}H_2CHSF_5$), 59.3 (s, $N\underline{C}H_2Ph$), 85.2 ($q_t$, $^2J_{C,F}$ = 9.9 Hz, $\underline{C}HSF_5$), 127.4 (s, $\underline{C}H$ Ph), 128.47 (s, 2 x $\underline{C}H$ Ph), 128.50 (s, 2 x $\underline{C}H$ Ph), 137.6 (s, $\underline{C}_q$ Ph).

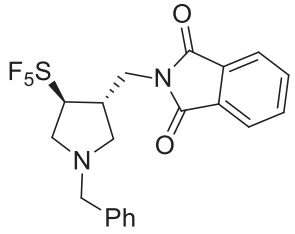
### 3.2.3.4. Synthesis of pyrrolidinyl phthalimide 59




**58** **59**

Chloride **58** (60 mg, 1.0 equiv, 0.19 mmol) was dissolved in anhydrous DMF (0.5 mL) and phthalimide potassium salt (42 mg, 1.2 equiv, 0.23 mmol) was added. The reaction mixture was stirred at 60°C for 3 days (conversion: ~40%). The reaction mixture was then cooled to room temperature, $CH_2Cl_2$ (0.6 mL) was added and the latter was poured into water (0.6 mL). The phases were separated and the aqueous phase was then extracted with $CH_2Cl_2$ (2 x 2 mL). The combined organic phases were washed with 1 M $NaOH_{aq.}$ solution (0.2 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Crude product was purified by silica gel column chromatography (EP/AcOEt = 70:30 + 2% $Et_3N$) giving the desired product **59** (18 mg, 22%) as a colourless oil.

**(±)-N-((1-Benzyl-4-pentafluorosulfanylpyrrolidin-3-yl)methyl)phthalimide 59**




**$C_{20}H_{19}F_5N_2O_2S$**
**M = 446.43 g/mol**

**Rf** = 0.30 (EP/$Et_2O$ = 70:30)

**IR ($cm^{-1}$)**: 2920, 2847, 1773, 1710, 1467, 1455.

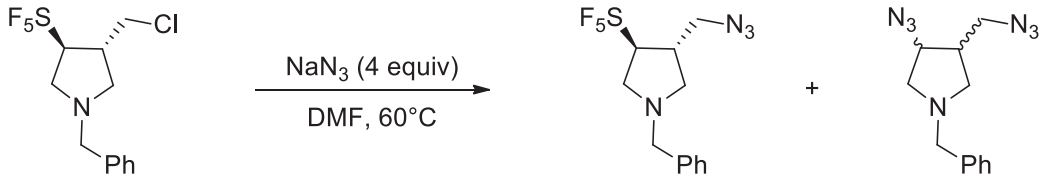
**HRMS ($ESI^+$)**: calcd for $C_{20}H_{20}F_5N_2O_2S$ (*m/z*) 447.1166 $[M+H]^+$, found 447.1165.

**$^{19}$F NMR ($CDCl_3/CFCl_3$, 282 MHz)**: δ 59.0 (dd, 4F, $^2J_{F,F}$ = 143.9 Hz, $^3J_{F,H}$ = 5.2 Hz), 85.7 (m, 1F).

**$^1$H NMR ($CDCl_3$, 300 MHz)**: δ 2.62 (m, 1H, C$\underline{H}_A$H$_B$CHCH$_2$N-phtalimido), 2.72 (m, 1H, CH$_A\underline{H}_B$CHCH$_2$N-phtalimido), 2.85 (m, 1H, C$\underline{H}_A$H$_B$CHSF$_5$), 3.1-3.4 (m, 2H, CH$_A\underline{H}_B$CHSF$_5$ + C$\underline{H}$CH$_2$N-phtalimido), 3.57 (d, 1H, $^2J_{H,H}$ = 13.0 Hz, NC$\underline{H}_A$H$_B$Ph), 3.65 (d, 1H, $^2J_{H,H}$ = 13.0 Hz, NCH$_A\underline{H}_B$Ph), 3.82 (dd, 1H, $^2J_{H,H}$ = 13.8 Hz, $^3J_{H,H}$ = 5.9 Hz, CHC$\underline{H}_A$H$_B$N-phtalimido), 3.95 (dd, 1H, $^2J_{H,H}$ = 13.8 Hz, $^3J_{H,H}$ = 7.8 Hz, CHCH$_A\underline{H}_B$N-phtalimido), 4.47 (m, 1H, C$\underline{H}$SF$_5$), 7.2-7.5 (m, 5H, Ph), 7.7-7.8 (m, 2H, Ar), 7.8-8.0 (m, 2H, Ar).

***Selected* $^{13}$C NMR ($CDCl_3$, 75 MHz)**: δ 41.3 (s, CH$\underline{C}$H$_2$N-phtalimido), 41.5 (q$_t$, $^3J_{C,F}$ = 2.8 Hz, $\underline{C}$HCH$_2$N-phtalimido), 56.4 (s, $\underline{C}$H$_2$CHCH$_2$N-phtalimido), 57.4 (q$_t$, $^3J_{C,F}$ = 5.0 Hz, $\underline{C}$H$_2$CHSF$_5$), 59.3 (s, N$\underline{C}$H$_2$Ph), 86.1 (q$_t$, $^2J_{C,F}$ = 10.0 Hz, $\underline{C}$HSF$_5$).

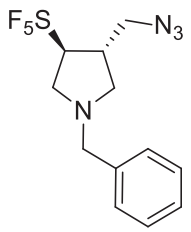
### 3.2.3.5. Synthesis of $SF_5$-pyrrolidinyl azide 60




**58** **60** **63**

$NaN_3$ (194 mg, 4 equiv, 2.98 mmol) was added to a solution of chloride **58** (250 mg, 1 equiv, 0.74 mmol) in DMF (5 mL) and it was stirred at 60°C for 16 h. After cooling to room temperature the reaction mixture was poured into water (15 mL) and extracted with AcOEt (2 x 12 mL). The organic phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure. Crude product was purified by silica gel column chromatography (EP/AcOEt = 96:4) giving the desired product **60** (72 mg, 28%) as a yellow oil, accompanied with the diazido derivative **63** (95 mg, 50%) as a colourless oil.

**(±)-3-(Azidomethyl)-1-benzyl-4-pentafluorosulfanylpyrrolidine 60**




**$C_{12}H_{15}F_5N_4S$**
**M = 342.33 g/mol**

**Rf** = 0.33 (EP/AcOEt = 96 :4)

**IR ($cm^{-1}$)**: 2923, 2805, 2099, 1496, 1455.

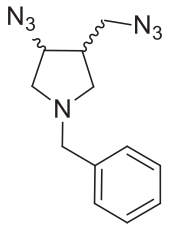
**HRMS ($ESI^+$)**: calcd for $C_{12}H_{16}F_5N_4S$ (*m/z*) 343.1016 $[M+H]^+$, found 343.1022.

**$^{19}F$ NMR ($CDCl_3/CFCl_3$, 282 MHz)**: δ 59.4 (dd, 4F $^2J_{F,F}$ = 143.9 Hz, $^3J_{F,H}$ = 5.2 Hz), 85.4 (m, 1F).

**$^1H$ NMR ($CDCl_3$, 300 MHz)**: δ 2.66-2.68 (m, 2H, $CHC\underline{H}_2N_3$), 2.92 (dd, 1H, $^2J_{H,H}$ = 10.3 Hz, $^3J_{H,H}$ = 8.1 Hz, $C\underline{H}_AH_BCHSF_5$), 3.0-3.1 (m, 1H, $C\underline{H}CH_2N_3$), 3.17 (m, 1H, $CH_A\underline{H}_BCHSF_5$), 3.42 (dd, 1H, $^2J_{H,H}$ = 12.2 Hz, $^3J_{H,H}$ = 7.9 Hz, $C\underline{H}_AH_BCHCH_2N_3$), 3.53-3.69 (m, 3H, $CH_A\underline{H}_BCHCH_2N_3$ + $NC\underline{H}_2Ph$), 4.18 (m, 1H, $C\underline{H}SF_5$), 7.3-7.4 (m, 5H, Ph).

**$^{13}C$ NMR ($CDCl_3$, 75 MHz)**: δ 41.8 ($q_t$, $^3J_{C,F}$ = 3.0 Hz, $\underline{C}HCH_2N_3$), 53.6 (s, $\underline{C}H_2CHCH_2N_3$), 56.1 (s, $CH\underline{C}H_2N_3$), 57.0 ($q_t$, $^3J_{C,F}$ = 4.7 Hz, $\underline{C}H_2CHSF_5$), 59.4 (s, $N\underline{C}H_2Ph$), 85.0 ($q_t$, $^2J_{C,F}$ = 10.2 Hz, $\underline{C}HSF_5$), 127.5 (s, $\underline{C}H$ Ph), 128.48 (s, 2 x $\underline{C}H$ Ph), 128.54 (s, 2 x $\underline{C}H$ Ph), 137.6 (s, $\underline{C}_q$ Ph).

**(±)-3-Azido-4-(azidomethyl)-1-benzylpyrrolidine 63**



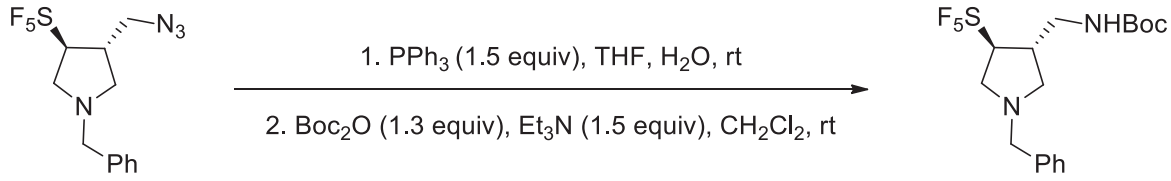
**$C_{12}H_{15}N_7$**
**M = 257.29 g/mol**

**Rf** = 0.11 (EP/AcOEt = 96 :4)

**$^1$H NMR ($CDCl_3$, 300 MHz)**: δ 2.49 (m, 1H, C$\underline{H}_A$H$_B$CHCH$_2$N$_3$), 2.6-2.8 (m, 2H, C$\underline{H}$CH$_2$N$_3$ + C$\underline{H}_A$H$_B$CHN$_3$), 2.87 (m, 1H, CH$_A\underline{H}_B$CHCH$_2$N$_3$), 3.08 (dd, 1H, $^2J_{H,H}$ = 10.6 Hz, $^3J_{H,H}$ = 5.7 Hz, CH$_A\underline{H}_B$CHN$_3$), 3.55 (dd, 1H, $^2J_{H,H}$ = 11 Hz, $^3J_{H,H}$ = 7.8 Hz, CHC$\underline{H}_A$H$_B$N$_3$), 3.69 (s, 2H, NC$\underline{H}_2$Ph), 3.73 (dd, 1H, $^2J_{H,H}$ = 11.0 Hz, $^3J_{H,H}$ = 7.8 Hz, CHCH$_A\underline{H}_B$N$_3$), 4.12 (m, 1H, C$\underline{H}$N$_3$), 7.3-7.4 (m, 5H, Ph).

***Selected* $^{13}$C NMR ($CDCl_3$, 75 MHz)**: δ 43.4 (s, CH$\underline{C}$H$_2$N$_3$), 45.1 (s, $\underline{C}$HCH$_2$N$_3$), 56.2 (s, $\underline{C}$H$_2$CHCH$_2$N$_3$), 59.1 (s, $\underline{C}$H$_2$CHN$_3$), 60.0 (s, N$\underline{C}$H$_2$Ph), 61.9 (s, $\underline{C}$HN$_3$), 127.3 (s, $\underline{C}$H Ph), 128.4 (s, 2 x $\underline{C}$H Ph), 128.7 (s, 2 x $\underline{C}$H Ph).

### 3.2.3.6. Synthesis of $SF_5$-pyrrolidinyl N-Boc amine 62



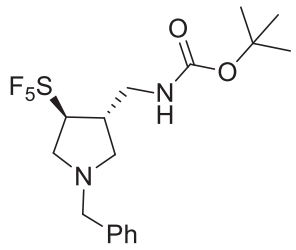

**60** **62**

Azide **60** (67 mg, 1.0 equiv, 0.20 mmol) was dissolved in anhydrous THF (1.3 mL) and the solution was cooled to 0°C. $PPh_3$ (77 mg, 1.5 equiv, 0.30 mmol) and $H_2O$ (0.01 mL) was then added and the reaction mixture was allowed to reach room temperature. After stirring for 27 h, $H_2O$ (0.5 mL) was added and the reaction mixture was extracted

with $Et_2O$ (3 x 1 mL). The combined organic phases were washed with brine (1 mL), dried over $MgSO_4$ and concentrated under reduced pressure.

The crude was then dissolved in anhydrous $CH_2Cl_2$ (0.8 mL), $Et_3N$ (0.04 mL, 1.5 equiv, 0.30 mmol) was then added dropwise to this solution, followed by $Boc_2O$ (0.06 mL, 1.3 equiv, 0.26 mmol). The reaction mixture was stirred for 1.5 h at room temperature. $CH_2Cl_2$ (5 mL) was then added to the reaction mixture and the latter was washed successively with $H_2O$ (2 x 3 mL), 10% citric $acid_{aq.}$ solution (2 x 3 mL), saturated $NaHCO_{3aq.}$ solution (2 x 3 mL) and brine (3 mL). The organic phase was separated and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the crude product was purified by silica gel column chromatography (EP/AcOEt = 80:20) giving the product **62** (17 mg, 21%) as a white solid.

**(±)-*Tert*-butyl ((1-benzyl-4-pentafluorosulfanylpyrrolidin-3-yl)methyl)carbamate 62**




**$C_{17}H_{25}F_5N_2O_2S$**
**M = 416.45 g/mol**

**Rf** = 0.11 (EP/AcOEt = 90:10)

**IR ($cm^{-1}$)**: 3387, 2975, 2807, 1691, 1517, 1368, 1271, 1250, 1168.

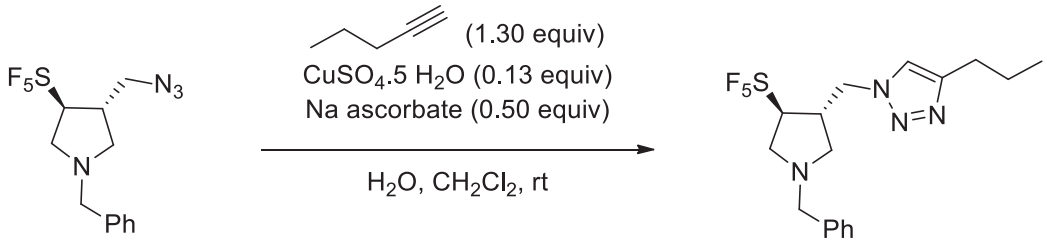
**HRMS ($ESI^+$)**: calcd for $C_{17}H_{26}F_5N_2O_2S$ (*m/z*) 417.1631 $[M+H]^+$, found 417.1635.

**$^{19}F$ NMR ($CDCl_3/CFCl_3$, 282 MHz)**: δ 59.2 (dm, 4F, $^2J_{F,F}$ = 143.9 Hz), 85.8 (m, 1F).

**$^1H$ NMR ($CDCl_3$, 300 MHz)**: δ 1.46 (s, 9H, $C(C\underline{H}_3)_3$), 2.5-2.6 (m, 1H, $C\underline{H}_AH_BCHCH_2NH$-Boc), 2.6-2.8 (m, 1H, $CH_A\underline{H}_BCHCH_2NHBoc$), 2.83 (m, 1H, $C\underline{H}_AH_BCHSF_5$), 3.0 (m, 1H, $C\underline{H}CH_2NHBoc$), 3.2-3.4 (m, 3H, $CH_A\underline{H}_BCHSF_5$ + $CHC\underline{H}_2NHBoc$), 3.58 (d, 1H, $^2J_{H,H}$ = 12.7 Hz, $NC\underline{H}_AH_BPh$), 3.68 (d, 1H, $^2J_{H,H}$ = 12.7 Hz, $NCH_A\underline{H}_BPh$), 4.26 (m, 1H, $C\underline{H}SF_5$), 5.14 (br s, 1H, $N\underline{H}Boc$), 7.3-7.4 (m, 5H, Ph).

**$^{13}$C NMR ($CDCl_3$, 75 MHz)**: δ 28.4 (s, 3 x $\underline{C}H_3$ Boc), 41.6 (m, $\underline{C}HCH_2NHBoc$), 44.1 (s, $CH\underline{C}H_2NHBoc$), 56.3 (s, $\underline{C}H_2CHCH_2NHBoc$), 57.3 (m, $\underline{C}H_2CHSF_5$), 59.4 (s, $N\underline{C}H_2Ph$), 79.5 (s, $\underline{C}_q$ Boc), 85.5 (m, $\underline{C}HSF_5$), 127.5 (s, $\underline{C}H$ Ph), 128.5 (s, 2 x $\underline{C}H$ Ph), 128.6 (s, 2 x $\underline{C}H$ Ph), 137.5 (s, $\underline{C}_q$ Ph), 156.2 (s, $\underline{C}$=O).

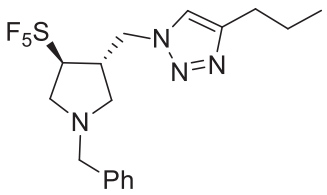
### 3.2.3.7. « Click » reaction of $SF_5$-pyrrolidinyl azide 60




**60** **64**

To the solution of azide **60** (70 mg, 1.00 equiv, 0.21 mmol) in $CH_2Cl_2$ (0.5 mL), pent-1-yne (26 µL, 1.30 equiv, 0.27 mmol) was added, followed by $H_2O$ (0.4 mL), $CuSO_4.5\,H_2O$ (7 mg, 0.13 equiv, 0.03 mmol) and Na ascorbate (19 mg, 0.50 equiv, 0.10 mmol). The reaction mixture was stirred for 24 h at room temperature. The phases were then separated and the organic phase was dried over $MgSO_4$. The solvent was removed and the crude product was purified by silica gel column chromatography (EP/$Et_2O$ = 30:70) giving product **64** (44 mg, 53%) as a yellow solid.

**(±)-1-((1-Benzyl-4-pentafluorosulfanylpyrrolidin-3-yl)methyl)-4-(*n*-propyl)-1*H*-1,2,3-triazole 64**




**$C_{17}H_{23}F_5N_4S$**
**M = 410.45 g/mol**

**Rf** = 0.28 (EP/$Et_2O$ = 30:70)

**IR ($cm^{-1}$)**: 2962, 2928, 2847, 2800, 1456, 1378.

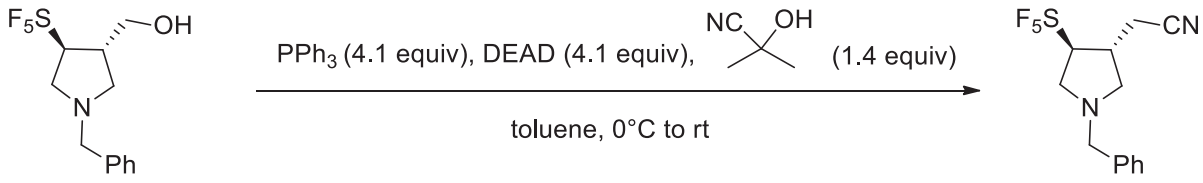
**HRMS ($ESI^+$)**: calcd for $C_{17}H_{24}F_5N_4S$ (*m/z*) 411.1642 $[M+H]^+$, found 411.1638.

**$^{19}F$ NMR ($CDCl_3/CFCl_3$, 282 MHz)**: δ 59.4 (dd, 4F, $^2J_{F,F}$ = 144.8 Hz, $^3J_{F,H}$ = 6.1 Hz), 85.1 (m, 1F).

**$^1H$ NMR ($CDCl_3$, 300 MHz)**: δ 1.03 (t, 3H, $^3J_{H,H}$ = 7.3 Hz, $CH_2CH_2C\underline{H}_3$), 1.76 (m, 2H, $CH_2C\underline{H}_2CH_3$), 2.62 (m, 1H, $C\underline{H}_AH_BCHCH_2$N-triazole), 2.7-2.8 (m, 3H, $C\underline{H}_2CH_2CH_3$ + $CH_A\underline{H}_BCHCH_2$N-triazole), 2.90 (m, 1H, $C\underline{H}_AH_BCHSF_5$), 3.2-3.3 (m, 2H, $CH_A\underline{H}_BCHSF_5$ + $C\underline{H}CH_2$N-triazole), 3.65 (s, 2H, $NC\underline{H}_2$Ph), 4.34 (m, 1H, $C\underline{H}SF_5$), 4.5-4.6 (m, 2H, $CHC\underline{H}_2$N-triazole), 7.3-7.4 (m, 6H, Ph + 1H-triazole).

**$^{13}C$ NMR ($CDCl_3$, 75 MHz)**: δ 13.7 (s, $CH_2CH_2\underline{C}H_3$), 22.6 (s, $CH_2\underline{C}H_2CH_3$), 27.6 (s, $\underline{C}H_2CH_2CH_3$), 42.7 ($q_t$, $^3J_{C,F}$ = 3.0 Hz, $\underline{C}HCH_2$N-triazole), 52.4 (s, $CH\underline{C}H_2$N-triazole), 55.9 (s, $\underline{C}H_2CHCH_2$N-triazole), 56.9 ($q_t$, $^3J_{C,F}$ = 5.0 Hz, $\underline{C}H_2CHSF_5$), 59.1 (s, $N\underline{C}H_2$Ph), 84.9 ($q_t$, $^2J_{C,F}$ = 10.5 Hz, $\underline{C}HSF_5$), 121.1 (s, $\underline{C}$H triazole), 127.5 (s, $\underline{C}$H Ph), 128.45 (s, 2 x $\underline{C}$H Ph), 128.51 (s, 2 x C$\underline{H}$ Ph), 137.5 (s, $\underline{C}_q$ Ph), 148.6 (s, $\underline{C}_q$ triazole).

### 3.2.3.8. Synthesis of $SF_5$-pyrrolidinyl nitrile 65

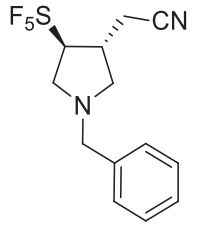



**55** **65**

Alcohol **55** (105 mg, 1.0 equiv, 0.33 mmol) was dissolved in anhydrous toluene (2 mL) and this solution was cooled to 0°C. $PPh_3$ (353 mg, 4.1 equiv, 1.35 mmol) was then added portionwise and the mixture was stirred for 10 min. at 0°C. DEAD (0.21 mL, 4.1 equiv, 1.35 mmol) was added dropwise and the orange-colored reaction mixture was stirred for 20 min., then acetone cyanhydrin (0.04 mL, 1.4 equiv, 0.47 mmol) was added dropwise. The reaction mixture was allowed to reach room temperature and it was stirred for 19 h. The reaction

mixture was poured into $Et_2O$/pentane (1:1, 26 mL) mixture. The precipitate was removed by filtration and the filtrate was concentrated under reduced pressure. Crude product was purified by silica gel column chromatography (EP/AcOEt = 85:15) giving the desired product **65** (68 mg, 63%) as a colourless oil.

**(±)-1-Benzyl-3-(cyanomethyl)-4-pentafluorosulfanylpyrrolidine 65**




**$C_{13}H_{15}F_5N_2S$**
**M = 326.33 g/mol**

**Rf** = 0.17 (EP/$Et_2O$ = 90:10)

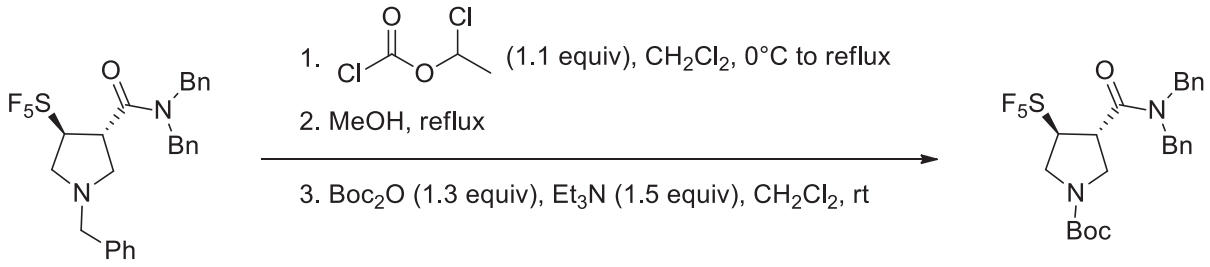
**HRMS (ESI$^+$)**: calcd for $C_{13}H_{16}F_5N_2S$ (*m/z*) 327.0955 $[M+H]^+$, found 327.0954.

**$^{19}$F NMR ($CDCl_3$/$CFCl_3$, 282 MHz)**: δ 59.6 (dd, 4F, $^2J_{F,F}$ = 143.9 Hz, $^3J_{F,H}$ = 5.2 Hz), 84.7 (m, 1F).

**$^1$H NMR ($CDCl_3$, 300 MHz)**: δ 2.56-2.81 (m, 4H, C$\underline{H}_2$CHC$H_2$CN + $CH_2$CHC$\underline{H}_2$CN), 2.95 (m, 1H, C$\underline{H}_A$$H_B$CH$SF_5$), 3.11 (m, 1H, C$\underline{H}$$CH_2$CN), 3.23 (m, 1H, $CH_A\underline{H}_B$CH$SF_5$), 3.61 (d, 1H, $^2J_{H,H}$ = 13.0 Hz, NC$\underline{H}_A$$H_B$Ph), 3.62 (d, 1H, $^2J_{H,H}$ = 13.0 Hz, N$CH_A\underline{H}_B$Ph), 4.15 (m, 1H, C$\underline{H}SF_5$), 7.3-7.4 (m, 5H, Ph).

**$^{13}$C NMR ($CDCl_3$, 75 MHz)**: δ 22.0 (s, CHC$\underline{H}_2$CN), 38.5 ($q_t$, $^3J_{C,F}$ = 3.3 Hz, $\underline{C}$HC$H_2$CN), 57.1 ($q_t$, $^3J_{C,F}$ = 5.0 Hz, $\underline{C}H_2$CH$SF_5$), 57.2 (s, $\underline{C}H_2$CHC$H_2$CN), 59.1 (s, N$\underline{C}H_2$Ph), 86.7 ($q_t$, $^2J_{C,F}$ = 11.0 Hz, $\underline{C}HSF_5$), 117.5 (s, $\underline{C}$N), 127.5 (s, $\underline{C}$H Ph), 128.5 (s, 4 x $\underline{C}$H Ph), 137.4 (s, $\underline{C}_q$ Ph).

### 3.2.3.9. Synthesis of $SF_5$ N-Boc protected pyrrolidine 70

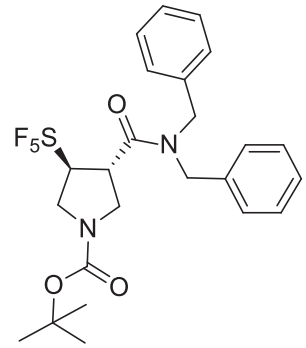



**43a** **70**

Pyrrolidine **43a** (110 mg, 1.0 equiv, 0.22 mmol) was dissolved in anhydrous $CH_2Cl_2$ (0.5 mL) and this solution was cooled to 0°C. 1-Chloroethyl chloroformate (26 µL, 1.1 equiv, 0.24 mmol) was added dropwise and the reaction mixture was then stirred at reflux for 3 h. After cooling to room temperature, the solvent was removed under reduced pressure and the remaining oil was then dissolved in anhydrous MeOH (1 mL). The reaction mixture was stirred at reflux for 2.5 h. Then, the reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure.

The crude product was dissolved in anhydrous $CH_2Cl_2$ (0.5 mL) and $Et_3N$ (50 µL, 1.5 equiv, 0.33 mmol) was added dropwise to this solution, followed by $Boc_2O$ (60 µL, 1.3 equiv, 0.29 mmol). After stirring the reaction mixture for 3 h at room temperature, $CH_2Cl_2$ (4 mL) was added and this solution was washed with $H_2O$ (2 x 2 mL), 10% citric $acid_{aq.}$ solution (2 x 2 mL), saturated $NaHCO_{3aq.}$ solution (3 x 2 mL) and brine (2 mL). The organic phase was separated, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was then purified by silica gel column chromatography (EP/$Et_2O$ = 70:30) giving the product **70** (25 mg, 24%) as a white solid.

**(±)-*Tert*-butyl 3-(*N*,*N*-dibenzylcarbamoyl)-4-pentafluorosulfanylpyrrolidine-1-carboxylate 70**




**$C_{24}H_{29}F_5N_2O_3S$**
**M = 520.56 g/mol**

**Rf** = 0.35 (EP/$Et_2O$ = 70 :30)

**IR ($cm^{-1}$)**: 2921, 2854, 1689, 1654, 1455, 1364, 1398.

**HRMS ($ESI^+$)**: calcd for $C_{24}H_{29}F_5N_2O_3SNa$ (*m/z*) 543.1720 $[M+Na]^+$, found 543.1717.

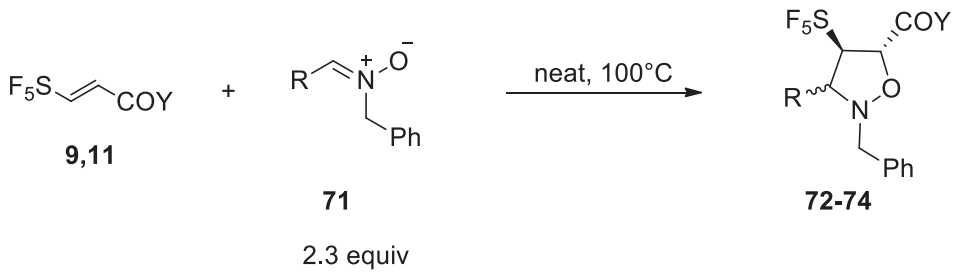
**$^{19}F$ NMR ($CDCl_3/CFCl_3$, 282 MHz)**: δ 59.6 (dm, 4F, $^2J_{F,F}$ = 143.9 Hz), 83.8 (m, 1F).

**$^1H$ NMR ($CDCl_3$, 300 MHz)**: δ 1.58 (s, 9H, $C(C\underline{H}_3)_3$), 3.2-3.6 (m, 1H, $C\underline{H}_AH_BCHSF_5$), 3.7-4.1 (m, 3H, $CH_A\underline{H}_BCHSF_5$ + $C\underline{H}_AH_BCHCON$ + $CH_AH_BC\underline{H}CON$), 4.1-4.3 (m, 1H, $CH_A\underline{H}_BCHCON$), 4.5-5.2 (m, 4H, $N(C\underline{H}_2Ph)_2$), 5.42 (m, 1H, $C\underline{H}SF_5$), 7.2-7.6 (m, 10H, 2 x Ph).

**$^{13}C$ NMR ($CDCl_3$, 75 MHz)**: δ 28.3 (s, 3 x $\underline{C}H_3$ Boc), 43.8 (m, $\underline{C}HCONBn_2$), 48.5 (s, $\underline{C}H_2CHCONBn_2$), 48.9 (s, $CON\underline{C}H_2Ph$), 49.9 (s, $CON\underline{C}H_2Ph$), 50.1 (m, $\underline{C}H_2CHSF_5$), 80.7 (s, $\underline{C}_q$ Boc), 82.6 (m, $\underline{C}HSF_5$), 126.3 (s, 2 x $\underline{C}H$ Ph), 127.8 (s, $\underline{C}H$ Ph), 128.1 (s, $\underline{C}H$ Ph), 128.2 (s, 2 x $\underline{C}H$ Ph), 128.8 (s, 2 x $\underline{C}H$ Ph), 129.2 (s, 2 x $\underline{C}H$ Ph), 135.6 (s, $\underline{C}_q$ Ph), 136.5 (s, $\underline{C}_q$ Ph), 153.3 (s, $\underline{C}$=O Boc), 170.1 (s, $\underline{C}$=O amide).

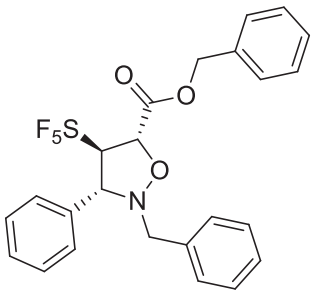
## 3.4. Pentafluorosulfanylated isoxazolidines

### 3.4.1. General procedure for the synthesis of isoxazolidines 72-74




Ester **9** or amide **11** (1.0 equiv, 0.18 mmol) and nitrone **71** (2.3 equiv, 0.42 mmol) were stirred without solvent in a sealed tube at 100°C. The reaction was followed by $^{19}F$ NMR. After completion, the reaction mixture was cooled to room temperature and the crude was directly purified by silica gel column chromatography leading to isoxazolidines **72-74**.

**(±)-2-Benzyl-5-(benzyloxycarbonyl)-4-pentafluorosulfanyl-3-phenylisoxazolidine 72a**




**$C_{24}H_{22}F_5NO_3S$**
**M = 499.49 g/mol**

The title compound was prepared according to the general procedure. The resulting crude product was purified by silica gel column chromatography (PE/AcOEt = 97:3) to afford **72a** in 13% yield (conversion: ~50%) as one diastereoisomer (colourless oil).

**Rf** = 0.37 (PE/AcOEt = 96:4)

**IR ($cm^{-1}$)**: 3034, 2923, 2854, 1735, 1456, 1262, 1211.

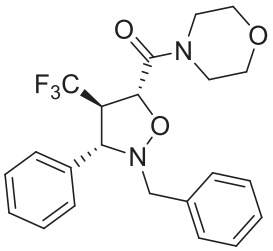
**HRMS ($ESI^+$)**: calcd for $C_{24}H_{23}F_5NO_3S$ (*m/z*) 500.1321 $[M+H]^+$, found 500.1319.

**$^{19}$F NMR ($CDCl_3/CFCl_3$, 282 MHz)**: δ 62.0 (dd, 4F, $^2J_{F,F}$ = 147.4 Hz, $^3J_{F,H}$ = 5.2 Hz), 83.8 (m, 1F).

**$^1$H NMR ($CDCl_3$, 300 MHz)**: δ 3.74 (d, 1H, $^2J_{H,H}$ = 14.9 Hz, NC$\underline{H}_A$H$_B$), 3.90 (d, 1H, $^2J_{H,H}$ = 14.9 Hz, NCH$_A\underline{H}_B$), 4.25 (d, 1H, $^3J_{H,H}$ = 8.2 Hz, C$\underline{H}$Ph), 5.15 (d, 1H, $^3J_{H,H}$ = 3.2 Hz, C$\underline{H}$COOBn), 5.25 (d, 1H, $^2J_{H,H}$ = 12.2 Hz, COOC$\underline{H}_A$H$_B$Ph), 5.30 (d, 1H, $^2J_{H,H}$ = 12.2 Hz, COOCH$_A\underline{H}_B$Ph), 5.44 (m, 1H, C$\underline{H}$SF$_5$), 7.2-7.4 (m, 15H, 3 x Ph).

**$^{13}$C NMR ($CDCl_3$, 75 MHz)**: δ 58.6 (s, N$\underline{C}$H$_2$Ph), 68.0 (s, COO$\underline{C}$H$_2$Ph), 74.2 (q$_t$, $^3J_{C,F}$ = 3.8 Hz, $\underline{C}$HPh), 78.3 (q$_t$, $^3J_{C,F}$ = 5.3 Hz, $\underline{C}$HCOOBn), 95.0 (q$_t$, $^2J_{C,F}$ = 10.1 Hz, $\underline{C}$HSF$_5$), 127.3 (s, $\underline{C}$H Ph), 128.1 (s, 2 x $\underline{C}$H Ph), 128.25 (s, 2 x $\underline{C}$H Ph), 128.31 (s, 2 x $\underline{C}$H Ph), 128.5 (s, $\underline{C}$H Ph), 128.60 (s, 2 x $\underline{C}$H Ph), 128.62 (s, 2 x $\underline{C}$H Ph), 129.0 (s, 2 x $\underline{C}$H Ph), 129.2 (s, $\underline{C}$H Ph), 134.5 (s, $\underline{C}_q$ Ph), 135.0 (s, $\underline{C}_q$ Ph), 136.2 (s, $\underline{C}_q$ Ph), 169.7 (s, $\underline{C}$=O).

**(±)-*N*-Morpholino-2-benzyl-4-pentafluorosulfanyl-3-phenylisoxazolidin-5-ylcarboxamide 72b**




**$C_{21}H_{23}F_5N_2O_3S$**
**M = 478.48 g/mol**

The title compound was prepared according to the general procedure. The resulting crude product was purified by silica gel column chromatography (PE/AcOEt = 86:14) to afford **72b** in 16% yield (conversion: ~50%) as one diastereoisomer (colourless oil).

**Rf** = 0.14 (PE/AcOEt = 88:12)

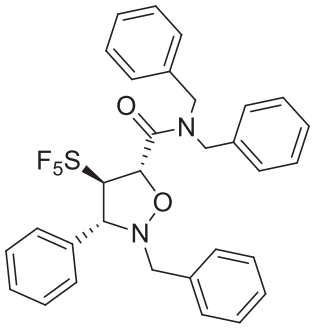
**IR (cm$^{-1}$)**: 2925, 2861, 1647, 1456, 1234.

**$^{19}$F NMR ($CDCl_3/CFCl_3$, 282 MHz)**: δ 62.4 (dd, 4F, $^2J_{F,F}$ = 146.5 Hz, $^3J_{F,H}$ = 6.1 Hz), 85.0 (m, 1F).

**$^1$H NMR ($CDCl_3$, 300 MHz)**: δ 2.61-2.69 (m, 1H, C$\underline{H}_A$H$_{Bmorpholino}$), 3.24-3.51 (m, 5H, CH$_A\underline{H}_{Bmorpholino}$ + 2 x C$\underline{H}_{2morpholino}$), 3.62 (d, 1H, $^2J_{H,H}$ = 14.2 Hz, NC$\underline{H}_A$H$_B$Ph), 3.74-3.79 (dm, 1H, $^2J_{H,H}$ = 12.5 Hz, C$\underline{H}_A$H$_{Bmorpholino}$), 3.89 (d, 1H, $^2J_{H,H}$ = 14.2 Hz, NCH$_A\underline{H}_B$Ph), 3.98 (dm, 1H, $^2J_{H,H}$ = 12.5 Hz, CH$_A\underline{H}_{Bmorpholino}$), 4.31 (d, 1H, $^3J_{H,H}$ = 8.3 Hz, C$\underline{H}$Ph), 5.22 (d, 1H, $^3J_{H,H}$ = 3.0 Hz, C$\underline{H}$COmorpholino), 6.25 (m, 1H, C$\underline{H}SF_5$), 7.3-7.7 (m, 10H, 2 x Ph).

**$^{13}$C NMR ($CDCl_3$, 75 MHz)**: δ 43.4 (s, N$\underline{C}$H$_{2morpholino}$), 46.3 (s, N$\underline{C}$H$_{2morpholino}$), 58.8 (s, N$\underline{C}$H$_2$Ph), 65.9 (s, O$\underline{C}$H$_{2morpholino}$), 66.5 (s, O$\underline{C}$H$_{2morpholino}$), 74.9 (q$_t$, $^3J_{C,F}$ = 3.0 Hz, $\underline{C}$HPh), 77.4 (q$_t$, $^3J_{C,F}$ = 4.8 Hz, $\underline{C}$HCOmorpholino), 93.6 (q$_t$, $^2J_{C,F}$ = 9.6 Hz, $\underline{C}$HSF$_5$), 127.6 (s, $\underline{C}$H Ph), 128.2 (s, 2 x $\underline{C}$H Ph), 128.6 (s, 2 x $\underline{C}$H Ph), 128.9 (s, 2 x $\underline{C}$H Ph), 129.0 (s, 2 x $\underline{C}$H Ph), 129.2 (s, $\underline{C}$H Ph), 134.7 (s, $\underline{C}_q$ Ph), 137.7 (s, $\underline{C}_q$ Ph), 166.1 (s, $\underline{C}$=O).

**(±)-*N*,*N*-Dibenzyl-2-benzyl-4-pentafluorosulfanyl-3-phenylisoxazolidin-5-ylcarboxamide 72c**




**$C_{31}H_{29}F_5N_2O_2S$**
**M = 588.63 g/mol**

The title compound was prepared according to the general procedure. The resulting crude product was purified by silica gel column chromatography (PE/AcOEt = 96:4) to afford **72c** in 24% yield (conversion: ~50%) as one diastereoisomer (colourless oil).

**Rf** = 0.32 (PE/AcOEt = 94:6)

**IR (cm$^{-1}$)**: 3013, 1646, 1495, 1439, 1210.

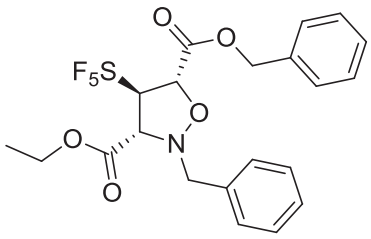
**HRMS (ESI$^+$)**: calcd for $C_{31}H_{30}F_5N_2O_2S$ (*m/z*) 589.1948 $[M+H]^+$, found 589.1946.

**$^{19}$F NMR ($CDCl_3/CFCl_3$, 282 MHz)**: δ 62.5 (dd, 4F, $^2J_{F,F}$ = 146.6 Hz, $^3J_{F,H}$ = 6.1 Hz), 84.9 (m, 1F).

**$^1$H NMR ($CDCl_3$, 300 MHz)**: δ 3.75 (d, 1H, $^2J_{H,H}$ = 14.5 Hz, NC$\underline{H}_A$H$_B$Ph), 3.99 (d, 1H, $^2J_{H,H}$ = 14.5 Hz, NCH$_A\underline{H}_B$Ph), 4.18 (d, 2H, $^2J_{H,H}$ = 15.8 Hz, CONC$\underline{H}_2$Ph), 4.36 (d, 1H, $^3J_{H,H}$ = 8.4 Hz, C$\underline{H}$Ph), 4.84 (d, 1H, $^2J_{H,H}$ = 16.0 Hz, CONC$\underline{H}_A$H$_B$Ph), 5.22 (d, 1H, $^2J_{H,H}$ = 16.0 Hz, CONCH$_A\underline{H}_B$), 5.38 (d, 1H, $^3J_{H,H}$ = 3.3 Hz, C$\underline{H}$CONBn$_2$), 6.41 (m, 1H, C$\underline{H}$SF$_5$), 7.10-7.12 (m, 2H, Ph), 7.20-7.23 (m, 2H, Ph), 7.2-7.3 (m, 5H, Ph), 7.3-7.5 (m, 6H, Ph), 7.5-7.6 (m, 3H, Ph), 7.6-7.7 (m, 2H, Ph).

**$^{13}$C NMR ($CDCl_3$, 75 MHz)**: δ 49.0 (s, CON$\underline{C}$H$_2$Ph), 49.6 (s, CON$\underline{C}$H$_2$Ph), 59.1 (s, N$\underline{C}$H$_2$Ph), 74.7 (q$_t$, $^3J_{C,F}$ = 3.0 Hz, $\underline{C}$HPh), 77.6 (q$_t$, $^3J_{C,F}$ = 5.2 Hz, $\underline{C}$HCONBn), 94.0 (q$_t$, $^2J_{C,F}$ = 9.6 Hz, $\underline{C}$HSF$_5$), 126.8 (s, 2 x $\underline{C}$H Ph), 127.3 (s, $\underline{C}$H Ph), 127.4 (s, $\underline{C}$H Ph), 127.7 (s, $\underline{C}$H Ph), 128.0 (s, 2 x $\underline{C}$H Ph), 128.2 (s, 2 x $\underline{C}$H Ph), 128.5 (s, 2 x $\underline{C}$H Ph), 128.7 (s, 2 x $\underline{C}$H Ph), 128.96 (s, 2 x $\underline{C}$H Ph), 128.97 (s, 2 x $\underline{C}$H Ph), 128.99 (s, 2 x $\underline{C}$H Ph), 129.1 (s, $\underline{C}$H Ph), 135.0 (s, $\underline{C}_q$ Ph), 136.0 (s, $\underline{C}_q$ Ph), 136.5 (s, $\underline{C}_q$ Ph), 136.6 (s, $\underline{C}_q$ Ph), 167.9 (s, $\underline{C}$=O).

**(±)-2,5-Dibenzyl-3-ethyl-4-pentafluorosulfanylisoxazolidine-3,5-dicarboxylate 73a**




**$C_{21}H_{22}F_5NO_5S$**
**M = 495.46 g/mol**

The title compound was prepared according to the general procedure. The resulting crude product was purified by silica gel column chromatography (PE/AcOEt = 94:6) to afford **73a** in 15% yield (conversion: ~80%). Two diastereoisomers were initially present in reaction crude (67:33) but only one diastereoisomer was isolated as a white solid.

**Rf** = 0.25 (PE/AcOEt = 90:10)

**IR (cm$^{-1}$)**: 2918, 2850, 1739, 1726, 1456, 1271, 1225.

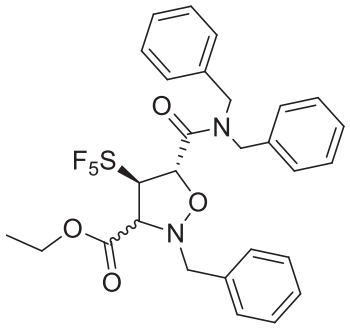
**HRMS (ESI$^+$)**: calcd for $C_{21}H_{23}F_5NO_5S$ (*m/z*) 496.1217 $[M+H]^+$, found 496.1218.

**$^{19}$F NMR ($CDCl_3/CFCl_3$, 282 MHz)**: δ 61.4 (dd, 4F, $^2J_{F,F}$ = 147.4 Hz, $^3J_{F,H}$ = 5.2 Hz), 82.6 (m, 1F).

**$^1$H NMR ($CDCl_3$, 300 MHz)**: δ 1.29 (t, 3H, $^3J_{H,H}$ = 7.1 Hz, $COOCH_2C\underline{H}_3$), 4.05 (d, 1H, $^3J_{H,H}$ = 7.8 Hz, C<u>H</u>COOEt), 4.11 (d, 1H, $^2J_{H,H}$ = 14.5 Hz, $NC\underline{H}_AH_BPh$), 4.22 (q, 2H, $^3J_{H,H}$ = 7.1 Hz, $COOC\underline{H}_2CH_3$), 4.39 (d, 1H, $^2J_{H,H}$ = 14.5 Hz, $NCH_A\underline{H}_BPh$), 5.08 (d, 1H, $^3J_{H,H}$ = 4.0 Hz, C<u>H</u>COOBn), 5.23 (d, 1H, $^2J_{H,H}$ = 12.3 Hz, $COOC\underline{H}_AH_BPh$), 5.29 (d, 1H, $^2J_{H,H}$ = 12.3 Hz, $COOCH_A\underline{H}_BPh$), 5.75 (m, 1H, C<u>H</u>$SF_5$), 7.3-7.4 (m, 10H, 2 x Ph).

**$^{13}$C NMR ($CDCl_3$, 75 MHz)**: δ 13.9 (s, $COOCH_2\underline{C}H_3$), 60.9 (s, $N\underline{C}H_2Ph$), 62.7 (s, $COO\underline{C}H_2CH_3$), 68.0 (s, $COO\underline{C}H_2Ph$), 71.0 ($q_t$, $^3J_{C,F}$ = 4.1 Hz, <u>C</u>HCOOEt), 77.6 ($q_t$, $^3J_{C,F}$ = 4.6 Hz, <u>C</u>HCOOBn), 89.3 ($q_t$, $^2J_{C,F}$ = 12.6 Hz, <u>C</u>H$SF_5$), 127.7 (s, <u>C</u>H Ph), 128.1 (s, 2 x <u>C</u>H Ph), 128.3 (s, 2 x <u>C</u>H Ph), 128.4 (s, <u>C</u>H Ph), 128.6 (s, 2 x <u>C</u>H Ph), 128.8 (s, 2 x <u>C</u>H Ph), 134.8 (s, $\underline{C}_q$ Ph), 135.1 (s, $\underline{C}_q$ Ph), 166.1 (s, <u>C</u>=O), 168.5 (s, <u>C</u>=O).

**<u>(±)-*N*,*N*-Dibenzyl-2-benzyl-3-(ethoxycarbonyl)-4-pentafluorosulfanylisoxazolidinyl-5-carboxamide 73b</u>**




**$C_{28}H_{29}F_5N_2O_4S$**
**M = 584.60 g/mol**

The title compound was prepared according to the general procedure. The resulting crude product was purified by silica gel column chromatography (PE/AcOEt = 95:5) to afford product **73b** as a mixture of two diastereoisomers (57:43) in 50% overall yield (conversion: 91%) (white solid).

**Rf** = 0.51 (PE/AcOEt = 86:14)

**IR ($cm^{-1}$)**: 2936, 1739, 1651, 1451, 1207.

**HRMS ($ESI^+$)**: calcd for $C_{28}H_{30}F_5N_2O_4S$ (*m/z*) 585.1846 $[M+H]^+$, found 585.1854.

*Selected data for diastereoisomer n°1*:

**$^{19}F$ NMR ($CDCl_3/CFCl_3$, 282 MHz)**: δ 62.2 (dd, 4F, $^2J_{F,F}$ = 146.5 Hz, $^3J_{F,H}$ = 6.1 Hz), 83.7 (m, 1F).

**$^1H$ NMR ($CDCl_3$, 300 MHz)**: δ 1.33 (t, 3H, $^3J_{H,H}$ = 7.1 Hz, $COOCH_2C\underline{H}_3$), 4.04 (d, 1H, $^2J_{H,H}$ = 13.7 Hz, $NC\underline{H}_AH_BPh$), 4.16 (d, 1H, $^3J_{H,H}$ = 7.2 Hz, $C\underline{H}COOCH_2CH_3$), 4.29 (d, 1H, $^2J_{H,H}$ = 13.7 Hz, $NCH_A\underline{H}_BPh$), 4.59 (d, 1H, $^2J_{H,H}$ = 16.8 Hz, $CONC\underline{H}_AH_B{}^1$), 4.94 (d, 1H, $^2J_{H,H}$ = 14.9 Hz, $CONC\underline{H}_AH_B{}^2$), 5.26 (d, 1H, $^3J_{H,H}$ = 5.3 Hz, $C\underline{H}CONBn_2$), 6.48 (m, 1H, $C\underline{H}SF_5$), 7.0-7.2 (m, 5H, Ph), 7.3-7.5 (m, 10H, 2 x Ph).

**$^{13}C$ NMR ($CDCl_3$, 75 MHz)**: δ 13.9 (s, $COOCH_2\underline{C}H_3$), 48.8 (s, $CON\underline{C}H_2Ph^1$), 49.5 (s, $CON\underline{C}H_2Ph^2$), 60.9 (s, $N\underline{C}H_2Ph$), 62.5 (s, $COOCH_2\underline{C}H_3$), 70.6 ($q_t$, $^3J_{C,F}$ = 3.5 Hz, $\underline{C}HCOOCH_2CH_3$), 77.2 ($q_t$, $^3J_{C,F}$ = 4.6 Hz, $\underline{C}HCON$), 88.0 ($q_t$, $^2J_{C,F}$ = 24.0 Hz, $\underline{C}HSF_5$), 126.7 (s, 2 x $\underline{C}$H Ph), 127.5 (s, $\underline{C}$H Ph), 127.8 (s, 2 x $\underline{C}$H Ph), 128.1 (s, 2 x $\underline{C}$H Ph) , 128.3 (s, 2 x $\underline{C}$H Ph), 128.7 (s, 2 x $\underline{C}$H Ph), 128.9 (s, 2 x $\underline{C}$H Ph), 129.0 (s, 2 x $\underline{C}$H Ph), 135.2 (s, $\underline{C}_q$ Ph), 135.8 (s, $\underline{C}_q$ Ph), 136.3 (s, $\underline{C}_q$ Ph), 166.2 (s, $\underline{C}$=O), 166.6 (s, $\underline{C}$= O).

S*elected data for diastereoisomer n°2*:

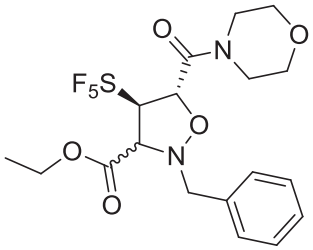
**$^{19}F$ NMR ($CDCl_3/CFCl_3$, 282 MHz)**: δ 68.7 (dm, 4F, $^2J_{F,F}$ = 147.4 Hz), 81.9 (m, 1F).

**$^1H$ NMR ($CDCl_3$, 300 MHz)**: δ 1.27 (t, 3H, $^3J_{H,H}$ = 7.1 Hz, $COOCH_2C\underline{H}_3$), 4.07 (d, 1H, $^2J_{H,H}$ = 14.0 Hz, $NC\underline{H}_AH_BPh$), 4.36 (d, 1H, $^3J_{H,H}$ = 6.5 Hz, $C\underline{H}COOEt$), 4.66 (d, 1H, $^2J_{H,H}$ = 17.4 Hz, $CONC\underline{H}_AH_B{}^1$), 4.92 (d, 1H, $^2J_{H,H}$ = 14.8 Hz, $CONC\underline{H}_AH_B{}^2$), 5.52 (d, 1H, $^3J_{H,H}$ = 7.9 Hz, $C\underline{H}CONBn_2$), 6.1 (m, 1H, $C\underline{H}SF_5$), 7.0-7.2 (m, 5H, Ph), 7.3-7.5 (m, 10H, 2 x Ph).

**$^{13}C$ NMR ($CDCl_3$, 75 MHz)**: δ 13.8 (s, $COOCH_2\underline{C}H_3$), 48.6 (s, $CON\underline{C}H_2Ph^1$), 49.7 (s, $CON\underline{C}H_2Ph^2$), 61.8 (s, 2C, $N\underline{C}H_2Ph$ + $COO\underline{C}H_2CH_3$), 68.1 ($q_t$, $^3J_{C,F}$ = 2.0 Hz, $\underline{C}HCOOCH_2CH_3$), 75.6 (m, $\underline{C}HCON$), 85.6 ($q_t$, $^2J_{C,F}$ = 13.3 Hz, $\underline{C}HSF_5$), 126.9 (s,

2 x CH Ph), 127.6 (s, CH Ph), 127.9 (s, 2 x CH Ph), 128.0 (s, 2 x CH Ph) , 128.6 (s, 2 x CH Ph), 128.8 (s, 2 x CH Ph), 129.0 (s, 2 x CH Ph), 129.1 (s, 2 x CH Ph), 135.4 (s, 2 x $C_q$ Ph), 136.2 (s, $C_q$ Ph), 167.0 (s, C=O), 167.4 (s, C=O).

**(±)-*N*-Morpholino-2-benzyl-3-(ethoxycarbonyl)-4-pentafluorosulfanylisoxazolidin-5-ylcarboxamide 73c**



**$C_{18}H_{23}F_5N_2O_5S$**
**M = 474.44 g/mol**

The title compound was prepared according to the general procedure. The resulting crude product was purified by silica gel column chromatography (PE/AcOEt = 75:25) to afford product **73b** as a mixture of two diastereoisomers (55:45) in 46 % yield (conversion: 86 %) (colourless oil).

**Rf** = 0.16 (PE/AcOEt = 80:20)

**IR ($cm^{-1}$)**: 2925, 1747, 1645, 1444, 1240, 1216.

**HRMS ($ESI^+$)**: calcd for $C_{18}H_{24}F_5N_2O_5S$ (*m/z*) 475.1326 $[M+H]^+$, found 475.1321.

*Selected data for diastereoisomer n°1*:

**$^{19}F$ NMR ($CDCl_3/CFCl_3$, 282 MHz)**: δ 61.7 (dd, 4F, $^2J_{F,F}$ = 146.5 Hz, $^3J_{F,H}$ = 6.1 Hz), 83.8 (m, 1F).

**$^1H$ NMR ($CDCl_3$, 300 MHz)**: δ 1.2-1.4 (m, 3H, $COOCH_2CH_3$), 2.7-4.4 (m, 13H, 4 x $CH_{2morpholino}$ + $CHCOOCH_2CH_3$ + $NCH_2Ph$), 5.09 (d, 1H, $^3J_{H,H}$ = 4.2 Hz, CHCON), 6.40 (m, 1H, $CHSF_5$), 7.32 (m, 5H, Ph).

**$^{13}$C NMR ($CDCl_3$, 75 MHz)**: δ 14.0 (s, $COOCH_2\underline{C}H_3$), 61.9 (s, $N\underline{C}H_2Ph$), 62.6 (s, $COO\underline{C}H_2CH_3$), 71.3 ($q_t$, $^3J_{C,F}$ = 3.9 Hz, $\underline{C}HCOOCH_2CH_3$), 77.1 ($q_t$, $^3J_{C,F}$ = 4.4 Hz, $\underline{C}HCON$), 87.8 ($q_t$, $^2J_{C,F}$ = 11.8 Hz, $\underline{C}HSF_5$), 127.9 (s, $\underline{C}H$ Ph), 128.3 (s, 2 x $\underline{C}H$ Ph), 129.0 (s, 2 x $\underline{C}H$ Ph), 136.0 (s, $\underline{C}_q$ Ph), 164.8 (s, $\underline{C}$=O), 166.2 (s, $\underline{C}$=O).

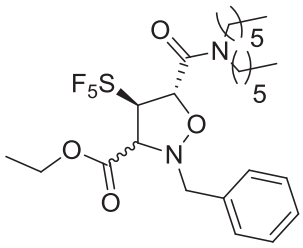
*Selected data for diastereoisomer n°2*:

**$^{19}$F NMR ($CDCl_3/CFCl_3$, 282 MHz)**: δ 68.2 (dm, 4F, $^2J_{F,F}$ = 145.7 Hz), 81.9 (m, 1F).

**$^1$H NMR ($CDCl_3$, 300 MHz)**: δ 1.2-1.4 (m, 3H, $COOCH_2C\underline{H}_3$), 2.7-4.4 (m, 13H, 4 x $C\underline{H}_{2morpholino}$ + $C\underline{H}COOC\underline{H}_2CH_3$ + $NC\underline{H}_2Ph$), 5.31 (d, 1H, $^3J_{H,H}$ = 7.2 Hz, $C\underline{H}CON$), 5.97 (m, 1H, $C\underline{H}SF_5$), 7.32 (m, 5H, Ph).

**$^{13}$C NMR ($CDCl_3$, 75 MHz)**: δ 13.9 (s, $COOCH_2\underline{C}H_3$), 61.0 (s, $N\underline{C}H_2Ph$), 62.6 (s, $COO\underline{C}H_2CH_3$), 67.9 (m, $\underline{C}HCOOCH_2CH_3$), 75.4 (m, $\underline{C}HCON$), 85.3 ($q_t$, $^2J_{C,F}$ = 13.8 Hz, $\underline{C}HSF_5$), 128 (s, $\underline{C}H$ Ph), 128.5 (s, 2 x $\underline{C}H$ Ph), 129.1 (s, 2 x $\underline{C}H$ Ph), 135.2 (s, $C_q$ Ph), 165.3 (s, $\underline{C}$=O), 166.9 (s, $\underline{C}$=O).

**(±)-*N,N*-Dihexyl-2-benzyl-3-(ethoxycarbonyl)-4-pentafluorosulfanylisoxazolidin-5-ylcarboxamide 73d**




**$C_{26}H_{41}F_5N_2O_4S$**
**M = 572.67 g/mol**

The title compound was prepared according to the general procedure. The resulting crude product was purified by silica gel column chromatography (PE/AcOEt = 96:4) to afford product **73d** as a mixture of two diastereoisomers (66:34) in 31% yield (conversion: 80%) (white solid).

**Rf** = 0.23 (PE/AcOEt = 95:5)

**IR ($cm^{-1}$)**: 2936, 1739, 1651, 1451, 1207.

**HRMS ($ESI^+$)**: calcd for $C_{26}H_{42}F_5N_2O_4S$ (*m/z*) 573.2785 $[M+H]^+$, found 573.2797.

*Selected data for diastereoisomer n°1*:

**$^{19}F$ NMR ($CDCl_3/CFCl_3$, 282 MHz)**: δ 62.2 (dd, 4F, $^2J_{F,F}$ = 145.7 Hz, $^3J_{F,H}$ = 5.2 Hz), 83.9 (m, 1F).

**$^1H$ NMR ($CDCl_3$, 300 MHz)**: δ 4.20 (d, 1H, $^2J_{H,H}$ = 14.0 Hz, NC$\underline{H}_A$H$_B$), 5.33 (d, 1H, $^3J_{H,H}$ = 5.6 Hz, C$\underline{H}$CON), 6.50 (m, 1H, C$\underline{H}$SF$_5$), 7.4-7.6 (m, 5H, Ph).

**$^{13}C$ NMR ($CDCl_3$, 75 MHz)**: δ 61.8 (s, N$\underline{C}$H$_2$Ph), 70.3 (q$_t$, $^3J_{C,F}$ = 3.3 Hz, $\underline{C}$HCOOCH$_2$CH$_3$), 77.0 (q$_t$, $^3J_{C,F}$ = 4.6 Hz, $\underline{C}$HCON), 87.9 (q$_t$, $^2J_{C,F}$ = 11.1 Hz, $\underline{C}$HSF$_5$), 127.7 (s, $\underline{C}$H Ph), 128.3 (s, 2 x $\underline{C}$H Ph), 128.8 (s, 2 x $\underline{C}$H Ph), 135.6 (s, $\underline{C}_q$ Ph), 164.8 (s, $\underline{C}$=O), 166.7 (s, $\underline{C}$=O).

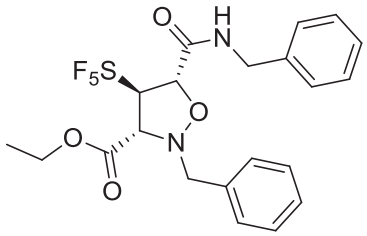
S*elected data for diastereoisomer n°2*:

**$^{19}F$ NMR ($CDCl_3/CFCl_3$, 282 MHz)**: δ 68.5 (dm, 4F, $^2J_{F,F}$ = 147.4 Hz), 82.2 (m, 1F).

**$^1H$ NMR ($CDCl_3$, 300 MHz)**: δ 4.17 (d, 1H, $^2J_{H,H}$ = 13.1 Hz, NC$\underline{H}_A$H$_B$), 5.55 (d, 1H, $^3J_{H,H}$ = 7.9 Hz, C$\underline{H}$CON), 6.04 (m, 1H, C$\underline{H}$SF$_5$), 7.4-7.6 (m, 5H, Ph).

**$^{13}C$ NMR ($CDCl_3$, 75 MHz):** δ 60.5 (s, N$\underline{C}$H$_2$Ph), 67.6 (q$_t$, $^3J_{C,F}$ = 2.6 Hz, $\underline{C}$HCOOCH$_2$CH$_3$), 75.4 (q$_t$, $^3J_{C,F}$ = 4.8 Hz, $\underline{C}$HCON), 85.8 (q$_t$, $^2J_{C,F}$ = 12.6 Hz, $\underline{C}$HSF$_5$), 127.8 (s, $\underline{C}$H Ph), 128.4 (s, 2 x $\underline{C}$H Ph), 129.1 (s, 2 x $\underline{C}$H Ph), 135.4 (s, $\underline{C}_q$ Ph), 166.3 (s, $\underline{C}$=O), 167.1 (s, $\underline{C}$=O).

**(±)-*N*-Benzyl-2-benzyl-3-(ethyloxycarbonyl)-4-pentafluorosulfanylisoxazolidin-5-ylcarboxamide 73e**




**$C_{21}H_{23}F_5N_2O_4S$**
**M = 494.48 g/mol**

The title compound was prepared according to the general procedure. The resulting crude product was purified by silica gel column chromatography (PE/AcOEt = 90:10) to afford product **73e** as one diastereoisomer, slightly contaminated by starting amide **11a**, in 17% yield (calculated from $^{1}$H NMR) (conversion: 50%) (colourless oil).

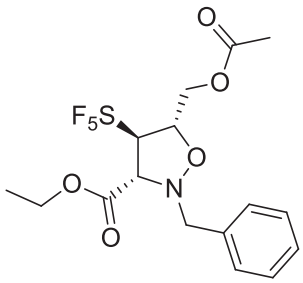
**Rf** = 0.25 (PE/AcOEt = 90:10).

**$^{19}$F NMR ($CDCl_3$/$CFCl_3$, 282 MHz)**: δ 60.6 (dd, 4F, $^{2}J_{F,F}$ = 146.5 Hz, $^{3}J_{F,H}$ = 6.1 Hz, 4F), 82.6 (m, 1F).

**$^{1}$H NMR ($CDCl_3$, 300 MHz)**: δ 1.33 (t, 3H, $^{3}J_{H,H}$ = 7.1 Hz, $COOCH_2C\underline{H}_3$), 3.89 (d, 1H, $^{2}J_{H,H}$ = 13.9 Hz, $NC\underline{H}_AH_BPh$), 4.06 (d, 1H, $^{3}J_{H,H}$ = 7.9 Hz, $C\underline{H}COOCH_2CH_3$), 4.23 (dd, 1H, $^{2}J_{H,H}$ = 14.8 Hz, $^{3}J_{H,H}$ = 5.8 Hz, $CONHC\underline{H}_AH_BPh$), 4.30 (q, 2H, $^{3}J_{H,H}$ = 7.1 Hz, $COOC\underline{H}_2CH_3$), 4.38 (d, 1H, $^{2}J_{H,H}$ = 13.9 Hz, $NCH_A\underline{H}_BPh$), 4.42 (dd, 1H, $^{2}J_{H,H}$ = 14.8 Hz, $^{3}J_{H,H}$ = 5.8 Hz, $CONHCH_A\underline{H}_BPh$), 4.93 (d, 1H, $^{3}J_{H,H}$ = 3.1 Hz, $C\underline{H}CONHBn$), 5.59 (m, 1H, $C\underline{H}SF_5$), 6.39 (m, 1H, $N\underline{H}$), 7.1-7.2 (m, 5H, Ph), 7.3-7.4 (m, 5H, Ph).

**$^{13}$C NMR ($CDCl_3$, 75 MHz)**: δ 14.0 (s, $COOCH_2\underline{C}H_3$), 43.3 (s, $NH\underline{C}H_2Ph$), 61.4 (s, $CONH\underline{C}H_2Ph$), 62.8 (s, $COO\underline{C}H_2CH_3$), 71.5 ($q_t$, $^{3}J_{C,F}$ = 4.0 Hz, $\underline{C}HCOOCH_2CH_3$), 78.4 ($q_t$, $^{3}J_{C,F}$ = 4.0 Hz, $\underline{C}HCONHBn$), 89.9 (m, $\underline{C}HSF_5$), 127.6 (s, $\underline{C}H$ Ph), 127.8 (s, 2 x $\underline{C}H$ Ph), 128.0 (s, $\underline{C}H$ Ph), 128.5 (s, 2 x $\underline{C}H$ Ph), 128.6 (s, 4 x $\underline{C}H$ Ph), 135.5 (s, $\underline{C}_q$ Ph), 137.3 (s, $\underline{C}_q$ Ph), 165.8 (s, $\underline{C}$=O), 168.5 (s, $\underline{C}$=O).

**(±)-[2-Benzyl-3-(ethoxycarbonyl)-4-pentafluorosulfanylisoxazolidin-5-yl)]methyl acetate 73f**




**$C_{16}H_{20}F_5NO_5S$**
**M = 433.39 g/mol**

The title compound was prepared according to the general procedure. The resulting crude product was purified by silica gel column chromatography (PE/AcOEt = 90:10) to afford **73f** in 23% yield (conversion: 50 %) as one diastereoisomer (white solid).

**Rf** = 0.23 (PE/AcOEt = 90:10)

**IR ($cm^{-1}$)**: 3007, 2921, 2868, 1742, 1384, 1232.

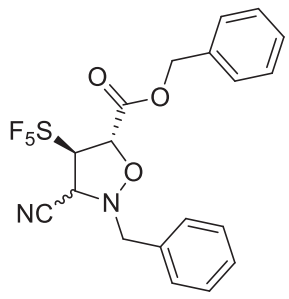
**HRMS ($ESI^+$)**: calcd for $C_{16}H_{21}F_5NO_5S$ (*m/z*) 434.1061 $[M+H]^+$, found 434.1055.

**$^{19}F$ NMR ($CDCl_3/CFCl_3$, 282 MHz)**: δ 62.0 (dd, 4F, $^2J_{F,F}$ = 146.5 Hz, $^3J_{F,H}$ = 6.1 Hz), 83.1 (m, 1F).

**$^1H$ NMR ($CDCl_3$, 300 MHz)**: δ 1.27 (t, 3H, $^3J_{H,H}$ = 7.1 Hz, $COOCH_2C\underline{H}_3$), 2.08 (s, 3H, $C\underline{H}_3COO$), 4.07 (d, 1H, $^3J_{H,H}$ = 7.1 Hz, $C\underline{H}COOCH_2CH_3$), 4.1-4.2 (m, 4H, $COOC\underline{H}_2CH_3$ + $NC\underline{H}_2Ph$), 4.30 (dd, 1H, $^2J_{H,H}$ = 11.8 Hz, $^3J_{H,H}$ = 5.6 Hz, $C\underline{H}_AH_BOAc$), 4.40 (dd, 1H, $^2J_{H,H}$ = 11.8 Hz, $^3J_{H,H}$ = 5.6 Hz, $CH_A\underline{H}_BOAc$), 4.85 (m, 1H, $C\underline{H}CH_2OAc$), 5.09 (m, 1H, $C\underline{H}SF_5$), 7.3-7.5 (m, 5H, Ph).

**$^{13}C$ NMR ($CDCl_3$, 75 MHz)**: δ 13.9 ($COOCH_2\underline{C}H_3$), 20.6 (s, $\underline{C}H_3COO$), 60.6 (s, $N\underline{C}H_2Ph$), 62.53 (s, $COO\underline{C}H_2CH_3$), 62.58 (s, $\underline{C}H_2OAc$), 70.4 ($q_t$, $^3J_{C,F}$ = 3.9 Hz, $\underline{C}HCOOCH_2CH_3$), 76.7 ($q_t$, $^3J_{C,F}$ = 4.2 Hz, $\underline{C}HCH_2OAc$), 88.7 ($q_t$, $^2J_{C,F}$ = 10.9 Hz, $\underline{C}HSF_5$), 127.8 (s, $\underline{C}H$ Ph), 128.4 (s, 2 x $\underline{C}H$ Ph), 128.9 (s, 2 x $\underline{C}H$ Ph), 135.2 (s, $\underline{C}_q$ Ph), 167.1 (s, $\underline{C}$=O), 170.5 (s, $\underline{C}$=O).

**(±)-2-Benzyl-5-(benzyloxycarbonyl)-3-cyano-4-pentafluorosulfanylisoxazolidine 74a**




**$C_{19}H_{17}F_5N_2O_3S$**
**M = 448.41 g/mol**

The title compound was prepared according to the general procedure. The resulting crude product was purified by silica gel column chromatography (PE/AcOEt = 95:5) to afford **74a** in 13% yield (conversion: 85%). Two diastereoisomers were initially present in reaction crude (77:23) but only one diastereoisomer was isolated as a white solid.

**Rf** = 0.28 (PE/AcOEt = 95:5)

**IR ($cm^{-1}$)**: 2925, 2229, 1721, 1499, 1456, 1269.

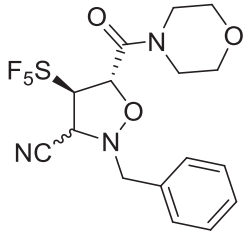
**HRMS ($ESI^+$)**: calcd for $C_{19}H_{18}F_5N_2O_3S$ (*m/z*) 471.0778 $[M+H]^+$, found 471.0772.

**$^{19}F$ NMR ($CDCl_3/CFCl_3$, 282 MHz)**: δ 61.7 (dd, 4F, $^2J_{F,F}$ = 147.4 Hz, $^3J_{F,H}$ = 3.5 Hz), 80.4 (m, 1F).

**$^1H$ NMR ($CDCl_3$, 300 MHz)**: δ 4.06 (d, 1H, $^2J_{H,H}$ = 13.8 Hz, NC$\underline{H}_A$H$_B$Ph), 4.14 (m, 1H, C$\underline{H}$CN), 4.44 (d, 1H, $^2J_{H,H}$ = 13.8 Hz, NCH$_A$$\underline{H}_B$Ph), 5.05 (d, 1H, $^3J_{H,H}$ = 4.5 Hz, C$\underline{H}$COOBn), 5.23 (d, 1H, $^2J_{H,H}$ = 12.3 Hz, COOC$\underline{H}_A$H$_B$Ph), 5.28 (d, 1H, $^2J_{H,H}$ = 12.3 Hz, COOCH$_A$$\underline{H}_B$Ph), 5.39 (m, 1H, C$\underline{H}$SF$_5$), 7.3-7.4 (m, 10H, 2 x Ph).

***Selected* $^{13}C$ NMR ($CDCl_3$, 75 MHz)**: δ 58.0 ($q_t$, $^3J_{C,F}$ = 4.4 Hz, $\underline{C}$HCN), 59.3 (s, N$\underline{C}$H$_2$Ph), 68.5 (COO$\underline{C}$H$_2$Ph), 78.1 ($q_t$, $^3J_{C,F}$ = 4.7 Hz, $\underline{C}$HCOOBn), 88.4 ($q_t$, $^2J_{C,F}$ = 13.5 Hz, $\underline{C}$HSF$_5$), 113.3 (s, $\underline{C}$N), 128.3 (s, 2 x $\underline{C}$H Ph), 128.5 (s, $\underline{C}$H Ph), 128.67 (s, 2 x $\underline{C}$H Ph), 128.72 (s, 3 x $\underline{C}$H Ph), 129.1 (s, 2 x $\underline{C}$H Ph), 133.2 (s, $\underline{C}_q$ Ph), 134.4 (s, $\underline{C}_q$ Ph).

**(±)-N-Morpholino-2-benzyl-3-cyano-4-pentafluorosulfanylisoxazolidin-5-ylcarboxamide 74b**




**$C_{16}H_{18}F_5N_3O_3S$**
**M = 427.39 g/mol**

The title compound was prepared according to the general procedure. The resulting crude product was purified by silica gel column chromatography (PE/AcOEt = 75:25) to afford product **74b** in 20% yield (conversion 55%) as a mixture of two diastereoisomers (75:25) (white solid).

**Rf** = 0.15 (PE/AcOEt = 75:25)

**IR ($cm^{-1}$)**: 2992, 2978, 2921, 2863, 2237, 1644, 1469, 1443, 1237.

**HRMS ($ESI^+$)**: calcd for $C_{16}H_{19}F_5N_3O_3S$ (*m/z*) 428.1067 $[M+H]^+$, found 428.1060.

*Diastereoisomer n°1*:

**$^{19}F$ NMR ($CDCl_3/CFCl_3$, 282 MHz)**: δ 61.9 (dm, 4F, $^2J_{F,F}$ = 147.4 Hz), 81.5 (m, 1F).

**$^1H$ NMR ($CDCl_3$, 300 MHz)**: δ 3.0-3.9 (m, 8H, 4 x $C\underline{H}_{2morpholino}$), 3.94 (d, 1H, $^2J_{H,H}$ = 13.3 Hz, $NC\underline{H}_AH_BPh$), 4.44 (d, 1H, $^2J_{H,H}$ = 13.3 Hz, $NCH_A\underline{H}_BPh$), 4.3-4.5 (m, 1H, C<u>H</u>CN), 5.08 (d, 1H, $^3J_{H,H}$ = 5.2 Hz, C<u>H</u>CON), 6.00 (m, 1H, C<u>H</u>$SF_5$), 7.3-7.5 (m, 5H, Ph).

**$^{13}C$ NMR ($CDCl_3$, 75 MHz)**: δ 43.4 (s, $N\underline{C}H_{2morpholino}$), 46.3 (s, $N\underline{C}H_{2morpholino}$), 58.4 (m, <u>C</u>HCN), 59.3 (s, $N\underline{C}H_2Ph$), 66.5 (s, 4 x $O\underline{C}H_{2morpholino}$), 77.9 ($q_t$, $^3J_{C,F}$ = 4.8 Hz, <u>C</u>HCON), 87.6 (m, <u>C</u>$HSF_5$), 113.5 (s, <u>C</u>N), 128.6 (s, <u>C</u>H Ph), 128.7 (s, 2 x <u>C</u>H Ph), 129.1 (s, 2 x <u>C</u>H Ph), 134.0 (s, $\underline{C}_q$ Ph), 162.6 (s, <u>C</u>=O).

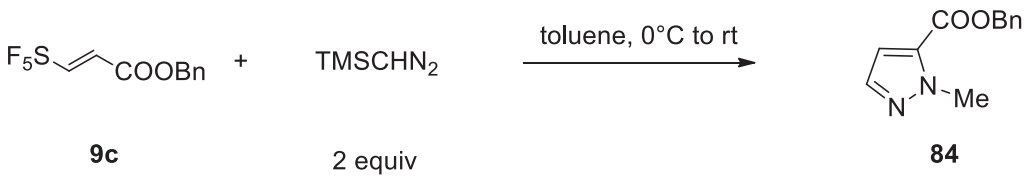
D*iastereoisomer n°2*:

**$^{19}F$ NMR ($CDCl_3/CFCl_3$, 282 MHz)**: δ 66.4 (dm, 4F, $^2J_{F,F}$ = 145.7 Hz), 80.9 (m, 1F).

**$^1H$ NMR ($CDCl_3$, 300 MHz)**: δ 3.0-3.9 (m, 8H, 4 x $C\underline{H}_{2morpholino}$), 4.07 (d, 1H, $^2J_{H,H}$ = 12.9 Hz, $NC\underline{H}_AH_BPh$), 4.24 (d, 1H, $^2J_{H,H}$ = 12.9 Hz, $NCH_A\underline{H}_BPh$), 4.56 (d, 1H, $^3J_{H,H}$ = 6.5 Hz, C<u>H</u>CN), 5.08 (d, 1H, $^3J_{H,H}$ = 5.2 Hz, C<u>H</u>CON), 6.18 (m, 1H, C<u>H</u>$SF_5$), 7.3-7.5 (m, 5H, Ph).

**$^{13}C$ NMR ($CDCl_3$, 75 MHz)**: δ 43.5 (s, $N\underline{C}H_{2morpholino}$), 46.3 (s, $N\underline{C}H_{2morpholino}$), 57.5 (m, <u>C</u>HCN), 59.3 ($N\underline{C}H_2Ph$), 66.3 (s, 4 x $O\underline{C}H_{2morpholino}$), 75.2 (m, <u>C</u>HCON), 84.4 (m, <u>C</u>$HSF_5$), 113.5 (s, <u>C</u>N), 128.6 (s, <u>C</u>H Ph), 128.8 (s, 2 x <u>C</u>H Ph), 129.1 (s, 2 x <u>C</u>H Ph), 133.8 (s, $\underline{C}_q$ Ph), 164.3 (s, <u>C</u>=O).

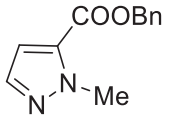
## 3.5. 1,3-Dipolar cycloaddition with TMS-diazomethane




**9c** 2 equiv **84**

Ester **9c** (75 mg, 1 equiv, 0.26 mmol) was dissolved in anhydrous toluene (1.5 mL) and this solution was cooled to 0°C. $TMSCHN_2$ (0.26 mL, 2 equiv, 0.52 mmol, 2 M solution in hexanes) was added dropwise. The reaction mixture was then allowed to reach room temperature and it was stirred for 5 h. Solvents were then removed under reduced pressure and the crude product was purified by silica gel column chromatography (EP/AcOEt = 90:10) giving the non-fluorinated pyrazole **84** (23 mg, 54%) as a colourless oil.

**Benzyl 1-methyl-1*H*-pyrazole-5-carboxylate 84**




**$C_{12}H_{12}N_2O_2$**
**M = 216.24 g/mol**

**Rf** = 0.18 (PE/AcOEt = 95:5)

**MS (ESI$^+$)**: 217 $[M+H]^+$

**$^1$H NMR ($CDCl_3$, 300 MHz)**: δ 4.20 (s, 3H, NC<u>H</u>$_3$), 5.34 (s, 2H, C<u>H</u>$_2$Ph), 6.89 (d, 1H, $^3J_{H,H}$ = 2.0 Hz, C<u>H</u>), 7.3-7.4 (m, 5H, Ph), 7.47 (d, 1H, $^3J_{H,H}$ = 2.0 Hz, C<u>H</u>).

**$^{13}$C NMR ($CDCl_3$, 75 MHz)**: δ 39.6 (s, N<u>C</u>H$_3$), 66.6 (s, COO<u>C</u>H$_2$Ph), 111.5 (s, <u>C</u>H), 128.2 (s, 2 x <u>C</u>H Ph), 128.5 (s, <u>C</u>H Ph), 128.7 (s, 2 x <u>C</u>H Ph), 132.2 (s, <u>C</u>$_q$ Ar), 135.5 (s, <u>C</u>$_q$ Ar), 137.8 (s, <u>C</u>H), 159.7 (s, <u>C</u>=O).

# Annex

# CURRICULUM VITAE


## EWELINA FALKOWSKA

| | |
|---|---|
| Address: | 23 Avenue Jean Rondeaux, 76100 Rouen |
| Mobile: | +33 665 95 98 99 |
| E-mail: | ewelinafalko@gmail.com |
| Date and place of birth: | 30 October 1986, Bytom (Poland) |


## Education:

| | |
|---|---|
| 2012 – 2015 | **PhD in Organic Chemistry**<br>**National Institute for Applied Sciences, Rouen, France** |
| 2005 – 2011 | **Master of Science**<br>**Warsaw University of Technology**, **Poland**<br>Faculty of Chemistry, Division of Technology of Biologically Active Compounds and Cosmetics |
| 2002 – 2005 | **Bilingual High School in Warsaw, Poland** |

## Experience:

| | |
|---|---|
| 10/2012 – 09/2015 | **INSA Rouen, UMR CNRS 6014 (IRCOF)**<br>PhD Student in Organic Chemistry |
| 10/2013 – 06/2015 | **INSA Rouen, STPI department (Science and Technology for Engineers)**<br>Contractual teacher (assistant) for practical work in general chemistry |
| 10/2010 – 06/2011 | **University of Paris-Sud XI**, **Orsay, Laboratory of Bioorganic and Bioinorganic Chemistry**<br>Scholarship of Socrates-Erasmus program<br>Student internship in Organic Chemistry |
| 04/2010 – 06/2010 | **Silliker Polska Sp. z o. o., Warsaw**<br>Student internship in department of physico-chemical analysis |

## Languages:

| | |
|---|---|
| French | fluent |
| English | very good |
| Polish | mother tongue |

## Skills and competences:

| | |
|---|---|
| Scientific | NMR, IR, MS, chromatography |
| Computer | MS Office, ChemDraw, ChemSketch, SciFinder, TopSpin |

# Congresses

**21st International Symposium on Fluorine Chemistry & 6th International Symposium on Fluorous Technologies** (08/2015, Como, Italy)
Oral Communication: Ewelina Falkowska, Philippe Jubault, Jean-Philippe Bouillon, Xavier Pannecoucke, "*Synthesis of New Pentafluorosulfanylated Heterocycles"*

**Journées Nord-Ouest Européennes des Jeunes Chercheurs (North-East European Days of Young Researchers)** (05/2015, Mont-Saint-Aignan, France)

Poster: Ewelina Falkowska, Philippe Jubault, Jean-Philippe Bouillon, Xavier Pannecoucke, "*Synthesis of New Pentafluorosulfanylated Heterocycles*"

**Journées Nord-Ouest Européennes des Jeunes Chercheurs (North-East European Days of Young Researchers)** (06/2014, Villeneuve d'Ascq, France)
Oral Communication: Ewelina Falkowska, Philippe Jubault, Jean-Philippe Bouillon, Xavier Pannecoucke, "*Synthesis of New Pentafluorosulfanylated Building Blocks – Application to the Preparation of New $SF_5$-Substituted Pyrrolidines*" – Prize for the presentation

**Colloque Français de Chimie Fluor (French Seminar on Fluorine Chemistry)** (05/2014, Gif-sur-Yvette, France)
Oral Communication: Ewelina Falkowska, Philippe Jubault, Jean-Philippe Bouillon, Xavier Pannecoucke, *"Synthesis of New Pentafluorosulfanylated Building Blocks for Heterocyclic Chemistry"*

**Ecole d'Automne AICHEM/SYNORG (Autumn School AICHEM/SYNORG)** (10/2013, Merville-Franceville, France)
Oral Communication: Ewelina Falkowska, Philippe Jubault, Jean-Philippe Bouillon, Xavier Pannecoucke, *"Synthesis of New Pentafluorosulfanylated Building Blocks*"

**Journées de Chimie Organique (Days of Organic Chemistry)** (09/2013, Palaiseau, France)
Poster: Ewelina Falkowska, Philippe Jubault, Jean-Philippe Bouillon, Xavier Pannecoucke, *"Development of New Synthetic Methodologies for the Indroduction of Pentafluorosulfanyl Group ($SF_5$) into Carbocycles and Heterocycles*"

**Journées Nord-Ouest Européennes des Jeunes Chercheurs (North-East European Days of Young Researchers)** (06/2013, Le Havre, France)
Poster: Ewelina Falkowska, Philippe Jubault, Jean-Philippe Bouillon, Xavier Pannecoucke, "*Development of New Synthetic Methodologies for the Introduction of Pentafluorosulfanyl Group ($SF_5$) into Carbocycles and Heterocycles*"

# Publications

Ewelina Falkowska, Mathieu Y. Laurent, Vincent Tognetti, Laurent Joubert, Philippe Jubault, Jean-Philippe Bouillon, Xavier Pannecoucke, *Tetrahedron* **2015**, *71*, 8067.
*"Synthesis of $SF_5$-substituted isoxazolidines using 1,3-dipolar cycloaddition reactions of nitrones with pentafluorosulfanyl acrylic esters and amides"*

Ewelina Falkowska, Vincent Tognetti, Laurent Joubert, Philippe Jubault, Jean-Philippe Bouillon, Xavier Pannecoucke, *RSC Advances* **2015**, *5*, 6864.
*"First efficient synthesis of $SF_5$-substituted pyrrolidines using 1,3-dipolar cycloaddition of azomethine ylides with pentafluorosulfanyl-substituted acrylic esters and amides"*

Ewelina Falkowska, Franc Suzenet, Philippe Jubault, Jean-Philippe Bouillon, Xavier Pannecoucke, *Tetrahedron Lett.* **2014**, *55*, 4833.
*"A mild and efficient synthesis of new pentafluorosulfanyl-substituted electron-deficient alkenes and allylsilanes"*

# Trainings (Normandy Chemistry Doctoral School)

**English cursus :** 03-06/2013, 30 h
**Réunion des doctorants à mission d'enseignement :** 11/2013, 3 h
**Groupes d'analyses de situations professionnelles :** 11/2013 and 03/2014, 4 h
**Enseigner et former à l'université :** 01/2014, 3 h
**Structure et fonctionnement de l'université :** 01/2014, 3 h
**Ethique de l'enseignement :** 01/2014, 3 h
**Le système éducatif : un espace en mutation :** 03/2015, 3 h
**Gérer son corps, sa voix, sa communication, pour mieux enseigner :** 04/2015, 3 h
**Enseigner et former à l'université :** 04/2015, 3 h
**Groupes d'analyses de situations professionnelles :** 06/2015, 3 h

Due to its unique properties, the pentafluorosulfanyl ($SF_5$) group has recently reached much attention. This bulky, highly lipophilic and electron-withdrawing substituent is often called as a “super-trifluoromethyl group”. Currently, the $SF_5$-chemistry is becoming a fast growing field of the fluorine chemistry and the new pentafluorosulfanylated building-blocks are under continuous development. Nevertheless, the methods for the introduction of the $SF_5$-group into heterocycles remain still quite limited.

The aim of this thesis was to synthesize new pentafluorosulfanylated building-blocks, on the one hand, and to develop new synthetic approaches leading to original pentafluorosulfanylated nitrogen-containing heterocyles, on the other hand.

In the first part of our work, we have developed an efficient four-step synthesis of new $SF_5$-acrylic esters and amides, starting from commercially available allyl acetate derivatives. Using the same strategy, several new pentafluorosulfanylated allylsilanes were synthesized. We have also developed an In-mediated allylation reaction of aldehydes, using the $SF_5$-allyl bromide, leading to the corresponding pentafluorosulfanylated $\alpha$- and $\gamma$-homoallylic alcohols.

In the second part, two different strategies for the synthesis of new $SF_5$-substituted heterocycles were explored. The first one was the direct fluorination of heterocyclic thiols or disulfides, according to the Umemoto’s procedure. The second approach was based on the cycloaddition reactions of our pentafluorosulfanylated building-blocks. As a result, we have successfully developed the synthesis of the first $SF_5$-substituted pyrrolidines and isoxazolidines. Finally, post-functionalizations of $SF_5$-pyrrolidines were performed, leading to several pentafluorosulfanylated scaffolds which could be easily introduce into molecules of biological interest.

---

Grâce à ses propriétés uniques, le groupement pentafluorosulfanyle ($SF_5$) a récemment retenu beaucoup d'attention. Ce substituant encombrant, hautement lipophile et électro-attracteur est souvent considéré comme un "super groupement trifluorométhyl". Aujourd’hui, la chimie de groupement $SF_5$ est un domaine de la chimie du fluor qui se développe rapidement, et les méthodologies de synthèse des nouveaux « building-blocks » pentafluorosulfanylés sont constamment développées. Néanmoins, les méthodes permettant l'introduction du groupement $SF_5$ dans les hétérocycles restent encore assez limitées.

L’objectif de cette thèse était de synthétiser des nouveaux « building-blocks » pentafluorosulfanylés, d’une part, et de développer des nouvelles approches synthétiques, conduisant à des hétérocycles azotés originaux, substitués par un groupement $SF_5$, d’autre part.

Dans la première partie de notre travail, nous avons développé une synthèse en 4 étapes, conduisant à de nouveaux esters et amides acryliques substitués par un groupement $SF_5$, à partir des dérivés commerciaux de l’acetate allylique. En utilisant la même stratégie, quelques nouveaux allylsilanes pentafluorosulfanylés ont été synthétisés. Nous avons aussi développé une réaction d’allylation des aldéhydes, catalysée par indium, en utilisant le bromure $SF_5$-allylique, conduisant aux alcools $\alpha$- et $\gamma$-homoallyliques correspondants.

Dans la deuxième partie, deux stratégies différentes pour la synthèse de nouveaux hétérocycles $SF_5$-substitués, ont été explorées. La première était la fluoration directe des thiols ou disulfures hétérocycliques, suivant la procédure de Umemoto. La deuxième approche était basée sur les réactions de cycloaddition de nos "building-blocks" pentafluorosulfanylés. Ainsi, nous avons développé avec succès la synthèse des premières pyrrolidines et isoxazolidines pentafluorosulfanylées. Enfin, des post-fonctionnalisations des $SF_5$-pyrrolidines ont été effectuées, conduisant aux plusieurs "plateformes" pentafluorosulfanylées qui pourraient être facilement incorporées dans les molécules d’intérêt biologique.