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Metal-Free β-Fluoroamination of Allyl Carbamates: Towards the Synthesis of Fluorinated Sphingolipid Analogs

Master Thesis

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Abbreviation and acronyms

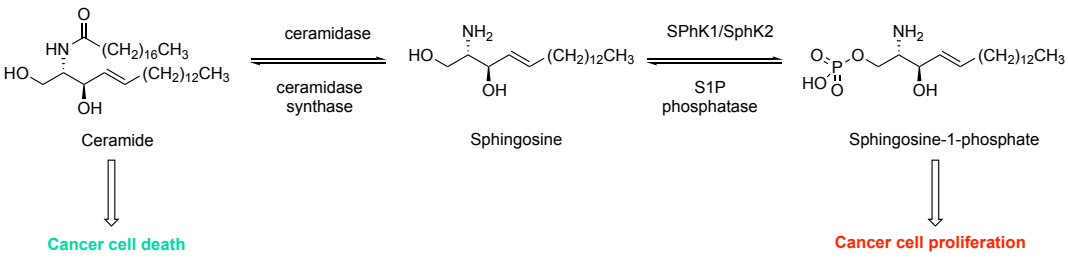
Bn	Benzyl	**PhIO**	Iodosylbenzene
CsF	Cesium Fluoride	**PIDA**	(Diacetoxyiodo)benzene
DCM	Dichloromethane	**Py**	Pyridine
DFT	Density Fuctional Theory	**S1P**	Sphingosine-1-phosphate
DMPU	N,N'-Dimethylpropyleneurea	**SphK**	Sphingosine Kinase
HF	Hydrofluoric acid	**SKIs**	Sphingosine Kinase Inhibitors
KF	Potassium Fluoride	**TAI**	Trichloroacetyl isocyanate
K_2CO_3	Potassium carbonate	**TBAF**	Tetrabutylammonium fluoride
MeOH	Methanol	**TEA**	Triethylamine
M.S.	Molecular Sieves	**THF**	Tetrahydrofurane
m/z	Mass under charge	**TLC**	Thin Layer Chromatography
$NaBH_4$	Sodium borohydride	**TMAF**	Tetramethylammonium fluoride
NMR	Nuclear Magnetic Resonance	**Ts**	Tosyl

1. Introduction

1.1. Sphingosine kinase inhibition toward the pharmacological approach to cancer intervention

Sphingolipids are essential molecules for human life as they play an important role in different cellular processes and physiological cell function. These structural components are founded in the eukaryotic membrane due to the amphipathic character. In addition to the structural role that play sphingolipids, they have crucial functions in the regulation of cell proliferation, differentiation, survival, trafficking and cell death.[1]

Sphingolipids are composed by a long carbon backbone containing 2-amino-1,3-diol functionality with a specific configuration (2S, 3R).[2] Different modifications in the structure of sphingolipids depending on a variety of charged, neutral, phosphorylated and/or acylated moieties gives rise to the different sphingolipid metabolites (Scheme 1). Chemically, the conversion of ceramide into sphingosine, a sphingoid base, is a deacylation produced by ceramidases. Sphingosine, in turn, can be phosphorylated on the alcohol at C-1 by sphingosine kinase to finally obtain sphingosine-1-phosphate (S1P). Cells also contain ceramide synthase and S1P phosphatase to convert sphingosine back to ceramide and sphingosine, respectively.



Scheme 1. Sphingolipid metabolism (Ceramide-Sphingosine-Sphingosine-1-phosphate).

In normal conditions there is a dynamic equilibrium in the cells between the levels of Ceramide, Sphingosine and Sphingosine-1-phosphate. The anomalous sphingolipid metabolism or an overexpression of one of the specific sphingolipids is related to diseases

1 a) X. Zheng, W. Li, L. Ren, J. Liu, X. Pang, X. Chen, D. Kang, J. Wang, G. Du. *Pharmacol. Ther.* **2019**, *195*, 85-89. b) Ogretmen, B. *Nature Rev. Cancer.* **2018**, *18*, 33-50.

2 Ridgway, N. and McLeod, R., **2015**. Biochemistry of Lipids, Lipoproteins and Membranes. 6th ed. Elsevier Science, pp.297-326.

such as cancer, Alzheimer's disease or sphingolipidoses.[3] Several studies have reported that a high concentration of S1P is detected in many tumor tissues as it stimulates cancer cell survival.[4] By contrast, an accumulation of Ceramide and Sphingosine promote apoptosis and inhibit proliferation.[5]

Sphingosine kinase (SphK) is a conserved lipid kinase, and it is responsible for the conversion of the sphingosine to sphingosine 1-phosphate (S1P). This enzyme, present in two possible isoforms (SphK1 and SphK2), is used to regulate the sphingolipid metabolism.[6] The crystal structure of SphK1 was reported in 2013 and its important role against cancer was confirmed by several studies.[7] Instead, at the moment there is not available structural information of SphK2. Concerning on these two kinases, it can be added that they are found in different places in the cell and they produce different functions.[8]

On the basis of these and many related studies, the study of promising inhibitors of SphK1 and SphK2 has become a novel approach for the treatment of cancers[9] such as breast, colon, kidney, rectum, ovary, stomach, uteri and prostate and including metastatic cancer. In recent years, many research groups have focused their attention on the development of new sphingolipid analogues by the chemical modification in the structure of sphingosine. The development of inhibitors of SphK1 and SphK2 (Figure 1) is expected to shift the equilibrium towards the formation of ceramide or sphingosine, favoring apoptosis. At the

3 Bu, Y.; Wu, H.; Deng, R.; Wang, Y. *Front. Pharmacol.* **2021**, *12*, 733387.

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5 J. W. Antoon, J. Liu, A. P. Ponnapakkam, M. M. Gestaut, M. Foroozesh, B. S. Beckman. *Cancer Chemother. Pharmacol.* **2010**, *65*, 1191–1195

6 Plano, D.; Amin, S.; Sharma, A. K. *J. Med. Chem.* **2014**, *57*, 5509-5524

7 Wang, Z.; Min, X.; Xiao, S.-H.; Johnstone, S.; Romanow, W.; Meininger, D.; Xu, H.; Liu, J.; Dai, J.; An, S.; Thibault, S.; Walker, N. *Structure*. **2013**, *21*, 798–809

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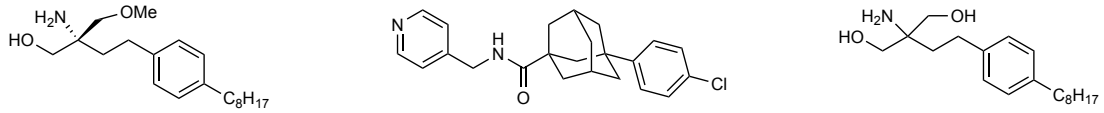
moment, it has been reported that the inhibition of SphK2 has a greater anti-tumor effect than SphK1. [10]



(R)-FTY720-OCH$_3$	**ABC294640**	**FTY720**
Ki (SphK1) : 50 μM Ki (SphK2) : 16.5 μM	Ki (SphK1) : > 100 μM Ki (SphK2) : 9.8 μM	Ki (SphK1) : 2 μM Ki (SphK2) : N.D

Figure 1. Examples of inhibitors of SphK and the inhibitor potency.

1.2. Organofluorine compounds

Henri Moissan was the first scientist to discover the fluorine[11] atom in 1886, isolating it in gas form by electrolysis of a solution of potassium hydrogen fluoride in anhydrous hydrofluoric acid (HF). This element is considered the 13th in the terrestrial abundance and the most electronegative. The importance of fluorine in the medicinal chemistry is increasing as it provides unusual properties and behavior. This small atom gives a library of potential applications in a variety of fields.

This chemical element has a Van der Waals radius very similar to that of hydrogen (1.39Å and 1.20Å), so there is no important consideration in terms of sterics. Although this change produces a totally different electronic effect, the C-F bond presents a greater stability. Moreover, fluorine is also considered an isostere of the hydroxyl group due to the similarity of the C-F and C-O bonds (1.39 Å and 1.43Å). The difference on this substitution can be explained since fluorine can act as a hydrogen bond acceptor but not as a donor, in comparison with hydroxyl group that is a good hydrogen bond donor.

On one hand, fluorine substituents are strong electron-withdrawing groups enabling the activation of nucleophilic attack on the center reaction and forming a σ-bond. On the other hand, the lone pair of electrons of fluorine give an electron-donor character despite their high electronegativity, opening up the possibility of controlling the regiochemistry and the reaction rates forming π-bond with the center reaction.

10 Gao, P.; Smith, C. D. *Mol. Cancer Res*. **2011**, *9*, 1509-1519

11 Uneyama, K., **2008**. Organofluorine Chemistry. John Wiley & Sons.

With all this context, many biologically active molecules and pharmaceuticals contain at least one fluorine atom in its structure.[12] Two examples of fluorinated drugs that obtained the worldwide top 20 best selling drugs of 1993 are shown in Figure 2 (Fluoxatine and Ciprofloxacine). Fluoxatine is used as an antidepressant drug and Ciprofloxacin as an antibiotic drug.

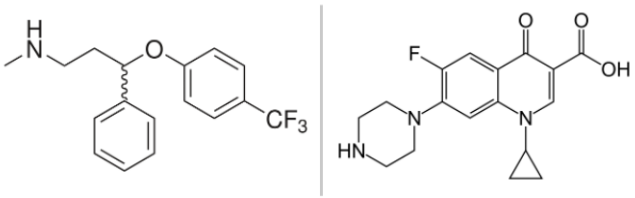


Figure 2. Structure of fluoxetine on the left and ciprofloxacin on the right.

1.3. The formation of aziridines by nitrene-mediated reactions

The synthesis of aziridines was highly studied in organic chemistry and used as intermediates by the ability to be opened by a large number of nucleophiles.[13] This fact makes this precursor of great interest since its opening by the use of any nucleophile allows us to have the anti-vicinal hetero-amino moieties, similar to the original structure of sphingosine, as shown in Figure 3.

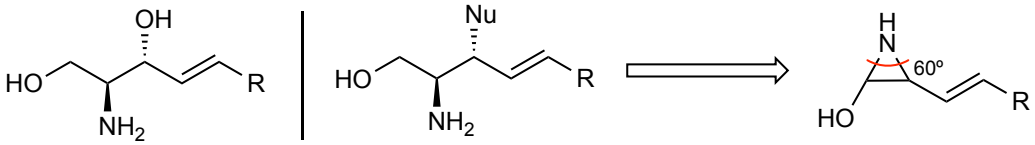


Figure 3. On the left Sphingosine fragment and on the right ring-opening of aziridines.

Aziridines are considered as equivalents of epoxides and they are the smallest class of *N*-substituted heterocycles.[14] The reactivity of this type of compounds is explained by the strained angles of 60 º, instead of the usual 109.5 º. They are used as synthetic targets for

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13 a) Stankovic, S.; D'hooghe, M.; Catak, S.; Eum, H.; Waroquier, M.; Van Speybroeck, V.; De Kimpe, N.; Ha, H. Chem. Soc. Rev. **2012**, *41*, 643-665. b) Okoromoba, O.E.; Li, Z.; Robertson, N.; Mashuta, M.S.; Couto, U.R.; Tormena, C.F.; Xu, B.; Hammond, G.B. *Chem. Commun*. **2016**, *52*, 13353-13356.

[14] B. Zwanenburg, P. ten Holte, In *Stereoselective Heterocyclic Synthesis III*; P. Metz, Ed.; *Top. Curr. Chem.* **2001**, *216*, 93–124

natural products[15], pharmaceutical drugs[16], chiral auxiliaries[17] and chiral ligands[18]. The electron withdrawing nitrogen makes an interesting intermediate for the formation of amines, amino alcohols, amino acids, amino sugars or azaheterocycles.

The first studies in which the formation of an aziridine took place appeared in the 80's, in the presence of an olefinic substrate using PhI=NTs and Fe or Mn as catalysts.[19] Nowadays, this type of reaction involving a nitrogen source and an alkene is well known that proceeds via nitrene. Nitrenes are molecular fragments with six electrons in their valence shell.[20] The traditional formation of this univalent nitrogen is yielded thermally or photochemically from hydrazoic acid or organic azides.[21]

General methods to obtain asymmetric aziridines from alkenes rely on the addition of metal-nitrenes to olefins (a, Scheme 2).[22] In the last years, the strong appearance of hypervalent iodine as an alternative to metals, have emerged for the preparation of iminoiodanes such as PhI=NTs.[23] In 2005, Che and coworkers developed a method that used a hypervalent iodine species to mediate the aziridination (b, Scheme 2).[24] Afterwards,

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[15] a) Fukuyama, T.; Yang, L. *J. Am. Chem. Soc*. **1987**, *109*, 7881-7882. b) Naganawa, H.; Usui, N.; Takita, T.; Hamada, M.; Umezawa, H. *J. Antibiot*. **1975**, *28*, 828-829. c) Breuning, A.; Vicik, R.; Schirmeister, T. *Tetrahedron Asymmetry*. **2003**, *14*, 3301-3312.

[16] a) Ismail, F.M.D.; Levistky, D.O.; Dembitsky, V.M. *Eur. J. Med. Chem.* **2009**, *44*, 3373-3387. b) S. Fürmeier, J. O. Metzger, *Eur. J. Org. Chem.* **2003**, 649–659.

[17] a) Tanner, D.; Birgersson, C.; Gogoll, A. *Tetrahedron*. **1994**, *50*, 9797-9824.

[18] a) Watson, I.D.G.; Yu, L.; Yudin, A.K. *Acc. Chem. Res.* **2006**, *39*, 194-206. b) Tanner, D.; Andersson, P.G.; Harden, A.; Somfai, P. *Tetrahedron Lett*. **1994**, *35*, 4631-4634.

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[20] Dequirez, G.; Pons, V.; Dauban, P. *Angew. Chem. Int. Ed*. **2012**, *51*, 7384-7395.

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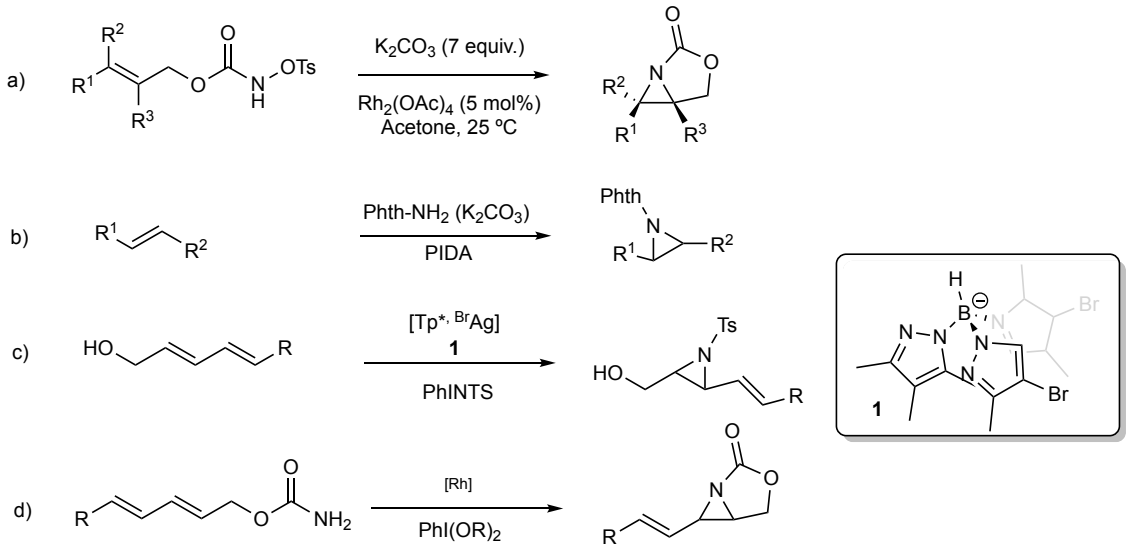
[22] a) Halfen, J. A. Curr. *Org. Chem.* **2005**, *9*, 657-669. b) Jeffs, L.; Arquier, D.; Kariuki, B.; Bethell, D.; Page, P. C. B.; Hutchings, G. *J. Org. Biomol. Chem*. **2011**, *9*, 1079-1084. c) Dauban, P.; Dodd, R. H. *Synlett*. **2003**, 1571-1586. d) Dhanalakshmi, T.; Suresh, E.; Palaoniandavar, M. *Inorg. Chim. Acta*. **2011**, *365*, 143-151. e) Hilt, G. *Angew. Chem. Int. Ed.* **2002**, *41*, 3586- 3588. f) Lebel, H.; Huard, K.; Lectard, S. *J. Am. Chem. Soc.* **2005**, *127*, 14198-14199.

[23] a) Llaveria, J.; Beltrán, A.; Díaz-Requejo, M. M.; Matheu, M. I.; Castillón, S.; Pérez, P. J. *Angew. Chem. Int. Ed*. **2010**, *49*, 7092-7095. b) Llaveria, J.; Beltrán, A.; Díaz Requejo, M. M.; Matheu, M. I.; Castillón, S.; Pérez, P. J. *Angew. Chem. Int. Ed*. **2010**, *49*, 7092-7095.

[24] Li, J.; Hong Chan, P.W.; Che, C. *Org. Lett.* **2005**, *7*, 5801-5804.

many research groups reported efficient and mild processes to obtain nitrene-mediated aziridines. Che and coworkers also introduced the addition of K_2CO_3 to avoid the ring-opening of the aziridine due to the nucleophilic attack of one of the acetates of PIDA.[25] Professor Pedro Pérez carried out a study on the aziridination of simple alkenes using different complexes as catalysts and PhINTs as nitrenes transfer agent. In 2010 our group in collaboration with this professor reported a regio- and stereospecific aziridination of silver-catalyzed dienes with a characteristic bromine and methyl substituent on the pyrrole ring (c, Scheme 2). Other alternative proposed by our group to obtain a regio- and enantioselective aziridination of vinyl alkenes mediated by rhodium catalysts and in the presence of PIDA and the subsequent ring-opening of the aziridine (d, Scheme 2). In this reaction rhodium plays a center role for the formation of the metallonitrene and also serves as Lewis acid during the S_N2 opening process. Furthermore, it was also found that this reaction works also without the use of metals.

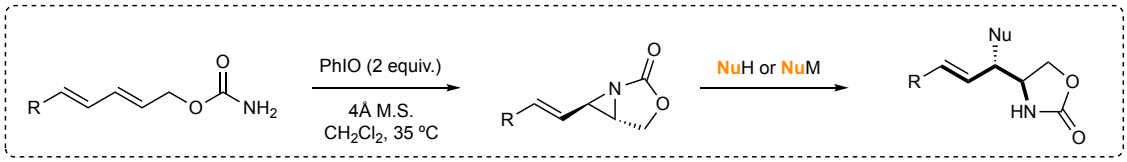


Scheme 2. Different approaches reported in the aziridination reactions.

Inspired by the last-mentioned studies, Dr. Giménez-Nueno performed the aziridination of dienyl carbamates using PhIO as oxidizing agent and under metal-free conditions. The subsequent ring-opening was carried out by the introduction of external nucleophiles as shown in Scheme 3, giving access to a single diastereomer in all cases. In general ring-opening of the vinyl aziridine under typical basic/nucleophilic conditions took place regio- and stereoselectively giving rise to a single regioisomeric oxazolidinone corresponding to

[25] Li, J.; Liang, J-L.; Chan, P.W.H.; Che, C.-M. *Tetrahedron Lett*. **2004**, *45*, 2685-2688.

the S_N2-anti ring-opening product. Only when weakly basic or acidic nucleophiles were used such as water of thiophenols, a regioisomeric mixture of S_N2 and S_N2'ring-opened products was obtained.



Scheme 3. General scheme of the reaction studied by Dr. Giménez-Nueno.

1.4. Metal-free Fluoroamination using hypervalent iodine

Nowadays, many efforts are being carried out to increase green chemistry and sustainability. Iodine is recognized as an eco-friendly element of the periodic table and it is highly used in chemical research. It was discovered in the 19th century during the Napoleonic Wars from brown algae, the highest iodine accumulator of all living systems. Today, the production of iodine is carried out in countries like Chile or Japan where there are high concentrations of petroleum or natural gas. Iodine offers a high versatility in organic synthesis due to its existence in different oxidation states from -I to +VII, being the +III and +V considered as hypervalent iodine (Figure 4).

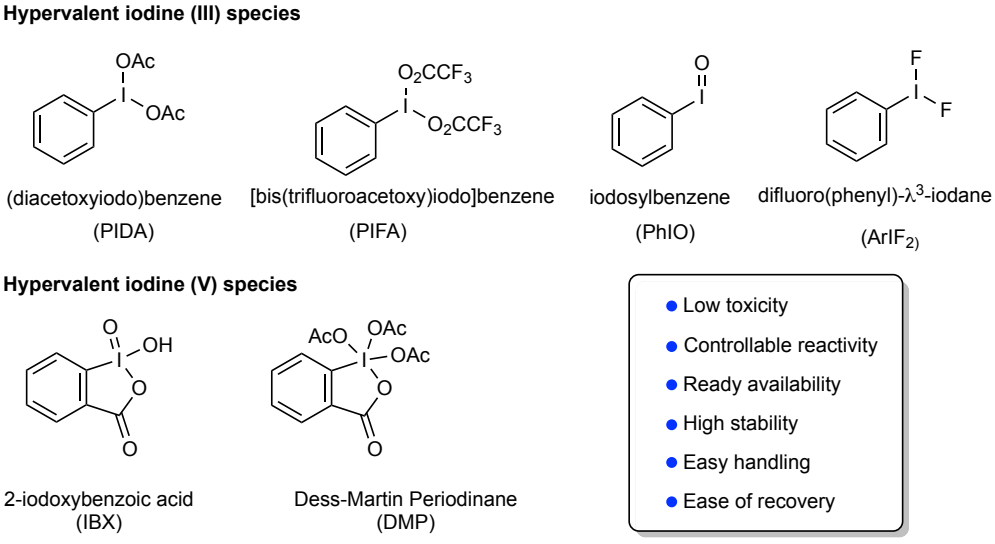


Figure 4. Most famous hypervalent iodine species and its specific properties.

In this context, the choice of a hypervalent iodine instead of a metal compound is a promising system for oxidative coupling reactions avoiding the formation of hazard substances. Hypervalent iodine was first synthesized in 1886 by the german Conrad

Willgerodt and despite the study of this scientist in this type of chemistry, it was not until 1960 that the development of new highly charged iodine cation species and their application were explored.[26] The low toxicity, controllable reactivity, ready availability, high stability, easy handling and ease of recovery has led to a depth study in new greener synthetic processes. The high oxidation state that presents hypervalent iodine makes it unstable in air and in the presence of light as it can be easily reduced.

The general structure among the hypervalent iodine compounds is presented in Figure 4. To mention some of the examples, it can be distinguished $ArIF_2$ as is a great fluorinating reagent or $PhI(OAc)_2$ as the most stable hypervalent iodine reagent. The highly electrophilic nature of these unstable compounds in air and in the presence of light can be explained by the geometry. The general structure of hypervalent iodine unfold a T-shaped structure within a pseudo trigonal bipyramidal as can be shown in Figure 5. In a trivalent iodine RIL_2, the less electronegative carbon is placed in an equatorial position along with iodine lone pairs. Instead, heteroatomic ligands are located in apical positions. The nearly linear L-I-L is considered as the hypervalent bond and is the responsible for the electrophilic reactivity.

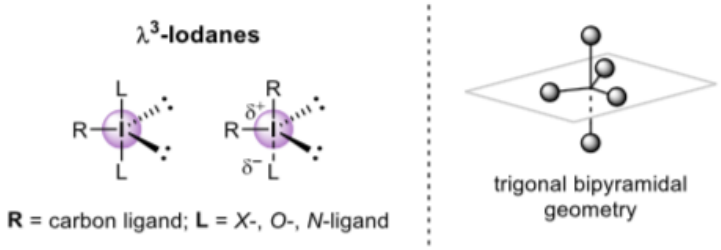
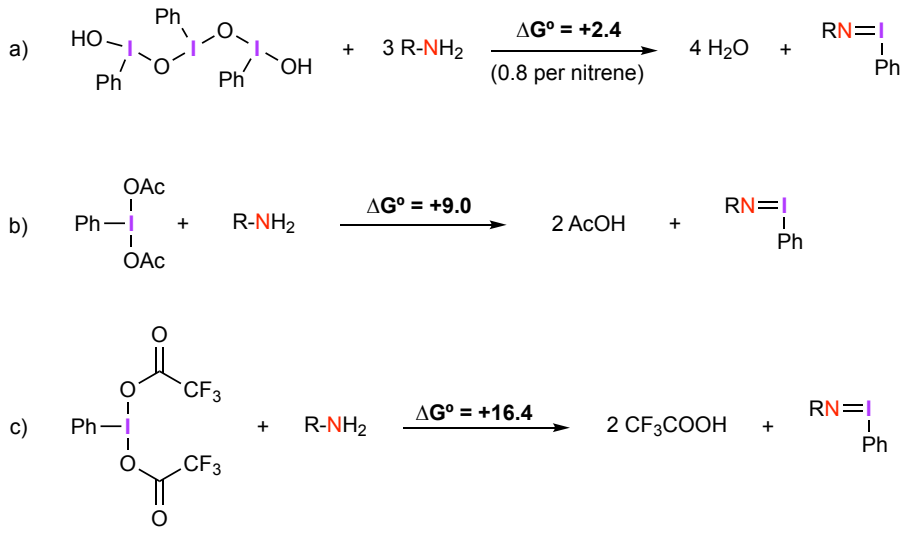


Figure 5. General structure of hypervalent iodine.

Professor Feliu Maseras has carried out a computational study that accounts for the thermodynamics of the formation of the iminoiodane intermediate as the nitrene transfer agent (Scheme 4).[27] The hypervalent iodine specie reacted with an amine producing an endothermic reaction ($\Delta G°$= +2.4) and forming as a products water and an iminoiodane. With this knowledge on hand, our research group suggests that the mechanism of this reaction proceeds through the intermediacy of an iminoiodane as intermediate for the

[26] Livingston, H.K.; Sullivan, J.W.; Musher, J.I. *J. Polym. Sci., Part C: Polym. Symp*. **1968**, *22*, 195-202.
[27] Barea, G.; Maseras, F.; Lledós. A. *New. J. Chem.* **2003**, *27*, 811-817.

formation of the aziridine. Also, this study for accounts for the need to use molecular sieves in the reaction so as to shift the equilibrium towards the products.



Scheme 4. Computational studies carried out by Prof. Feliu Masseras.

In order to gain insight more mechanistic details, Prof. Maseras and Dr. I. Funes-Ardoiz performed a DFT calculation which supports our idea that the mechanism is via iminoiodane, as shown in Figure 6. They proposed a first step (A → B) in which there is a reorganization of the dienyl carbamate to bring the nitrogen close to the double bond. Then, the obtention of the aziridine C goes through the intermediate TS B-C stabilized by dispersion interactions between phenyl ring at hypervalent iodine reagent and distal double bond from dienyl moiety. Finally, as can be seen, the aziridine D is obtained as the reaction is favored due to the decrease in energy.

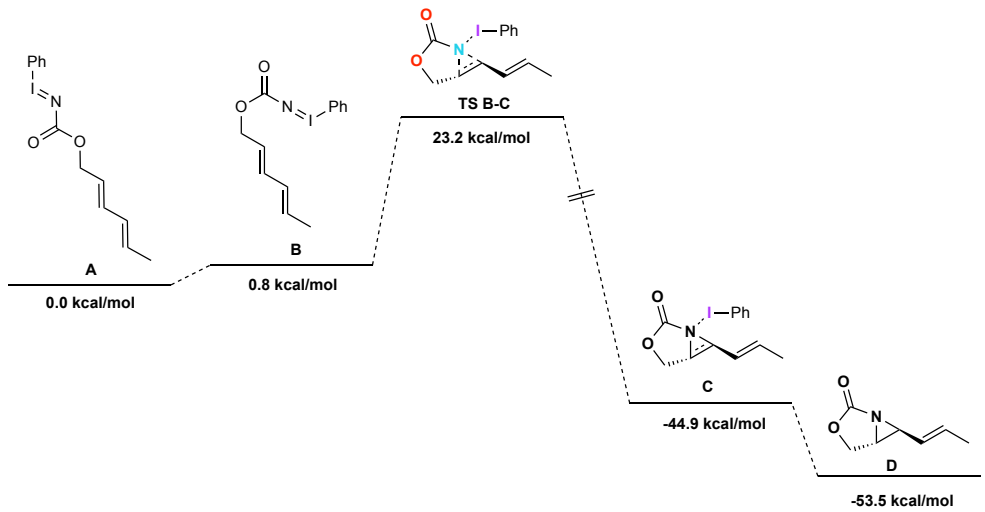
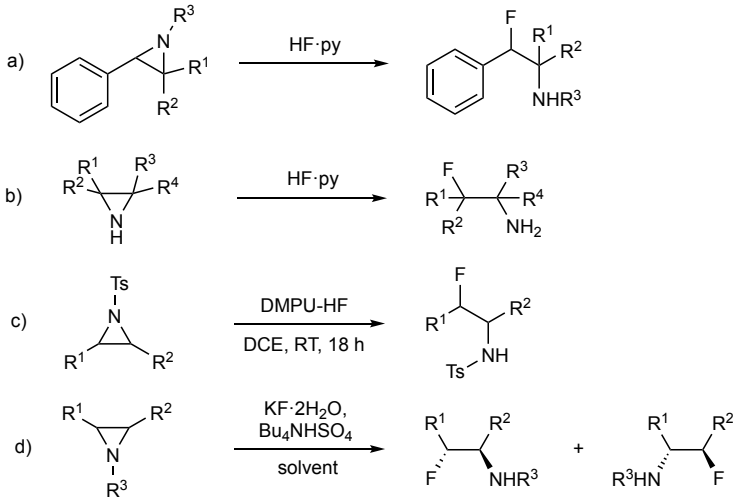


Figure 6. Free energy profile for aziridine formation from iminoiodane.

Once it has been shown that aziridines are easily accessible under metal-free conditions, our interest focuses on their opening by nucleophilic attack of fluorine equivalents. For this purpose, a convenient procedure for the formation of fluoroamines using Olah's reagent (a, Scheme 5) was discovered in 1978 with good yields.[28] At that time, another study of opening of aziridines with different fluorine sources was reported where the different stereoselectivities and the synthetic advantages of each reagent could be observed (b, Scheme 5).[29] Okoromoba and coworkers developed an efficient method for the conversion of aziridines to β-Fluoroamines using HF·DMPU as a fluorine source (c, Scheme 5).[30] The opening of aziridine does not need to be carried out in acid medium, as was demonstrated in 2003 with the use of potassium fluoride dihydrate in the presence of Bu_4NHSO_4 (d, Scheme 5).



Scheme 5. Fluoroamination reactions reported in the bibliography.

1.5. Fluoroamination reactions.

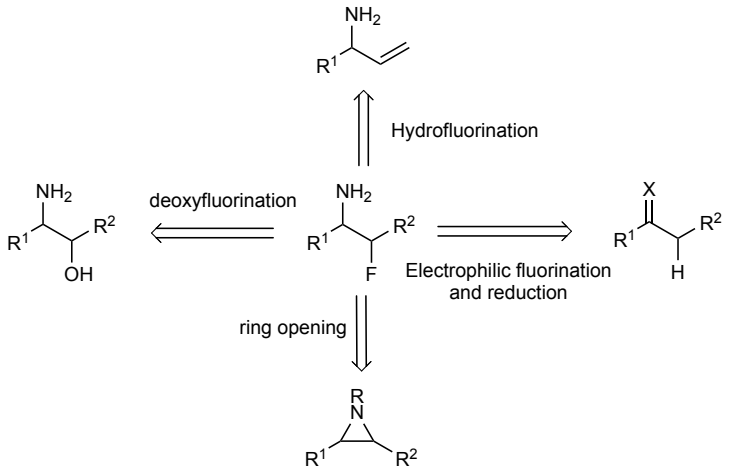
As commented before, the utility of aziridines is focused on the selective ring-opening reactions. The interest to obtain an anti-vicinal fluoro-amines instead of the amino-alcohol fragment of the sphingosine has led us to study the ring opening of aziridines with different fluorine sources. Among all the organofluorinated compounds, β-

[28] Wade, T. N.; Guedj, R.; *Tetrahedron Lett*. **1978**, *19*, 3247-3250.

[29] Alvernhe, G. M.; Ennakoua, C. M.; Lacombe, S. M.; Laurent, A. J. *J. Org. Chem*. **1981**, *46*, 4938-4948.

[30] Okoromoba, O.E.; Li, Z.; Robertson, N.; Mashuta, M.; Couto, U.R.; Tormena, C.F.; Xu, B.; Hammond, G.B. *Chem. Commun*. **2016**, *55*, 13353-13356.

fluoroaminated compounds are very important by its properties as an anticancer, anti-inflammatory and anticholinergic drugs as well as enzyme inhibitors. This fact is explained by the electron-withdrawing β-fluoro group that is able to decrease the pK_a of the amine, improving the bio-availability and increasing the blood-brain barrier penetration.



Scheme 6. Methods to generate vicinal fluoroamination moiety.

In 1996, Stojan Stavber and his research group presented a Rytter-type fluorofunctionalization to introduce a vicinal fluoramides using an electrophilic fluorine sources (e.g. Selectfluor), although the scope of the reaction was low.[31] In 2011, Véronique Gouverneur and her research group develop a method to promote a catalytic enantioselective fluorocyclization using nitrogen-containing activated olephins.[32] Many processes rely on the use of metals to produce the fluoroamination of alkenes.[33]

Usually, fluorine reagents present low nucleophilicity, high toxicity and often produces side reactions. They can act also as electrophilic reagents, although they are considered more expensive. For the current work nucleophilic fluorinating reagent will be considered (HF·DMPU, HF·triethylamine, etc.), as were they are able to release one fluoride ion. Hydrogen fluorides are one of the most inexpensive sources of fluorides, but it presents a

[31] Stavber, S.; Sotler, T.; Papez, M.; Zupan, M. *Chem. Commun.* **1996**, 2247-2248.

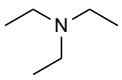
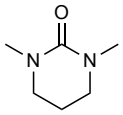
[32] Lozano, O.; Blessley, G.; Martinez, T.; Thompson, A.L.; Giuffredi, G.T.; Bettati, M.; Walker, M.; Borman, R.; Gouverneur, V. Organocatalyzed Enantioselective Fluorocyclizations. *Angew. Chem. Int. Ed.* **2011**, *50*, 8105-8109.

[33] a) Wu, T.; Yin, G.; Liu, G. *J. Am. Chem. Soc.* **2009**, *131*, 16354-16355. b) · Hull, K.L.; Anani, W.Q.; Sanford, M.S. *J. Am. Chem.* Soc. **2006**, *128*, 7134-7135. c) · Qiu, S.; Xu, T.; Zhou, J.; Guo, Y.; Liu, G. *J. Am. Chem. Soc.* **2010**, *132*, 2856-2857. d) Furuya, T.; Kaiser, H.M.; Ritter, T. *Angew. Chem. Int. Ed*. **2008**, *47*, 5993-5996. e) · Xu, T.; Mu, X.; Peng, H.; Liu, G. *Angew. Chem*. **2011**, *123*, 8326-8329.

high toxicity, corrosivity and low boiling point (b.p. 19 °C). Nevertheless, ring-opening of aziridines by the addition of HF provides an efficient and economic method to obtain α,β-fluoroamines, a very stable compound.

Hirschmann and coworkers reported the importance of the addition of a base to form a stable solution in the reactivity of HF.[34] Controlling the amount of base used (triethylamine, pyridine…) it is possible to influence in the yield of the reaction. It was demonstrated that varying the nature of the Lewis base and the stoichiometric amount of HF, a different range of properties can be achieved. [35] The use of a base hampered can influence in the acidity of the medium and it can interact with many metal catalysts. Trying to avoid this problem, Okoromoba reported a new HF nucleophilic reagent composed by HF·DMPU.[36]

Table 1. Comparison of the properties of Et_3N and DMPU.

	Et_3N	DMPU
Compound		
pK_{BHX}[a]	1.98	2.82
pK_{AH}[b]	10.7	<0
nucleophilicity	weaker	higher

[a] Hydrogen bond basicity. [b] Acid dissociation constant.

The interaction of HF with an organic base is performed with hydrogen bonding. This strong interaction allows an increase in the boiling point, where most of the HF·complex are liquids or solids. On one hand, analyzing the Table 1, triethylamine and pyridine are considered as Bronsted bases and in both cases, they are hydrogen bond acceptors. On the

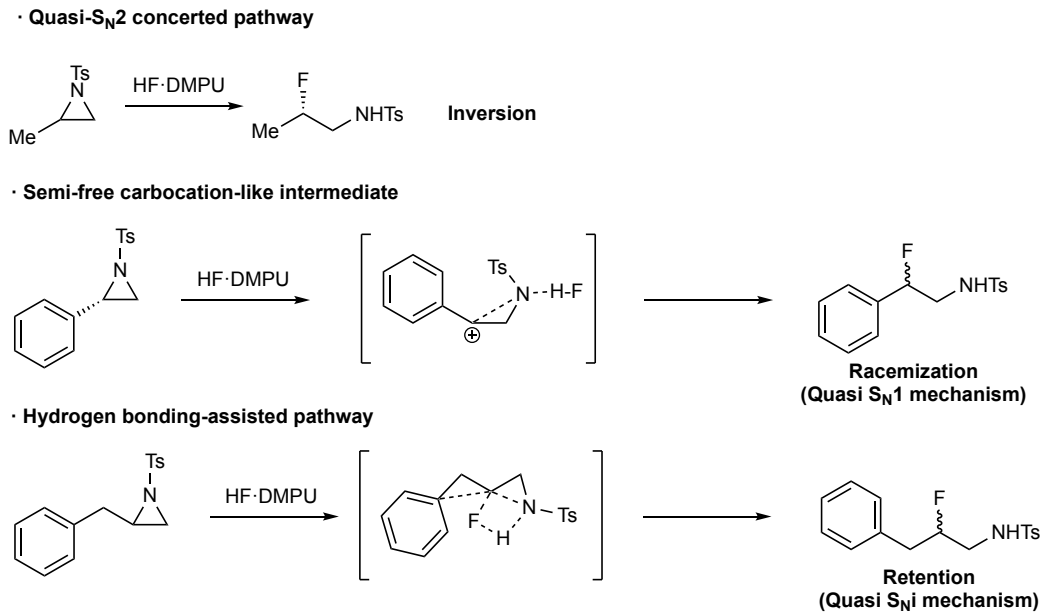
[34] Hirschmann, R.F.; Miller, R.; Wood, J.; Jones, R. *J. Am. Chem. Soc.* **1956**, *78*, 4956-4959.

[35] Yoneda, N. *Tetrahedron*. **1991**, *47*, 5329-5365.

[36] a) Okoromoba, O.E. ThinkIR: The University of Louisville's Institutional Repository. PhD Thesis. Development and Applications of Novel HF-Based Fluorination Reagents: DMPU-HF. **2016**. b) Okoromoba, O.E.; Li, Z.; Robertson, N.; Mashuta, M.S.; Couto, U.R.; Tormena, C.F.; Xu, B.; Hammond, G.B. *Chem. Commun*. **2016**, *52*, 13353-13356. c) Okoromoba, O.E.; Han, J.; Hammond, G.B.; Xu, B. *J. Am. Chem. Soc.* **2014**, *136*, 14381-14384.

other hand, DMPU presents a clear differentiation with these two bases. DMPU is a better hydrogen bond acceptor with properties of a Bronsted acid.[37]

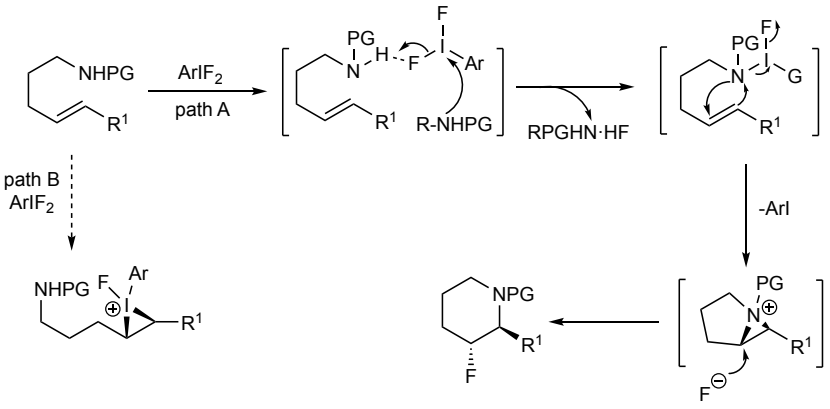
Okoromoba et al. reported the differences in the mechanism for the ring-opening of alkyl aziridines when HF·DMPU and HF·NEt_3 were used. When DMPU was used, the mechanism goes through a SN1-type regioselectivity accompanied with inversion of stereochemical configuration. The mechanistic proposed by Okoromoba is related with the acidic medium of the reaction where the aziridine is protonated and form a carbocation-like intermediate as shown in Scheme 7. This intermediate gives rise to a mechanism that is a pathway between the idealized S_N2 and S_N1 because the nucleophile (HF) will preferentially attack the most substitute carbon, being a property of S_N1, and will perform an inversion of the center, characteristic of S_N2 reactions. The stereochemical outcome of the aziridine opened by HF·DMPU varies with the substrate used. By contrast, the use of triethylamine or pyridine, basic organic molecules, only allows the S_N2 reaction. The kind of substrates where we will focus are generally aryl aziridines where the phenyl group is the responsible to stabilize strongly the corresponding carbocation intermediate, giving rise to a regiospecific reaction for both HF·DMPU and HF·NEt_3.



Scheme 7. Proposed mechanisms for fluoroamination reaction.

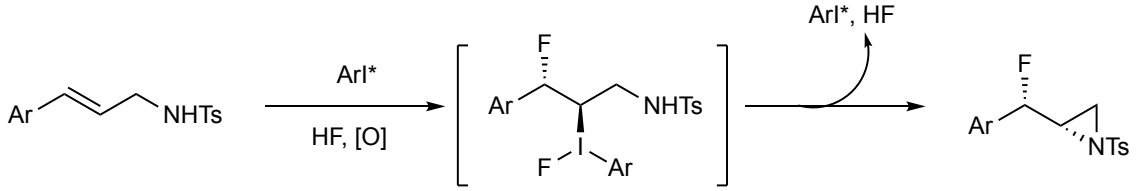
[37] Gilli, P.; Pretto, L.; Bertolasi, V.; Gilli, G. *Acc. Chem. Res.* **2009**, *42*, 33-44.

Dr. Cristina Nevado in 2013 reported a regioselective metal-free fluoroamination of alkenyl tosylamides by using difluoroiodonium salts (Scheme 8).[38] In this study she proposed a mechanism reaction in which the reaction proceeds via an aminoiodane intermediate. Nitrene transfer generates an aziridinium intermediate that is subsequently opened by fluoride. Nevado accounts for the requirement of an acidic hydrogen directly bonded to N such as in tosylamides in order to activate the $ArIF_2$ reagent for oxidation. Also, Richardson et al. proposed the same reasoning for his studies in the aziridination of alkenes.[39]



Scheme 8. Proposal mechanism by Dr. Cristina Nevado.

More studies related with an fluoroamination were presented by Eric N. Jacobsen, in which he reported that the mechanism of the reaction proceeds via the oxidation of the alkene and the subsequent nucleophilic attack of the nitrogen to form the aziridine (Scheme 9).[40]



Scheme 9. Mechanistic proposal by Dr. Jacobsen.

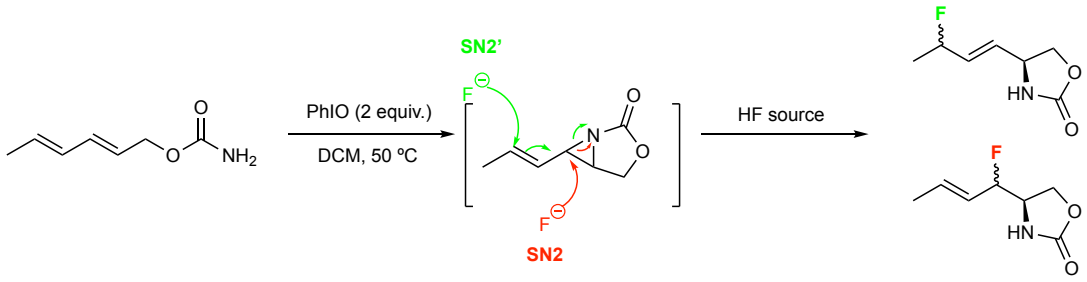
[38] Kong, W.; Feige, P.; de Haro, T.; Nevado, C. *Angew. Chem. Int. Ed*. **2013**, *52*, 2469-2473.

[39] Richardson, R.D.; Desaize, M.; Wirth, T. *Chem. Eur. J*. **2007**, *13*, 6745-6754.

[40] Mennie, K.M.; Banik, S.M.; Reichert, E.C.; Jacobsen, E.N. *J. Am. Chem. Soc.* **2018**, *140*, 4797-4802.

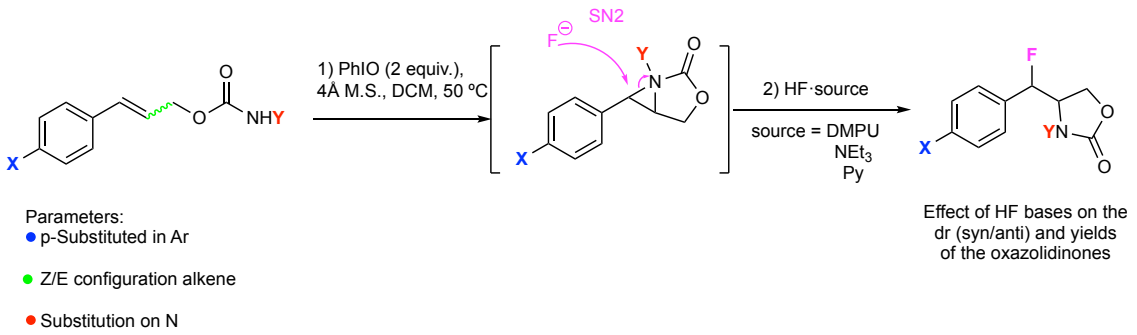
2. Objectives

Following the experience and knowledge learned by our group during the last years on alkene aziridination and ring-opening of aziridines, we envisaged the synthesis of *β*-Fluoroamine scaffolds aiming at synthesizing sphingolipid analogs from dienyl carbamates. To this purpose, a hypervalent iodine species (PhIO) is envisaged as oxidant of the nitrogen functional group on dienyl carbamates to render a nitrene source capable of performing intramolecular aziridination on the proximal alkene moiety. Different Fluorine sources will be explored in the subsequent ring-opening of the aziridine intermediate. As vinyl aziridines are generated in the first step, these can undergo ring-opening at different sites, that is, through S_N2 or S_N2' reaction path, leading to different regioisomeric fluoro oxazolidinones (Scheme 10). Additionally, the stereoselectivity outcome of the ring-opening process with fluorine sources deserves to be studied.



Scheme 10. General scheme of the fluoroamination of dienyl carbamates.

Since dienyl carbamates pose regioselectivity problems, we first sought to study the one-pot fluoroamination process using simpler substrate models, and for that purpose we focused on cinnamic substrates (**Scheme 11**). More specifically, the goals of this master thesis are the following ones:



Scheme 11. General scheme for the different parameters studied in our fluoroamination reaction of cinnamyl substrates.

· Synthesize a library of cinnamyl carbamates:

- Modifying the electronic properties of the substrates by installing substituents in p-position of the aryl moiety.

- Modifying the configuration of the double bond.

- Using *N*-substituted carbamates (tosyl and benzyl).

· Explore the fluoroamination of cinnamyl carbamates by one-pot I(III)-mediated intramolecular aziridination and ring opening of the aziridine intermediate using PhIO as a hypervalent iodine reagent and HF·Base reagents such as HF·Net3, HF·py, HF·DMPU, studying the following parameters:

· Explore the role of the configuration (*E* vs *Z*) of the alkene in the stereoselectivity of the one-pot aziridination/ring opening.

· Study how the outcome (yield and anti/syn stereoselectivity) of the one-pot aziridination/ring opening of *p*-substituted cinnamyl carbamates is affected by the electronic properties of the substituents in the fluoroamination reaction.

· Screen the effect of the substitution of the carbamate in the feasibility of the one-pot fluoroamination reaction of *N*-substituted carbamates. Furthermore, the role of acidity of the NH group in the *N*-substituted carbamate will be also studied.

· Exploration on the reactivity of other non-acidic fluorine sources such as TMAF, TBAF, CsF and KF on the one-pot fluoroamination of cinnamyl carbamates.

· Study the regio- and stereoselectivity of the one-pot fluoramination process of dienyl carbamates, comparing the effect of the fluorine source.

3. Results and discussion

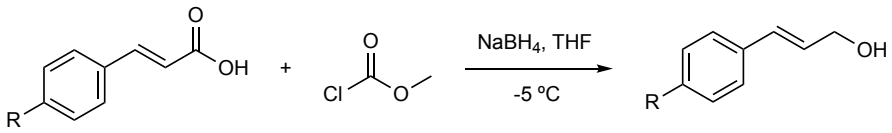
3.1. Synthesis of carbamates starting from cinnamyl alcohols

With the idea of synthesizing β-Fluoroamines in mind, different carbamates substrates were chosen to be studied for a one-pot sequential I(III)-mediated aziridination/ring-opening reaction. On one hand, cinnamyl carbamates were identified as simple model substrates of the more complex dienyl carbamates for the optimization of the reaction conditions, as the latter may afford regioisomeric products as a consequence of the ring-opening in an S_N2' fashion. To the purpose of initially studying the feasibility and stereoselectivity of the aziridination/ring-opening of cinnamyl carbamates, a library of substrates was envisioned to be used as starting materials, trying to determine the scope of the reaction. Cinnamyl carbamates are available from the corresponding alcohols, which can be synthesized from the commercially available cinnamyl acids.[41,42]

3.1.1. Reduction of cinnamyl acids to alcohols

As discussed in section **1.5**, and taking into account the study performed in our group by Gimenez-Nueno, who showed that *E,E*-dienyl and *E*-cinnamyl carbamates are stereospecifically aziridinated and stereospecifically ring-openened to give the anti-configured 2-aminol-ol products of the different cinnamyl substrates with a trans-alkene configuration were prepared.

The reduction conditions of cinnamyl acids were previously studied in our research group (Scheme 12). The best conditions for this reaction involve the reduction of the acid with excess NaBH4 in dry methanol in the presence of dry TEA, methyl chloroformate and dry THF as a solvent.[41]



Scheme 12. General procedure for the reduction of cinnamyl acids to alcohols.

The use of methyl chloroformate increases the reaction yield due to the formation of a transient acyl carbonate that facilitates its subsequent reduction to alcohol by the use of a

[41] Krätzschmar, F.; Kabel, M.; Delony, D.; Breder, A. *Chem. Eur. J.* **2015**, *21*, 7030-7034

reducing agent like $NaBH_4$ in MeOH. $NaBH_4$ is considered as a softer reducing agent and for this reason it can also attack the double bond. The chemoselectivity towards the reduction of the acid were improved with respect to the reduction of the double bond, obtaining yields between 40 and 80% after successfully purification by flash chromatography and obtaining a white solid in most cases (Figure 8).

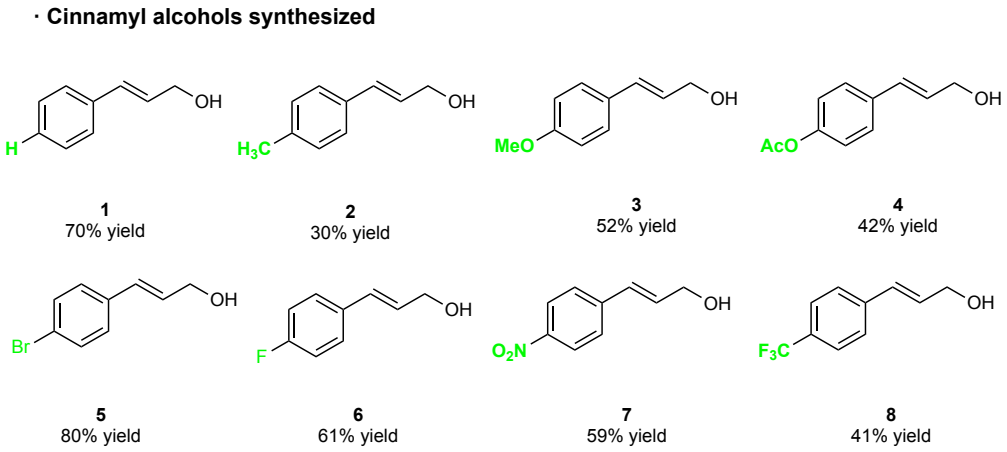
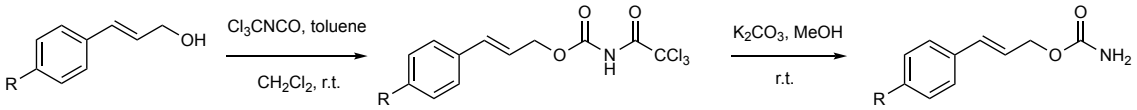


Figure 8. Cinnamyl alcohols synthesized and the respective yields from the cinnamic acids.

3.1.2. Synthesis of cinnamyl carbamates: Carbamoylation of cinnamyl alcohols

Following with the synthesis of carbamates, the second stage is the carbamoylation of cinnamyl alcohols (Scheme 13).



Scheme 13. General procedure for the carbamoylation of cinnamyl alcohols.

The synthesis of carbamates takes place by addition of a solution of trichloro isocyanate in dry toluene to a solution of the corresponding alcohol in CH_2Cl_2 to render an imido carboxylate intermediate that is subsequently submitted to a methanolysis.[42] The final carbamate product was purified by flash chromatography and recrystallized by slow diffusion obtaining a solid compound (Figure 9).

[42] Espino, C. G.; Du Boif, J. *Angew. Chem. Int. Ed.* **2001**, *40*, 598-600.

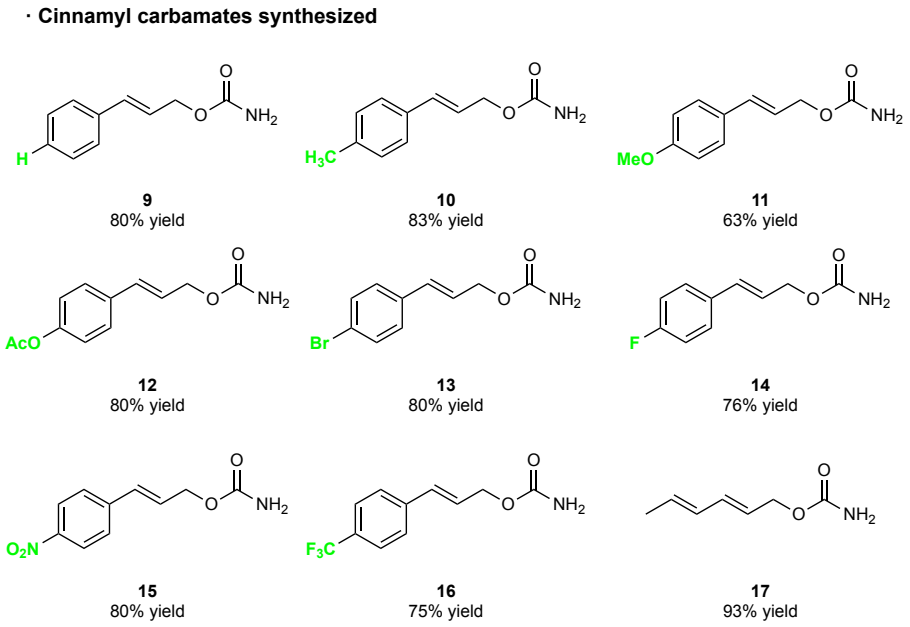


Figure 9. Cinnamyl carbamates synthesized and the respective yields obtained from the corresponding alcohols.

The synthesis of carbamates was confirmed by NMR spectroscopy and by HRMS. All the starting materials for the fluoroamination reaction follow the same pattern that can be seen in Figure 10. When the carbamate is formed, the signal from the diastereotopic protons CH_2 bounded to the oxygen appears more deshielded. Through ^{13}C it can also be distinguished from alcohol since a new signal is formed between 150-160 ppm corresponding to the carbon of the carbamate group. Analyzing HSQC spectrum, there is a signal corresponding to NH_2 that is not coupled with any other of the ^{13}C spectrum.

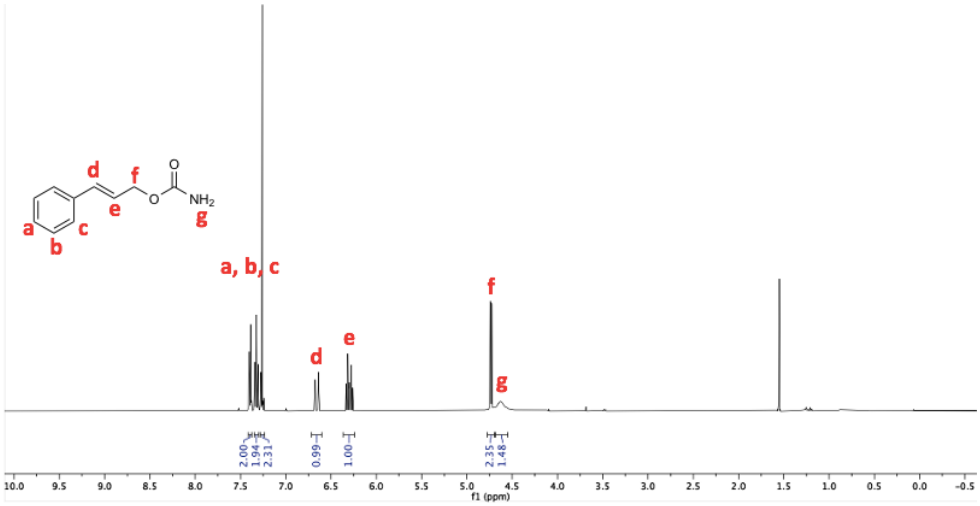


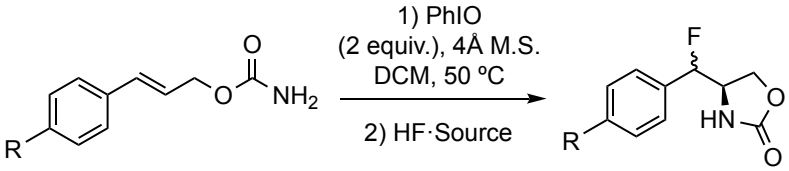
Figure 1. ^{1}H NMR spectra for cinnamyl carbamate **9**.

3.2. Study of the one-pot sequential fluoroamination reaction of cinnamyl carbamates with PhIO and HF·Base reagents.

Inspired by the previous study in our group by Gimenez-Nueno relative to the one-pot I(III)-aziridination of dienyl carbamates followed by stereospecific ring-opening with O, N, and S-nucleophiles (Scheme 3), we sought to extend the scope of this protocol to the study of fluoroamination reaction of dienyl carbamate substrates. To this purpose, we initially explored the fluoroamination process of cinnamyl carbamates as simple model substrates involving one-pot I(III)-mediated intramolecular aziridination followed by ring-opening of the aziridine intermediate with HF·base reagents as a HF source.

In this context, we applied the best reaction conditions for the intramolecular aziridination of cinnamyl carbamate described by Gimenez-Nueno, that involve the use of PhIO as metal-free oxidant, 4Å molecular sieves, dichloromethane as solvent, and 50 ºC. Unlike the reaction conditions previously explored in our group, where ring-opening step was explored in essentially nucleophilic (basic) conditions, the ring-opening of the aryl aziridine with F sources such as HF·NEt_3 or HF·DMPU is expected to be challenging, given the acidic nature and the low nucleophilicity of these reagents.

Table 2. One-pot fluoroamination of *p*-substituted cinnamyl carbamates. [a]



9, R = H
10, R = CH_3
11, R = OMe
12, R = OAc
13, R = Br
14, R = F
15, R = NO2
16, R = CF3

(±)-19, R = H
(±)-20, R = CH_3
(±)-21, R = OMe
(±)-22, R = OAc
(±)-23, R = Br
(±)-24, R = F
(±)-25, R = NO_2
(±)-26, R = CF_3

	Substrate	HF·Source	Yield (%)[b]	dr (anti/syn)[c]
Entry 1	9	HF·DMPU	58	71:29
Entry 2	9	HF·NEt_3	40	15:85
Entry 3	9	HF·py	43	26:74
Entry 4	10	HF·DMPU	25	85:15
Entry 5	10	HF·NEt_3	52	40:60
Entry 6	11	HF·DMPU	-[d]	-
Entry 7	11	HF·NEt_3	-[d]	-
Entry 8	12	HF·DMPU	25	82:18
Entry 9	12	HF·NEt_3	12	44:56
Entry 10	13	HF·DMPU	34	70:30
Entry 11	13	HF·NEt_3	16	64:36
Entry 12	14	HF·DMPU	32	74:26
Entry 13	14	HF·NEt_3	16	58:42
Entry 14	15	HF·DMPU	16	83:17
Entry 15	15	HF·NEt_3	-[e]	-
Entry 16	16	HF·DMPU	10	76:24
Entry 17	16	HF·NEt_3	-[e]	-

[a] Carbamate **9** (1 equiv.), PhIO (2 equiv.), 4Å M.S. (100 mg per 0.1 mmol carbamate **9**), CH_2Cl_2 (0.04M), 35 ºC. HF·DMPU (26 equiv.). or HF·NEt_3 (26 equiv.) [b] Determined after isolation by flash chromatography column. [c] Determined by ^{19}F NMR spectroscopy.[d] Aziridination decomposes. [e] Formation of a byproduct.

The carbamate substrate initially probed in the one-pot I(III)-mediated aziridination/ring opening was cinnamyl carbamate itself (**9**), which was submitted to general conditions for aziridination. The reaction was monitored by TLC until disappearance of the starting material. The mixture was then treated with HF·NEt_3 (26 equiv. HF) as a fluorinating agent at room temperature until disappearance of the aziridine intermediate by TLC. After work-

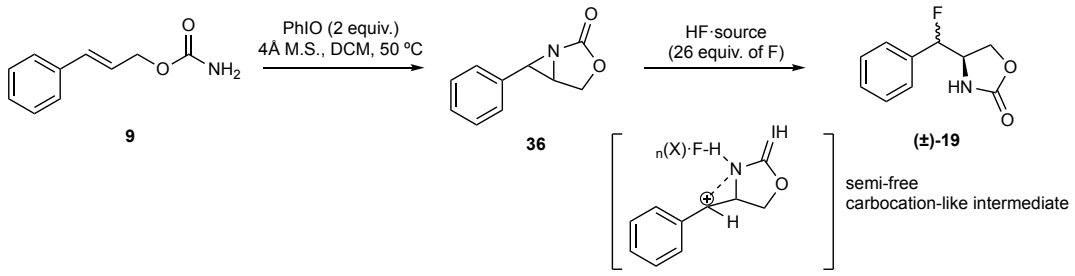
up and chromatographic purifications the fluoro oxazolidinone **19** was isolated as a 15/85 anti/syn diastereomeric mixture in 40% yield (Table 2, entry 2). The analogous reactions using the same amounts of HF equivalents with HF·Py (Table 2, entry 3) and HF·DMPU (Table 2, entry 1) furnished **19** in 43% yield as dr 26:74 anti:syn diastereomeric mixture and dr 71:29 anti:syn diastereomeric mixture in 58% yield, respectively. As HF·py provided similar results from those of $HF{\cdot}NEt_3$, we decided to continue the study only with $HF{\cdot}NEt_3$ and HF·DMPU as fluorinating agents.

The one-pot fluoroamination reaction was also assayed starting from *p*-substituted cinnamyl carbamates in order to explore whether the electronics has an impact on the outcome of the process. The conversion of the carbamate to aziridine was complete in all cases, and in general full conversion of the aziridine intermediate was also observed for the subsequent ring-opening process with F sources, except for reactions with $HF{\cdot}NEt_3$, which, as judged by ^{1}H NMR, revealed traces of aziridine after work-up. Instead, HF·DMPU showed full consumption of the aziridine for all the *p*-substituted cinnamyls. The yields obtained were moderated to low, being higher with HF·DMPU than with $HF{\cdot}NEt_3$. NMR Analysis of the reaction crudes revealed the formation of a byproduct, which could not be fully characterized but possibly corresponding to a ring-opened product, whose amount increased when electron-withdrawing *p*-substituents were used. Besides, this byproduct was the only product formed when CF_3 or NO_2 were used as *p*-substituents in the presence of $HF{\cdot}NEt_3$. Different NMR methods were analyzed to define the structure. No signal was observed by ^{19}F NMR spectroscopy, and the ^{1}H and ^{13}C NMR spectrum pattern was very similar to those obtained for ring-opened products, thus leading to the conclusion that a ring-opened product was obtained, probably by ring-opening process with a nucleophile present in the reaction mixture or the work-up. HRMS analysis of the sample did not provide the molecular peak but revealed some peaks with a mass to charge ratio that could be compatible with the presence of a chlorine. This fact led us to think that this byproduct could correspond to the chloro-oxazolidinone product resulting from the ring-opening process of the aziridine with a chloride anion.

Moreover, when electron-donating groups such as MeO- were used as *p*-substituents in the aryl moiety, the problem arose in the first aziridination stage of the process, which furnished complex mixtures.

One-pot sequential aziridination of cinnamyl carbamates/ring opening of the aziridines with basic O-, N-, and S- nucleophiles studied by Dr. Giménez-Nueno provided the 3-heteoatomic-oxazolidinones in a stereospecific way, both for the aziridination and the ring-opening process leading to the formation of S_N2-anti products.

By contrast, ring-opening of the aziridine intermediates by HF sources did not result stereospecific but led to diastereomeric mixtures of anti/syn ring-openened products. Stereoselectivities could be easily determined by ^{19}F NMR spectroscopy of the crude of the reaction. As commented above, reactions using HF·DMPU proceeded with a moderate degree of 3:1 anti/syn stereoselectivity, affording the anti-product as a major diastereomer. By contrast, reactions with HF·NEt_3 exhibited a complementary behavior in terms of stereoselectivity, affording in most cases the syn-product as a major diastereomer. Taking into account the acidic nature of these reagents, these results could appear counterintuitive. As already described by Okoromoba[30] these HF·base reagents are expected to activate the aziridine intermediate by protonation of hydrogen-bonding to the nitrogen atom at the same time that provide fluorine delivery. The fact that the substrate is an aryl aziridine provides a perfect control of the regioselectivity of the ring-opening process, that could be explained by generation of a semi-free benzylic carbocation-like intermediate, and subsequent nucleophilic attack of fluoride at that position, in a process that proceeds through quasi-racemization (Scheme 14).



Scheme 14. Mechanistical proposal for the stereochemical behavior of our cinnamyl substrates.

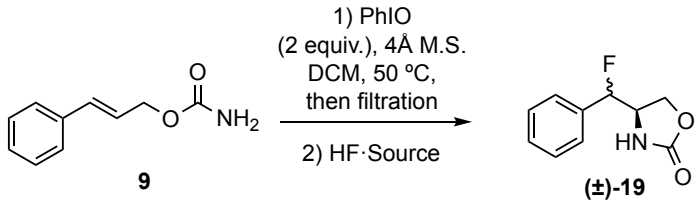
Additionally, the almost invariable diastereomeric ratios provided by the ring-opening of *p*-substituted cinnamyl carbamates with HF·DMPU reveal that the reaction is not sensitive to the electronic properties of the *p*-aryl substituents. In light of the rationale described above, we could think that HF·DMPU, which is more acidic and a better hydrogen-bonding donor than HF·NEt3 is able to activate all the aziridines towards ring-opening in an efficient way, regardless the presence of an electron-withdrawing or electron-donating group. The slight anti stereoselectivity obtained in these reactions could be explained

through a pseudo-carbocation where back site attack could be preferred over front-side attack by hindrance provided by the leaving group.

More intriguing are the results obtained with HF·NEt_3. On one hand, being less acidic than HF·DMPU, HF-NEt_3 should be expected to activate the aziridine in a poorer way, thus leading to lower yields, as it really happens. On the other hand, a worse activation should discard or rest importance to a pseudo-carbocation, therefore expecting to obtain the anti-diastereoselectivity obtained for typical S_N2 processes. In contrast, the complementary syn-diastereoselectivity observed for HF-NEt_3 suggests another operating mechanism, which could involve syn-delivery of fluoride by hydrogen-bonding or by intermediacy of another species.

Taking into account that the aziridination step is performed without any work-up process from the first aziridination step, we suspected that the ring-opening process could be affected by the presence of PhIO in excess, and that in combination with an excess HF·base reagent, it could give rise to $PhIF_2$ reagent. To prove this hypothesis, we decided to explore the one-pot fluoroamination reaction, filtering off the excess PhIO and molecular sieves after the aziridination step. The ring-opening step using either HF·NEt_3 or HF·DMPU was then performed under the general conditions.

Table 3. PhIO-mediated intramolecular aziridination and subsequent ring-opening with HF sources in absence of PhIO



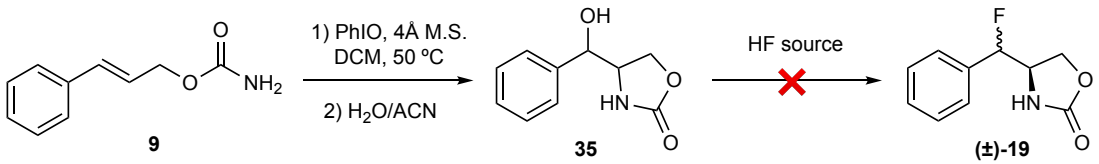
9 **(±)-19**

	Substrate	HF·Source	Yield (%)[b]	dr (anti/syn)[c]
Entry 1	**9**	HF·DMPU	63	74:26
Entry 2	**9**	HF·NEt_3	0[d]	-

[a] Carbamate **9** (1 equiv.), PhIO (2 equiv.), 4Å M.S. (100 mg per 0.1 mmol carbamate **9**), CH_2Cl_2 (0.04M), 50 °C. HF·DMPU (26 equiv.). or HF·NEt_3 (26 equiv.) [b] Determined after isolation by flash chromatography column. [c] Determined by ^{19}F NMR spectroscopy. [d] Unaltered aziridine

The reaction starting from the aziridine derived from **9** using HF·DMPU (26 equiv. HF) as fluorinating agent at room temperature rendered fluoro oxazolidinone **19** which was isolated as a 74:26 anti/syn diastereomeric mixture in a 63% yield (Table 3, entry 1). This

result is in agreement with that obtained in Table 2, entry 1. The analogous procedure with HF·NEt_3 (Table 3, entry 2) did not provide transformation of the aziridine, which remained unaltered along the reaction time. This result showed that HF·NEt_3 itself is not the actual reagent promoting ring-opening of the aziridine intermediate. This result leads us to the idea that HF·NEt_3 is not acidic enough or not such an efficient hydrogen-bonding donor to protonate/activate the aziridine. Therefore, in the reactions where HF·NEt_3 was used in the presence of PhIO, the formation of another species must have been formed, which could correspond to $ArIF_2$, probably responsible for the ring-opening process. Actually, the results obtained with the one-pot fluoroamination of cinnamyl carbamates using PhIO and HF·NEt_3 are very similar in terms of yields and stereoselectivities to those obtained using preformed $ArIF_2$ as only reagent for the tandem aziridination/ring-opening reactions of cinnamyl carbamates, also performed in our group by Albert Granell.



Scheme 15. PhIO-mediated intramolecular aziridination of cinnamyl carbamate **9** and in situ ring-opening with O-nucleophiles.

To gain insight on the ring-opening mechanism, we attempted an experiment to gain evidence on the intermediacy of a carbocation-like intermediate. To this purpose, we envisaged that a solvolysis reaction of hydroxy-oxazolidinone **35** through the activation of the hydroxyl group in the presence of HF·bases could lead to a carbocation species, which could be trapped by fluoride rendering the fluoride oxazolidinone 19 (Scheme 15). We hypothesized that if the diastereoselectivities were similar to those obtained in Table 2, we could say that the mechanism could proceed via semi-free carbocation-like intermediate. Synthesis of the hydroxy-oxazolidinone **35** (58% yield) was performed applying the PhIO–mediated aziridination/ring-opening reaction conditions studied by Dr. Giménez-Nueno with H2O/ACN. Regretally, solvolysis reactions of compound 35 with either HF·DMPU or HF·NEt_3, respectively, in DCM as solvent did not take place and the starting material **35** was unaltered.

3.3. Elucidation of the structural determination.

All the products were characterized by NMR spectroscopy (^{1}H, ^{13}C, ^{19}F) and the spectroscopic data were similar to the one founded in the literature[43] by Xu. Xu described that these compounds are characterized by the signal for the proton in geminal place to the fluor that is founded between 5.30-5.60 ppm as a doublet of doublet with a characteristic constant coupling of 46.00 Hz approximately. The aromatic protons are founded in the range 6.80-8.00 ppm. Diastereotopic protons (Figure 11 and 12, f and f') displayed different chemical shifts for the anti- (4.21-4.33 and 4.14-4.17 ppm) (Figure 11) and syn-product (4.45-4.60 ppm and 4.19-4.11) (Figure 12). Consequently, structure anti/syn can be attributed in each case.

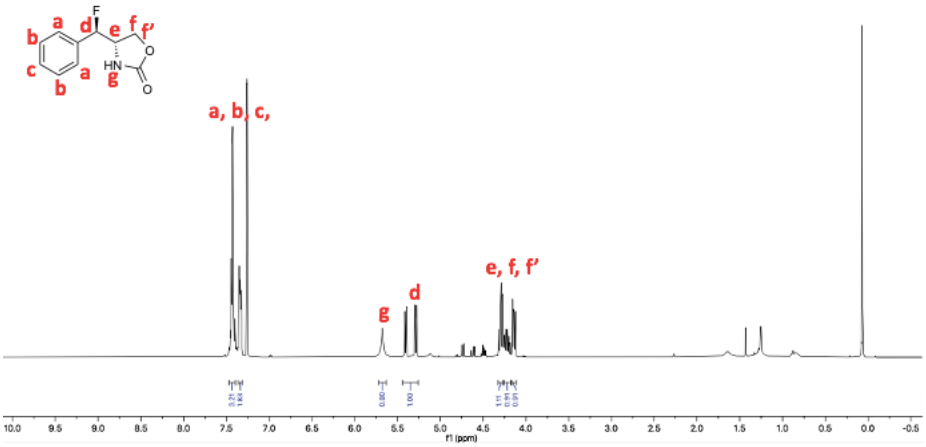


Figure 11. Example of ^{1}H NMR spectra for the anti-oxazolidinone in $CDCl_3$.

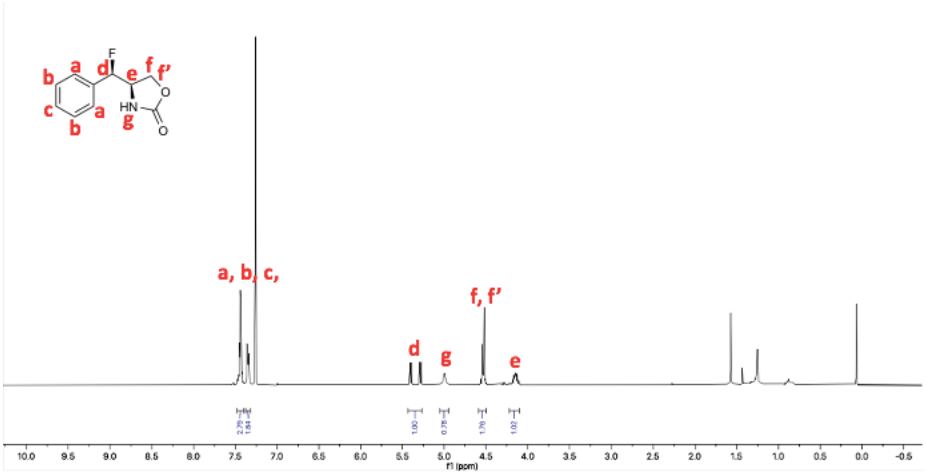


Figure 12. Example of ^{1}H NMR spectra for the syn-oxazolidinone in $CDCl_3$.

[43] Lu, D.; Zhu, C.: Sears, J.; Xu, H. *J. Am. Chem. Soc*. **2016**, *138*, 35, 11360-11367.

By ^{19}F NMR spectroscopy there is the possibility to differentiate between the diastereoisomers (Figure 13). The ppm range in which the two desired products are measured between -180 and -190 ppm, characteristic of a secondary alkyl fluoride with the anti-compound being the most deshielded. This characteristic signal is confirmed with the aforementioned one in ^{1}H NMR since both contain the $^{2}J_{HF}$ coupling constant of 46 Hz.

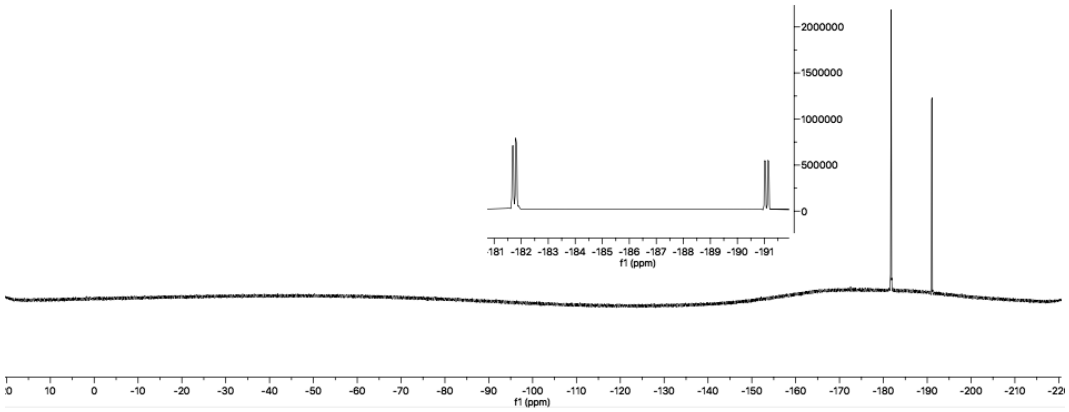
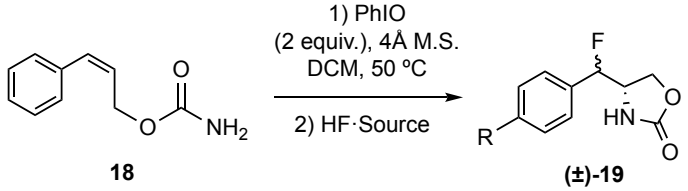


Figure 13. Example of ^{19}F NMR of diastereomeric oxazolidinones.

3.4. Study of the configuration (*E* vs *Z*) of alkenes in the one-pot fluoroamination of cinnamyl carbamates.

Table 4. One-pot fluoroamination of (Z)-cinnamyl carbamates.



18 **(±)-19**

	HF·Source	Conversion (%)[b]	Yield (%)[c]	dr (anti/syn)
Entry 1	HF·DMPU	15	1	46:54
Entry 2	$HF{\cdot}NEt_3$	18	8	75:25

[a] Carbamate **9** (1 equiv.), PhIO (2 equiv.), 4Å M.S. (100 mg per 0.1 mmol carbamate **9**), CH_2Cl_2 (0.04M), 35 ºC, HF·DMPU (26 equiv.). or $HF{\cdot}NEt_3$ (26 equiv.) [b] Determined by ^{1}H NMR spectroscopy. [c] Determined after isolation by flash chromatography column. [d] Determined by ^{19}F NMR spectroscopy.

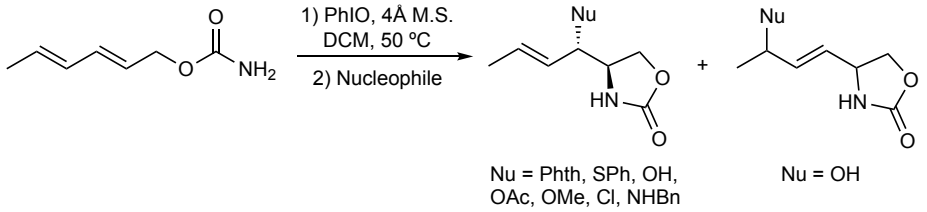
To prove whether this process could proceed through the intermediacy of a carbocation-like species, we decided to explore the reaction starting from cis-cinnamyl carbamate **18**, with the idea that if that was the case, the reaction would be stereoconvergent and thus

lead to fluoro-oxazolidinones with the same diastereoselectivity. The *cis* cinnamyl carbamate was tested with PhIO (2 equiv.) in the presence of 4Å M.S. and CH_2Cl_2. The reaction was monitored by TLC in which it was observed that the reaction did not go to complete conversion. The reaction was left to react for 7 days and by means of ^{1}H NMR spectroscopy conversion to aziridine was estimated in 15-18%. The low conversion obtained is in agreement with the DFT calculations carried out by Prof. Feliu Masseras, who described that when there is a trans alkene, π-stacking interactions are produced in the transition state between the aromatic ring of the substrates and the phenyl group of the hypervalent iodine specie. In this case, the existence of a cis alkene considerably decreases these interactions, making it difficult for the reaction to take place.

Despite the low conversion to aziridine, it was decided to add HF·DMPU and HF·NEt_3 to understand how the role of the alkene configuration can affect the fluoroamination reaction. After work-up, the diastereomeric ratio was analyzed by ^{19}F NMR spectroscopy obtaining the two diastereoisomers of the oxazolidinone **19** for both cases. When HF·DMPU was used, no stereoselectivity was obtained, obtaining an approximately equimolar mixture of anti and syn 19 (Table 4, Entry 1). Instead, rection from HF·NEt_3 resulted slightly stereoselective towards **anti-19** (dr 75:25) (Table 4, Entry 2). Finally, chromatographic column for reaction with HF·DMPU and HF·NEt_3 was performed to analyze the yield for each reaction obtaining a 1% and an 8%, respectively. The extremely low yields obtained in these assays discard conclusion from these experiments.

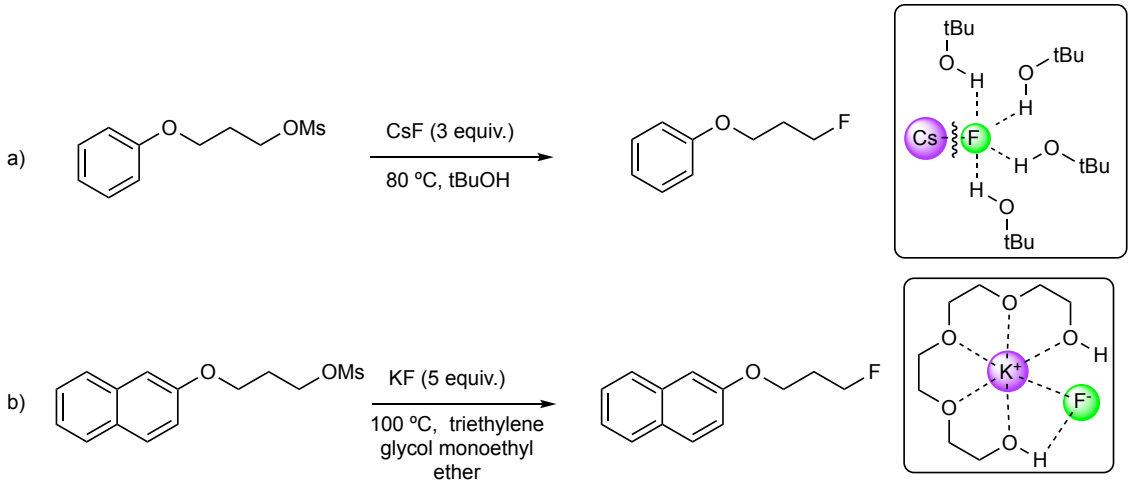
3.5. Use on non-acidic fluor sources in the ring-opening reaction of cinnamyl carbamates: TMAF, CsF, KF…

According to previous studies in our group by Dr. Giménez-Nueno to provide different substituted oxazolidinones, several nucleophiles in basic medium were tested to explore the scope of the ring-opening of the aziridine intermediate. Under those conditions, the reaction produced a single diastereoisomer as shown in Scheme 16, resulting from a typical S_N2 mechanism. Only a regioisomeric mixture was obtained when water was used as a nucleophile forming the corresponding alcohol group.



Scheme 16. Iodine(III)-mediated metal-free intermolecular aziridination and subsequent ring-opening by an external nucleophile studied by Giménez-Nueno.

In this context, the use of new fluorinating agents such as alkali metals or ammonium fluorides has been tested. These new reagents provide a different reactivity than hydrofluoric acid due to the basic conditions of the reaction, as well as being commercially available and safer. The main problem of them lies in the low solubility of these compounds in organic solvents.[44] To solve this problem, the use of crown ether for the generation of "naked" fluoride ion from KF was discovered.[45] Alternatively, ammonium fluorides are used to bring fluoride to the organic phase.[46]



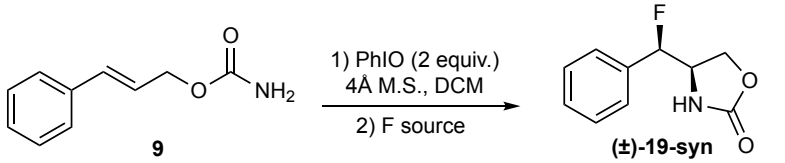
Scheme 17. Nucleophilic fluorination using alkali metals.

In 2008 a nucleophilic fluorination reaction in presence of tert-alcohol as a reaction medium was reported (a, Scheme 17).[47] The existence of hydrogen bonds surrounding the fluoride anion reduces the ionic bond strength of the alkali metal with the fluoride, increasing the nucleophilicity. In 2009, Chi and coworkers designed a method to introduce

[44] Neumann, C.N.; Ritter, T. *Angew. Chem. Int. Ed.* **2015**, *54*, 3216-3221.
[45] Kim, D.W.; Song, C.E.; Chi, D.Y. *J. Am. Chem. Soc.* **2002**, *124*, 10278-10279.
[46] Pilcher, A.S.; Ammon, H.L.; DeShong, P. *J. Am. Chem. Soc.* **1995**, *117*, 5166-5167.
[47] Kim, D.W.; Lim, S.T.; Sohn, M.; Katzenellenbogen, J.A.; Chi, D.Y. *J. Org. Chem.* **2008**, *73*, 957-962.

a fluoride ion from KF in a S_N2 reaction (b, Scheme 17)[48]. For this purpose, they proposed a crown ether mimic such as tetraethylene glycol that is able to surround the potassium with the ether groups, releasing the fluoride ion that will generate a hydrogen bond with one of the OH groups.

Table 5. One-pot sequential fluoroamination using basic fluorination reagents.



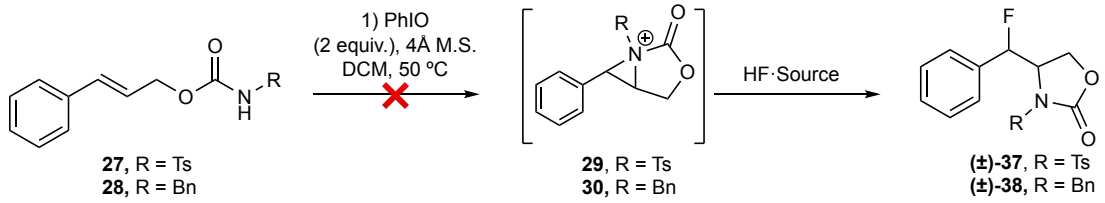
Entry	Fluoride source	Solvent	Yield (%)[b]
1	TMAF	DCM	C.M.
2	CsF	tBuOH	12
3	KF	triethylene glycol monoethyl ether	13

[a] Carbamate **9** (1 equiv.), PhIO (2 equiv.), 4Å M.S. (100 mg per 0.1 mmol carbamate **9**), CH_2Cl_2 (0.04M), 35 ºC. TMAF (5 equiv.), CsF (3 equiv., tBuOH), KF (5 equiv., tryethylene glycol monoethyl ether) [b] Determined after isolation by flash chromatography column [c] C.M. = Complex mixture.

With all this in hand, carbamate **9** was explored in a one-pot sequential reaction using the standard conditions of PhIO and the fluorinating agents mentioned in this section. TMAF reagent was used for the fluoroamination reaction and judged by TLC, the aziridine disappeared. By ^{1}H and ^{19}F NMR spectroscopy signals from oxazolidinone **19-syn** could be detected as a single diastereoisomer. After work-up and column chromatography, a complex mixture of different fluorine compounds presents in the crude appeared in the same fraction than our oxazolidinone, not allowing us to determine the yield in a proper way. For the case of CsF and KF (Table 5, entry 3 and 4), dichloromethane had to be evaporated under reduced pressure to subsequently add the alkaline metal followed by the dry solvent used to generate the hydrogen bonds. The reactions afforded in all cases the syn-oxazolidinone **19** and in no cases the anti-product. Due to time constrains we could not optimize this process to finally test it in dienyl carbamates.

[48] Lee, J.W.; Yan, H.; Jang, H.B.; Kim, H.K.; Park, S.W.; Lee, S.; Chi, D.Y. *Angew. Chem. Int. Ed.* **2009**, *48*, 7683-7686.

3.6. Aziridination reaction for substituted Carbamates



Scheme 18. I(III)-mediated aziridination of *N*-substituted carbamates.

Nevado and coworkers reported the fluoroamination of alkenyl sulfonamides by reaction with $ArIF_2$.[38] The process was envisaged to proceed through the initial activation of the I(III) reagent by hydrogen bonding with the acidic proton at the sulfonamide moiety (Scheme 8). Subsequent intramolecular aziridination from an aminoiodane then furnishes an aziridinium ion that is ultimately opened by a fluoride ion. Taking into account these results, we investigated the PhIO mediated aziridination of Ts-substituted carbamates with the idea that, on one hand, the presence of an acidic proton would favor the activation of the I(III) reagent and, on the other hand, it could generate an analogous aminoiodane intermediate, instead of an iminoiodane, that could serve as a nitrene source for aziridination. Besides, the formation of an aziridinium intermediate would also favor ring-opening without the need of further activation. Benzyl-carbamates were also tested as a blank assay for substituted carbamates, as the acidity of the proton on NBn is similar to unsubstituted carbamates.

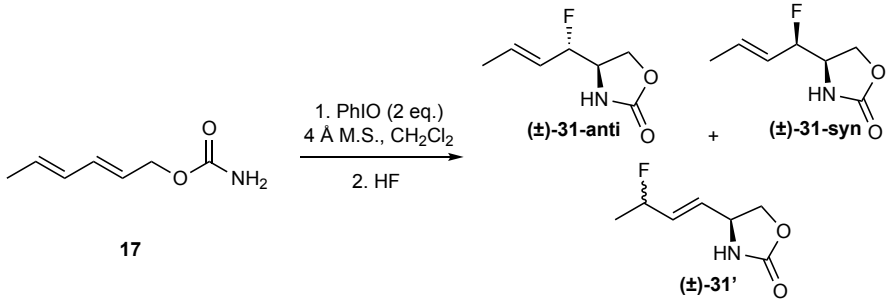
In our hands, PhIO-mediated aziridination of substituted cinnamyl carbamates did not afford any product and unaltered starting materials were recovered, thus discarding the aminoiodane intermediate as and actual nitrene source.

3.7. Study of the regio- and stereoselectivity in dienyl carbamates

Having explored the one pot sequential fluoroamination reaction of cinnamyl carbamates, we next investigated the analogous process starting from dienyl carbamates, aiming at synthesizing unsaturated 2-amino-3-fluoro-1-alcohols en route to sphingosine analogues. According to previous work developed by Dr. Joan Guasch, dienyl carbamate **I7** was synthesized from commercially available (2*E*,4*E*)-hexa-2,4-dien-1-ol and treated with the general procedure of the carbamoylation. These types of substrates are more challenging in terms of regioselectivity since their aziridine intermediate can undergo, as well as a S_N2-like ring-opening, and S_N2' ring opening leading to unsaturated 4-fluoro-1 amino products. Furthermore, studies in our group showed that ring opening of the vinyl aziridine

intermediates with non-basic O or S nucleophiles afforded by-products arising from S_N2' attack. This fact anticipates that S_N2' ring-opening of vinyl aziridines arising from dienyl carbamates may be a feasible reaction path using HF·base reagents (HF·NEt_3 and HF·DMPU), altogether with the S_N2-like ring opening reaction path. This reaction outcome would then lead to a combination of regioisomeric (S_N2 vs S_N2') products, each one as a diastereomeric mixture of anti- or syn configured compounds (Table 6).

Table 6. PhIO mediated intramolecular aziridination of model dienyl carbamate and in situ ring-opening with HF sources.



Entry	Hypervalent iodine	HF source	Temperature (ºC)	SN_2 product ratio (%)[b]	SN_2' product ratio (%)[b]	Yield (%)[c]
1	PhIO	DMPU	25	53 (anti/syn dr: 65:35)	47 (dr 51:49)	28
2	PhIO	NEt_3	25	50 (anti/syn dr: 48:52)	50 (dr 53:47)	17
3	PIDA	DMPU	25	54 (anti/syn dr: 64:36)	46 (dr 63:37)	33
4	PIDA	NEt_3	25	66 (anti/syn dr: 33:67)	34 (dr 54:46)	17
5	PhIO	DMPU	0	63 (anti/syn dr: 75:25)	37 (dr 51:49)	27

[a] Carbamate **17** (1 equiv.), PhIO (2 equiv.), 4Å M.S. (100 mg per 0.1 mmol carbamate **9**), CH_2Cl_2 (0.04M), 35 ºC. Nu = F, HF·DMPU (26 equiv.). Nu = F, HF·NEt_3 (10 equiv.) [b] Determined after isolation of the 4 diastereoisomers by flash chromatography column. [c] Determined by 19F NMR spectroscopy.

When dienyl carbamate **17** was submitted to one-pot sequential fluoroamination using the standard conditions using PhIO or PIDA as an oxidative agent, and HF·DMPU or HF·NEt3 as a fluorinating agent in the aziridination step, the reaction proceeded with apparent full conversion of the starting carbamate and the vinyl aziridine intermediate as judged by TLC (Table 6, entry 1) but afforded moderate to low yields of the fluorinated products. Note that the mixture of products resulted difficult to separate by chromatographic techniques and because they have no bibliographic reference, we could not fully characterize them. Temptative assignment of S_N2 product were performed by analogy of the chemical shifts observed with those observed for cinnamyl-derived products. Thus, signals at 178.7 ppm and 182.6 ppm in the ^{19}F NMR spectrum were assigned to S_N2-anti

and S_N2-syn products, respectively. Additional signals appearing at 170.3 and 170.6 ppm, as dtt, partly due to the fact that they are vicinal to a CH_3 group, were hence attributed to the S_N2'-products, although no assignment to the syn or anti diastereomeric nature of each product could be done.

The reactions afforded approximately equimolar mixtures of regiosiomeric S_N2 and S_N2' ring-opened products (Table 6, entries 1-3), except for reaction with PIDA and HF·NEt_3, which resulted in a moderate regioselectivity towards the S_N2-regioisomer (Table 6, entry 4). As far as the stereoselectivity outcome is concerned, no clear trend can be described for this process. On one hand, the major diastereoisomer product for the S_N2 products depends on the fluorinating agent, so that when HF·DMPU was used, the SN2-anti isomer was obtained in a modest diastereoselectivity, whereas when HF·NEt3 was used, either no stereoselectivity was observed using PhIO or a moderately selectivity towards the syn-diastereoisomer was observed using PIDA. As for the S_N2'-product is concerned, the stereoselectivity outcome was in almost all cases null (Table 6, entries 1,2 and 4) except for the reaction using PIDA and HF·DMPU which provided a 2:1 diastereomeric ratio towards the anti (Table 6, entry 3).

Some tests carried out in our research group by Albert Granell with dienyl carbamates and $ArIF_2$ as oxidant species revealed that reactions at 0 ºC, resulted in an increase in the anti-S_N2 stereoselectivity. We therefore explored the ring-opening step of the aziridine derived from **17** by addition of HF·DMPU at 0 °C and stirring the resulting mixture at that temperature. This reaction afforded fluoro-oxazolidinones in a moderate regioselectivity towards S_N2 products (Table 6, entry 5), as expected. Additionally, the stereoselectivity for the S_N2-anti also increased at low temperatures as expected. By contrast, for the S_N2'-product, the stereoselectivity outcome was null.

4. Conclusions

The present work aimed at developing a practical protocol for synthesizing β-Fluoroamine scaffolds from cinnamyl carbamates as simple model substrates of dienyl carbamates, which will be ultimately used for the synthesis of fluorinated sphingolipid analogs. The proposed synthetic fluoroamination route relied on a metal-free intramolecular aziridination by I(III)-reagents and the subsequent ring-opening of the vinyl aziridine intermediate with different fluorine sources.

A library of cinnamyl carbamates were prepared in good synthetic yields from the corresponding cinnamyl alcohols which, in turn, where synthesized from the corresponding commercially available cinnamic acid.

The one-pot sequential fluoroamination of cinnamyl carbamates using PhIO as hypervalent iodine reagent in the presence of 4A molecular sieves in dichloromethane followed by addition HF·bases (DMPU, NEt_3, Py) led to the synthesis of fluoro-oxazolidone products in good to moderate yields. More specifically the conclusions were:

· Fluoroamination from **9** using HF·DMPU led to a diastereomeric mixture of fluoro-oxazolidinones **19** in moderately good yield, with a 3:1 preference towards the anti-isomer.

· Analogous reactions from p-substituted cinnamyl carbamates furnished the corresponding oxazolidinones in comparable lower yields, with almost the same degree of stereoselectivity towards the anti-product.

· In contrast, one-pot fluroamination starting from **9** with HF·NEt_3 led to the preferential formation of fluoro-oxazolidinone syn **19**. Analogous reactions from *p*-substituted cinnamyl carbamates led to the fluorinated products in low yield and lower stereoselectivity.

· Ring-opening step with HF·NEt_3 in the absence of PhIO did not produce the fluoro-oxazolidinone products, thus suggesting that HF·NEt_3 itself is not capable of promoting ring-opening of the aryl aziridine intermediate, and that the mechanism of this reaction might proceed via the intermediacy of $ArIF_2$.

· The cis-cinnamyl carbamate was almost unreactive under the one-pot sequential fluoroamination reaction conditions, thus stating the importance of the alkene configuration.

· *N*-Substituted carbamates were not aziridinated using PhIO as a promoter

· The use of basic fluorine nucleophiles for the ring-opening stage of cinnamyl substrates exclusively affords the syn-oxazolidinone, although in low yields. The optimization of this new fluorine reagents and the respective tests with dienyl carbamates can be a promising system to specifically obtain one of those diastereoisomers.

· The one-pot sequential intramolecular aziridination/ring-opening of dienyl carbamate **17** furnished a mostly equimolar regiosiomeric mixture of S_N2 and S_N2'-openend fluoro-ozadolidinones **3l** and **3l'**, which were obtained as anti/syn diastereomeric mixtures. Both reactions using HF·NEt_3 or HF·DMPU proceeded in low to moderate yields.

· Use of HF·DMPU at 0 ºC improves the S_N2 selectivity, and lead room for a future optimization.

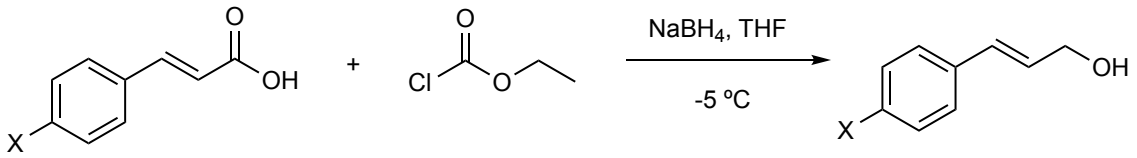
5. Experimental part

5.1. General methods

Proton (^{1}H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were recorded on a 400 MHz (for 1H) and 100.6MHz (for ^{13}C) Varian VNMR-S400 NMR instrument at 25°C in CDCl3. All chemical shifts are quoted on the δ scale in ppm using the residual solvent as internal standard (^{1}H NMR: CDCl3=7.26ppm) and ^{13}C NMR: $CDCl_3$=77.16ppm). Coupling constant (J) are reported in Hz with the following splitting abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, bs = broad singlet. Infrared (IR) spectra were recorded on a JASCO FTIR-680 plus Fourier Transform Infrared Spectrophotometer, wavenumbers ($\tilde{\nu}$) in cm^{-1}. ESI MS were run on an Agilent® 1200 Series HPLC-TOF instrument. Thin layer chromatography (TLC) was carried out on 0.25 mm E. Merck® aluminium backed sheets coated with 60 F_{254} silica gel. Visualization of the silica plates was achieved using a UV lamp (λ_{max} = 254 nm).

5.2. General procedures

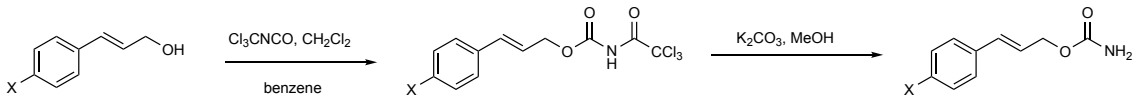
5.2.1. General procedure for the reduction of cinnamic acids (1-8).



***Scheme 19**. General procedure for the reduction of cinnamic acids.*

Cinnamic acid (9 mmol) was dissolved in dry THF (12 mL) in an Schlenk tube at -5 ºC. Then, triethylamine (9 mmol) is added to the solution and the reaction is allowed to stir for 1h. Ethyl chloroformate (13.5 mmol) is added to the solution and the reaction is stirred for 1 hour. Finally, sodium borohydride (33.86 mmol) was introduced followed by an addition of methanol (8.4 mL) drop by drop. The reaction remains stirring at room temperature until showing totally conversion. Saturated NH_4Cl (16.2 mL) was added to quench the reaction and it was performed a liquid-liquid extraction with dichloromethane (3x20mL). The solution is dried with anhydrous Na_2SO_4 and filtered. The solvent is removed under reduced pressure. The crude was purified by flash chromatography using hexane/AcOEt mixture to give the final product.

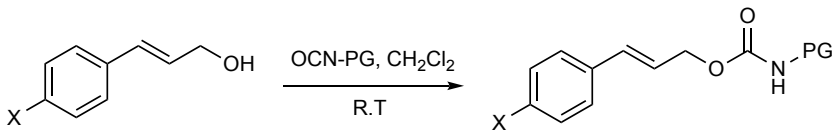
5.2.2. General procedure for the carbomoylation of alcohols (9-18)



***Scheme 20**. General procedure for the carbamoylation of alcohols.*

Cinnamyl alcohol (1 mmol) was dissolved in dichloromethane (2 mL). Dry toluene (1 mL) and trichloroacetyl isocyanate (1.3 mmol) was added to the Schlenk tube. The reaction was stirred at room temperature until TLC shows totally conversion. Then, the addition of K_2CO_3 (%20 mol) in methanol (3 mL) produces the second step of the reaction called methanolysis. The reaction is followed by TLC and when it is finished the solvent is removed under reduced pressure. The residue was dissolved in a mixture 1:1 of diethylether and water. The aqueous phase was extracted with diethylether (3x10 mL) and washed with brine. The combined organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude was purified by flash chromatography using hexane/AcOEt mixture and then it was recrystallized by slow diffusion of pentane into a solution of the carbamate in THF.

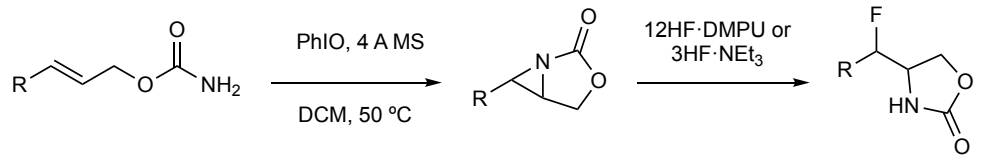
5.2.3. General procedure for the synthesis of *N*-substituted carbamates (27-28)



***Scheme 21**. General procedure for the synthesis of Tosyl/Benzyl carbamates.*

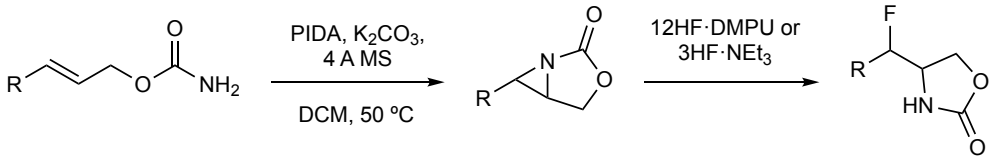
To a Schlenk tube is dissolved the corresponding alcohol in dry dichloromethane followed by the addition of benzyl or tosyl isocyanate dropwise. The reaction is stirred until TLC shows complete consumption of the starting material. The crude was treated with saturated NH_4Cl solution. The organic phase is separated by an extraction liquid-liquid and the solution is dried with anhydrous $MgSO_4$ and filtrated. The solvent is removed under reduced pressure. The product is purified by silica chromatography using a mobile phase of Hexane:EtOAc. The corresponding carbamates are crystallized by slow diffusion after purification.

5.2.4. General procedure for the fluoroamination with HF sources (19-26,31)



***Scheme 22**. PhIO-mediated intramolecular aziridination and subsequent ring-opening with HF·Sources.*

Procedure 1. To a Schlenk tube it was added 4 Å M.S. and it was flame dried under vacuum for 2 minutes. Dry dichloromethane was added under argon atmosphere and the solution was stirred for 20 minutes. Then, carbamate and powdered PhIO were added and the reaction was stirred at 50 °C. When TLC shows complete conversion of the carbamate to aziridine, it was added the corresponding fluorine source (12 HF·DMPU or 3HF·NEt_3). The reaction is controlled by TLC. When the reaction was finished, saturated $NaHCO_3$ was added in the Schlenk tube to neutralize the acidic medium. Then, it was done an extraction liquid-liquid with CH_2Cl_2. Na_2SO_4 was added to remove water and it was filtered. The solvent was reduced under pressure. The corresponding crude was purified with a column chromatography of ether/hexane.

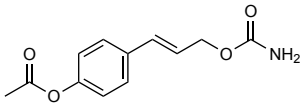


***Scheme 23**. PIDA-mediated intramolecular aziridination and subsequent ring-opening with HF·sources.*

Procedure 2. To a Schlenk tube it was added 4 Å M.S. and it was flame dried under vacuum for 2 minutes. Dry dichloromethane was added under argon atmosphere and the solution was stirred for 20 minutes. Then, K_2CO_3 is added to favor the formation of the aziridine. Powdered PIDA and carbamate were added, and the reaction was stirred at 50 °C. When TLC shows complete conversion of the carbamate to aziridine, it was added the corresponding fluorine source. The reaction is controlled by TLC. When the reaction was finished, saturated $NaHCO_3$ was added in the Schlenk tube to neutralize the acidic medium. Then, it was done an extraction liquid-liquid with CH_2Cl_2. Na_2SO_4 was added to remove water and it was filtered. The solvent was reduced under pressure. The corresponding crude was purified with a column chromatography of ether/hexane.

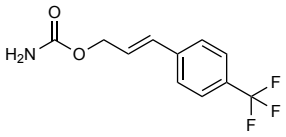
5.2.5. Characterization data.

· (*E*)-4-(3-(carbamoyloxy)prop-1-en-1-yl)phenyl acetate (**12**)



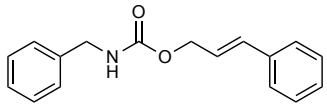
Cinnamyl alcohol **4** (1000 mg, 5.20 mmol), DCM (10.40 mL), toluene (5.2 mL) and TAI (651 μL, 5.46 mmol) were stirred at room temperature in a Schlenk tube. Then, K_2CO_3 (144 mg, 1.04 mmol) and methanol (15.60 mL) were added to the mixture and the reaction was stirred until TLC shows totally conversion. The crude was purified by chromatography column using a mobile phase of hexane/AcOEt (6:4). Recrystallization by slow diffusion rendered **12** as a white solid in an 80% yield. **m.p.** 138-139 °C. **IR (neat):** 3419, 3335, 3255, 3210, 2966, 2364, 1754, 1683, 1617, 1508, 1350, 1214, 1062 cm^{-1}. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.42 – 7.37 (m, 2H), 7.07 – 7.03 (m, 2H), 6.63 (d, *J* = 15.9 Hz, 1H), 6.25 (dt, *J* = 15.9, 6.4 Hz, 1H), 4.72 (dd, *J* = 6.3, 1.4 Hz, 2H), 2.30 (s, 2H). **^{13}C NMR** (100 MHz, CDCl3) δ 169.6 (CH3CO), 156.6 (OCONH2)150.5 (Car), 134.2 (Car), 133.0 (C3), 127.7 (C2), 124.0 (Car), 121.9 (Car), 65.7 (C1), 21.3 (CH3CO). **HR ESI-TOF MS** for [M+Na+] $C_{12}H_{13}NNaO_3$+ (m/z): 242.0788; found: 242.0735.

· (*E*)-3-(4-(trifluoromethyl)phenyl)allyl carbamate (**16**)



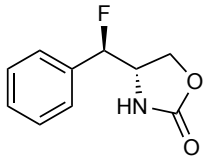
Cinnamyl alcohol **8** (374 mg, 1.85 mmol), DCM (3.70 mL), toluene (1.85 mL) and TAI (287 μL, 2.4 mmol) were stirred at room temperature in a Schlenk tube. Then, K_2CO_3 (52 mg, 0.37 mmol) and methanol (5.6 mL) were added to the mixture and the reaction was stirred until TLC shows totally conversion. The crude was purified by chromatography column using a mobile phase of hexane/AcOEt (6:4). Recrystallization by slow diffusion rendered **16** as a white solid in a 75% yield. **m.p.** 118-120 °C. **IR (neat):** 3443, 3327, 3268, 3197, 3038, 2966, 2359, 2327, 1740, 1686, 1321, 1065 cm^{-1}. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.58 (d, *J* = 8.2 Hz, 2H), 7.48 (d, *J* = 8.1 Hz, 2H), 6.68 (d, *J* = 16.0 Hz, 1H), 6.38 (dt, *J* = 15.9, 6.0 Hz, 1H), 4.76 (dd, *J* = 6.1, 1.4 Hz, 2H), 4.65 (s, 2H). **^{13}C NMR** (100 MHz, CDCl3) δ 156.5 (OC(O)NH2), 139.9 (Car), 132.1 (C3), 129.9 (q, J = 32.2 Hz, Car), 127.0 (apparent d, J = 271.9 Hz, CF3) 126.9 (Car), 126.6 (C2), 125.73 (q, J = 4.5 Hz, Car), 65.3 (C1). **^{19}F NMR** (377 MHz, CDCl3) δ -62.6. **HR ESI-TOF MS** for [M-H] $C_{11}H_9F_3NO_2$- (m/z): 244.0585; found: 244.0590.

· Cinnamyl benzylcarbamate (**28**)



The title compound was synthesized following the general procedure for the synthesis of substituted carbamates. Cinnamyl alcohol **1** (1106 mg, 8.00 mmol), DCM (10 mL) and benzyl isocyanate (1090 μL, 8.80 mmol) were stirred at room temperature in a Schlenk tube until TLC shows totally conversion. The crude was purified by chromatography column using a mobile phase of hexane/AcOEt (6:4). Recrystallization by slow diffusion rendered **28** as a white solid in a 80% yield. **IR (neat):** 3301, 1683, 1653, 1538, 1260, 1056. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.61 – 7.18 (m, 10H, H_{ar}), 6.64 (d, *J* = 15.9 Hz, 1H, H_3), 6.30 (dt, *J* = 15.8, 6.3 Hz, 1H, H_2), 5.20 (s, 1H, H_{NH}), 4.77 (t, *J* = 7.7 Hz, 2H, H_1), 4.39 (d, *J* = 5.9 Hz, 1H, H_4). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 156.38 (CO), 138.48 (C_{ar}), 136.32 (C_{ar}), 133.64 (C_3), 128.66 (C_{ar}), 128.58 (C_{ar}), 127.97 (C_{ar}), 127.52 (C_{ar}), 127.48 (C_{ar}), 126.60 (C_{ar}), 123.89 (C_2), 65.58 (C_1), 45.11 (C_4). **HR ESI-TOF MS** for [M+Na+] $C_{17}H_{17}NNaO_2$ (m/z): 290.1157; found: 290.117.

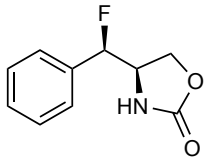
· *u*-4-((*R*)-fluoro(phenyl)methyl)oxazolidin-2-one ((+)-**19-anti**)



The title compound was synthesized following the procedure 1 of the fluoroamination of carbamates. 4 Å M.S. (280 mg) were added to a Schlenk tube and dissolved in dry dichloromethane (7.00 mL) under an argon atmosphere. Carbamate **9** (50 mg, 0.28 mmol) and powdered PhIO (124 mg, 0.56 mmol) were introduced in one portion and the reaction was stirred at 50 °C. When the starting material was consumed, the corresponding fluorine source (26 eq of fluorine) was added and controlled by TLC. The crude was purified by chromatography column using a mobile phase of Et_2O/Hexane (75:25) mixtures. Compound **19** was isolated in a 58% yield with a dr 71/29 (anti/syn) when HF·DMPU was used and in a 40% yield with a dr 15/85 (anti/syn) when HF·NEt_3 was used. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.48 – 7.40 (m, 3H), 7.35 (p, *J* = 2.2 Hz, 2H), 5.68 (s, 1H), 5.35 (dd, *J* = 46.9, 6.7 Hz, 1H), 4.32 – 4.18 (m, 2H), 4.16 – 4.11 (m, 1H). **^{19}F NMR** (377 MHz, CDCl3) δ -181.62 (dd, J= 47.1, 13.8 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$) *δ* 158.9, 134.4 (d, J=20.2 Hz), 129.9, 129.8, 126.3 (d, J=6.1 Hz), 94.6 (d, J=177.8 Hz), 65.3 (d, J=7.1 Hz), 56.6 (d, J=25.3 Hz). **IR ν_{max} (neat)/cm^{-1}:** 3264 (w), 1753 (s), 1410 (m), 1266 (s), 1236 (s), 1026 (s), 934 (m), 733

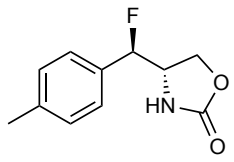
(s), 699 (s). **HR ESI-TOF MS** for [M+H+] $C_{10}H_{11}NO_2F^+$ (m/z): 196.0774, found 196.0769. The analytical data matched with the previously reported.[49]

· *l*-4-(fluoro(phenyl)methyl)oxazolidin-2-one ((+)-**19-syn**)



The title compound was synthesized following the procedure 1 of the fluoroamination of carbamates. 4 Å M.S. (280 mg) were added to a Schlenk tube and dissolved in dry dichloromethane (7.00 mL) under an argon atmosphere. Carbamate **9** (50 mg, 0.28 mmol) and powdered PhIO (124 mg, 0.56 mmol) were introduced in one portion and the reaction was stirred at 50 °C. When the starting material was consumed, the corresponding fluorine source (26 eq of fluorine) was added and controlled by TLC. The crude was purified by chromatography column using a mobile phase of Et_2O/Hexane (75:25) mixtures. Compound **19** was isolated in a 58% yield with a dr 71/29 (anti/syn) when HF·DMPU was used and in a 40% yield with a dr 15/85 (anti/syn) when HF·NEt_3 was used. **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.52 – 7.40 (m, 3H), 7.40 – 7.30 (m, 2H), 5.34 (dd, *J* = 46.3, 7.1 Hz, 1H), 5.00 (s, 1H), 4.59 – 4.47 (m, 2H), 4.18 – 4.08 (m, 1H). **^{13}C NMR** (100 MHz, CDCl3) δ 158.8 (C2), 135.1 (d, J =19.7 Hz, Car), 129.9 (d, J = 1.8 Hz, Car), 129.3 (Car), 126.3 (d, J = 6.7 Hz, Car), 93.6 (d, J = 178.6 Hz, C1'), 66.9 (d, J = 2.8 Hz, C5), 56.3 (d, J = 31.5 Hz, C4). **^{19}F NMR** (377 MHz, CDCl3) δ –186.26 (dd, J= 46.1, 10.4 Hz). **HR ESI-TOF MS** for [M+Na+] C10H10FNNaO2+ (m/z): 218.0588; found: 218.0593. The analytical data matched with the previously reported.[49]

· *u*-4-(fluoro(*p*-tolyl)methyl)oxazolidin-2-one ((+)-**20-anti**)

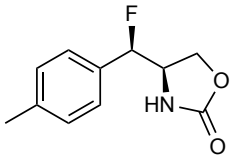


The title compound was synthesized following the procedure 1 of the fluoroamination of carbamates. 4 Å M.S. (260 mg) were added to a Schlenk tube and dissolved in dry dichloromethane (6.50 mL) under an argon atmosphere. Carbamate **10** (50 mg, 0.26 mmol) and powdered PhIO (116 mg, mmol) were introduced in one portion and the reaction was stirred at 50 °C. When the starting material was consumed, the corresponding fluorine source (26 eq of fluorine) was added and controlled by TLC. The crude was purified by chromatography column using a mobile phase of Et_2O/Hexane (80:20) mixtures. Compound **20** was isolated in a 25% yield

[49] Lu, D.; Liu, G.; Zhu, C.; Yuan, B.; Xu, Hao. *Org. Lett.* **2014**, *16*, 2912-2915.

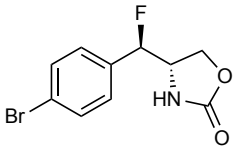
with a dr 85/15 (anti/syn) when HF·DMPU was used and in a 52% yield with a dr 60/40 (anti/syn) when HF·NEt_3 was used. **IR ν_{max} (neat)/cm^{-1}:** 3305 (w), 1756 (s), 1722 (s), 1408 (m), 1284 (s), 1113 (s), 1020 (m), 767 (m), 736 (m). **^{1}H NMR (400 MHz, Chloroform-*d*) δ** 7.25 – 7.22 (m, 4H), 5.30 (dd, *J* = 47.1, 7.0 Hz, 1H), 4.31 – 4.15 (m, 2H), 4.16 – 4.08 (m, 1H), 2.38 (d, *J* = 1.7 Hz, 4H). **^{19}F NMR (377 MHz, Chloroform-*d*) δ** -179.07 (dd, *J* = 47.1, 13.2 Hz).**^{13}C NMR (100 MHz, $CDCl_3$): δ** 166.3, 159.0, 139.7 (d, J=20.0 Hz), 131.3, 130.26, 125.9 (d, J=7.0 Hz), 92.8 (d, J=179.0 Hz), 66.2 (d, J=4.0 Hz), 56.2 (d, J=29.0 Hz). **^{13}C NMR (100 MHz, $CDCl_3$): δ** 166.3, 159.0, 139.7 (d, J=20.0 Hz), 131.3, 130.26, 125.9 (d, J=7.0 Hz), 92.8 (d, J=179.0 Hz), 66.2 (d, J=4.0 Hz), 52.37. **HR ESI-TOF MS** for [M+H$^-$] $C_{12}H_{13}NO_4F^+$ (m/z): 254.0829, found 254.0835. The analytical data matched with the previously reported.[49]

· *l*-4-(fluoro(*p*-tolyl)methyl)oxazolidin-2-one ((±)-**20-syn**)



The title compound was synthesized following the procedure 1 of the fluoroamination of carbamates. 4 Å M.S. (260 mg) were added to a Schlenk tube and dissolved in dry dichloromethane (6.50 mL) under an argon atmosphere. Carbamate **10** (50 mg, 0.26 mmol) and powdered PhIO (116 mg, mmol) were introduced in one portion and the reaction was stirred at 50 °C. When the starting material was consumed, the corresponding fluorine source (26 eq of fluorine) was added and controlled by TLC. The crude was purified by chromatography column using a mobile phase of Et_2O/Hexane (80:20) mixtures. Compound **20** was isolated in a 25% yield with a dr 85/15 (anti/syn) when HF·DMPU was used and in a 52% yield with a dr 60/40 (anti/syn) when HF·NEt_3 was used. **^{1}H NMR (400 MHz, Chloroform-d): δ** 7.24 (s, 4H), 5.28 (dd, J=46.2, 7.5 Hz, 1H), 4.60-4.49 (m, 2H), 4-18.4-08 (m, 1H), 2.38 (d, J=1.5 Hz, 3H). **^{19}F NMR (377 MHz, Chloroform-d): δ** -183.47 (d, J=49.0 Hz). **^{13}C NMR (100 MHz, $CDCl_3$): δ** 166.25, 158.8, 139.1 (d, J=20.0 Hz), 131.5, 130.32, 126.1 (d, J=7.0 Hz), 93.6 (d, J=179.0 Hz), 65.3 (d, J=7.0 Hz), 56.5 (d, J=24.0 Hz). The analytical data matched with the previously reported.[49]

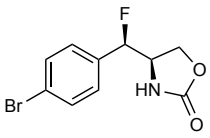
· *u*-4-(4-bromophenyl)fluoromethyl)oxazolidin-2-one ((±)-**23-anti**)



The title compound was synthesized following the procedure 1 of the fluoroamination of carbamates. 4 Å M.S. (290 mg) were added to a Schlenk tube and dissolved in dry dichloromethane (7.25 mL) under an argon atmosphere. Carbamate **13** (75 mg, 0.29 mmol) and powdered PhIO (129 mg, 0.59 mmol) were introduced in one portion and the reaction was stirred at 50 °C. When

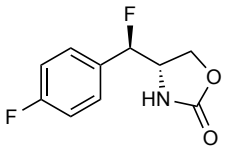
the starting material was consumed, the corresponding fluorine source (26 eq of fluorine) was added and controlled by TLC. The crude was purified by chromatography column using a mobile phase of Et_2O/Hexane (80:20) mixtures. Compound **23** was isolated in a 34% yield with a dr 70/30 (anti/syn) when HF·DMPU was used and in a 12% yield with a dr 36/64 (anti/syn) when HF·NEt_3 was used. **IR (neat):** 3251, 2954, 2921, 2851, 1766, 1641, 1239, 1203, 1027 cm^{-1}. **^{1}H NMR (400 MHz, Chloroform-*d*) δ** 7.34 (ddt, *J* = 6.4, 5.1, 1.3 Hz, 2H), 7.17 – 7.09 (m, 2H), 6.00 (s, 1H), 5.34 (dd, *J* = 46.6, 6.8 Hz, 1H), 4.34 – 4.14 (m, 2H), 4.14 – 4.06 (m, 1H)**. ^{13}C NMR (101 MHz, Chloroform-*d*) δ** 163.59 (dd, *J* = 249.6, 2.2 Hz), 159.00, 130.41 (dd, *J* = 20.6, 3.3 Hz), 128.48 (dd, *J* = 8.5, 6.1 Hz), 116.42 (d, *J* = 21.8 Hz), 94.11 (d, *J* = 177.9 Hz), 65.38 (d, *J* = 6.5 Hz), 56.66 (d, *J* = 24.6 Hz). **HR ESI-TOF MS** for [M+Na+] $C_{10}H_9BrFNNaO_2$+ (m/z): 295.9698; found 295.9693.

· *l*-4-(4-bromophenyl)fluoromethyl)oxazolidin-2-one ((±)-**23-syn**)



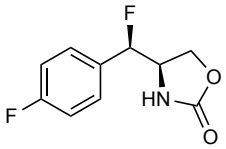
The title compound was synthesized following the procedure 1 of the fluoroamination of carbamates. 4 Å M.S. (290 mg) were added to a Schlenk tube and dissolved in dry dichloromethane (7.25 mL) under an argon atmosphere. Carbamate **13** (75 mg, 0.29 mmol) and powdered PhIO (129 mg, 0.59 mmol) were introduced in one portion and the reaction was stirred at 50 °C. When the starting material was consumed, the corresponding fluorine source (26 eq of fluorine) was added and controlled by TLC. The crude was purified by chromatography column using a mobile phase of Et_2O/Hexane (80:20) mixtures. Compound 23 was isolated in a 34% yield with a dr 70/30 (anti/syn) when HF·DMPU was used and in a 12% yield with a dr 36/64 (anti/syn) when HF·NEt_3 was used. **m.p.** 118-120 °C. **IR (neat):** 3242, 3142, 2958, 2924, 2359, 1750, 1489, 1402, 1234, 1010, 802 cm^{-1}. **^{1}H NMR (400 MHz, CDCl3) δ** 7.59 (d, J = 8.4 Hz, 2H, Har), 7.23 (d, J = 8.4 Hz, 2H, Har), 5.32 (dd, J = 46.1, 7.1 Hz, 1H, H1'), 4.81 (bs, 1H, HNH), 4.64 – 4.42 (m, 2H, H5), 4.20 – 4.05 (m, 1H, H4). **^{13}C NMR (100 MHz, CDCl3) δ** 159.0 (C2), 134.1 (d, J = 20.2 Hz, Car), 132.4 (Car), 127.8 (d, J = 6.8 Hz, Car), 124.1 (d, J = 2.1 Hz, Car), 92.97 (d, J = 179.6 Hz, C1'), 66.63 (d, J = 3.3 Hz, C5), 56.14 (d, J = 30.8 Hz, C4). **^{19}F NMR (377 MHz, CDCl3) δ** -186.3 (dd, J = 46.1, 11.5 Hz). **HR ESI-TOF MS** for [M+Na+] C10H9BrFNNaO2+ (m/z): 295.9693; found: 295.9702.

· *u*-4-(fluoro(4-fluorophenyl)methyl)oxazolidin-2-one ((±)-**24-anti**)



The title compound was synthesized following the procedure 1 of the fluoroamination of carbamates. 4 Å M.S. (440 mg) were added to a Schlenk tube and dissolved in dry dichloromethane (11.00 mL) under an argon atmosphere. Carbamate **14** (93.5 mg, 0.48 mmol) and powdered PhIO (193 mg, 0.88 mmol) were introduced in one portion and the reaction was stirred at 50 °C. When the starting material was consumed, the corresponding fluorine source (26 eq of fluorine) was added and controlled by TLC. The crude was purified by chromatography column using a mobile phase of Et_2O/Hexane (80:20) mixtures. Compound **24** was isolated in a 32% yield with a dr 74/26 (anti/syn) when HF·DMPU was used and in a 16% yield with a dr 42/58 (anti/syn) when HF·NEt_3 was used. **IR (neat):** 3280, 2956, 2952, 2852, 1749, 1494, 1229, 1024, 892. **^{1}H NMR (400 MHz, Chloroform-*d*) δ** 7.34 (ddt, *J* = 6.4, 5.1, 1.3 Hz, 2H), 7.17 – 7.09 (m, 2H), 6.00 (s, 1H), 5.34 (dd, *J* = 46.6, 6.8 Hz, 1H), 4.34 – 4.14 (m, 2H), 4.14 – 4.06 (m, 1H). **^{19}F NMR (377 MHz, Chloroform-*d*) δ** -110.67 (qd, *J* = 8.4, 4.3 Hz), -179.75 (dd, *J* = 46.6, 13.7 Hz). **^{13}C NMR (101 MHz, Chloroform-*d*) δ** 163.59 (dd, *J* = 249.6, 2.2 Hz, Car), 159.00 (C2), 130.41 (dd, *J* = 20.6, 3.3 Hz, Car), 128.48 (dd, *J* = 8.5, 6.1 Hz, Car), 116.42 (d, *J* = 21.8 Hz, Car), 94.11 (d, *J* = 177.9 Hz, C1'), 65.38 (d, *J* = 6.5 Hz, C5), 56.66 (d, *J* = 24.6 Hz, C4). **HR ESI-TOF MS** for [M+Na+] $C10H9F_2NNaO2+$ (m/z): 236.1730; found: 236.0495.

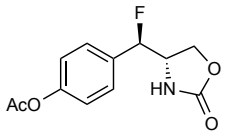
· *l*-4-(fluoro(4-fluorophenyl)methyl)oxazolidin-2-one ((±)-**24-syn**)



The title compound was synthesized following the procedure 1 of the fluoroamination of carbamates. 4 Å M.S. (440 mg) were added to a Schlenk tube and dissolved in dry dichloromethane (11.00 mL) under an argon atmosphere. Carbamate **14** (93.5 mg, 0.48 mmol) and powdered PhIO (193 mg, 0.88 mmol) were introduced in one portion and the reaction was stirred at 50 °C. When the starting material was consumed, the corresponding fluorine source (26 eq of fluorine) was added and controlled by TLC. The crude was purified by chromatography column using a mobile phase of Et_2O/Hexane (80:20) mixtures. Compound **24** was isolated in a 32% yield with a dr 74/26 (anti/syn) when HF·DMPU was used and in a 16% yield with a dr 42/58 (anti/syn) when HF·NEt_3 was used**. IR (neat):** 3276, 2955, 2920, 2851, 1751, 1513, 1229, 1033. **^{1}H NMR (400 MHz, Chloroform-*d*): δ** 7.61 – 7.57 (m, 1H), 7.25 – 7.20 (m, 1H), 5.47 (s, 1H), 5.32 (dd, *J* = 46.8, 6.7 Hz, 0H), 4.31 (td, *J* = 8.5, 2.3 Hz, 1H), 4.23 – 4.10 (m,

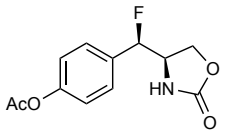
1H). **^{19}F NMR (377 MHz, Chloroform-d): *δ*** -183.35 (dd, J=46.0, 9.5 Hz). **HR ESI-TOF MS** for $[M+Cl]^-$ $C_{10}H_9ClF_2NO_2+$ (m/z)**:** 248.029502; found: 248.02924.

· *u*-4-(fluoro-2-oxooxazolidin-4-yl)methyl)phenyl acetate ((±)-**22-anti**)



The title compound was synthesized following the procedure 1 of the Fluoroamination of carbamates. 4 Å M.S. (210 mg) were added to a Schlenk tube and dissolved in dry dichloromethane (5.25 mL) under an argon atmosphere. Carbamate **12** (50 mg, 0.21 mmol) and powdered PhIO (94 mg, 0.43 mmol) were introduced in one portion and the reaction was stirred at 50 °C. When the starting material was consumed, the corresponding fluorine source (26 eq of fluorine) was added and controlled by TLC. The crude was purified by chromatography column using a mobile phase of Et_2O/Hexane (10:1) mixtures. Compound **22** was isolated in a 25% yield with a dr 82/18 (anti/syn) when HF·DMPU was used and in a 24% yield with a dr 56/44 (anti/syn) when HF·NEt_3 was used**. ^{1}H NMR (400 MHz, Chloroform-*d*) δ** 7.36 (dd, *J* = 8.5, 1.1 Hz, 1H), 7.21 – 7.14 (m, 1H), 5.52 – 5.48 (m, 0H), 5.35 (dd, *J* = 46.8, 6.8 Hz, 0H), 4.32 (td, *J* = 8.4, 2.4 Hz, 0H), 4.26 – 4.12 (m, 1H), 2.32 (s, 1H). **^{19}F NMR (377 MHz, CDCl3) δ** -181.46 (dd, J=46.3, 15.3 Hz). **HR ESI-TOF MS** for [M+Na+] $C_{12}H_{12}FNNaO_4+$ (m/z): 276.0643; found: 276.24814.

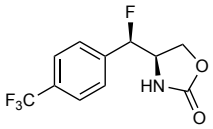
· *l*-4-(fluoro-2-oxooxazolidin-4-yl)methyl)phenyl acetate ((±)-**22-syn**)



The title compound was synthesized following the procedure 1 of the Fluoroamination of carbamates. 4 Å M.S. (210 mg) were added to a Schlenk tube and dissolved in dry dichloromethane (5.25 mL) under an argon atmosphere. Carbamate **12** (50 mg, 0.21 mmol) and powdered PhIO (94 mg, 0.43 mmol) were introduced in one portion and the reaction was stirred at 50 °C. When the starting material was consumed, the corresponding fluorine source (26 eq of fluorine) was added and controlled by TLC. The crude was purified by chromatography column using a mobile phase of Et_2O/Hexane (10:1) mixtures. **m.p.** 108-110 °C. Compound **22** was isolated in a 25% yield with a dr 82/18 (anti/syn) when HF·DMPU was used and in a 24% yield with a dr 56/44 (anti/syn) when HF·NEt_3 was used**. IR (neat):** 3290, 2923, 2851, 2349, 1742, 1509, 1408, 1370, 1192, 911 cm^{-1}. **^{1}H NMR (400 MHz, CDCl3) δ** 7.37 (d, J = 8.5 Hz, 2H, Har), 7.17 (d, J = 8.5 Hz, 2H, Har), 5.52 (bs, 1H, HNH), 5.36 (dd, J = 46.1, 6.8 Hz, 1H, H1'), 4.54 – 4.46 (m, 2H, H5), 4.22 – 4.06 (m, 1H, H4), 2.32 (s, 3H, CH3CO). **^{13}C NMR (100 MHz, CDCl3) δ** 169.4 (CH3CO), 158.9 (C2), 151.7 (d, J = 2.0 Hz, Car) 132.8 (d, J = 20.2 Hz,

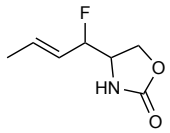
Car), 127.5 (d, J = 6.7 Hz, Car), 122.5 (Car), 93.1 (d, J = 179.2 Hz, Cl'), 66.8 (d, J = 2.9 Hz, C5), 56.3 (d, J = 31.5 Hz, C4), 21.3 (CH3CO). **^{19}F NMR (377 MHz, CDCl3) δ** -186.9 (dd, J = 46.1, 6.8 Hz). **HR ESI-TOF MS** for [M+Na+] C12H12FNNaO4+ (m/z): 276.0643; found: 276.0643.

· *l*-4-fluoro(4-(trifluoromethyl) phenyl)methyl)oxazolidin-2-one ((+)-**26-syn**)



The title compound was synthesized following the procedure 1 of the Fluoroamination of carbamates. 4 Å M.S. (200 mg) were added to a Schlenk tube and dissolved in dry DCM (5.00 mL) under an argon atmosphere. Carbamate **16** (50 mg, 0.20 mmol) and powdered PhIO (90 mg, 0.40 mmol) were introduced in one portion and the reaction was stirred at 50 °C. When the starting material was consumed, the corresponding fluorine source (26 eq of fluorine) was added and controlled by TLC. The crude was purified by chromatography column using a mobile phase of Et_2O/Hexane (8:2) mixtures. Compound **26** was isolated in a 10% yield with a dr 76/24 (anti/syn) when HF·DMPU was used**. m.p.** 108-110 °C. **IR (neat):** 3290, 2923, 2851, 2349, 1742, 1509, 1408, 1370, 1192, 911 cm^{-1}. **IR (neat):** 3292, 2922, 2852, 2359, 1748, 1417, 1324, 1253, 1067, 1017 cm^{-1}. **^{1}H NMR (400 MHz, CDCl3) δ** 7.72 (d, J = 8.1 Hz, 2H, Har), 7.49 (d, J = 81 Hz, 2H, Har), 5.44 (dd, J = 46.2, 6.6 Hz, 1H, H1'), 5.16 (bs, 1H, HNH), 4.59 – 4.44 (m, 2H, H5), 4.25 – 4.05 (m, 1H, H4). **^{19}F NMR (377 MHz, CDCl3) δ** -62.91 (s, CF3), -189.44 (dd, J = 46.1, 10.5 Hz, CF). **HR ESI-TOF MS** for [M+Na+] C11H9F4NNaO2+ (m/z): 286.0462; found: 286.0453.

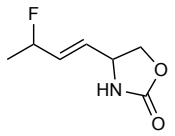
· u-4-[(*E*)-1-fluorobut-2-en-1-yl]oxazolidin-2-one ((±)-**31**)



The title compound was synthesized following the procedure 1 of the Fluoroamination of carbamates. 4 Å M.S. (350 mg) were added to a Schlenk tube and dissolved in dry dichloromethane (8.75 mL) under an argon atmosphere. Carbamate **17** (50 mg, 0.35 mmol) and powdered PhIO (156 mg, 0.71 mmol) were introduced in one portion and the reaction was stirred at 50 °C. When the starting material was consumed, the corresponding fluorine source (26 eq of fluorine) was added and controlled by TLC. The crude was purified by chromatography column using a mobile phase of Hexane/AcOEt (6:4) mixtures. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 5.99 (dq, 1H, J = 18.2, J = 5.7), 5.50 (dddq, 1H, J = 33.4, 15.2, 7.8, 1.5 Hz), 4.74 (dt, 1H, J = 47.2, 7.0 Hz), 4.48 (t, 1H, J = 8.8 Hz), 4.32 (dd, 1H, J = 9.2, 4.6), 3.98 (m, 1H), 1.80 (dddd, *J* = 6.7, 5.2, 3.6, 1.7 Hz, 3H).**^{19}F NMR** ($CDCl_3$, 400 MHz) δ: -177.77 (dtd, *J* = 48.9, 11.8, 6.0 Hz),-181.1 (ddd, J =

47.6, J = 10.8, J = 5.4); **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ: 159.4, 135.8 (J = 11.5), 124.1 (J = 19.3), 93.4 (J = 172.0), 66.4 (J = 4.4), 54.8 (J = 29.4), 29.8. **HR ESI-TOF MS** for [M+NH_4^+] $C_7H_{14}FN_2O_2$ (m/z)**:** 177.1034; found: 177.1030.

· *l*-4-[(*E*)-1-fluorobut-2-en-1-yl]oxazolidin-2-one ((+)-**3l'**)



The title compound was synthesized following the procedure 1 of the Fluoroamination of carbamates. 4 Å M.S. (350 mg) were added to a Schlenk tube and dissolved in dry dichloromethane (8.75 mL) under an argon atmosphere. Carbamate **I7** (50 mg, 0.35 mmol) and powdered PhIO (156 mg, 0.71 mmol) were introduced in one portion and the reaction was stirred at 50 °C. When the starting material was consumed, the corresponding fluorine source (26 eq of fluorine) was added and controlled by TLC. The crude was purified by chromatography column using a mobile phase of Hexane/AcOEt (6:4) mixtures. **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 5.84 (ddd, 1H, J = 29.5, J = 15.7, J = 5.1), 5.73 (m, 1H), 5.09 (dp, 1H, J = 48.3, J = 6.3), 4.55 (t, 1H, J = 8.5), 4.42 (m, 1H), 4.07 (dd, 1H, J = 8.6, 6.6 Hz); **^{19}F NMR** ($CDCl_3$, 400 MHz) δ: -170.9 (ddq, J = 47.1, J = 24.3, J = 13.2). **^{13}C NMR** ($CDCl_3$, 100.6 MHz) δ: 159.4, 134.2 (J = 19.8 Hz), 129.6 (J = 10.6 Hz), 88.5 (J = 168.0 Hz), 70.0 (J = 2.1 Hz), 54.2, 21.2 (J = 23.3 Hz). **HR ESI-TOF MS** for [M-H^+] $C_7H_{10}FNO_2^+$ (m/z): 158.0623, found: 158.0601.