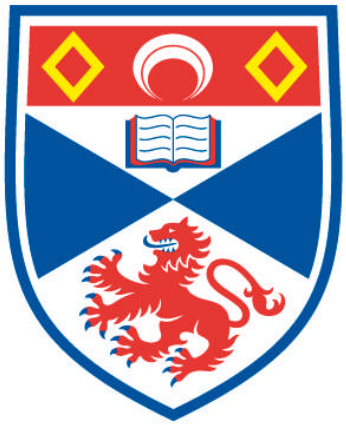
SYNTHESIS STUDIES TO SINGLE STEREOISOMERS OF THE VICINAL TRIFLUOROALKANE MOTIF

Vincent Brunet

A Thesis Submitted for the Degree of PhD
at the
University of St Andrews



2009

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Vincent Brunet

Ph.D. Thesis

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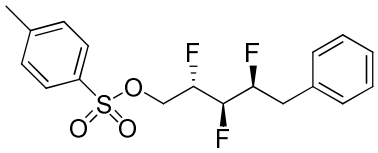
Abbreviations

BnOH	benzyl alcohol
Boc_2O	*tert*-butoxycarbonyl anhydride
Bn	benzyl
br	broad
BuLi	*n*-butyl lithium
C ar	aromatic carbon
CHP	cumene hydroperoxide
d	doublet
DAST	diethylaminosulfur trifluoride
DCC	dicyclohexyl carbodiimide
DCE	dichloroethane
DCM	dichloromethane
de	diastereomeric excess
DIEA	diisopropyl ethyl amine (Hunig's base)
DMAP	4-(*N*,*N*-dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide
dr	diastereoisomeric ratio
ee	enantiomeric excess
eq	equivalent
er	enantiomeric ratio
H ar	aromatic proton
Hz	Hertz
HRMS	high resolution mass spectroscopy
IR	infrared spectroscopy
J	coupling constant
LDA	lithium diisopropyl amine
m	multiplet
*m*CPBA	metachloroperbenzoic acid
MeCN	acetonitrile

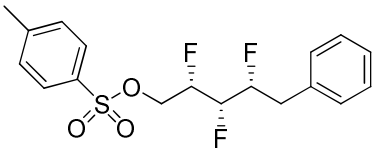
(-)-MIB	3-*exo*-morpholinoisoborneol
µM	micromolar (10^{-6} mol.L^{-1})
MOST	morpholinosulfur trifluoride
Mp	melting point
MsO	methanesulfonate (mesyl)
NBS	*N*-bromosuccinimide
NFSI	*N*-fluorobenzene sulfonimide
NFOBS	*N*-fluoro-O-benzenedisulfonimide
NMR	nuclear magnetic resonance
PG	protecting group
ppm	parts per million
PTFE	polytetrafluoroethylene
Pyr	pyridine
q	quartet
RT	room temperature
s	singlet
S_N	nucleophilic substitution
S_E	electrophilic substitution
t	triplet
TBAF	*N*-tetrabutylammonium fluoride
TBHP	*tert*-butyl hydroperoxide
Tempo	2,2,6,6-tetramethylpiperidin-*N*-oxyl radical
TfO	trifluoromethanesulfonate (triflate)
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TsO	*p*-methyl benzene sulfonate (tosyl)
V_w	Van der Waals volume
^{19}F-NMR	fluorine nuclear magnetic resonance
$^{19}F\{^1H\}$-NMR	proton decoupled fluorine nuclear magnetic resonance

Abstract

This thesis focuses on the construction of individual isomers of the R-CHF-CHF-CHF-R' motif. The multi-vicinal fluorine motif is new in organic chemistry and therefore stereoselective methods giving rapid access to these motifs and with flexibility need to be explored. The research in the thesis succeeded in the preparation of (*2S,3R,4S*)-**314** and (*2S,3S,4R*)-**328**.



(*2S,3R,4S*)-**314**



(*2S,3S,4R*)-**328**

In **Chapter 1**, an overview of the impact of fluorine in organic molecules is given. Recent developments in asymmetric electrophilic and nucleophilic fluorination are described, as well as the preparation of multivicinal fluoroalkane motifs.

Aldol reactions of either (*R*)- or (*S*)-*N*-(α-fluoropropyl)-2-oxazolidinones, mediated by $TiCl_4$ are reported in **Chapter 2**. Such aldol reactions gave rise to identical α-fluoro-β-hydroxy-aldol products with high diastereoselectivities (95% dr). After removal from the auxiliary α-fluoro-β-hydroxy- products were converted to the corresponding α,β-difluoro products.

The synthesis of non symmetric vicinal trifluoro motifs (*2S,3R,4S*)-**314** and (*2S,3S,4R*)-**328** is described in **Chapter 3**. They were prepared by direct fluorination in three steps of the corresponding (2*R,3R,4R*)-*erythro* and (2*R,3S,4S*)-*threo* enantio-enriched epoxy-alcohols. The two *erythro* and *threo* epoxy-alcohol isomers behave very differently during the first fluorination step and then an attempt to study and rationalise this difference in behaviour is made.

Table of contents

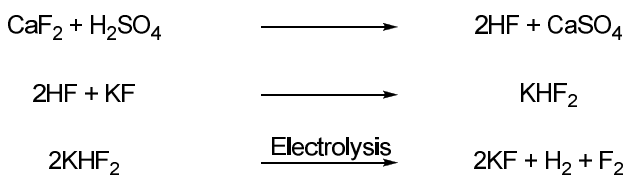
Chapter 1: The impact of fluorine in organic molecules

1.1 Introduction:

1.1.1) Historic:

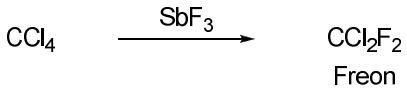
Fluorine in the form of calcium fluoride (CaF_2 also called fluorspar or fluorite) was used as early as the 16th century as a substance that promoted the fusion of metals or minerals. During the 17th century it was found that glass was etched when it was exposed to fluorspar previously treated with acid. Over the next 200 years many scientists would experiment with hydrofluoric acid, easily obtained by treating calcium fluoride with concentrated sulfuric acid. It was eventually realized that hydrofluoric acid contained a previously unknown element which was not isolated for many years, due to its extreme reactivity. Finally, elemental fluorine was isolated by Henri Moissan in 1886, by electrolysis of a mixture of potassium fluoride and hydrogen fluoride [1,2]. Moissan was awarded the Nobel Prize in chemistry in 1906 for his discovery of elemental fluorine. He died the year after, age 54, and it is not clear whether his fluorine work shortened his life.

Nowadays the method employed by Moissan is still used for industrial fluorine production. It starts with fluorspar (CaF_2), which is heated with sulfuric acid (H_2SO_4) to produce anhydrous hydrogen fluoride (HF). The hydrogen fluoride is added to potassium fluoride (KF) to form potassium bifluoride (KHF_2). Finally electrolysis of potassium bifluoride produces fluorine gas at the anode, and hydrogen gas at the cathode (Scheme 1.1) [3].



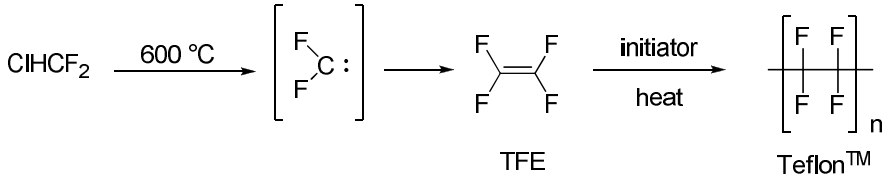
Scheme 1. 1 : Preparation of elemental fluorine.

Synthetic organofluorine chemistry debuted in 1892 when Frédéric Swarts performed the conversion of chlorocarbons to fluorocarbons using antimony trifluoride [4]. This directly led to the discovery of freon, by Thomas Midgley in 1928 [5] (Scheme 1.2). This scientific breakthrough constituted the first commercial application of organic fluorides and allowed the first widespread use of refrigerators and air conditioners.



Scheme 1. 2

In 1938, while working on the development of new refrigerants, Roy Plunkett discovered the polymerisation of perfluoroethylene (Scheme 1.3). This opened up the tremendous commercial application of organofluorine chemistry in the field of fluoropolymers. Such polymers have broad technological applications as thermoplastics, elastomers, fluids and membranes. These applications are well known in daily life, under the brands Teflon™, Tefal™ or Goretex™, etc…



Scheme 1. 3 : Formation and polymerisation of tetrafluoroethylene.

Fluorine chemistry benefited significantly from the development of nuclear weapons during the second World War [6,7]. Within the Manhattan project, volatile UF_6 was used as a gaseous carrier of uranium to separate the ^{235}U and ^{238}U isotopes. Thus the first large-scale production of hydrofluoric acid and elemental fluorine took place, as they were both required for the preparation of UF_6. After the second World War, fluorine chemistry experienced a rapid expansion in knowledge and technology. Fluorine chemists dedicated their efforts to increasing the number of methods for incorporating fluorine into organic molecules, as most of the synthetic methods used to insert other halogens into organic compounds were not transposable to fluorinated compounds. Therefore, new reagents were developed for the interconversion of functional groups into fluorine. Many efforts were also put forward for preparing new fluorinated building blocks, such as alkylic, vinylic or aryl monofluoro compounds, alkyl and vinyl CF_2 compounds and aliphatic and aromatic CF_3 compounds. This allowed chemists to target more complex molecules, such as biologically active fluorochemicals. In the 1950's, in addition to the discovery of new fluorinated non-flammable anaesthetics to replace diethyl ether [8], the synthetic breakthrough of the preparation of fluorocorticoids by Josef Fried marked the first step of fluorine into the medicinal field [9] (Figure 1.1) . The fluorocorticoid synthesised by Fried proved to be an order of magnitude more effective than its non fluorinated analogue, and also it had less side effects. This discovery introduced the new concept that a fluorine atom could change the biological properties of a molecule. Over the years many important drugs proved to have their biological activity enhanced by the presence of fluorine. For example, Fluorouracil and Prozac have been used since the 1980's in medicine as antitumor agents and antidepressants, respectively (Figure 1.1).

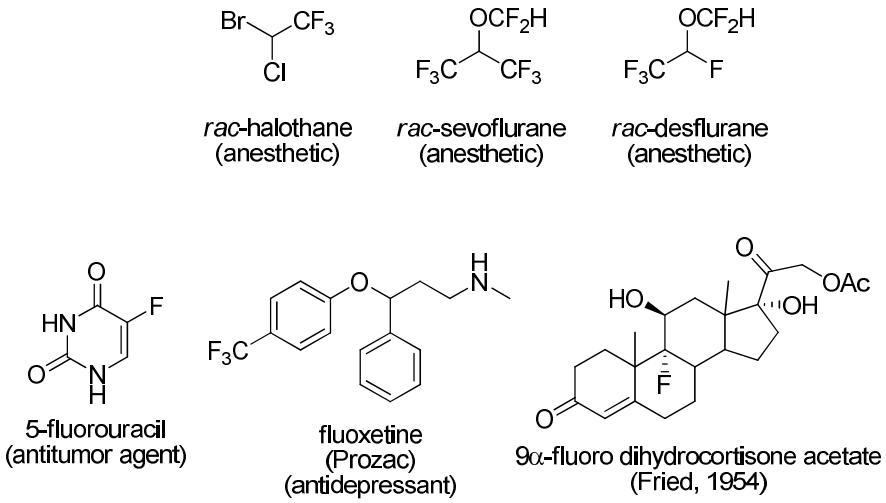


Figure 1. 1 : Example of fluorinated anesthetics and drugs.

Fluorocompounds are also involved in many other fields of research and technology: for instance the use bromofluorocarbons in extinguishers [10], perfluorocarbons as gas carrier and blood substitutes [11], polymers in automobile industry [12], artificial ^{18}F radioisotope in positron emission tomography (PET) such as **1** [13] or the use of fluorinated molecules such as **2** in liquid crystals displays technology (LCD) [14] (Figure 1.2).

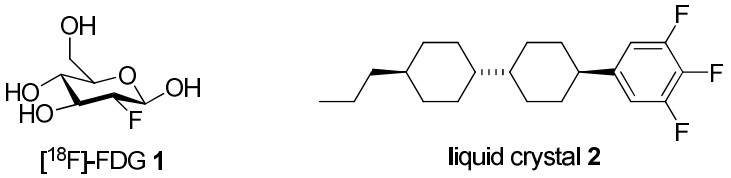


Figure 1. 2 : Fluorodeoxyglucose [^{18}F-FDG] and an example of a fluorinated liquid crystal motif.

Organofluorine chemistry is therefore a thriving field of research, only a few decades young. It is in constant expansion as shown by the current increase of fluorochemicals on the pharmaceutical and agrochemical markets. Fluorochemicals represented 18% of the market in the pharmaceutical industry in 2000 (2% in 1970, 8% in 1980 and 13% in 1990), and 50% of the market in the agrochemical industry (3% in 1970, 10% in 1980, 28% in 1990) [15].

1.1.2) Natural fluoro compounds:

In spite of the fact that fluorine is a significant element in the earth's crust (13th most abundant element and most abundant halogen), it is difficult to find naturally incorporated fluorine in organic molecules, perhaps because of the high energy of solvation of fluoride ion in water. Only about fifteen organometabolites have been isolated from plants, and half of them are derivatives of fluorofatty acids (some of them are shown in Figure 1.3) [16]. The toxic fluoroacetate can be biosynthesised and used by specific type of plants in Africa, South America and Australia, as a natural defence against herbivores. Fluorocitrate is responsible for the toxicity of fluoroacetate and arises as a result of the *in vivo* enzymatic transformation of fluoroacetate. ω-Fatty acids such as ω-fluoro-oleic acid are found in one plant in Africa, and are almost certainly arise as the result of the incorporation of fluoroacetyl-CoA instead of acetyl-CoA during the first step of the biosynthesis of fatty acids. Nucleosidine has been isolated from *Streptomyces clavus*, a bacteria found in India. The position of the fluorine at 4' tends to indicate that the biosynthesis of nucleosidine does not have a fluoroacetate origin.

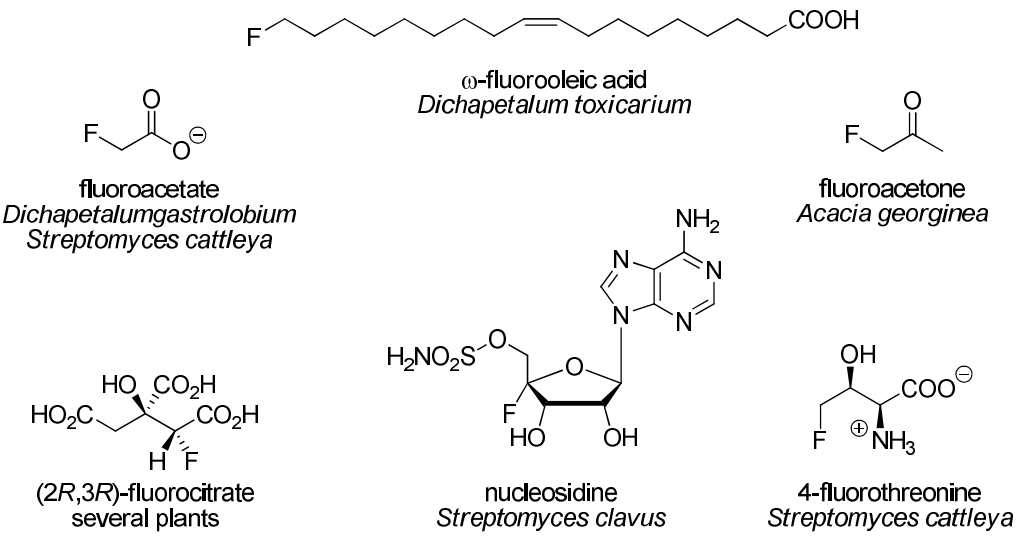
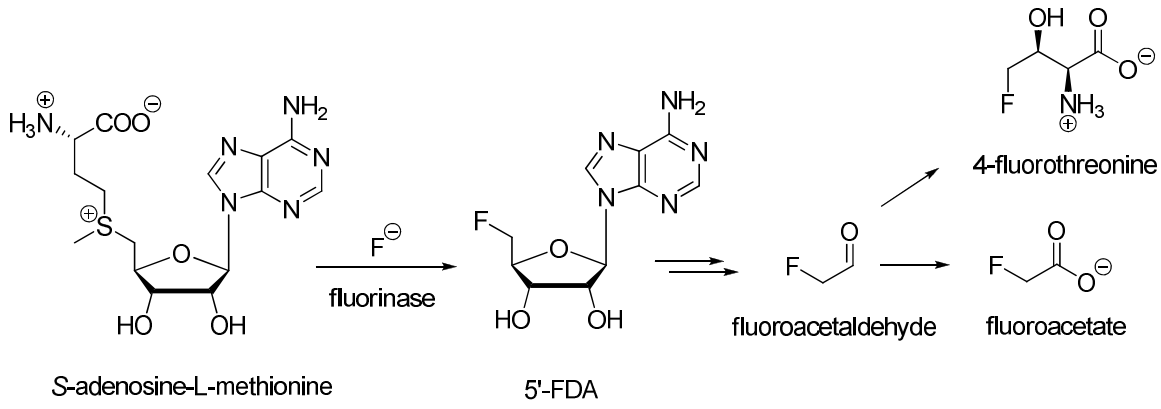


Figure 1. 3 : Example of natural fluorinated molecules.

4-Fluorothreonine was isolated from the bacterium *Streptomyces cattleya* in presence of fluoride ion [17,18]. In this bacterium, fluoroacetate and 4-fluorothreonine are both synthesised from the same precursor; fluoroacetaldehyde. The first step of the biosynthetic pathway in *Streptomyces cattleya* induces the conversion of *S*-adenosine-L-methionine to 5'-fluoro-5'-desoxyadenosine by a C-F bond forming enzyme, the fluorinase, in the presence of fluoride ion (Scheme 1.4). The fluorinase is the first native enzyme capable of forming a carbon-fluorine bond. With so few naturally occurring fluorine containing compounds, and none containing more than one fluorine atom, the field of organofluorine chemistry is essentially a synthetic field.



Scheme 1. 4: Formation of a C-F bond by the fluorinase in *Streptomyces cattleya* and biosynthesis of fluoroacetate and 4-fluorothreonine.

1.1.3) Toxicity:

Fluorine is sometimes, and for good reasons, affiliated with toxicity, but the number of toxic fluorinated molecules is in fact relatively limited and are a safety concern more in an industrial environment due to the large quantities employed.

Elemental fluorine (fluorine gas) is simply the most reactive element in the periodic table, and in this regard is a highly toxic, corrosive oxidant. Hydrogen fluoride and hydrofluoric acid are also highly toxic on contact with skin. The HF molecule is a weak acid which is significantly non-dissociated in water, and the intact molecule is capable of rapidly migrating through lipid layers of cells which would ordinarily stop an ion or partly ionized acid, and the burns it produces are typically deep. HF may react with calcium, permanently damaging the bone or create more serious hypocalcaemia. Hydrofluoric acid spills of just over 2.5% of the body's surface area (about 75 in^2 or 5 dm^2), have been fatal.

Perfluoroisobutene (PFIB) (Figure 1.4) is also a well known toxin. It is a highly reactive electrophile with a boiling point at 7 °C. PFIB is a product of the pyrolysis of Teflon^{TM} released when polytetrafluoroethylene (PTFE) is heated above 300 °C. In contact with water, PFIB undergoes rapid hydrolysis, producing various reactive compounds and fluorophosgene. PFIB is about 10 times as toxic as phosgene.

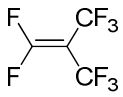
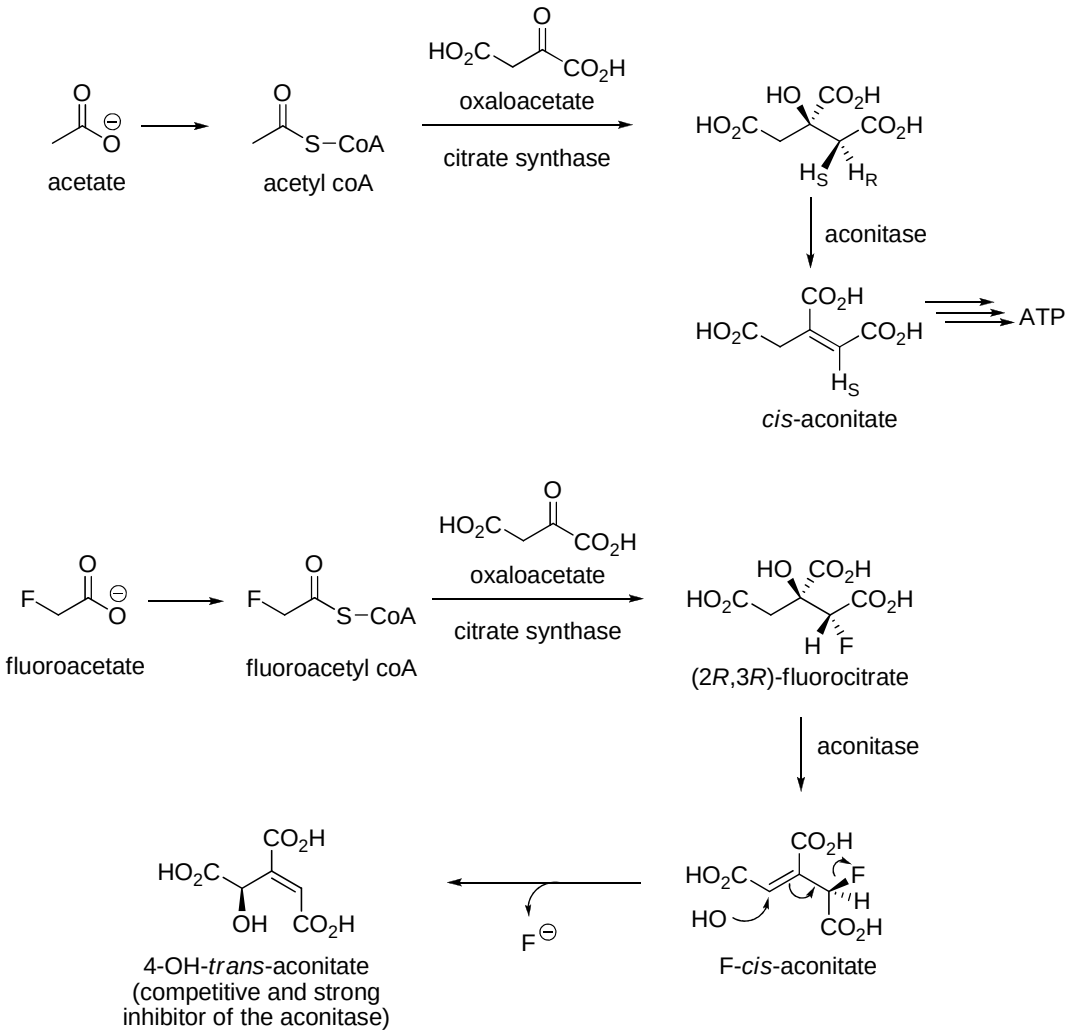


Figure 1. 4: Perfluoroisobutene (PFIB)

The toxicity of fluoroacetate historically played an important role because it showed that a fluorinated analogue of a natural product could have a totally different biological activity than its fluorodehydro-counterpart. The toxicity of fluoroacetate lies in its ability to block the Krebs cycle and therefore the production of ATP (adenosine triphosphate) in the mitochondria [19] (Scheme 1.5). Fluoroacetate is first transformed stereoselectively by citrate synthase into (*2R,3R*)-2-fluorocitrate which is then a substrate of the aconitase. The fluorine atom in the 2 position prevents the aconitase from synthetising *cis*-aconitate by the normal pathway, but it generates fluoro-*cis*-aconitate instead. After addition of water across the double bond, then β-

elimination with loss of a molecule of HF, the fluoro-*cis*-aconitate is transformed into 4-OH-*trans*-aconitate which is a powerful inhibitor of the aconitase. Nevertheless, it seems that the reversible inhibition of the aconitase by 4-OH-*trans*-aconitate does not fully explain the high irreversible toxicity of fluorocitrate. It has been suggested that fluorocitrate may also bind covalently to proteins in charge of the transport of citrate through the mitochondrial membranes.



Scheme 1. 5 : Inhibition of the Krebs cycle by fluoroacetate.

1.2) Influence of fluorine in organic molecules:

1.2.1) The fluorine atom:

Most of the effects induced by the presence of a fluorine atom in a molecule result from the structure and the fundamental properties of this atom [20,21,22,23]. Fluorine has an electronic configuration $1s^2 2s^2 2p^5$ and with a Van der Waals radius of 1.47Å, it is the second smallest atom in the periodic table after hydrogen (Table 1.1). Despite its small size, fluorine has a high nuclear charge (9 protons) that strongly attracts the electrons in the valence p-shell and makes fluorine the most electronegative atom of the periodic table (3.98 on the Pauling scale). The large ionisation energy of fluorine implies that an electron-deficient fluorine species is unlikely to be formed. Compared to the other halogen atoms, where the formation of chloronium, bromonium and iodonium ion is well established, a fluoronium ion has never been observed. Under its ionic form, fluorine is then found exclusively as a fluoride anion. In elemental fluorine (F_2), fluorine has a low bond energy (157 kJ/mol). Much lower in comparison to hydrogen (H_2 434 kJ/mol) or chlorine (Cl_2 242 kJ/mol). This explains the extreme reactivity of elemental fluorine.

atom	Van der Waals radius (Å)	Pauling electronegativity	Polarisability ($Å^3$)	Ionisation energy (kcal/mol)
H	1.20	2.20	0.667	313.6
F	**1.47**	**3.98**	**0.557**	**401.8**
O	1.52	3.44	0.82	314.0
N	1.55	3.04	1.10	335.1
C	1.70	2.55	1.76	240.5
Cl	1.75	3.16	2.18	299.0
Br	1.85	2.96	3.05	272.4
I	1.98	2.66	4.7	241.2

Table 1. 1 : Atomic parameters of the fluorine atom.

1.2.2) Physical properties of the C-F bond:

The physical properties of a molecule are usually greatly modified only when this molecule is highly fluorinated. The insertion of only one fluorine into aliphatic motifs does not usually have a huge impact on the physical properties of this molecule. However, when positioned on aromatic rings, the presence of only one fluorine atom can increase the lipophilicity. This is an important parameter in medicinal chemistry, where the lipophilicity of a potential drug determines its ability to go through biological barriers. As shown in Table 1.2, as the degree of fluorination of a molecule decreases the boiling point increases. The density, viscosity and compressibility, are also enhanced by the presence of fluorine atoms. Perfluorocarbons have a limited capacity for intra- and inter-molecular interactions [20]. Taken together theses properties make perfluorocarbons almost perfect fluids with a high compressibility and a low vapour pressure.

	C_6F_{14}	$CF_3(CF_2)(CH_2)_3H$	C_6H_{14}
boiling point (°C)	57	64	69
Density d^{25} (g/m^3)	1.672	1.265	0.655
Viscosity η^{25} (cP)	0.66	0.48	0.29
Compressibility β (10^{-6} atm^{-1})	254	198	150

Table 1. 2: Some physical properties of non-, partially- and poly-fluorinated compounds.

The degree of fluorination also influences the general polarity of a molecule, and therefore its ability to dissolve in organic solvents or water. For instance, perfluorocarbons are miscible neither in water nor hydrocarbon solvents, but rather form a third phase. On the other hand they are able to efficiently dissolve gases, and they have found applications as oxygen carrier blood substitutes.

1.2.3) Stereoelectronic properties of the C-F bond:

The following paragraphs will mainly focus on monofluorinated and/or partially fluorinated molecules.

1.2.3.1) Polarity and electronic dispersion:

The high electronegativity of the fluorine atom, its small size and the good overlap between 2s and 2p orbitals of the fluorine and the corresponding orbitals of the carbon atom, implies that a fluorine atom is always an inductive electron withdrawing substituent when bound to carbon. The C-F bond is then always polarised from a sp^3 carbon (δ^+) to the fluorine (δ^-) (Figure 1.5). When bound to a sp^2 carbon, fluorine is still an inductive electron withdrawing substituent, but it is also electron donating by the mesomeric effect, and to a greater extent

than the other halogens. Thus, when placed in unsaturated systems, a fluorine atom is globally less electron withdrawing than the other halogens.

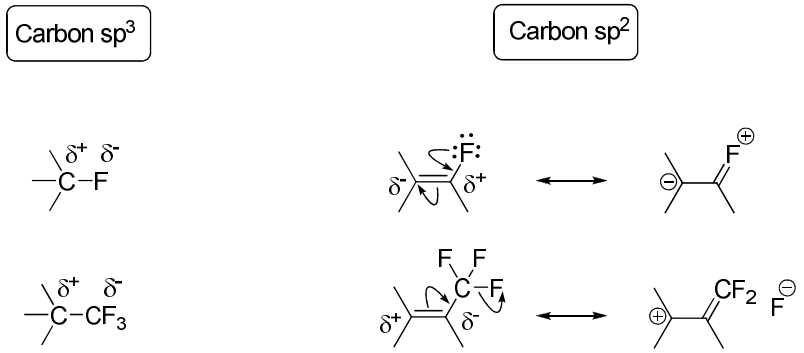


Figure 1. 5 : Inductive and mesomeric effects in the C-F bond.

1.2.3.2) Bond strength:

Fluorine forms the strongest bond to carbon. As shown in Table 1.3, carbon clearly forms a stronger bond with fluorine than with chlorine, bromine or even with another carbon (entry 1 to 4). The presence of fluorine in an organic compound also serves to strengthen the bonds between other proximate atoms in the molecule (comparison between entry 4 and 5 and 4 and 6). The bond strengthening effect of fluorine also increases upon accumulation of additional fluorine substituents. This is because the bond has some ionic character. The presence of fluorine also affects C-X bonds α or β to the fluorine. For example the C-O bond in the bis(trifluoromethyl) ether CF_3-O-CF_3 is stronger by 22 kcal.mol^{-1} compared to its non-fluorinated analogue, and the C-H bond in nonafluoroterbutane $(CF_3)_3$C-H is stronger by 15 kcal/mol compared to its non fluorinated analogue.

The strength of C-H, C-C and C-F bonds in highly fluorinated compounds gives rise to the extraordinary thermal and oxidative stability that generally characterises these compounds.

Entry	Molecule	Bond dissociation energy ($kcal.mol^{-1}$)
1	H_3C-F	108.3
2	H_3C-Cl	82.9
3	H_3C-Br	69.6
4	H_3C-CH_3	88.8
5	H_3C-CF_3	101.2
6	F_3C-CF_3	98.7
7	F_3C-F	130.5

Table 1. 3 : Bond dissociation energy of some halogenated simple compounds.

1.2.3.3) Acidity and basicity:

Due to the strong electron withdrawing effect, fluorine enhances the acidity of neighbouring hydrogen atoms. For example, the acidity of carboxylic acids increases significantly upon the presence and accumulation of fluorine (comparison Entry 1-4 Table 1.4). The acidity of other acid groups benefit from the presence of fluorine, for example esters (Entries 5, 6), alcohols (Entries 7, 8), and imides (Entries 9 and 10).

Entry	acid	pKa
1	CH_3-COOH	4.76
2	CH_2F-COOH	2.6
3	CHF_2-COOH	1.3
4	CF_3-COOH	0.5
5	CH_3-COOMe	24
6	FCH_2-COOMe	21
7	CH_3CH_2OH	15.9
8	CF_3CH_2OH	12.4
9	succinimide	9.6 0.493
10	F_4-succinimide	2.1 0.86

Table 1. 4 : The influence of fluorine on the pKas of different organic acids.

Fluorine also decreases the basicity of amines (Table 1.5), and perfluoroamines are not even able to form chlorohydrate salts.

amine	pKb	
$CH_3CH_2NH_2$	10.7	0.70
$CF_3CH_2NH_2$	3.3	0.36
C_6H_6-NH_2	4.3	0.38
C_6F_6-NH_2	0.36	-

Table 1. 5 : The influence of fluorine on the pKbs of different amines.

1.2.3.4) Hydrogen bonding:

Carbon bound fluorine is not a hydrogen bond donor, and despite its high electronegativity and its three lone pairs, fluorine is a weak hydrogen bond acceptor. But even if fluorine is not itself involved in hydrogen bonding, its strong inductive electron withdrawing effect can influence neighbouring atoms in their ability to strengthen hydrogen bonds. For example fluoroalcohols are strong hydrogen bond donors but weak acceptors. The proximity in size between a C-F (van der Waals molar volume = 6.2 $cm^3.mol^{-1}$) and and a C-OH group (van der Waals molar volume = 8.04 $cm^3.mol^{-1}$), combined with their different behaviour towards hydrogen bonding is widely used in medicinal chemistry. For example, the selective replacement of hydroxyl groups for fluorine in hydroxyproline, or sugars allowed the study of the role of hydroxyls and hydrogen bonding in the stability of collagen [24,25] and in interactions between proteins and sugars [26].

1.2.4) The influence of fluorine on reaction intermediates:

The strength of the C-F bond renders aliphatic fluoro compounds less prone to undergo nucleophilic substitution at fluorine, compared to the other halides. In fluoroalkenes the C-F bond is also strong and contributes to a strong π bond, less sensitive to electrophiles and more sensitive to nucleophiles.

Carbonyls are also affected by the presence of fluorine in an α position. For example fluoroaldehydes and fluoroketones react easily with amines, alcohols or even water and lead to stable imines, hemiketals and hydrates respectively.

The effect of fluorine on the stabilisation of carbocations depends on their position in the molecule. Although fluorine destabilises a carbocation when placed α by the inductive electron withdrawing effect, it also stabilises it by electron donation of one of its lone pairs (Figure 1.6). The competition between those two effects makes fluorine a moderate carbocation stabiliser but fluorine is for example a weaker stabiliser than a methyl substituent. Fluorine does not stabilise cabocations when placed at a β position because in that case, only the inductive effect operates.

Figure 1. 6 : Effect of fluorine on the stability of carbocations.

When placed α to a carbanion, fluorine has a destabilising effect due to repulsion between its lone pairs and the negative charge on the carbon (Figure 1.7). On the other hand fluorine can stabilise a negative charge when placed β to the carbanion due to its electron withdrawing inductive effect.

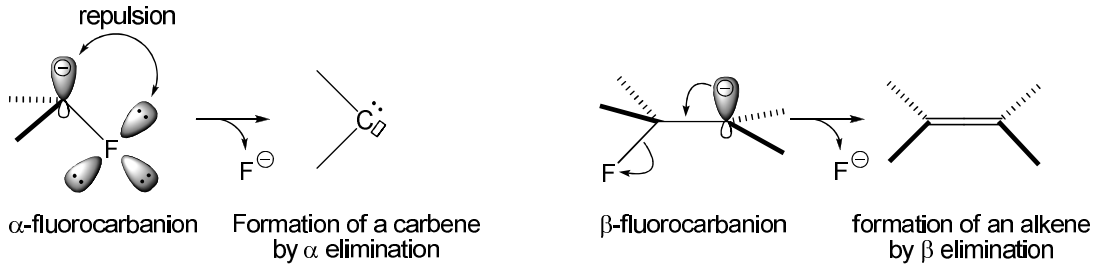
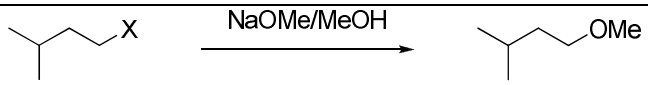


Figure 1. 7 : Destabilisation of α-carbocation and stabilisation of β-carbocation by fluorine.

These species can have a short life time and quickly undergo α and β elimination to form carbenes and alkenes. In fact the β elimination of fluoride ion *via* an E_{1CB} or concerted process is a common problem in organofluorine chemistry. As fluorine enhances the acidity of vicinal hydrogens, it is easy to understand that mono or partially fluorinated compounds are sensitive to base-mediated deprotonation.

As the C-F bond is the strongest bond to carbon, displacement of fluoride by nucleophilic substitution is more difficult than for other halides in aliphatic systems. As shown in Table 1.6, the displacement of fluoride by sodium methanolate is considerably slower than the displacement of chloride, and much slower than the displacement of bromide or iodide [15].



X	Relative reaction rate
F	1
Cl	71
Br	3500
I	4500

Table 1. 6 : Rates of halide ions as leaving groups in S_N2 reaction.

Fluoroalkyl groups also slow down nucleophilic substitutions (S_N1 or S_N2) at α, β, and even γ positions. The CF_3 group has a non negligible steric impact on proximal nucleophilic substitutiuons. As CF_3 is sometimes quoted to be as bulky as a tertbutyl group, its steric impact can seriously reduce the accessibility of a nucleophile, in addition to associated electronic effects.

1.2.5) Influence of fluorine on the conformation of molecules:

1.2.5.1) Dipole/dipole and dipole/charge interactions:

With the strong electron withdrawing effect of fluorine, the carbon fluorine bond has a dipole with large dipole moment (μ = 1.97 D in difluoromethane). As part of the C-F dipole, fluorine can then interact with other dipoles or with heteroatoms bearing a charge. These interactions are of great interest in academic research towards the use of fluorine for controlling the conformation of molecules or inducing stereoselectivity in a given reaction. As shown in Figure 1.8, α-fluorocarbonyls show a preferred *trans* conformation due to the dipole/dipole (C-F/C=O) repulsion [27,28,29,30]. This conformational preference increases with the strength of the carbonyl dipole. A stabilising interaction is also experienced between a C-F bond and a formal charge. As shown in Figure 1.8, fluorine prefers to align *gauche* to protonated amines or alcohols [31,32,33,34]. The conformation of a four membered ring 3-fluoro-azetidinium cation favours a more puckered structure compared to the non fluorinated analogue.

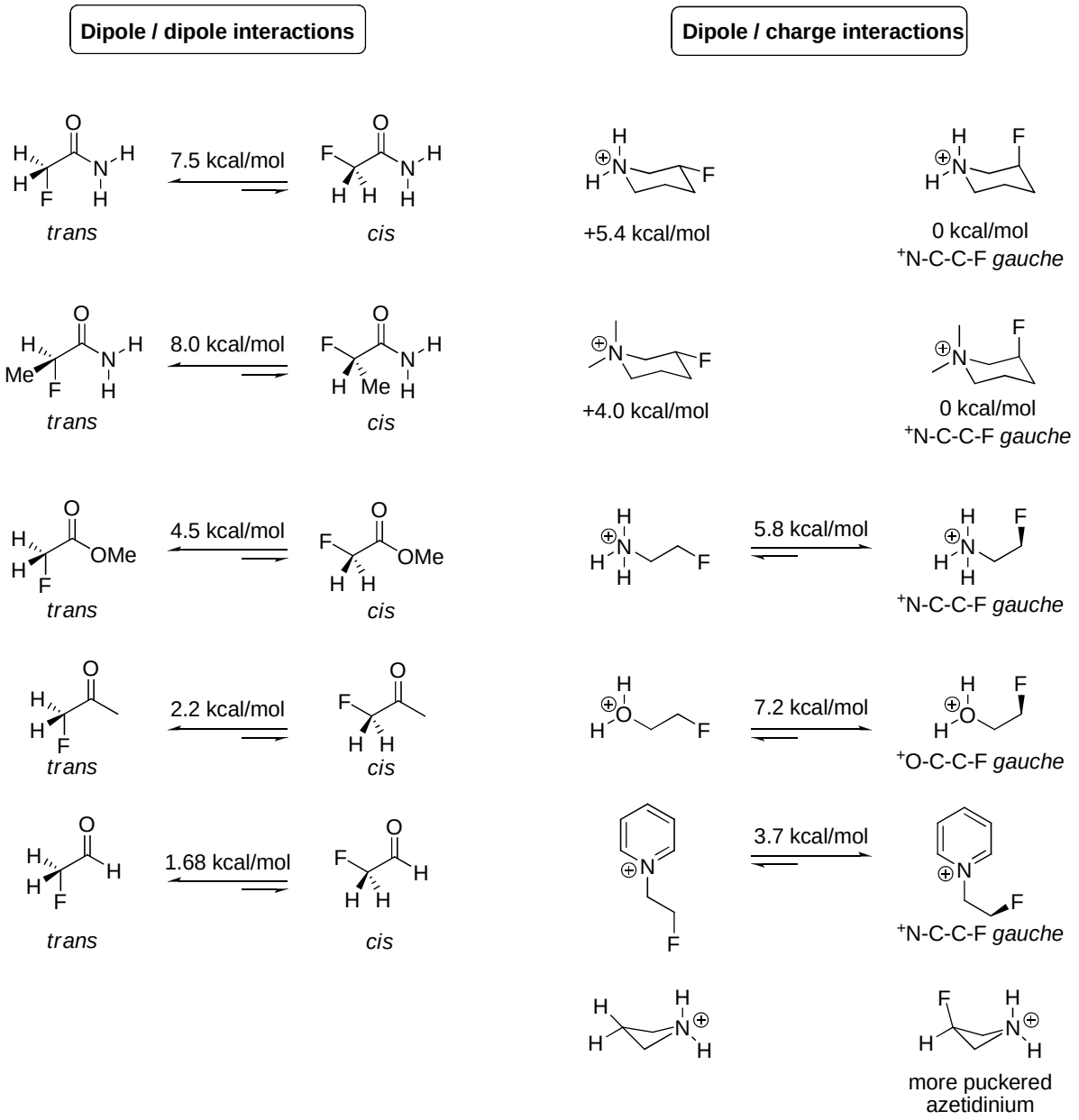
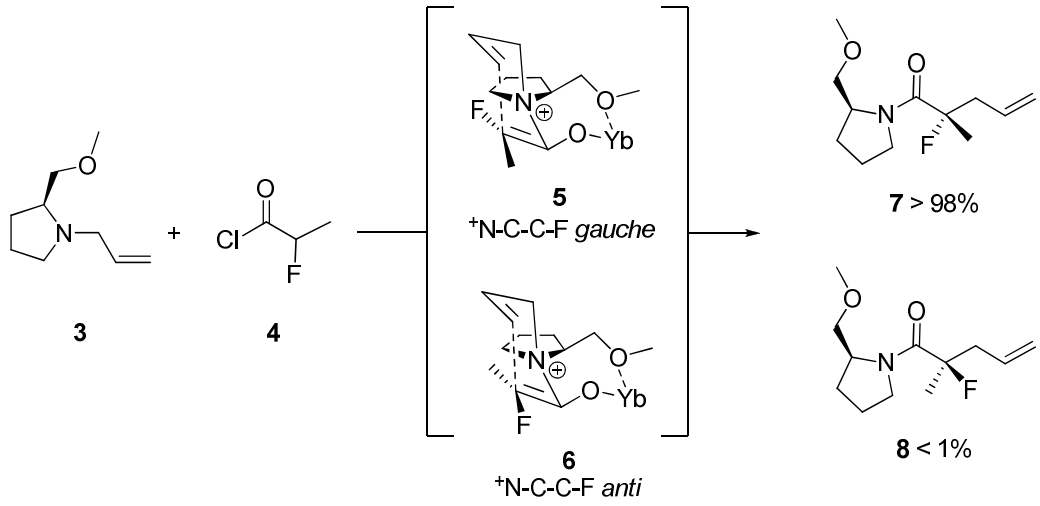


Figure 1. 8 : Examples of preferred conformations in F-C-C=O and F-C-C-X^+ interactions.

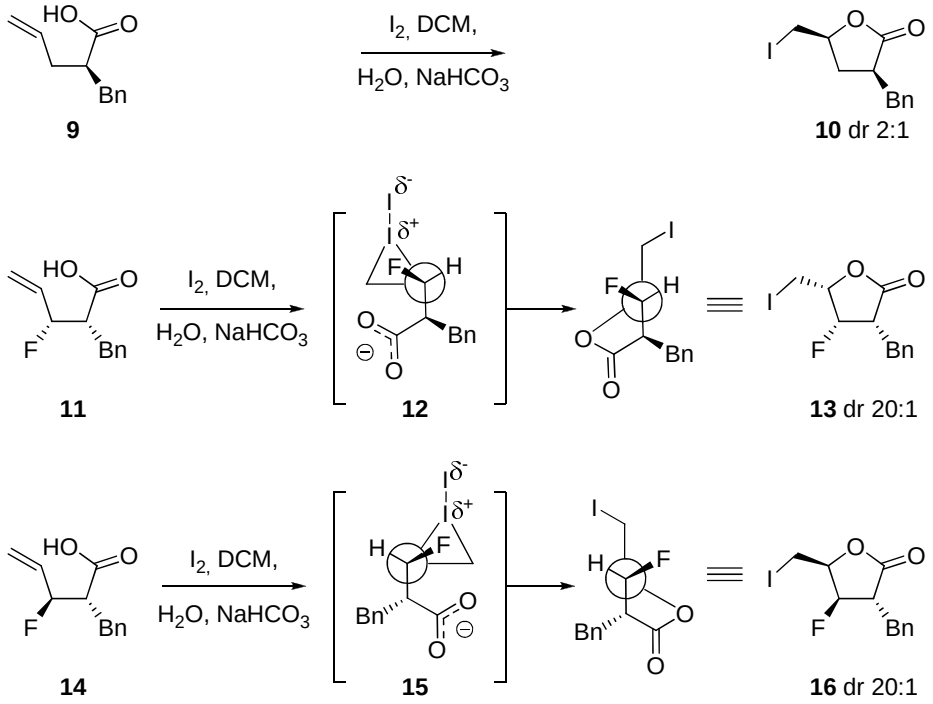
Dipolar interactions involving fluorine do not only influence the conformation of products but can also have a dramatic impact on the stereochemical outcome of a reaction. In 2005, O'Hagan and co-workers [35] reported the influence of fluorine in the zwitterionic *aza*-Claisen rearrangement of fluoroacetyl chloride with (*S*)-*N*-allyl-2-(methoxymethyl)-pyrrolidine in presence of ytterbium triflate (scheme 1.6). The reaction affords an amide product with a moderate 75% de, however, when 2-fluoropropionyl chloride is used, the

stereoselectivity is dramatically improved to a 98:2 dr (molecules **7** and **8**). This difference in stereoselectivity can be rationalised with a more stabilised transition state when the fluorine aligns *gauche* to the positively charged ammonium, adding a dipole-charge stabilising interaction.



Scheme 1. 6 : Effect of F-C-C-N^+ alignment in the zwitterionic *aza*-Claisen rearrangement.

In 2008, Gouverneur and co-workers [36] described fluorine as a highly efficient *syn*-stereodirecting group in an iodocyclization reaction. As shown in Scheme 1.7, the presence of fluorine in allylic position in molecules **11** and **14** improves the diastereoselectivity of the reaction by ten fold (2:1 dr for **10** compared to 20:1 dr for **13** and **16**). Calculations on the stability of reaction intermediates showed that rotamers **12** and **15** with the fluorine inside the I_2-π complex pocket is more stable by ~ 2 kcal/mol, compared to an outside or *anti* rotamer. This could be explained by improved stabilisation of the partially positively charged I_2-π complex by the charge density (dipole) of the fluorine and also by a better relaxation between partially positively charged I_2-π complex and the electron deficient $\sigma^*_{C\text{-}F}$.



Scheme 1. 7 : Fluorine as a *syn*-stereodirecting group in an iodocyclization reaction.

1.2.5.2) Fluorine / fluorine *gauche* effect:

In the case of molecules containing a 1,2-disubstituted ethane fragment, where substituents are electronegative atoms or groups, a *gauche* conformation was shown to be preferred to an *anti* conformation, although steric an electrostatic repulsion between substituents might suggest an *anti* preference. This unusual *gauche* preference has been observed for vicinal fluorines but not for vicinal chlorines or bromines. For example, infra red adsorption analysis [37], NMR data [38], *ab initio* calculations [39,40,41] and X- ray diffraction [42] have shown that for the 1,2-difluoroethane, the *gauche* rotamer is more stable by up to 1 kcal/mol compared to the *anti* rotamer (Figure 1.9).

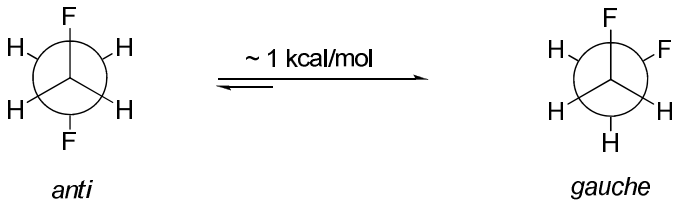


Figure 1. 9 : *Gauche* preference in the 1,2-difluoroethane.

Observations of a *gauche* preference have also been reported by Rittner and co-workers [43] in the study of 1,2-difluoropropane, and Speranza and co-workers [44] in the study of *threo* and *meso* 2,3-difluorobutane (Figure 1.10). In the case of the *threo* isomer, better stability is observed for rotamer **19A** benefiting both from relaxation between the two butyl groups and fluorine *gauche* stabilisation. In case of the *meso* isomer, the stabilisation of the rotamers **18A** and **18B** by the fluorine-fluorine *gauche* effect even overrides the steric hindrance of the two methyl groups being brought close one to another.

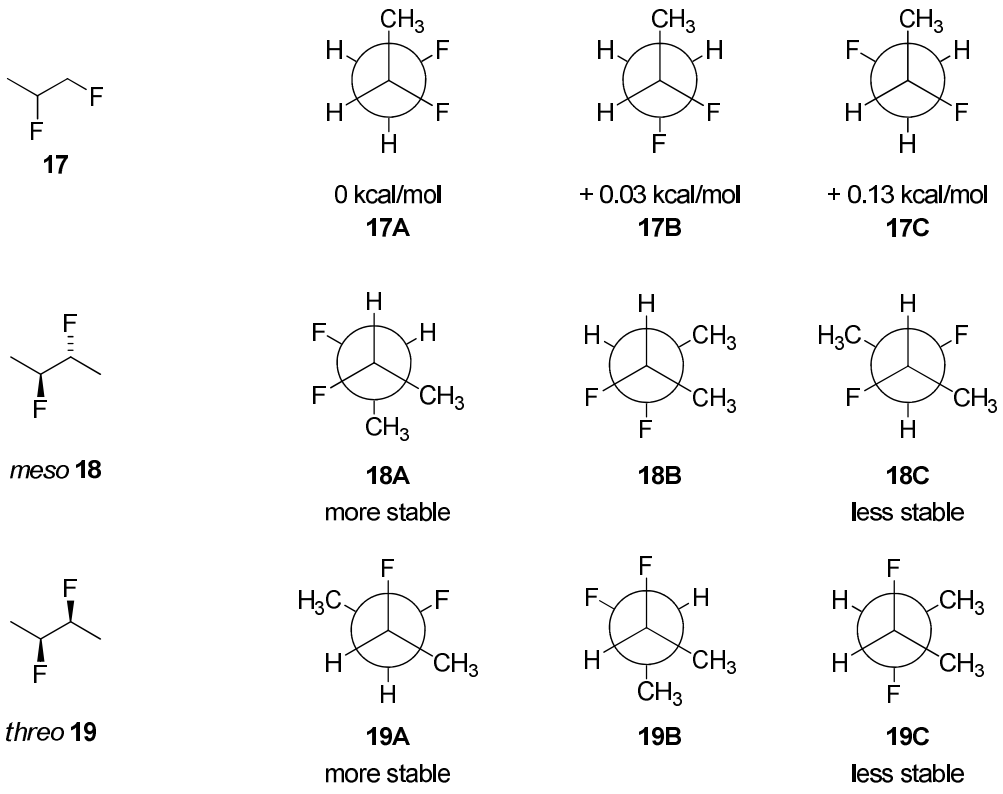


Figure 1. 10 : *Gauche* preference in the 2,3-difluorobutane and 1,2-difluoropropane.

Two different theories have been put forward to explain the *gauche* conformation of vicinal difluorines. The first explanation is based on bent bonds and was developed by Wiberg and co-workers [40]. In a 1,2-difluoroethane model, Wiberg argues that the strong polarisation of the carbon-fluorine bonds induces a distorsion of the carbon-carbon orbitals towards the fluorines (Figure 1.11). Thus Wiberg does not explain the fluorine *gauche* preference, by a better stabilisation of the *gauche* conformer but more by a destabilisation of the *anti* conformer. Indeed, in the bent bond analysis, the carbon-carbon orbitals of the *anti* conformer, bend in opposite directions, resulting in a poorer overlap. Better overlap occurs in the *gauche* conformer with the carbon-carbon orbitals bend in roughly the same direction.

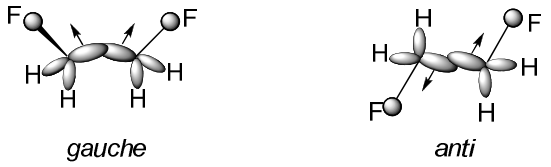


Figure 1. 11 : *Gauche* and *anti* conformers of 1.2-difluoroethane with bent bonds.

In their conformational analysis of 1,2-difluoropropane, Rittner and co-workers suggest that the *gauche* preference is better explained by hyperconjugation [43]. A consequence of the strong electronegativity of fluorine upon carbon, is the presence of a low energy antibonding orbital $\sigma^*_{C\text{-}F}$. In this regard, the polarised C-F bond can be considered as an electron acceptor through its electron-deficient $\sigma^*_{C\text{-}F}$ orbital. In 1,2-difluoroethane, the C-H bonds are better σ-donors than the C-C bond, thus the more stable *gauche* conformation can be explained by hyperconjugation between a $\sigma^*_{C\text{-}F}$ orbital and a $\sigma_{C\text{-}H}$ orbital of the vicinal carbon [45]. As shown in Figure 1.12, when the two fluorines align *gauche*, each $\sigma^*_{C\text{-}F}$ orbital lies antiperiplanar to a $\sigma_{C\text{-}H}$ orbital, and then stabilisation by hyperconjugation is favoured. In the *anti* conformer, $\sigma^*_{C\text{-}F}$ and $\sigma_{C\text{-}H}$ point in different directions and hyperconjugation is not possible.

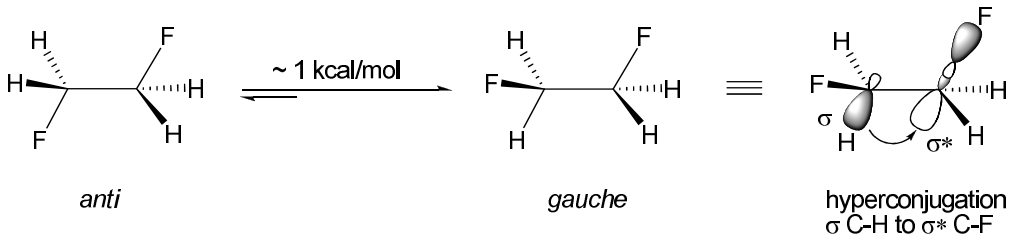


Figure 1. 12 : : *Gauche* and *anti* conformers of 1.2-difluoroethane in the hyperconjugation therory.

In a recent conformational study on 1,2-difluoroethane, Goodman and co-workers [41] state in accordance with Rittner [43], that the ~ 1 kcal/mol difference between the two conformers is better rationalised by hyperconjugation rather than the bent bond analysis. They also suggest that, not only *trans* $\sigma_{C\text{-}H}$ / $\sigma^*_{C\text{-}F}$ hyperconjugation but also a *cis* $\sigma_{C\text{-}H}$ / $\sigma^*_{C\text{-}F}$ hyperconjugation should be considered to fully explain the fluorine *gauche* affect. This could explain why the dihedral angle between fluorine atoms aligning *gauche* is often superior to 60°, and not equal to 60° as it ideally should be (Figure 1.13).

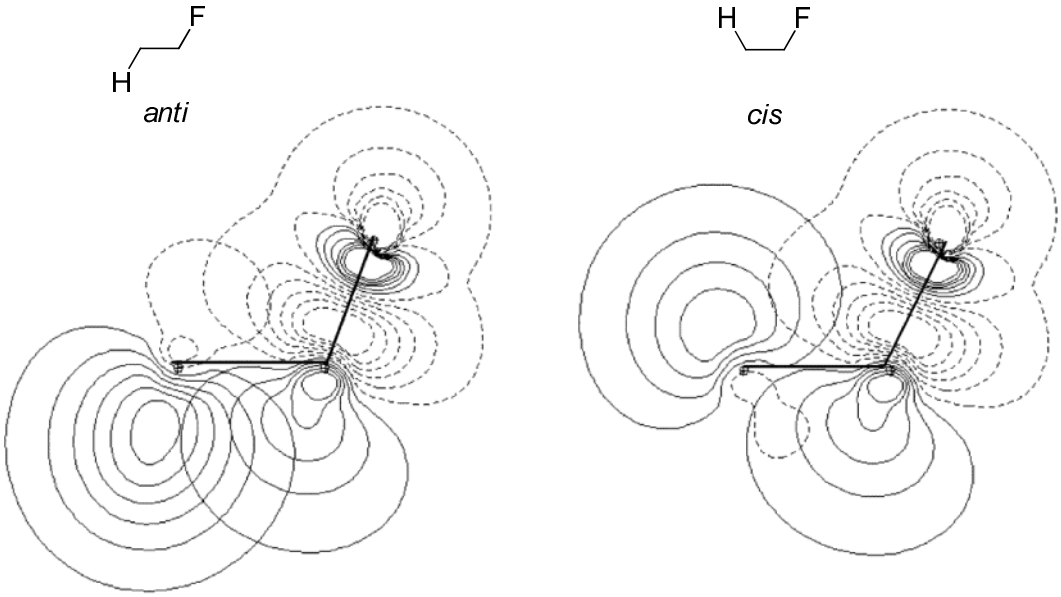


Figure 1. 13 : *Anti* and *cis* $\sigma_{C\text{-}H}$ / $\sigma^*_{C\text{-}F}$ orbital overlap, showing the greater overlap of the main lobe of the anti orbital C-H bond with the back lobe of the C-F antibond. The orbital contours are shown in the C-C-F plane.

1.2.5.3) 1,3-Fluorine/fluorine repulsion:

Sun and co-workers [46] discussed the conformational behaviour of 1,3-difluoropropane. *Ab initio* calculations predicted the order of conformational energies to be GG < AG < AA < G'G', as shown in Figure 1.14.

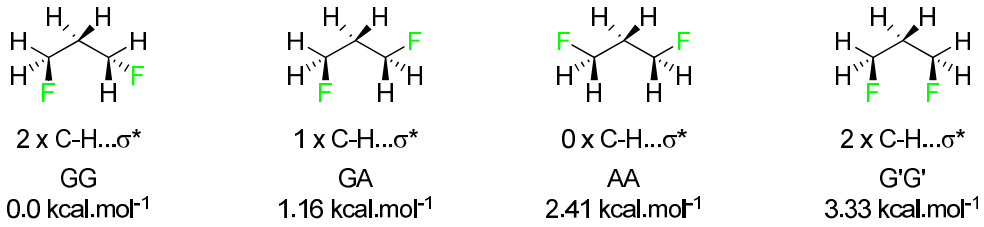


Figure 1. 14 : Conformers of the 1.3-difluoropropane.

This order of preference in conformations can be partially rationalised by hyperconjugative interactions, where conformer GG has two $\sigma_{C-H}/\sigma^*_{C-F}$ interactions and is therefore more stable than conformers GA and AA which have respectively one and no σ_{C-H} / σ^*_{C-F} interactions. However, hyperconjugation does not explain the significant difference in energy between GG and G'G' because the highest energy conformer G'G' has also two $\sigma_{C-H}/\sigma^*_{C-F}$ interactions. To explain that phenomenon, Sun proposed the existence of a 1,3-fluorine/fluorine repulsion calculated at 3.33 kcal.mol^{-1}, and thus higher in energy than the 1,2-fluorine/fluorine *gauche* effect (~1 kcal.mol^{-1}).

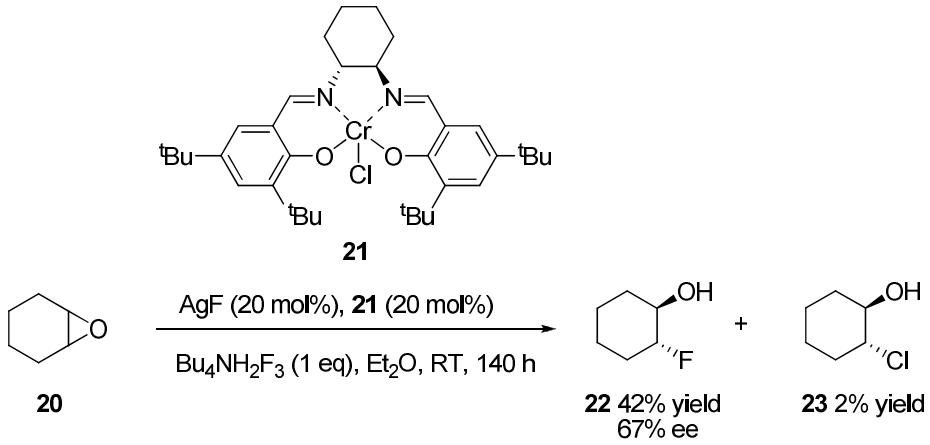
1.3) Stereoselective preparation of mono-fluorinated compounds; recent developments:

1.3.1) Strategies in asymmetric fluorination:

Three different approaches have been used to prepare mono-fluorinated compounds in a stereospecific manner. The first two involve the creation of a carbon-fluorine bond by either nucleophilic or electrophilic fluorination. The third approach is the creation of a carbon-fluorine bond using a synthon already bearing a fluorine atom [19].

1.3.1.1) Nucleophilic fluorination:

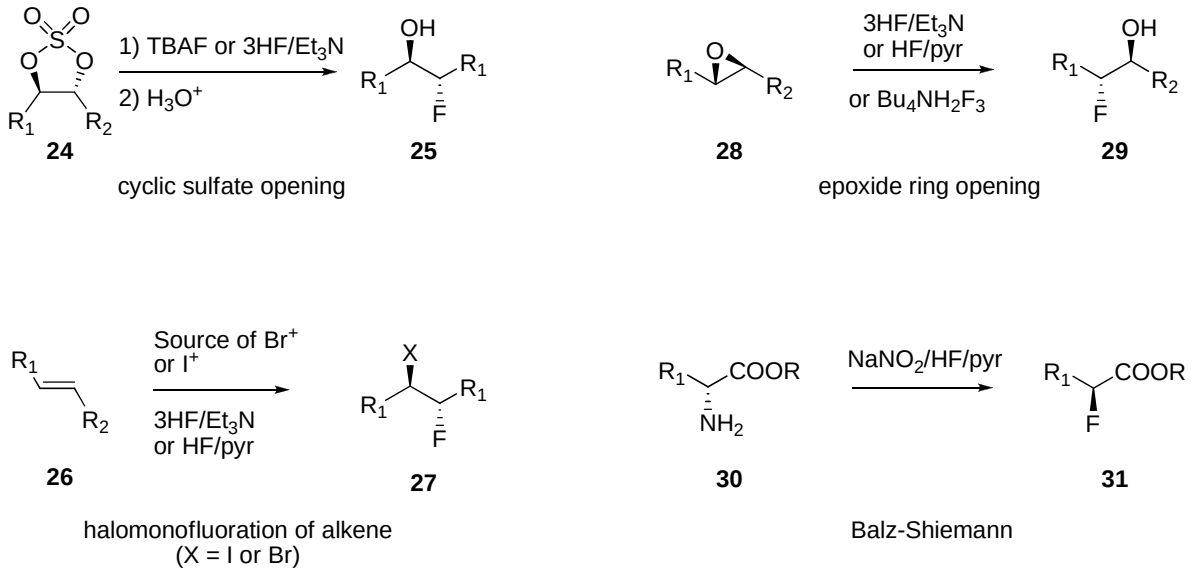
The small size (1.47 Å) and the low polarisability of the fluorine atom favour its ability to act as a base to the detriment of its nucleophilicity. Fluoride ion is also sensitive to solvation and is thus not a very reactive ion. For instance, Haufe and co-workers [47,48] reported an enantioselective disymmetrisation of *meso* epoxides with nucleophilic fluorinating reagents. As shown in Scheme 1.8, an epoxide ring opening is performed with a stoichiometric amount of $Bu_4H_2F_3$ combined with 20% of AgF and catalysed by 20 mol% of a Jacobsen's Cr-Salen Lewis acid. They obtained a fluoro-cyclohexanol **22** with an *anti* configuration, in 42% yield and a moderate 67% ee, together with traces of undesired chlorohydrin **23**.



Scheme 1. 8 : Enantioselective disymmetrisation of *meso* epoxides with nucleophilic fluorinating reagents.

Induction of asymmetry by a nucleophilic reaction on a racemate is then not an easy task, thus the strategy of stereoselective nucleophilic fluorination of an enantio-enriched starting material is usually preferred. In this regard the displacement of a leaving group (halide or sulfonate) at a stereogenic center can be carried out using metallic fluorides (KF, CsF, AgF) or ammonium fluorides (Bu_4NF (TBAF), Bu_4NHF_2 (TBABF) or $Bu_4NH_2F_3$), but these reactions sometimes require the presence of highly aprotic polar and toxic solvents, high temperatures, or the addition of crown ethers. These substitutions are substrate dependant and depending on the starting material, can be achieved in good yields or can suffer from elimination side reactions. The main reagents for performing nucleophilic fluorinations are metallic fluoride salts, quaternary ammonium fluorides (TBAF and derivatives), DAST (and its derivatives) or fluorohydric acid complexed with amines. As shown in Scheme 1.9, cyclic sulfates **24** and epoxides **28** can be stereoselectively and sometimes regioselectively opened with a source of fluoride ion. Cyclic sulfates react with TBAF in refluxing acetone or $3HF/Et_3N$ in refluxing THF or acetonitrile, to lead to α-fluoro alcohols in moderate to good yields. The opening of epoxides however can require much harsher conditions and extended reaction times. For example $3HF/Et_3N$ and $Bu_4NH_2F_3$ are frequently used neat at high temperatures. Olah's reagent (HF/pyridine complex) is more reactive and can open epoxides

at sub-zero temperatures but its high reactivity can sometimes lead to unwanted side reactions and is not compatible with some protecting groups [19].

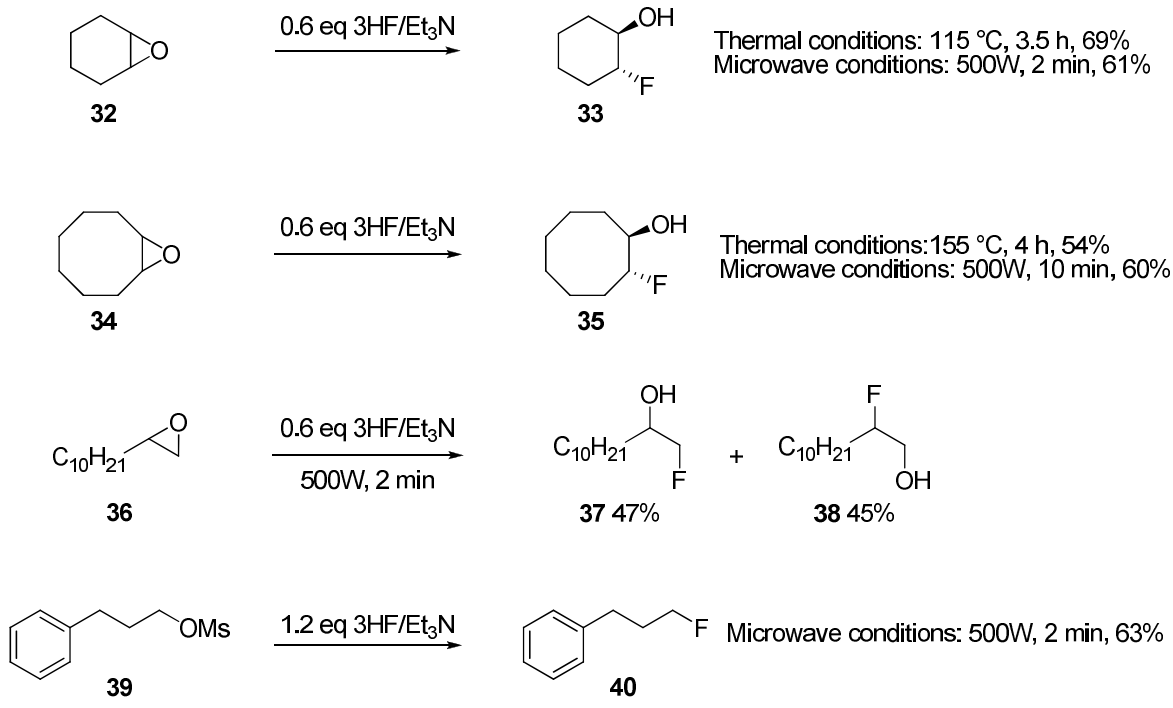


Scheme 1. 9 : Examples of stereoselective insertion of a fluorine atom.

Halomonofluoration of alkenes **26** is also possible *via* the opening of a bromonium or iodonium intermediate with HF/pyridine, $3HF/Et_3N$ or $Bu_4NH_2F_3$. But these reactions sometimes suffer from a lack of regioselectivity. It is also possible to perform a diazotisation/fluorination with an amine **30** in a Balz-Schiemann reaction, in the presence of sodium nitrite and HF/pyridine. This reaction has been used to transform derivatives of natural amino acids into enantioenriched α-fluorocarboxylic acid derivatives, but a loss in enantiopurity is sometimes observed due to the high lability of the diazonium intermediate. Retention of configuration is favoured when the reaction is performed on the amino acid and inversion of configuration is usually favoured with the amino ester derivative [19].

In 2003, Hara and co-workers [49] reported a dramatic reduction in time and HF reagent for epoxide openings (Scheme 1.10). Fluoroalcohols were obtained within a few minutes under microwave irradiation instead of hours under thermal conditions, using less than one

equivalent of $3HF/Et_3N$ in most of the cases studied. Given that $3HF/Et_3N$ is less acidic than HF associated with pyridine, and sometimes is considered to be close to a neutral source of fluorine, reactions of epoxides opening with $3HF/Et_3N$ sometimes suffers from a lack of regioselectivity. For instance, when **36** was treated with $3HF/Et_3N$, α-fluoroalcohols were obtained as a mixture of regioisomers **37** and **38**. They also applied their microwave methodology to the nucleophilic substitution on terminal mesylates by $3HF/Et_3N$, and observed dramatically shortened reaction times.



Scheme 1. 10 : Example of substitution by HF in thermal and microwave conditions.

Sulfur fluorides can also serve as nucleophilic fluorination sources. Diethylamino-sulfur trifluoride (DAST), was developed in the middle of the 1970's, as a less toxic and easier to handle source of fluorine than SF_4. But DAST can undergo explosive degradation when shock-heated, therefore safer derivatives have been developed in the 1980's such as 4-

morpholinosulfur trifluoride (MOST) and bis-(2methoxyethyl)aminosulfur trifluoride (Deoxo-Fluor®) (Figure 1.15) [50]**.**

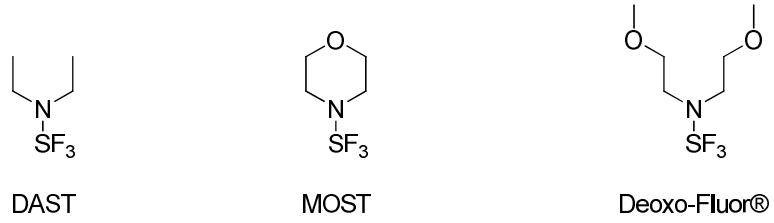
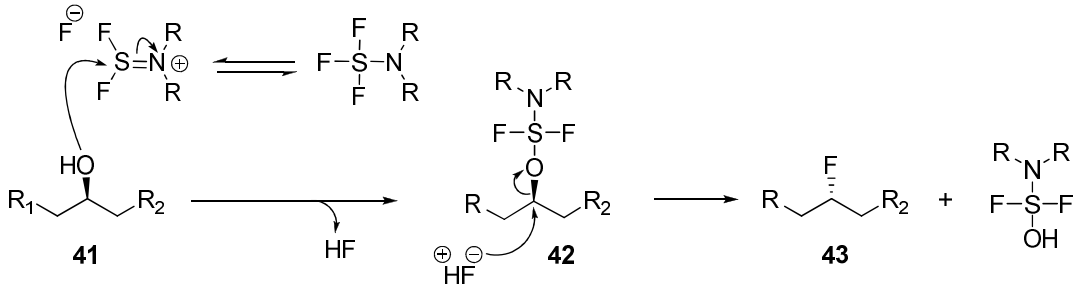


Figure 1. 15

Given their commercially availability, DAST and Deoxo-Fluor® are probably the most widely used nucleophilic fluorinating reagents. These two reagents allow the transformation of an hydroxyl group to fluorine in a stereoselective manner with inversion of configuration in most cases (Scheme 1.11) [51]. Due to the high lability of the reaction intermediate **42**, Deoxo-Fluor® and DAST have significant cationic character that can lead to rearrangements, poor stereoselectives, or complete retention of configuration depending on the participation of the nearby functional groups.



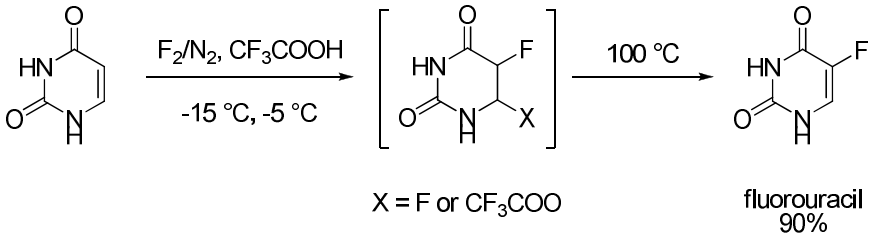
Scheme 1. 11 : Mechanism of reaction of DAST or Deoxo-Fluor® on an hydroxyl group.

This class of reagents can also react with carboxylic acids, aldehydes, ketones and sulfides to form respectively acid fluorides, *gem* difluoro compounds and other fluorinated products. The

reaction with 1,2- or 1,3-diols can also lead to a mixture of difluoro compounds with cyclic ethers as by-products [51].

1.3.1.2) Electrophilic fluorination:

Elemental fluorine is still used in industry for electrophilic fluorination, diluted in nitrogen gas, notably in the synthesis of fluorouracil (Scheme 1.12) [52]. But the use of elemental fluorine in an academic environment is more delicate. In the first instance, specific equipment is required due to its extreme toxicity, and in the second instance, its high reactivity is not in accordance with the great degree of control required for stereoselective fluorinations.



Scheme 1. 12 : Preparation of fluorouracil by electrophilic fluorination.

Other reagents such as hypofluorites (CF_3OF, CH_3COOF) or xenon fluoride are also known for their toxicity, and this has been a negative factor for the development of asymmetric electrophilic fluorination reactions. The development of a new class of safe, easy to handle N-F reagents (Figure 1.16) for electrophilic fluorination in the late 1980's marked the starting point of tremendous progress in asymmetric fluorination.

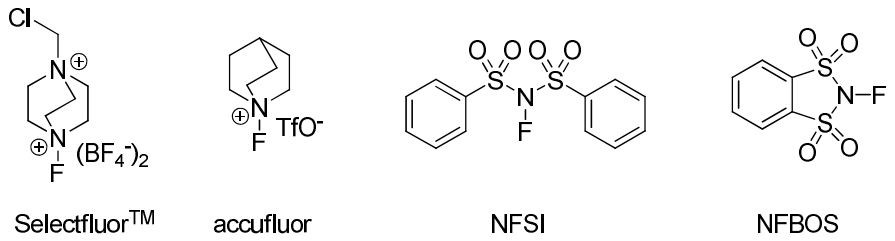
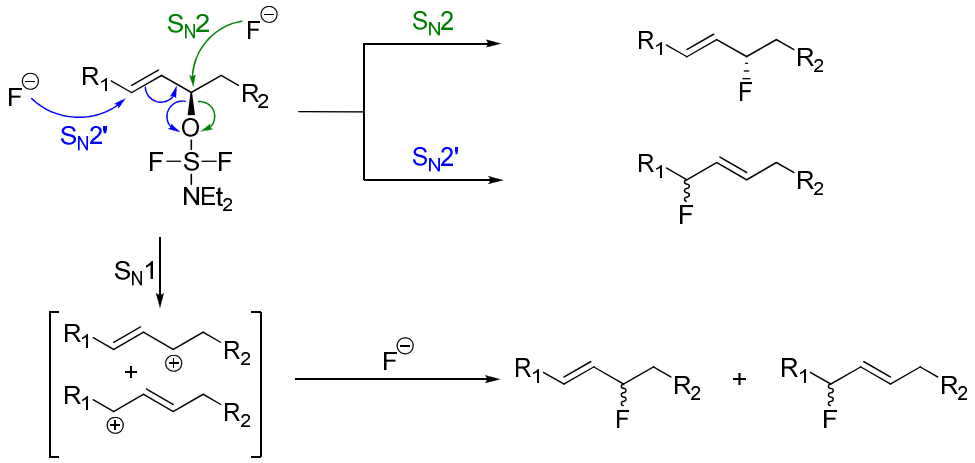


Figure 1. 16

Selectfluor™ (F-TEDA, 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo-[2.2.2]-octane bis-(tetrafluoroborate)), and NFSI (N-fluorosulfonimide) are commercially available. They probably are the most widely used electrophilic sources of fluorine nowadays in the academic environment. Examples of some of their applications are described in the paragraphs below.

1.3.2) Asymmetric fluorination α to π systems:

One of the challenges in organofluorine chemistry in the past few years has been to find highly stereoselective methods to insert a fluorine atom vicinal to π sytems. For example a direct attempt for the preparation of allylic fluoride by deshydroxyfluorination of an allylic alcohol is subjected to several substitution pathways. As shown in Scheme 1.13, the reaction can proceed with S_N1, S_N2 or S_N2' mechanisms depending on the structure of the substrate and it is therefore difficult to control both regio- and stereo-selectivity [53].

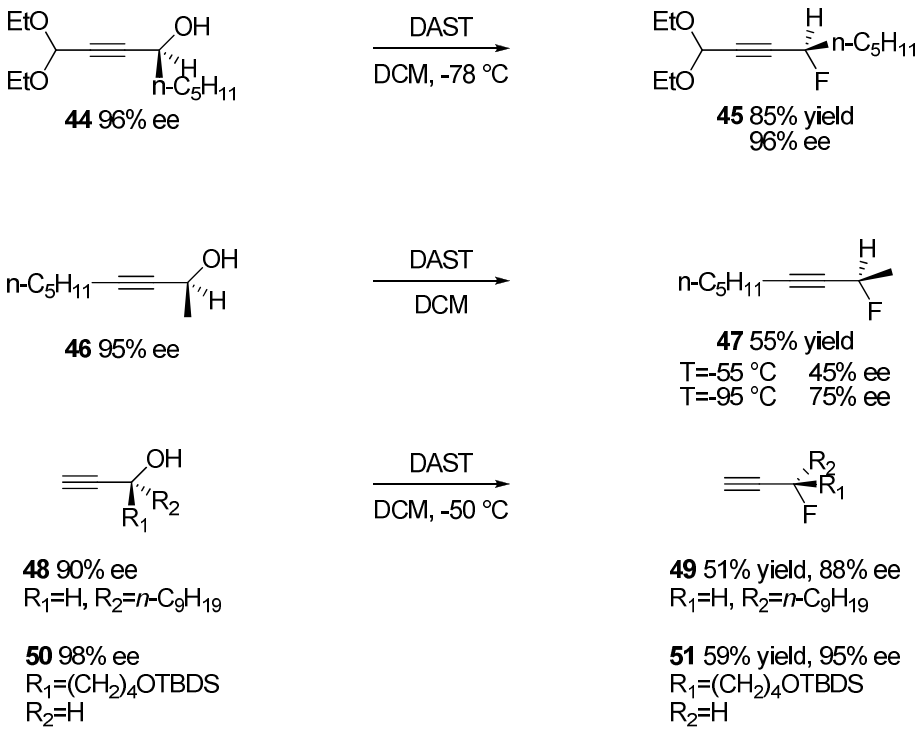


Scheme 1. 13 : Deshydroxyfluorination of an allylic alcohol mediated by DAST.

1.3.2.1) Deshydroxyfluorination of propargylic alcohols:

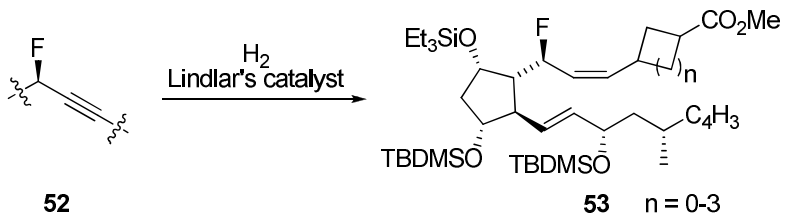
Among others, Grée and co-workers have shown that the fluorination of propargylic alcohols can be stereoselective when carried out at low temperature with DAST (Scheme 1.14) [54,55]. No loss in enantiopurity was observed when propargylic alcohol **44** was converted to a propargylic fluoride **45** with DAST at -78 °C. However this reaction proved to be substrate and temperature dependant. For example when the nearly enantiopure substrate **46** was reacted with DAST, a significant drop of the enantiopurity was observed when the reaction was carried out at -55 °C (**47** obtained in 45% ee) and even -95 °C (**47** obtained in 70% ee). However, the authors showed that the deshydroxyfluorination reaction of terminal propargylic alcohols was more stereoselective, as they didn't observe any significant loss of enantiopurity when substrates **48** and **50** were subjected to deshydroxyfluorination at -50 °C [56,57]. They used an NMR technique based on chiral liquid crystals (poly(γ-benzyl-L-glutamate)) to resolve the two enantiomers of propargylic fluoride in the ^{13}C spectra when the NMR spectra

is recorded in the liquid crystal. They assumed that the reaction proceeded mainly with inversion of configuration.



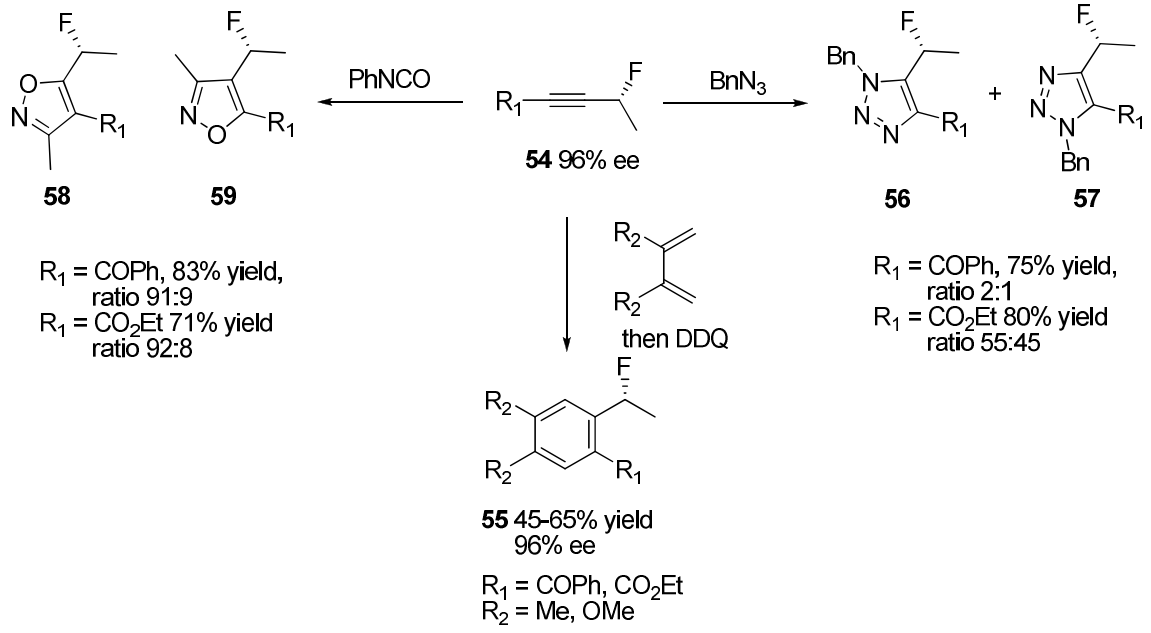
Scheme 1. 14 : DAST deshydroxyfluorination reaction over several propargylic alcohols.

Grée and co-workers also observed that a "protected" triple bond with a cobalt-carbonyl complex favoured a deshydroxyfluorination reaction with a rentention of configuration [58]. Propargylic fluorides like **52** could be reduced to (*Z*)-allyl fluorides using Lindlar's catalyst as shown in Scheme 1.15 for the preparation of fluorine containing prostacyclin precursor **53** [59,60,61].



Scheme 1. 15 : Examples of reduction of a propargylic fluoride with Lindlar's catalyst.

Grée and co-workers extended their methodology to the synthesis of enantio-enriched α-fluoro-aromatic and heteroaromatic compounds (Scheme 1.16) [62]. They used an enantio-enriched propargylic fluoride **54** as a dienophile in a Diels-Alder reaction followed by aromatisation with DDQ, and formed benzylic fluorides **55** without erosion of enantiopurity. Propargylic fluorides were also used in the formation of fluorinated triazoles **56** and **57**, and isoxazoles **58** and **59** upon 1,3-dipolar cycloaddition with azide and nitrile oxide. Regio-selectivities were good in the case of isoxazoles (up to 91:9) whereas moderate in case of triazoles (up to 2:1).

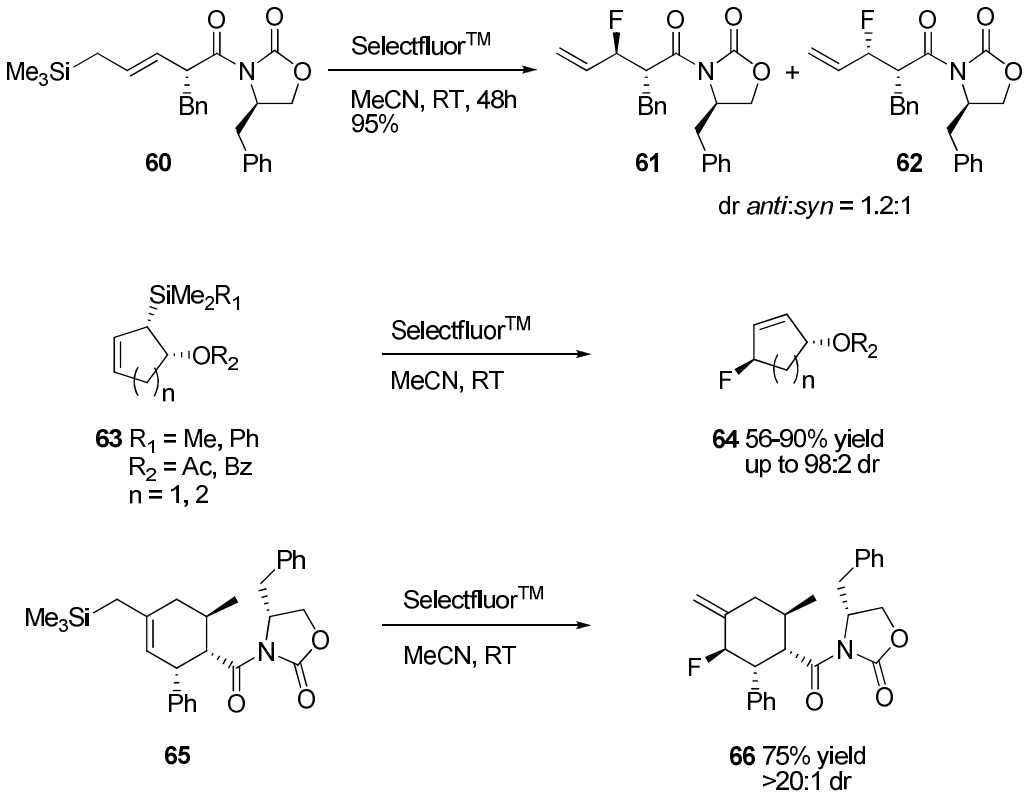


Scheme 1. 16 : Formation of aromatic fluorocompounds from propargylic fluoride.

1.3.2.2) Electrophyllic fluorodeslylation:

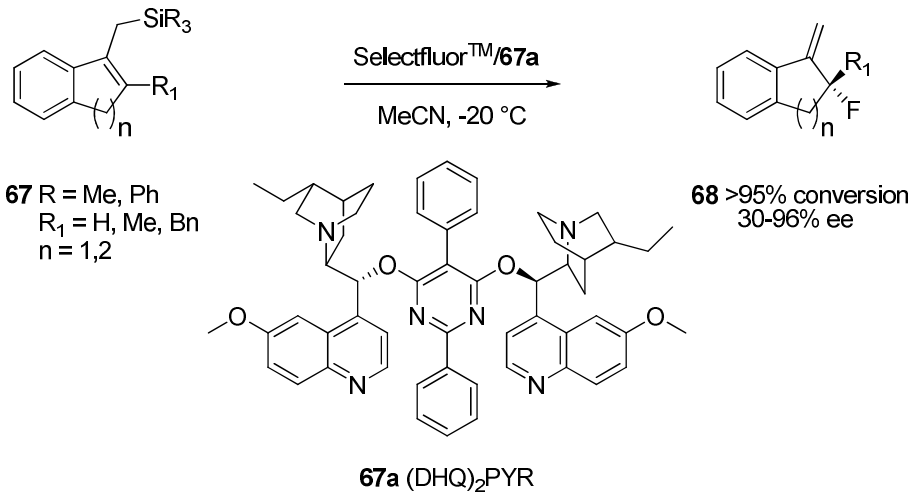
Gouverneur and co-workers developed the concept of electrophilic fluorodesilylation for the synthesis of allylic fluorides. In allylic silane motifs, the silyl group enhances the reactivity of the π bond as a nucleophile, and controls the regiochemistry of the addition of the electrophile. This is based on the ability of a carbon-silicon bond, in an allylic silane motif, to stabilise a β carbocation by approximatively 30 kcal.mol^{-1} and therefore allow the γ electrophillic addition of fluorine, with transposition of the double bond. The mechanism of this reaction is believed to be S_E2' [63]. Optimised reaction conditions appeared to involve Selectfluor^{TM} in MeCN, usually at RT.

After successfully testing their methodology for the preparation of racemate allylic fluorides, Gouverneur and co-workers applied their knowledge to the preparation of enantio-enriched allylic silanes for electrophilic fluorodesilylation reaction [64,65,66]. The reaction of the enantiopure **60** with Selectfluor^{TM}, afforded both *syn* **62** and *anti* **61** diastereoisomers in a 1:1.2 mixture, which were separated by silica gel chromatography (Scheme 1.17). It is noteworthy that although α fluorination of oxazolido-imide is well documented, examples of β fluorination remain rare. Gouverneur and co-workers also prepared a wide range of enantio-enriched fluorinated carbocycles such as **64** and **66**, with good yields and in excellent diastereoselectivities, by fluorodesilylation of enantio-enriched allylic silanes (some of their results are shown in Scheme 1.17).



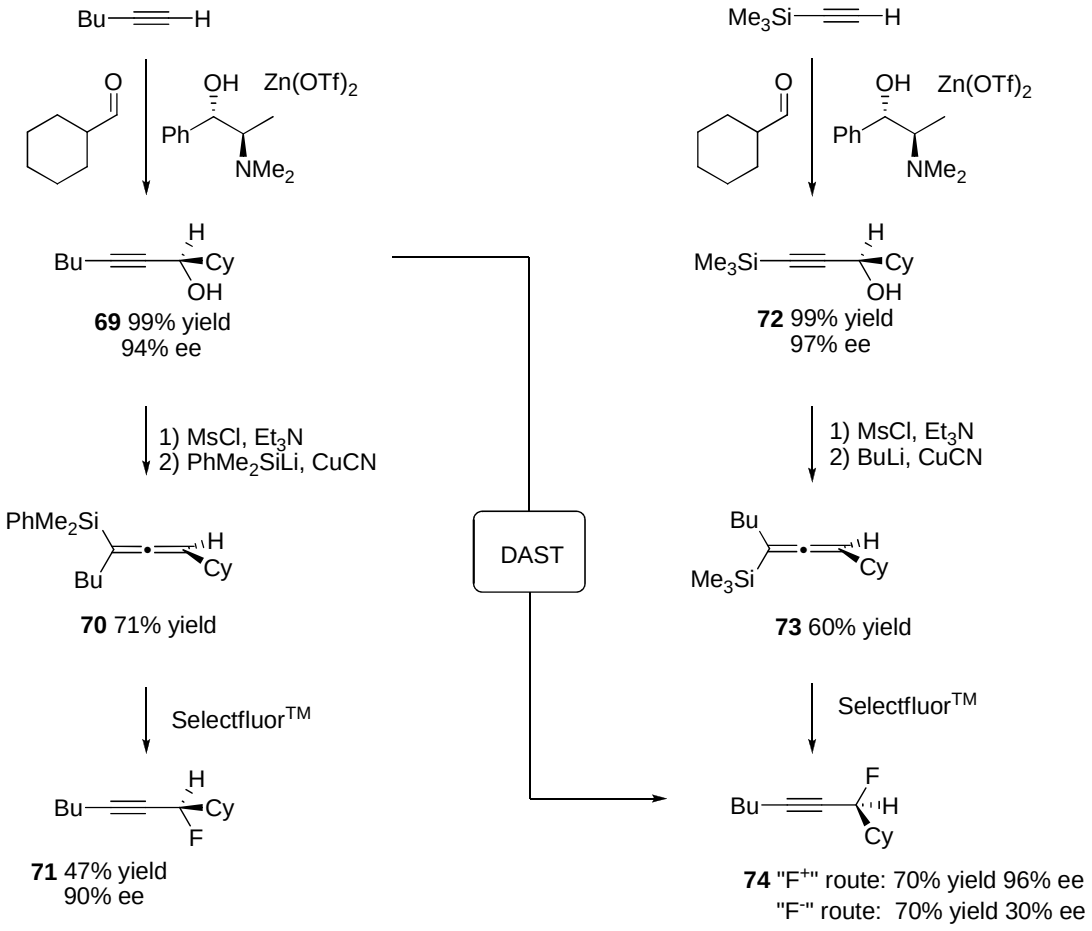
Scheme 1. 17 : Examples of allylic silanes for electrophilic fluorodesilylation reaction.

As an alternative to the reaction with enantiopure starting material, the authors also reported a catalytic version of the fluorodesilylation reaction (Scheme 1.18) [67]. They reacted a range of cyclic prochiral allylsilanes **67**, with Selectfluor™ combined with the commercially available cinchona alkaloid **67a**. Allylic fluorides such as **68** were obtained in good yields and high enantioselectivities, especially with indanones (n = 1, ee up to 96%).



Scheme 1. 18 : Example of catalytic electrophilic fluorodesilylation reaction.

In an effort to extend their methodology, Gouverneur and co-workers explored the preparation of enantio-enriched propargylic fluorides by fluorodesilylation of enantio-enriched allenylsilane [68] (Scheme 1.19). Propargylic alcohols **69** and **72** were first prepared in high enantioselectivity (up to 97% ee) following Carreras's method, and converted to allenyl silane **70** and **73** without loss of enantiopurity. Further reaction with Selectfluor™ afforded the propargylic fluorides **71** and **74** with efficient transfer of chirality, and an overall retention of stereochemistry. In parallel, propargylic fluoride **74** was also prepared from deshydroxyfluorination of propargylic alcohol **69**, and thus the two methods could be compared. In that case, electrophilic fluorodesilylation proved to be a more powerful method as it did not generate any erosion of enantiopurity. Alternatively, when propargylic fluoride **74** was prepared under Grée's conditions, a dramatic drop in enantiopurity from 94% ee to 30% ee was observed.



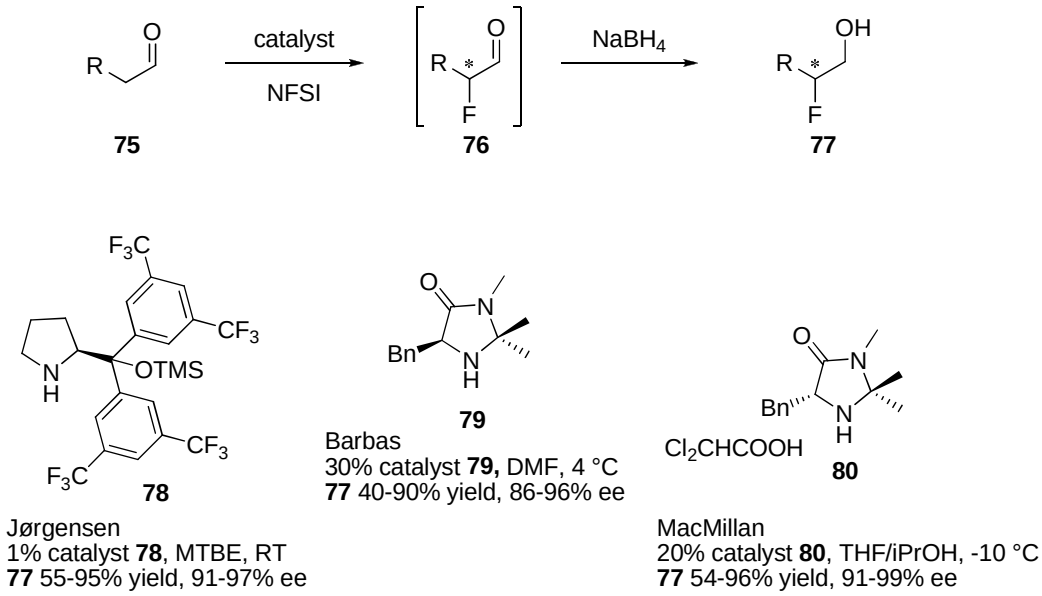
Scheme 1. 19 : Different routes to enantio-enriched propargylic fluorides.

1.3.3) Catalytic electrophilic fluorinations:

Introduction of fluorine in a diastereo- and enantio-controlled manner, presents a serious challenge under catalytic conditions. The catalyst must be stable in the presence of the fluorinating reagent and must also clearly differentiate the starting material from the product, which is not easy due to the small size of fluorine. The development of stable, easy to handle electrophilic reagents such as Selectfluor™ and NFSI have had a tremendous impact on the development of catalytic methods of asymmetric fluorination.

1.3.3.1) Preparation of α-fluoroaldehydes and ketones:

In 2005, Enders and Huettl [69] published the first organocatalytic fluorination of an aldehyde using L-proline as a catalyst and with Selectfluor^{TM} as the fluorinating reagent, but reactions proved slow and the ee's were low. The same year, and within a few weeks of each other, Jørgensen [70], Barbas [71] and MacMillan [72] published on the α fluorination of aldehydes, but this time, with NFSI and with significantly better results. Jørgensen and co-workers showed that the bulky silylated prolinol **78** was much more reactive than the original proline. They obtained α-fluoro derivatives of aldehydes in excellent enantioselectivities (up to 97% ee) and good yields (up to 85%) using only 1 mol% of catalyst (Scheme 1.20).

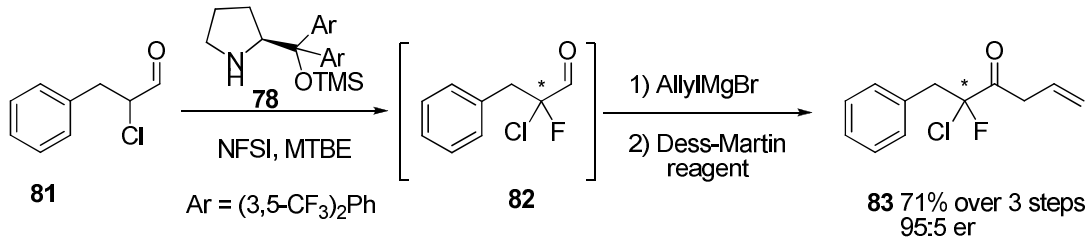


Scheme 1. 20 : Different catalytic methods for the asymmetric α-fluorination of aldehydes.

Barbas and MacMillan developed catalysts **79** and **80**. Derivatisation *in situ* of the α-fluoro aldehydes to an alcohol or hydrazone was necessary because purification of fluoroaldehydes over silica proved to be impossible. Jørgensen and Barbas also performed the fluorination of

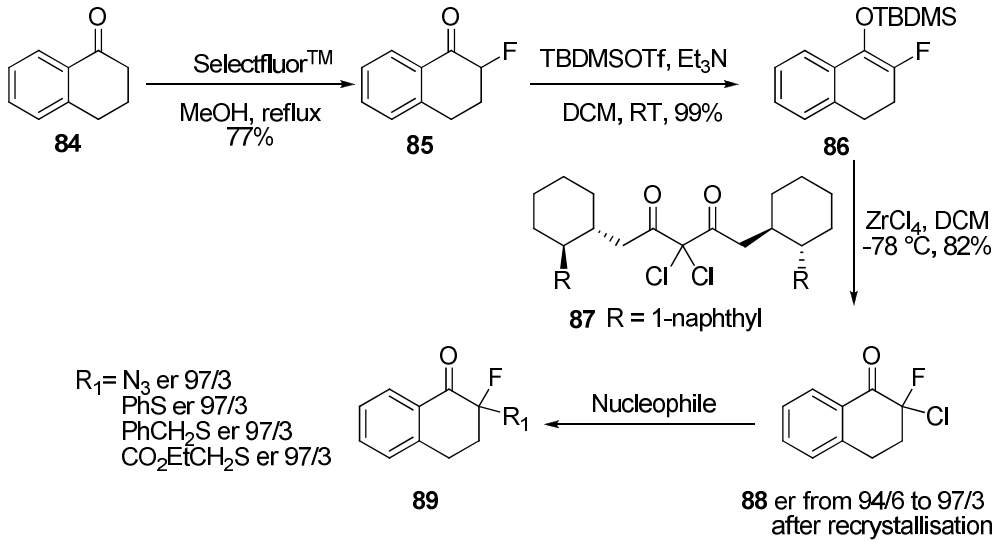
α-branched aldehydes leading to fluorine substituted quaternary stereogenic centers, but with only moderate ee's.

In 2008, Yamamoto and co-workers [73] published the stereoselective formation of fluorinated chiral quaternary carbon centers by either a fluorination / chlorination or a chlorination / fluorination reaction of aldehydes and ketones. As shown in Scheme 1.21, they first performed an asymmetric fluorination of α-chloro aldehydes **81** using Jørgensen's catalyst **78**, followed by the *in situ* addition of a Grignard reagent, and they obtained α-fluoro-α-chloroketone **84** with a 95:5 enantiomeric ratio.



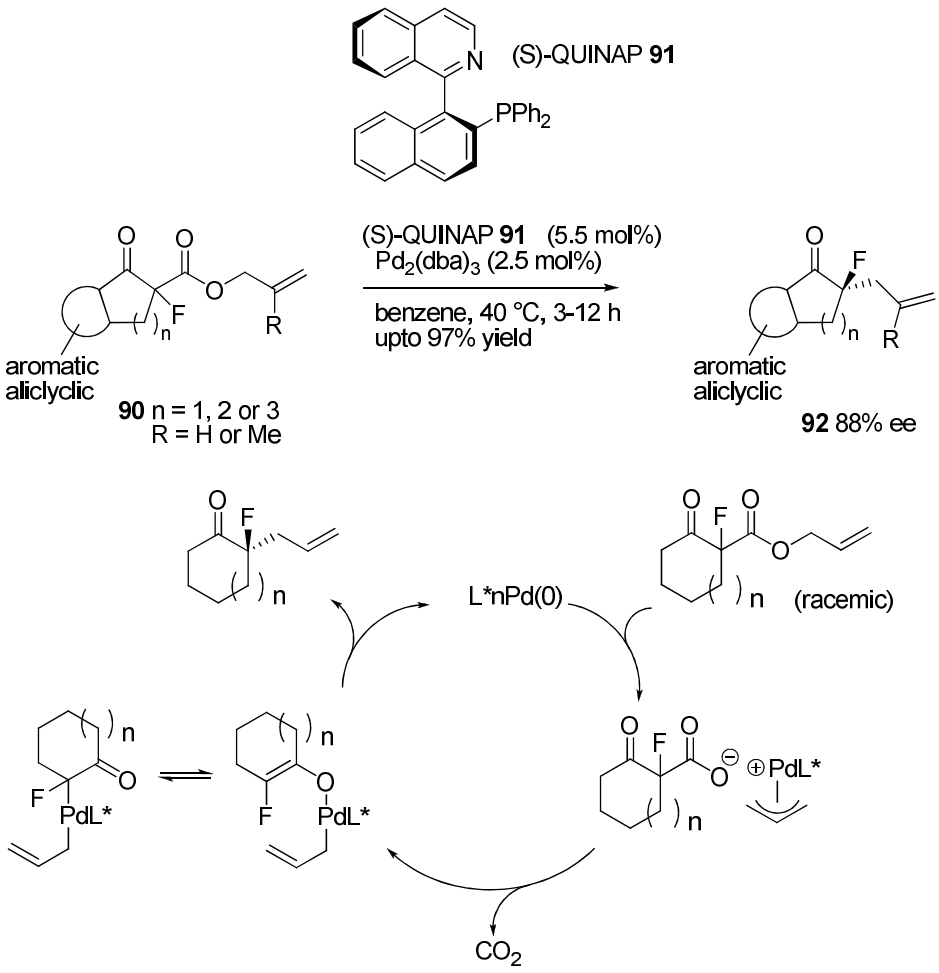
Scheme 1. 21 : Preparation of α-fluoro-α-chloroketone.

The authors also prepared an *O*-silylated α-fluorotetralone by electrophilic fluorination of tetralone **84** with Selectfluor^{TM}, followed by the conversion to its silyl ether **86** with TBDMSOTf in presence of triethyl amine. Then an asymmetric chlorination of the α-fluoro silyl ether was performed using the chiral ligand **87** and $ZrCl_4$ as a source of chlorine. This reaction proved to be highly stereoselective, as the α-fluoro-α-chlorotetralone **88** was obtained in a 94:6 enantiomeric ratio, which was improved to 97:3 after crystallisation. Chlorine was then selectively displaced by a range of soft nucleophiles without erosion of the enantiomeric ratio to form molecules such as **89** (scheme 1.22).



Scheme 1. 22 : Preparation of α-fluoro-α-substituted ketone.

In an indirect approach to the preparation of enantiomerically enriched α-fluoroketones, Tunge and co-workers [74] have recently investigated a Pd(II) mediated decarboxylative allylation reactions on already fluorinated (racemic) β-keto allyl esters such as **90** with ligands such as QUINAP **91**. A catalytic cycle is shown in Scheme 1.23 and for example this generated ketone **92** in 88% ee carrying a fluorinated quarternary stereogenic centre.

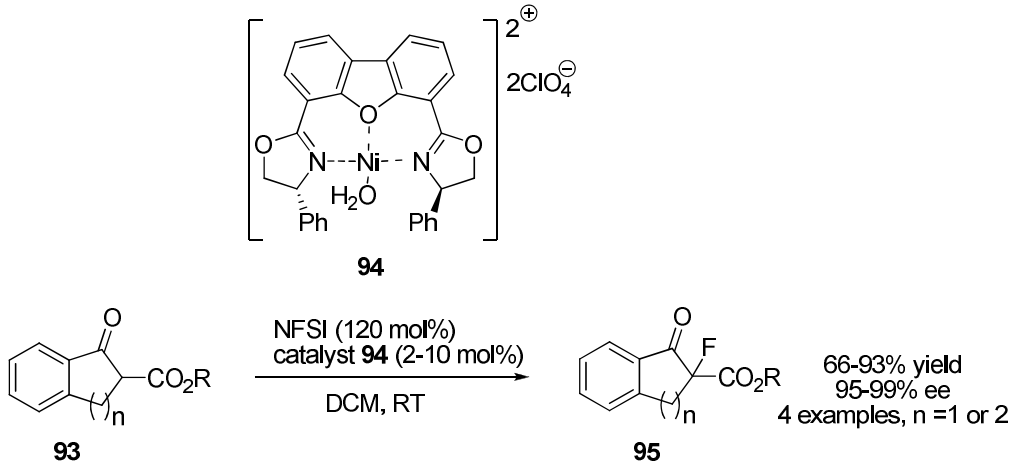


Scheme 1. 23 : Decarboxylative allylation to α-fluoroketones.

1.3.3.2) α-Fluoro-β-ketoesters:

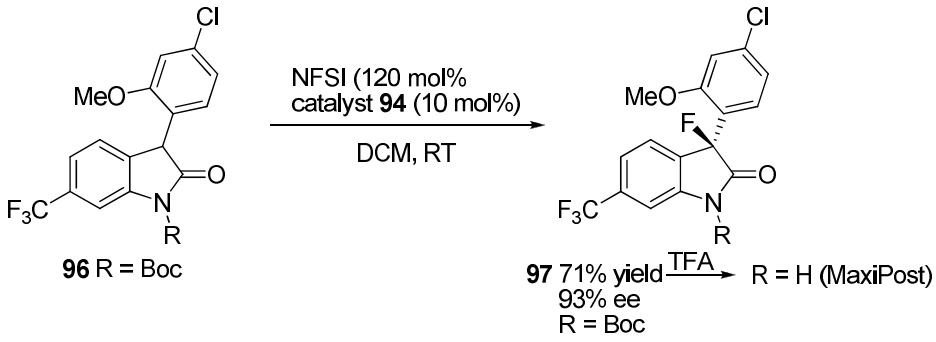
Examples of catalytic asymmetric fluorination of β-ketoesters are quite numerous compared to other motifs. It was first reported by Togni and Hintermann [75] in 2000 where α-fluoro-β-ketoesters where obtained good enantioselectivities (up to 90% ee), using a Taddol-titanium complex (5 mol%) in combination with Selectfluor™. Most recently Iwasa and co-workers [76] have explored enantiopure *N*,*N*,*N*-tridentate ligands at 5 mol%, with NFSI as the electrophilic fluorine source. The most impressive enantioselectivities (up to 94% ee) were found when $Ni(ClO_4)_2$ or $Mg(ClO_4)_2$ was used as the Lewis acid in association with the

N,*N*,*N*-tridentate ligands. One of the most impressive result was recently reported by the Shibata and Toru groups [77] to generate α-fluoro-β-ketoesters **95** in good yields, and in excellent enantiopurities (up to 99% ee) using NFSI and the Ni-bisoxazoline **94** complex (Scheme 1.24).



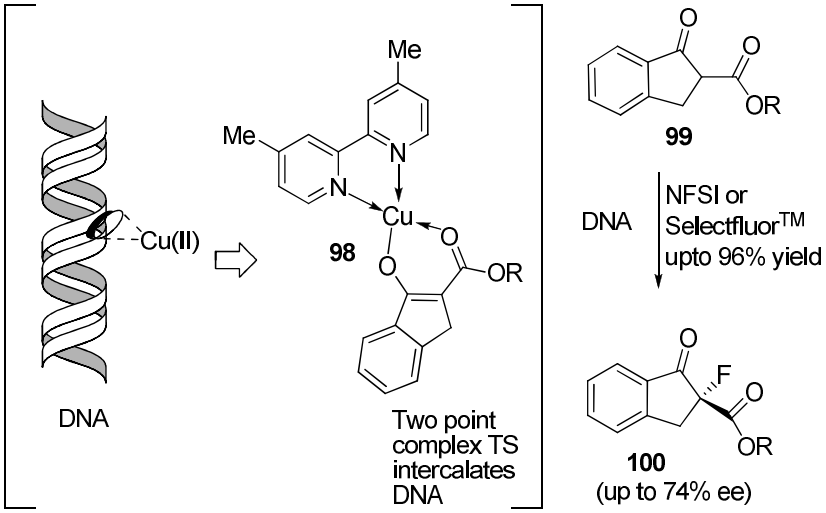
Scheme 1. 24 : Preparation of α-fluoro-β-ketoesters by Shibata [77].

The power of their methodology was proven not only by decreasing the catalyst loading to 2 mol% without loss of yield and enantioselectivity, but also by preparing the oxindole **97** (Scheme 1.25). Indeed, deprotection of the Boc group afforded MaxiPost, a potent opener of maxi-K channels. Shibata's approach was the first catalytic enantioselective route to this molecule.



Scheme 1. 25 : Preparation of MaxiPost.

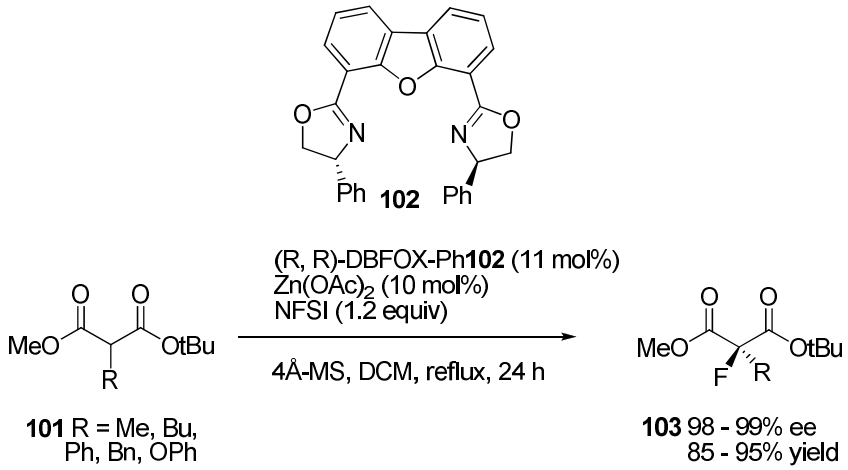
In an intriguing approach Shibata and co-workers [78] have used a catalytic ensemble involving a Cu-bound bispyridyl ligand, intercalated with DNA, for Cu(II) catalysed asymmetric fluorinations. These remarkable reactions, which were inspired by related methodology exploring asymmetric Diels-Alder reactions, utilise Selectfluor^{TM} as the fluorine transfer reagent to the catalyst, in an aqueous buffer. The DNA-intercalated Cu bound catalyst mediates fluorination of indanone β-keto esters with modest to good enantioselectivity (up to 74% ee) induced by the inherent chirality of the DNA molecule (Scheme 1.26).



Scheme 1. 26 : Asymmetric fluorination with DNA.

1.3.3.3) α-Fluoromalonate:

Shibata, Toru and their co-workers [79] have also explored a variety of Lewis acids complexed to the (*R,R*)-DBFOX-Ph ligand to explore catalytic (10 mol %) asymmetric fluorinations of nonsymmetrical malonate esters, considered one of the most challenging substrates to date for enantioselective fluorination. After optimisation $Zn(OAc)_2$ and $Ni(ClO_4)_2$ emerged as the best catalysts, and products are recovered in very high yields and with almost complete enantioselectivity (99% ee) (Scheme 1.27).



Scheme 1. 27 : Malonate catalytic asymmetric fluorination.

Shibata, Toru extended their method to the synthesis of more complex targets; some of them are shown in Scheme 1.17. Several of the substrates are progressed to relevant peptide and pharmaceutical analogues **104-107**, in each case with fluorine at a quarternary stereogenic centre.

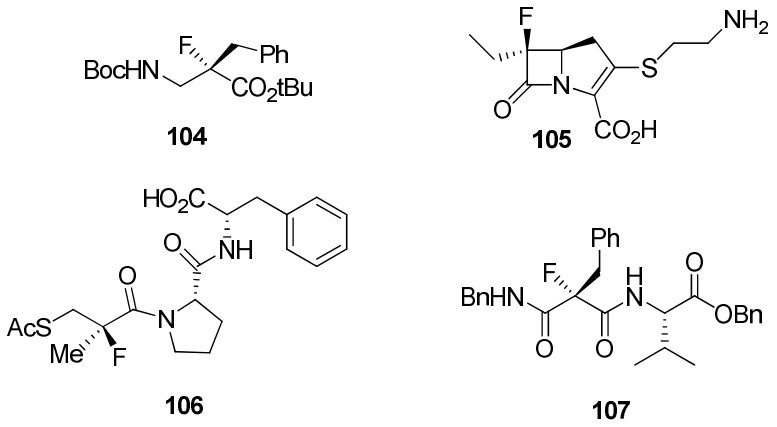
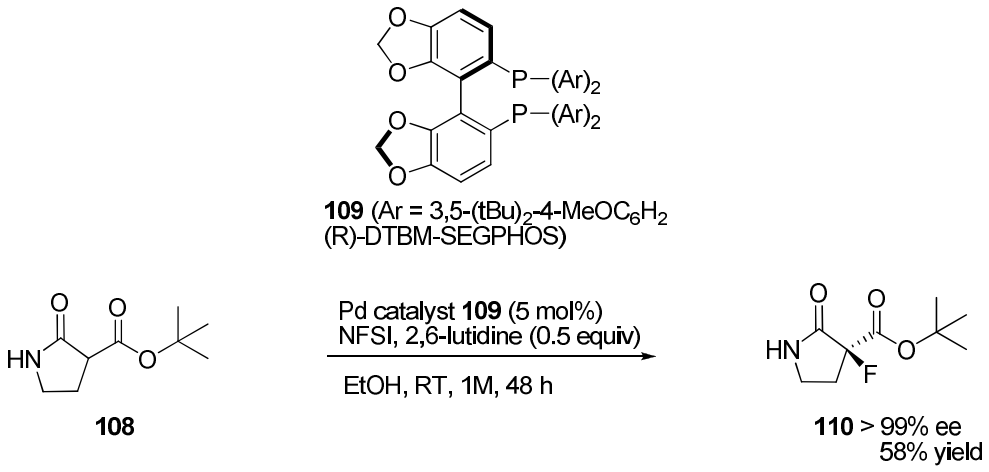


Figure 1. 17

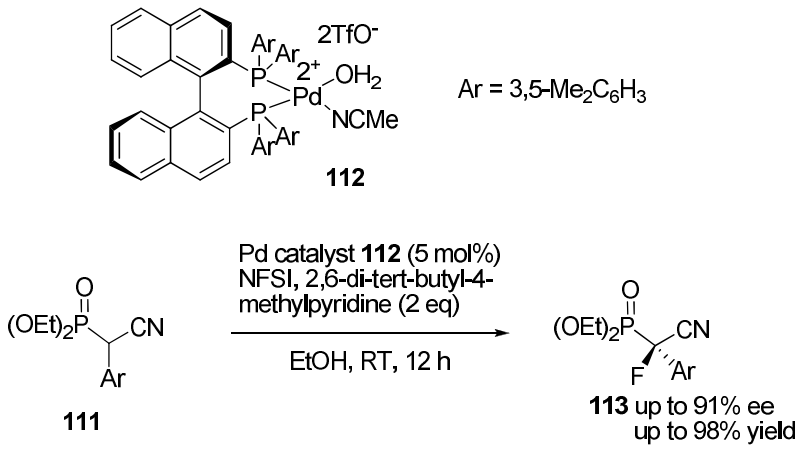
1.3.3.4) Fluorination of other motifs:

Sodeoka and co-workers [80] also reported impressive asymmetric α-fluorination reactions of *tert*-butoxycarbonyl lactones and lactams. As illustrated in scheme 1.28, they used the chiral *bis*-phosphine **109** complexed to Pd(II) (5 mol%) in presence of 2,6-lutidine.



Scheme 1. 28 : Pd(II) mediated fluorinations of lactams.

Lactame **108** was converted to fluorolactame **110** in moderate yield (58%) but with high enantioselectivity (ee > 99%). This general methodology has been extended by the groups of Sodeoka [81] and Kim [82] who have independently demonstrated the asymmetric fluorination of α-cyanophosphonates (Scheme 1.29). In this case, an organic base (eg. 2,6-lutidine or 2,6-di-*tert*-butyl-4-methylpyridine, 2 equivalents) was essential for the efficient fluorination of these substrates, and the method gave product α-fluorophosphonates with enantioselectivities in the high 80% ee's.

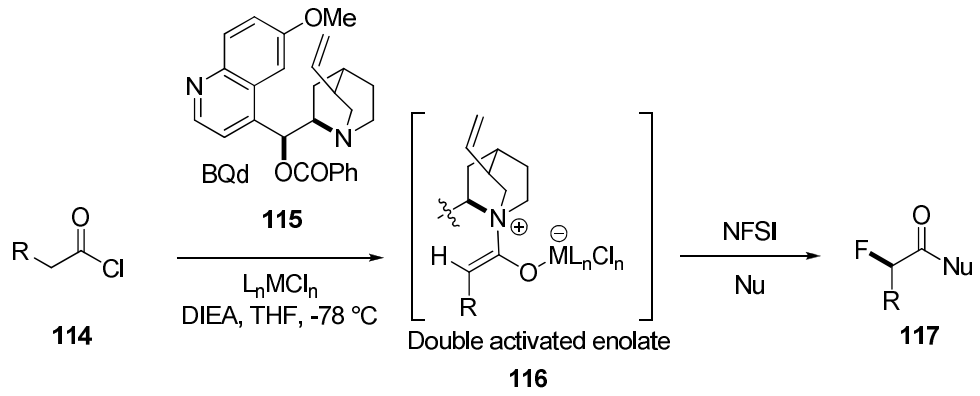


Scheme 1. 29 : Pd(II) mediated fluorinations of phosphonates.

Sodeoka and co-workers have also developed an efficient methodology based on the combination of Ni^{II} (*R*)-BINAP, trimethyl silyl triflate and 2,6-lutidine, for the preparation of enantioenriched α-fluorothiazolidinones and demonstrated their conversion to α-fluoroaryl acetic acid derivatives [83].

1.3.3.5) α-Fluorination of acid chlorides:

In 2009, Lectka and co-workers [84] described the preparation of enantiopure α-fluoro carboxylic acids and some of their derivatives with formation of a double activated enolate intermediate (Scheme 1.30). They reacted an acyl chloride with both a chiral catalyst **115** (benzoylquinidine: BQd), and a transition metal based Lewis acid co-catalyst to access a metal coordinated chiral ketene enolate. This intermediate could then react not only as a nucleophile in fluorination reaction with NFSI but also as an electrophile on its carbonyl center.



Scheme 1. 30 : Preparation of α-fluoro carboxylic acids derivatives from acyl chlorides.

Lectka and co-workers demonstrated the power of their method by preparing a broad range of carboxylic derivatives depending on the nucleophile used to quench the reaction. Some of their results are shown in Table 1.7. Thus, addition to the reaction mixture of water or methanol, an amine or a thiol led to the formation of α-fluoro carboxylic acids, esters, amides, petides and thioesters in very good yields (up to 83%) and excellent stereoselectivities (ee up to 99% and de >99%). Acid halides containing aromatic as well as heterocyclic substituents

proved to be good substrates and the reaction was also compatible with isomerisable carbon-carbon bonds.

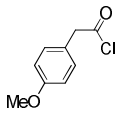
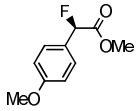
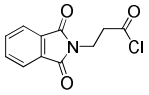
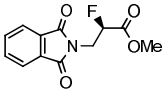
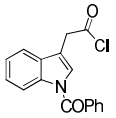
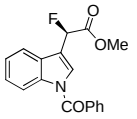
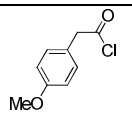
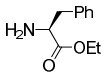
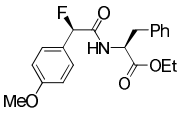
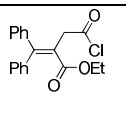
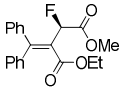
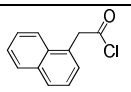
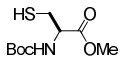
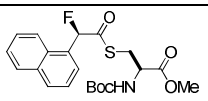
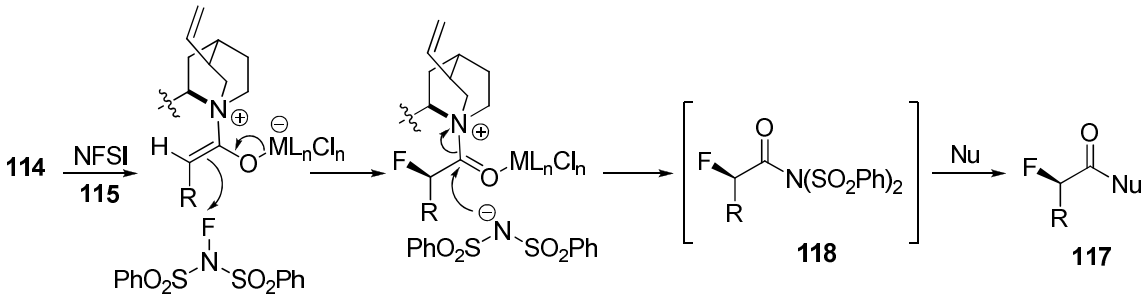
substrate	co-catalyst	nucleophile	product
	$(dppp)NiCl_2$	MeOH	 yield 83% ee 99%
	$(PPh_3)_3PdCl_2$	MeOH	 yield 74% ee 99%
	$(PPh_3)_3PdCl_2$	MeOH	 yield 58% ee 94%
	$(PPh_3)_3PdCl_2$		 yield 68% de >99%
	$(dppp)NiCl_2$	MeOH	 yield 71% ee 99%
	$(dppp)NiCl_2$		 80% yield >99% de

Table 1. 7 : Preparation of α-fluoro carboxylic acids derivatives from acyl chlorides.

Lectka and co-workers noticed the absence of free protonated dibenzenesulfonamide during the course of the reaction. They therefore suggested that the dibenzenesulfonamide ion liberated after fluorination could react with the α-fluoro acyl ammonium salt to form the active imide intermediate **118**. This would undergo a transacylation with added nucleophile to generate the final product (Scheme 1.31).



Scheme 1. 31 : Mechanism proposed by Lectka.

1.4) Multi-vicinal fluoro compounds:

As discussed earlier in this chapter, the presence of a fluorine atom can greatly modify the physical and chemical properties of a molecule. This is of special interest in our laboratory at St Andrews University, to explore the preparation and properties of molecules bearing multi-vicinal motifs in which each adjacent carbon is bonded to one fluorine atom (Figure 1.18).

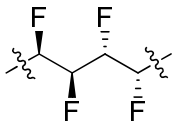


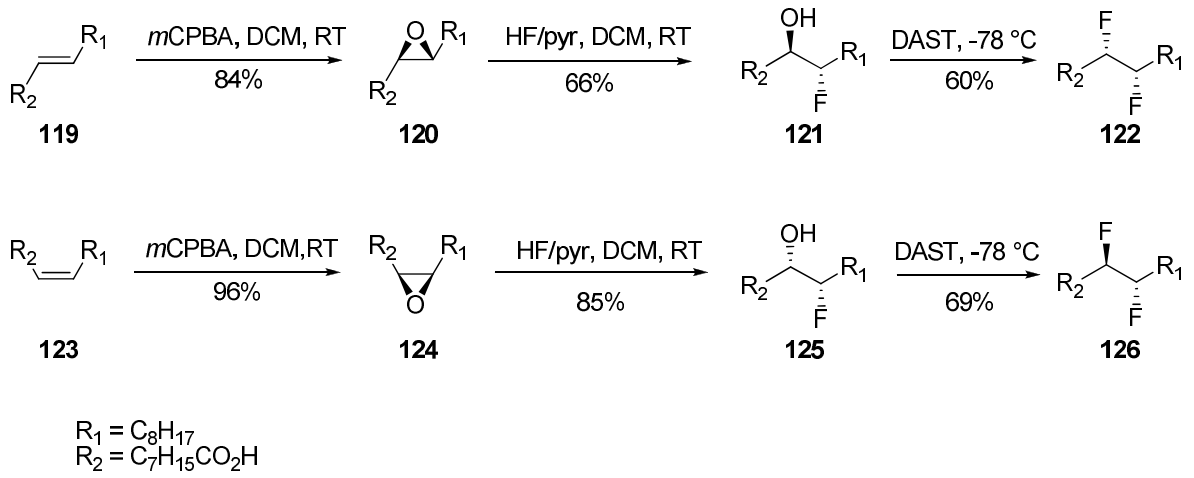
Figure 1. 18 : Example of a multi vicinal fluoro motif.

These compounds can be then considered as a new class of molecules with a degree of fluorination sitting between those of alkanes and perfluoroalkanes. The highly polar nature of the C-F is expected to greatly influence the chemical and physical properties of this new class of compound. In addition the preference for vicinal fluorines to align *gauche* to each other is expected to stabilise some conformations. Each insertion of fluorine generates a new stereogenic centre and therefore each diastereoisomer of a multi-vicinal compound is expected to have unique characteristics due to differently aligned C-F bonds. It is therefore a

requirement to develop flexible stereoselective synthetic methods allowing access to different diastereoisomers of multi-vicinal fluoro compounds.

1.4.1) Vicinal difluorocompounds:

In 2002, Tavasli and O'Hagan [85] reported the synthesis of racemate *threo* and *erythro*-9,10-difluorostearic acids (Scheme 1.32). Epoxidation of both *cis*- and *trans*-9,10-dehydrostearic esters, followed by epoxide ring opening with HF/pyridine and treatment with DAST afforded the *threo* and *erythro*-9,10-difluorostearic esters in good yields and diastereoselectivities.



Scheme 1. 32 : Preparation of vicinal difluoro fatty acids.

After conversion to the corresponding acids by treatment with sodium hydroxide, it appeared that the two diastereoisomers had significantly different physical properties (e.g. melting points) (Figure 1.19). The twenty degrees difference in melting points can be explained by a preferred *anti* zig-zag conformation where the C-F bonds align *gauche* to each other and the alkyl chains are *anti* for the *threo* diastereoisomer **122**. In the case of the *erythro* stereoisomer

126, a greater conformational disorder results from competition between conformers where fluorine prefer to align *gauche* or alkyl chains prefer to orient *anti* to each other.

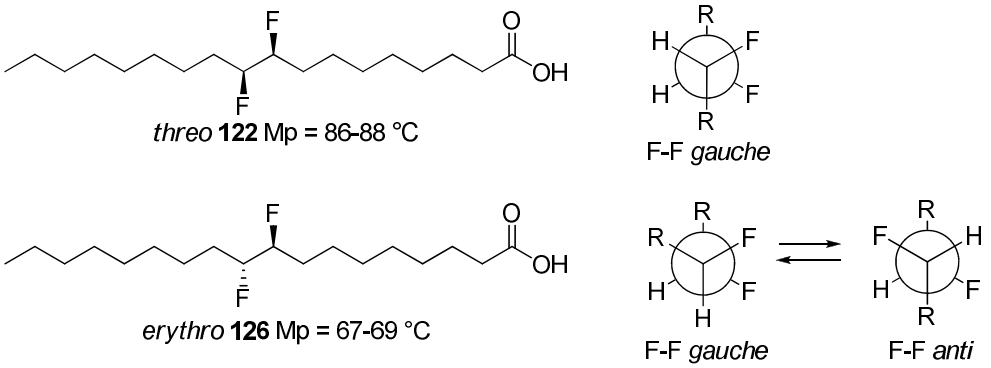
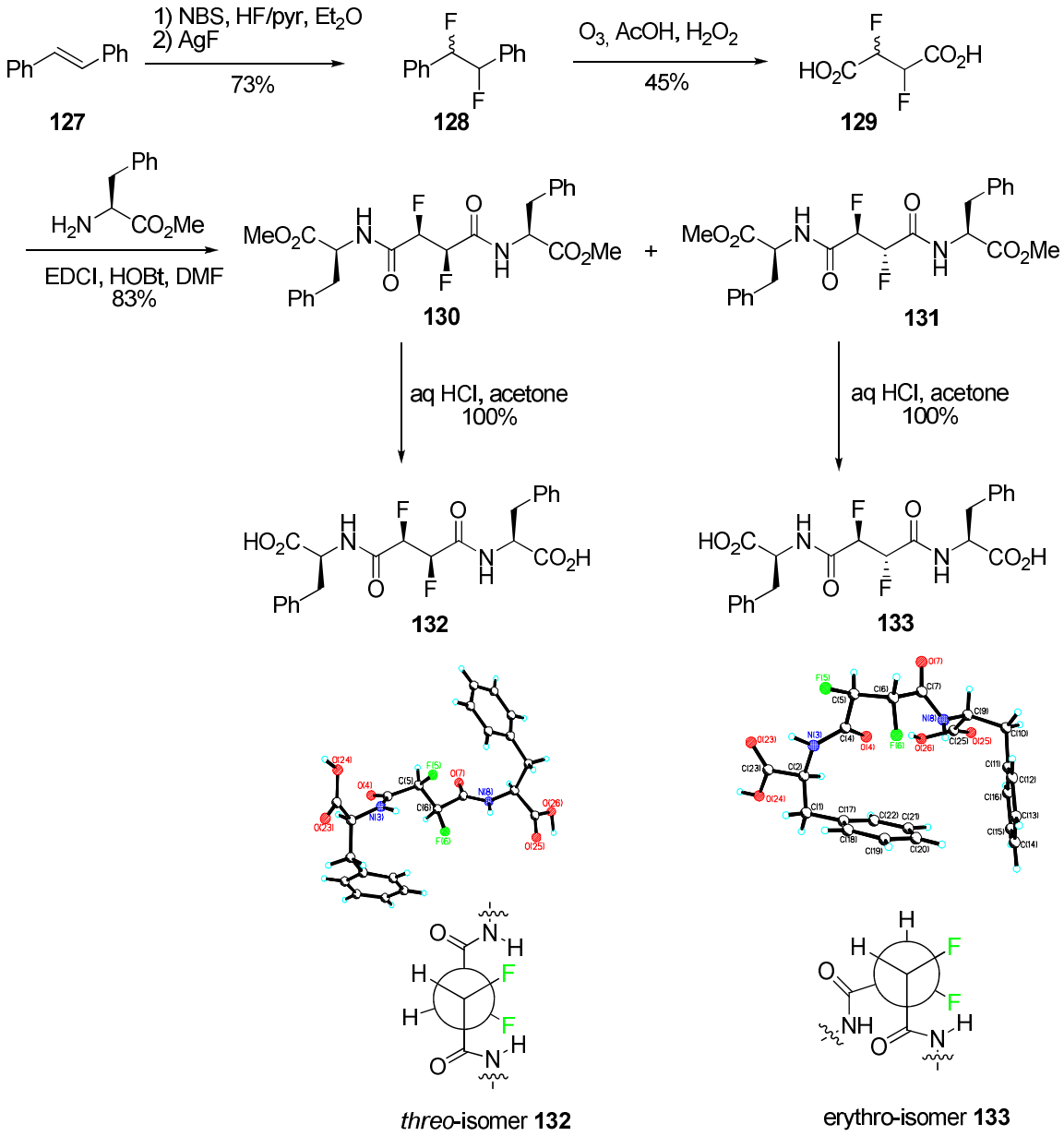


Figure 1. 19

Another example of the conformational influence by vicinal fluorines was reported by Shüeler and O'Hagan [86,87] in the synthesis of 2,3-difluorosuccinic acids and their incorporation into peptidic motifs. Treatment of *trans*-stilbene **127** with *N*-bromosuccinimide in the presence of HF/pyridine, followed by addition of silver fluoride generated *erythro*- and *threo*-stereoisomers of **128** in a 4:1 mixture (Scheme 1.33). It is noteworthy that the major isomer is the *erythro* and is formed by a double inversion with participation of the aromatic ring. Ozonolysis with oxidant work up afforded the diacids **129**, that were then coupled with (*S*)-phenyl alanine methyl ester. After hydrolysis to the corresponding acids, crystal structures of both diastereoisomers **132** and **133** were obtained. Both solid state and solution analyses confirmed that the two diastereoisomers have very different backbone conformations, governed by *gauche* alignment of the fluorine in both cases.

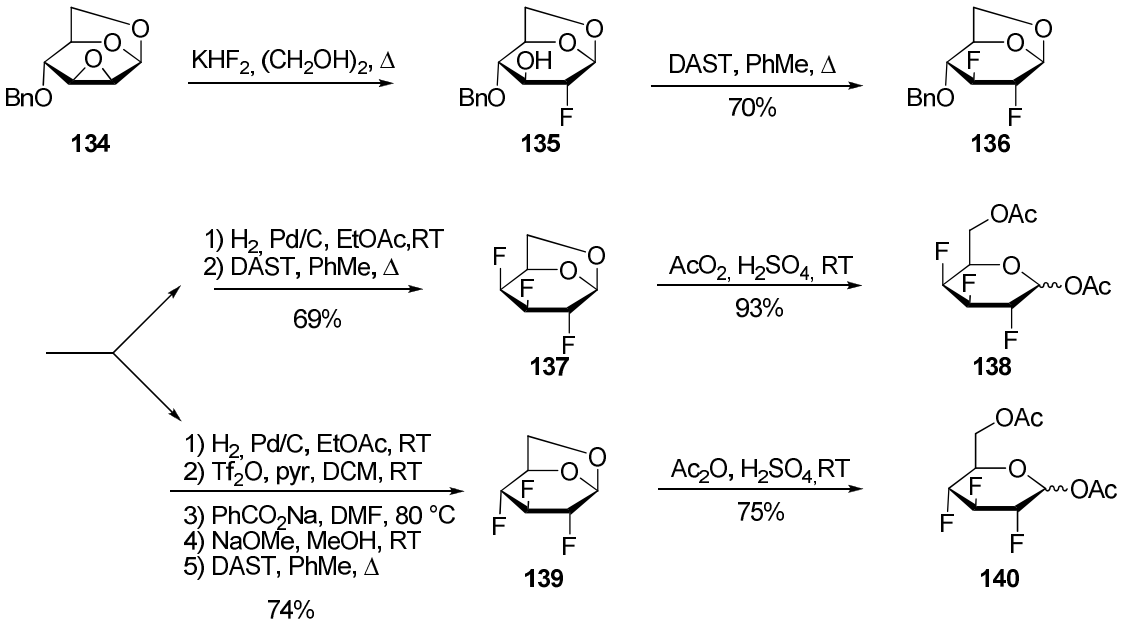


Scheme 1. 33 : Synthesis of 2,3-difluorosuccinic acids and their incorporation into peptidic motifs.

1.4.2) Vicinal trifluorocompounds:

In 1989, Sarda and co-workers [88] reported the preparation 1,6-diacetate-2,3,4-trifluoro analogues of galactose and glucose (Scheme 1.34). Starting from a benzylated epoxy-alcohol **134**, the fluorines at the C_2 and C_3 position were inserted by ring opening with potassium hydrogenofluoride followed by treatment with DAST. It is noteworthy that

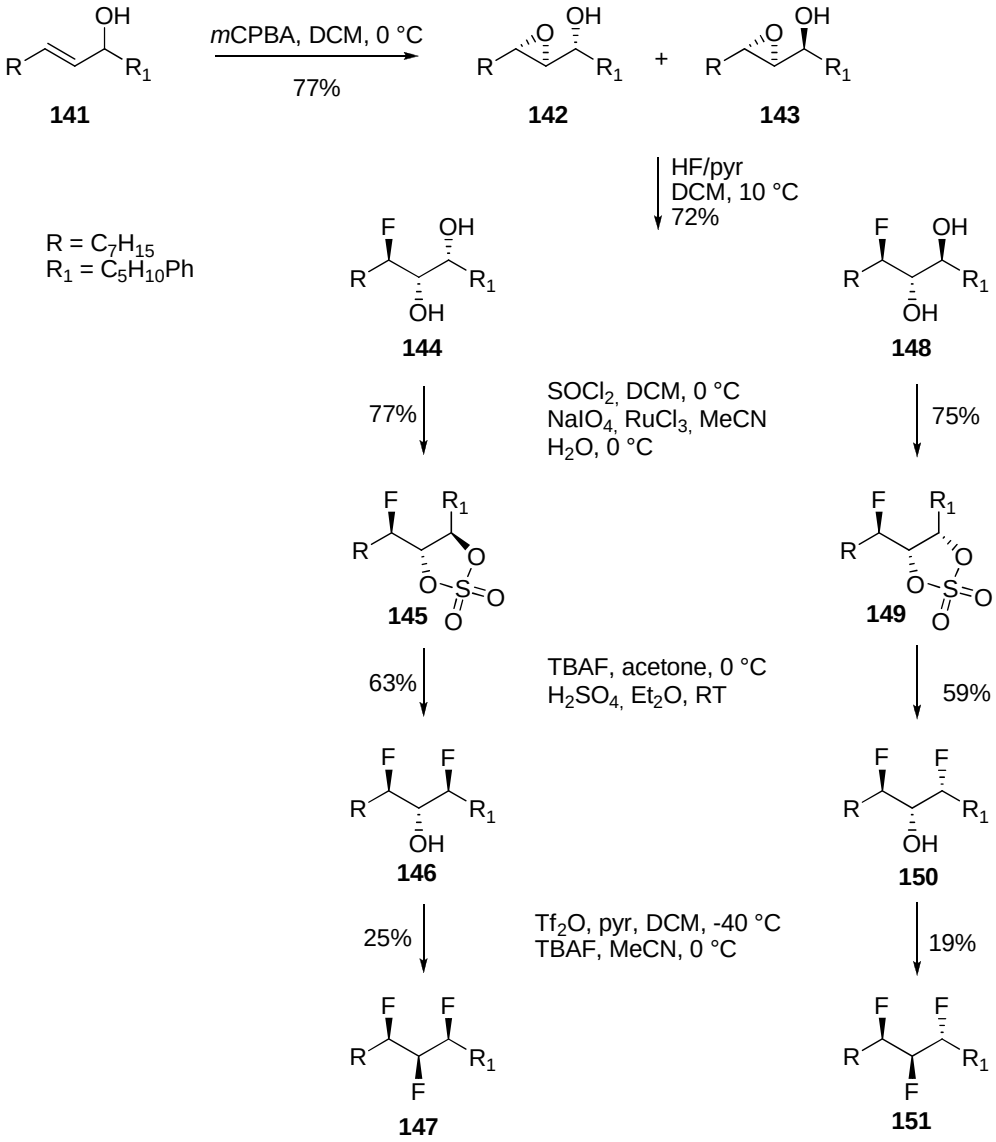
deshydroxyfluorination at the C_3 position occurred with participation of the *O*-benzyl group and with complete retention of configuration. Then hydrogenolysis of the *O*-benzyl group followed by subsequent deshydroxyfluorination at the C_3 position and formation of the acetates at the C_1 and C_6 afforded the 1,6-diacetate-2,3,4-trifluoro analogue of galactose **138**. Following the same pathway but with an inversion of configuration at the C_3 position, before treatment with DAST, led to the 1,6-diacetate-2,3,4-trifluoro analogue of glucose **140**. Sarda and co-workers did not describe deprotection of the acetate groups or applications of these fluorinated sugar analogues.



Scheme 1. 34 : Synthesis of 1,6-diacetate-2,3,4-trifluoro analogues of galactose **138** and glucose **140**.

A more flexible synthetic method to the vicinal trifluoromotif was reported by Nicoletti and O'Hagan [89] in 2005 (Scheme 1.35). After epoxidation of an allylic alcohol with *m*-CPBA, the *threo*-**142** and *erythro*-**143** diastereoisomers of the epoxy-alcohol were regio- and stereo-selectively opened with HF/pyridine and then separated by silica gel chromatography. Formation of a cyclic sulfates **145** and **149** under Sharpless' conditions, and subsequent

highly stereoselective ring opening mediated by TBAF afforded difluorocompounds **146** and **150**. The remaining hydroxyl was then activated by conversion to its triflate derivative, and then displacement by TBAF mediate insertion of the third fluorine atom towards **147** and **151**.



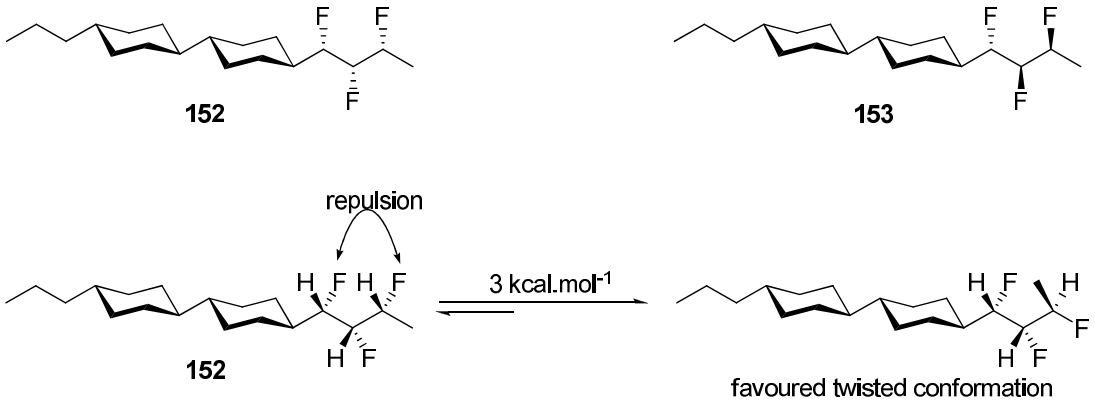
141 **142** **143** **144** **148** **145** **149** **146** **150** **147** **151**

Scheme 1. 35 : Preparation of vicinal trifluoro motifs from epoxy-alcohols.

This methodology was also applied to the synthesis of potential liquid crystal compounds **152** and **153** (Scheme 1.36) [90]. It was assumed that in a linear conformation with all fluorines *syn*, and pointing at the same direction, a molecule such as **152** would exhibit negative

dielectric anisotropy (Δε). Dielectric anisotropy reflects the ability of a liquid crystal to respond to an applied switching voltage. It is defined as the difference between the dielectric constant parallel and perpendicular to the molecular axis. Even though this characteristic is a property of the nematic phase, it correlates to the physical property of single molecules. This is of great importance for the targeted, rational design of novel liquid crystalline materials.

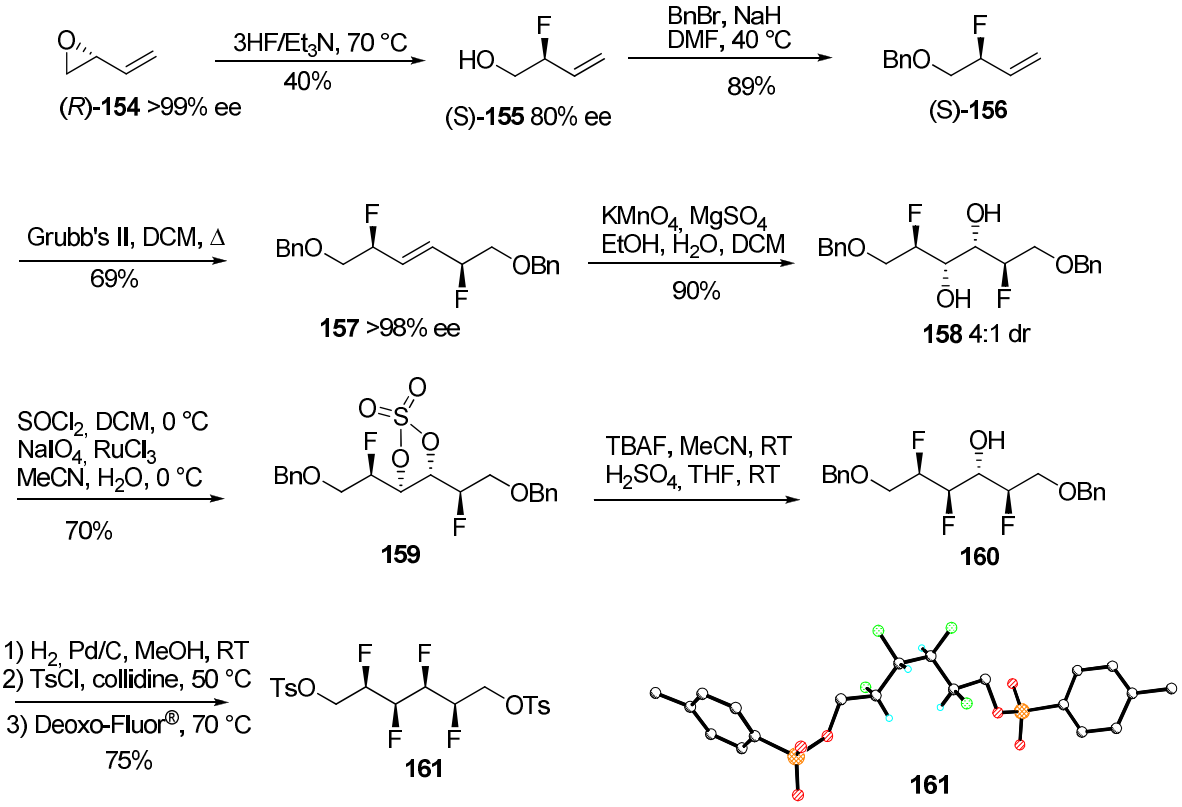
In the case of molecule **152**, it appeared that the measured dielectric anisotropy was lower than predicted. This suggested that the preferred conformation was not the linear one where all the fluorine atoms point at a same direction, but was rather a "twisted" due to repulsion between the C-F bonds at the C_1 / C_3 positions. The energy of this 1,3-F-F repulsion was calculated to be 3 kcal.mol^{-1}. This 1,3-F-F repulsion was also predicted in the calculated preferred conformations of 1,3-difluoropropane and *cis*-1,3-difluorocyclohexane. It is presumably due to the combination of dipole and lone pair repulsion.



Scheme 1. 36 : Example of 1,3-F-F repulsion in the vicinal trifluoro liquid crystal motif.

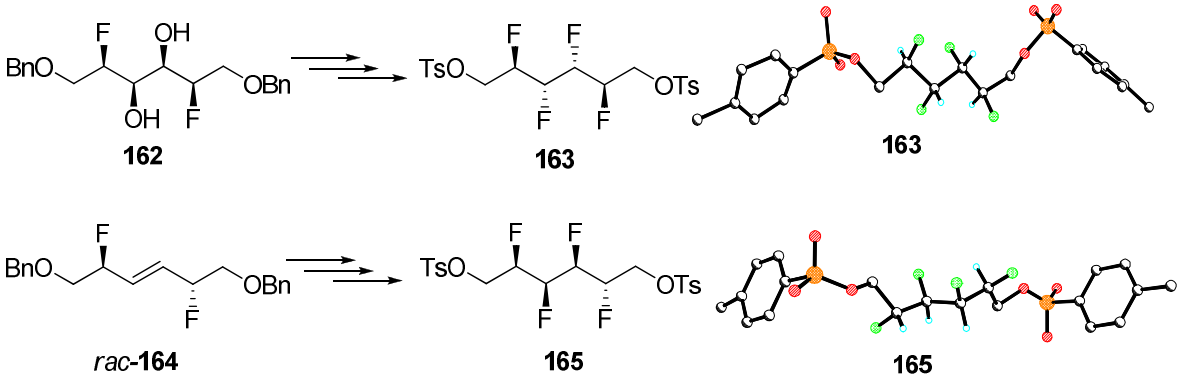
1.4.3) Vicinal tetrafluorocompounds:

The synthesis of the vicinal tetrafluoro motif was reported by Hunter and O'Hagan [91,92,93,94]. As illustrated in Scheme 1.37, the synthetic route started from the enantiopure (*R*)-butadiene oxide **154** directly obtained from hydrokinetic resolution of the racemate under Jacobsen's conditions. The epoxide was regioselectively opened with $3HF/Et_3N$, but with a significant erosion of the enantiopurity due to the partial S_N1 character of the reaction. However, this problem of loss of enantiopurity was circumvented two steps further ahead, when the 1-*O*-benzyl-2-allyl fluoride **156** was subjected to a homo-cross metathesis reaction and the (*S,S*)-difluoroalkene product **157** was recovered in 98% ee after separation from the (*S,R*) and (*R,R*) isomers by silica gel chromatography. The (*S,S*)-difluoroalkene **157** was then subjected to dihydroxylation with potassium permanganate to afford the difluoro diol **158** in 4:1 dr. After separation of the minor isomer, the cyclic sulfate **159** was formed under Sharpless' conditions and was stereoselectively opened with TBAF. Insertion of the fourth fluorine atom by treatment with Deoxo-Fluor®, occurred smoothly, but only after switching protecting groups from benzyl ethers to tosyl esters. The resultant ditosylated tetrafluoroalkane **161** proved to be crystalline and the absolute configuration of each stereocenter was conformed by X-ray crystal structure analysis.



Scheme 1. 37 : Synthesis of vicinal tetrafluoroalkane motifs.

A similar synthetic protocol was used to generate the tetrafluoro motifs **163** and **165** from the minor isomers which had arisen from the cross metathesis and dihydroxylation reactions (Scheme 1.38). The products from these two minor diastereoisomers proved to also be crystalline, and their stereochemistry was elucidated by X-ray crystal structure analysis.



Scheme 1. 38

The crystal structures of all three isomers showed that in the solid state, each diastereoisomer of the tetrafluoro motif adopt unique conformations. The all-*syn* stereoisomer **161** adopts a "helical" conformation in which each pair of C-F bonds align *gauche* to avoid all 1,3-F-F repulsions. By comparison, the *anti-syn-anti* stereoisomer **163** adopts an *anti* zig-zag conformation with only the two central fluorines aligning *gauche*. Finally, the *syn-syn-anti* isomer **165** adopts a conformation in which each pair of C-F bonds seems to be aligned *gauche*, but with torsion angles which vary considerably from the ideal value of 60°. Analysis of the ^{1}H- and ^{19}F-NMR spectra allowed a mapping of $^{3}J_{\text{H-H}}$ and $^{3}J_{\text{H-F}}$ values for each isomer and elucidation of the corresponding torsion angles in solution state. This analysis revealed that the helical and *anti* zig-zag conformations observed in the solid state for isomers **161** and **163** are also the preferred conformations in solution. The solution (NMR) and solid state (X-ray) structures of these isomers were also validated by molecular modelling experiments.

1.5) Aims and objectives:

The vicinal multifluoroalkane motif is a new motif in organic chemistry. Therefore stereoselective methods giving a rapid access to these motifs and with a maximum of flexibility still need to be explored.

The aim of my research during my PhD was to explore new stereoselective synthetic routes towards single diastereoisomers of vicinal trifluoroalkane motifs.

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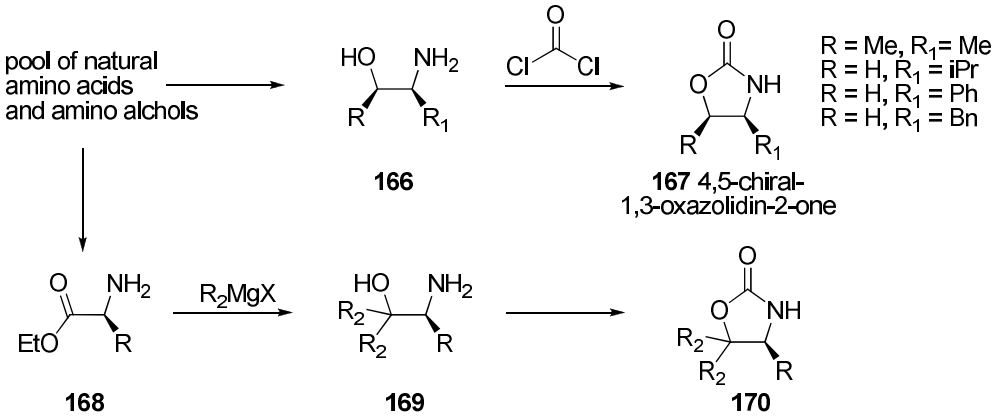
Chapter 2: Synthesis of vicinal fluoro motifs by asymmetric aldol reaction :

2.1) General informations about chiral oxazolidinones:

Among the many strategies used in asymmetric synthesis, one of the most effective involves a chiral oxazolidinone as a chiral auxiliary. Chiral oxazolidinones are easily accessible from the pool of natural chiral amino acids and amino alcohols (Scheme 2.1). For example an amino alcohol **166** can react with phosgene to form an oxazolidinone **167** bearing chiral substituents in position 4 and/or 5. An amino acid can also be transformed into the corresponding amino ester **168** and then be made to react with a Grignard reagent. This results, after cyclisation with phosgene, in an oxazolidinone such as **170**, disubstituted at the 5 position. This disubstitution is believed to prevent oxazolidinones from ring opening by nucleophilic attack at the carbamate group [1,2].

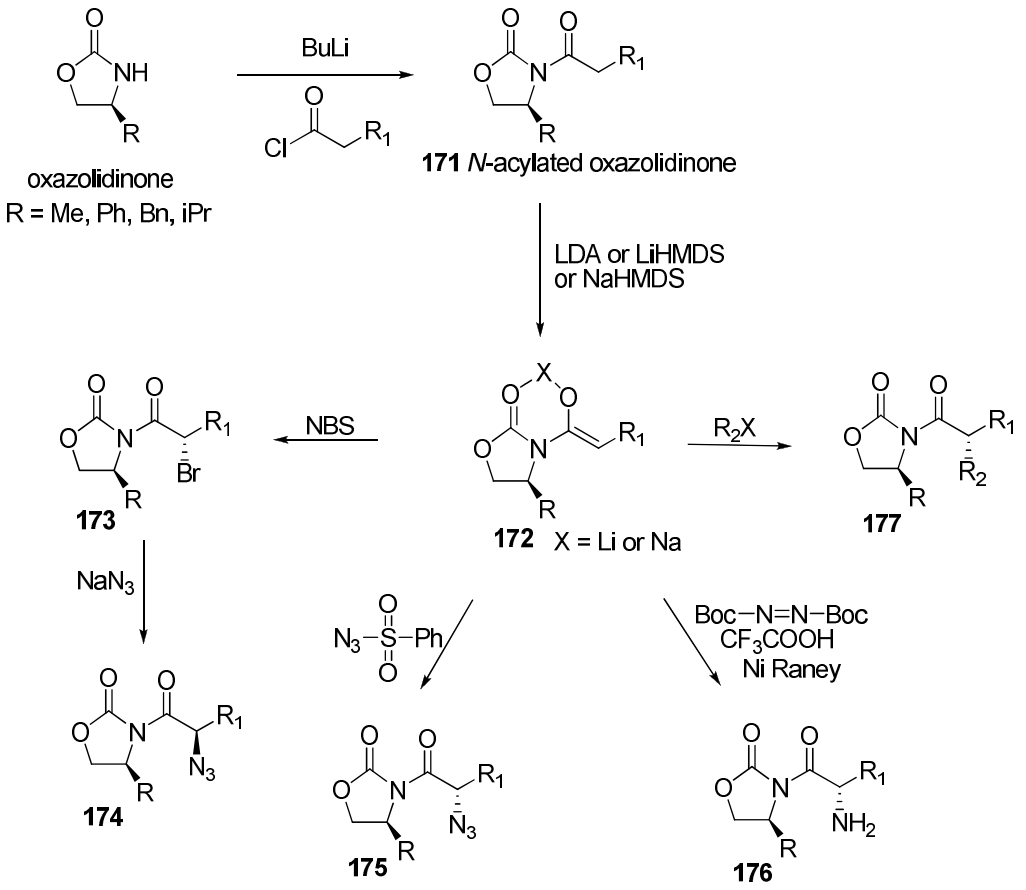


Scheme 2. 1: Preparation of chiral oxazolidinones from amino acids and amino amino alcohols.

Oxazolidinones have a heterocyclic core which is pretty much flat, and the presence of substituents (methyl, phenyl, benzyl or isopropyl) at position 4 and/or 5, renders one of the faces much more hindered [3]. This is the source of the induction of stereoselectivity in asymmetric synthesis. In the past twenty years, chiral oxazolidinones have shown wide applications in asymmetric synthesis, and notably in aldol reactions and in the addition of an electrophile α to a carbonyl group in enolate chemistry [4].

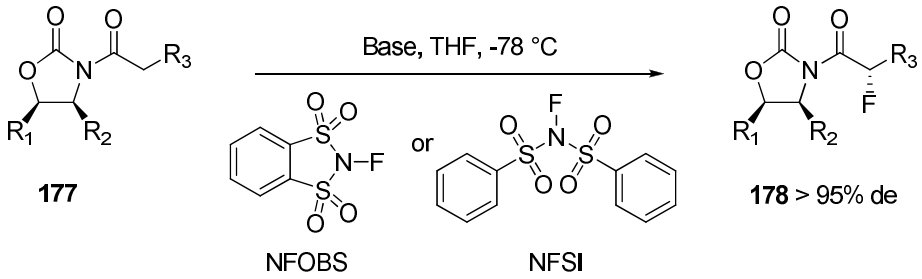
2.1.1) Addition of electrophiles α to carbonyls:

A chiral oxazolidino-imide such as **171** can easily be prepared by deprotonation of an oxazolidinone using a strong base such as BuLi, followed by reaction with an acyl chloride (Scheme 2.2). Subsequent deprotonation, α to the imide, allows the so formed enolate **172** to react with a wide range of electrophiles including *N*-bromosuccinimide [5], *diter*butylazodicarboxylate [6], tosyl azide [7], alkyl halide [8], resulting in the addition of bromine, azide, amine or a variety of alkyl groups. These reactions are often highly stereoselective, and lead to products with diastereoisomeric excesses (de) greater than 90%.



Scheme 2. 2: Examples of electrophilic insertion using oxazolidinone auxiliaries.

Insertion of a fluorine atom α to the oxazolido-imides has been studied by Davis and co-workers [9,10,11] and Staunton and co-workers [12] (Scheme 2.3). A base such as LDA, NaHMDS or LiHMDS was used to deprotonate the imide, and *N*-fluorobenzenedisulfonimide (NFSI) or *N*-fluoro-O-benzenedisulfonimide (NFOBS) were used as the electrophilic fluorinating reagents.



Scheme 2. 3: Electrophilic fluorination using oxazolidinone auxiliaries.

These studies demonstrate that α-fluorinated imides can be obtained in good yields (up to 86%) and high diastereoselectivities (de > 95%) (Table 2.1).

Entry	R_1	R_2	R_3	Base	F^+ reagent	**178** yield (%)	de (%)
1	H	*i*-Pr	*n*-Bu	LDA	NFOBS	85	96
2	H	*i*-Pr	*t*-Bu	LDA	NFOBS	80	97
3	Ph	Me	Ph	LDA	NFOBS	86	86
4	Ph	Me	Ph	NaHMDS	NFSI	85	97
5	H	Bn	C_5H_9	LiHMDS	NFSI	78	98

Table 2. 1: Selective electrophilic α-fluorination using oxazolidinone auxiliaries.

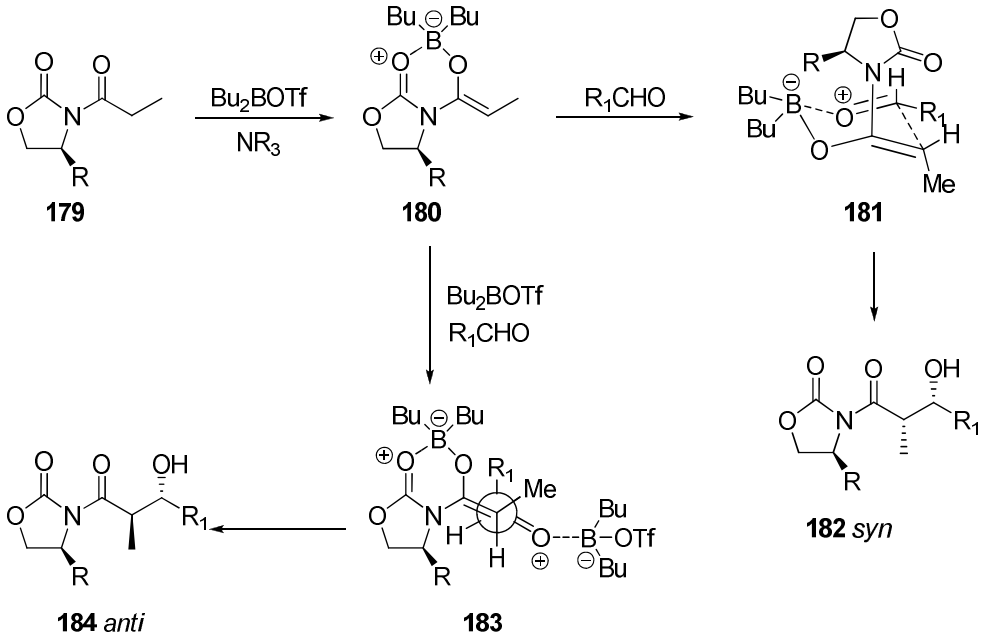
2.1.2) Asymmetric aldol reactions:

The aldol reaction is an efficient method by which to form carbon-carbon bonds. In its usual form it involves the nucleophilic addition of an enol ketone to an aldehyde, under acidic conditions, or a ketone enolate, under basic conditions. Reaction with an aldehyde generates a

β-hydroxyketone. Asymmetric versions of the aldol reaction have been the focus of a lot of attention. They involve the use of a chiral auxiliary either in a stoichiometric version or using chiral ligands in catalytic reactions.

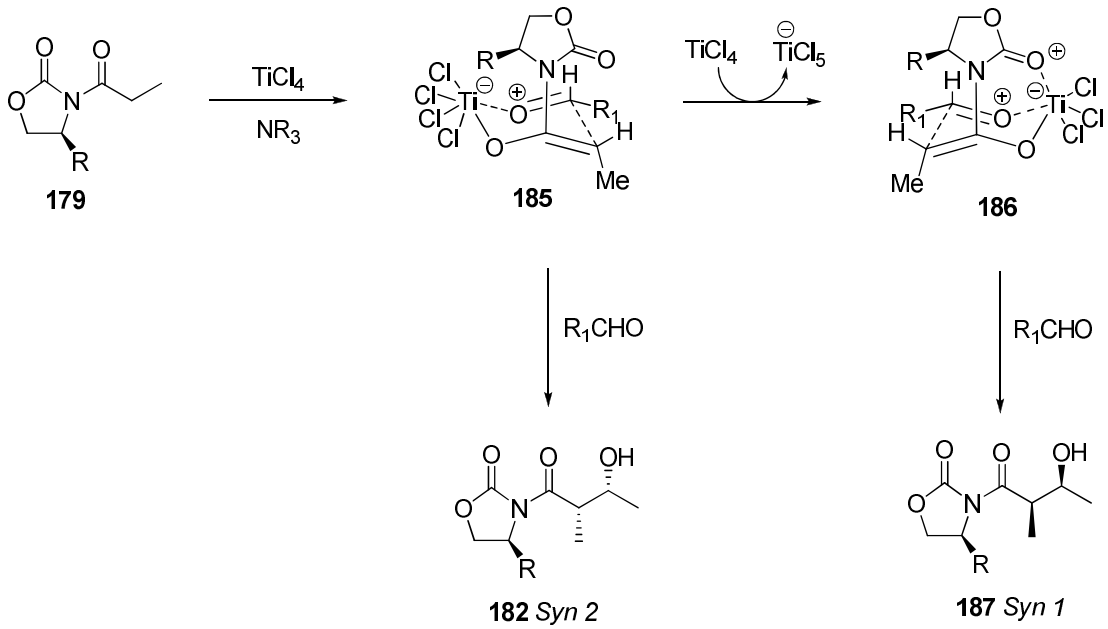
2.1.2.1) Controlling asymmetric aldol reactions:

Aldol reactions are often achieved in both good yields and very good stereoselectivities, but optimised conditions require several parameters to be controlled. Indeed, the nature of the base, of the Lewis acid, of the substrate, the solvent used, the temperature and the ratio of Lewis acid/substrate, all play a role in the stereochemical outcome of the reaction. Effective methods have been elaborated using titanium [13], tin [14,15], aluminium [16] or boron [17] as Lewis acids. The quantity of Lewis acid is key to control the stereoselective outcome of the reaction. As shown in Scheme 2.4, dibutylboron triflate first binds to both C-O bonds of the oxazolidinone. But after the aldehyde is added the complexation changes because of the greater polarity of the aldehyde, leading to an alcohol product such as **182** with a *syn* configuration. This selectivity can be explained by the six-membered ring transition state **181** shown in Scheme 2.4. When dibutylboron triflate is added in excess, the alcohol product **184** with an *anti* configuration is usually obtained. This can be explained if the second equivalent of the Lewis acid coordinates to the aldehyde and thus, an open transition state such as **183** is generated.



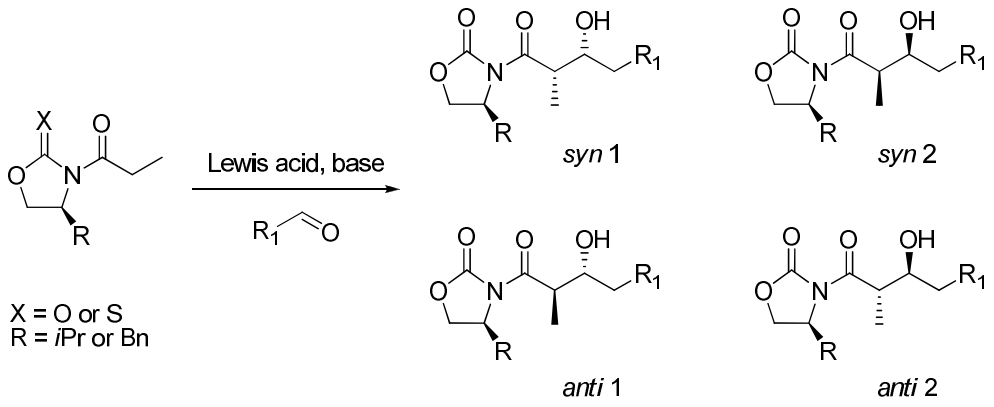
Scheme 2. 4: Stereochemical outcomes of boron mediated aldol reactions.

If the boron mediated aldol reaction is not sufficiently stereoselective, other Lewis acids with aluminium, titanium or tin can be deployed. Titanium tetrachloride associated to diisopropylethylamine (DIEA, Hunig's base) also offers excellent selectivities, but the stoichiometry of the Lewis acid is important (Scheme 2.5) [18]. As with dibutylboron triflate, the first equivalent of the Lewis acid complexes both the enolate and the aldehyde to lead to the alcohol product **182** with a *syn 2* configuration. When titanium tetrachloride is used in excess, the second equivalent of Lewis acid abstracts a chlorine of the titanium aldol complex, allowing the vacant site on titanium to bind to the carbamate of the oxazolidinone. This, leads to a product favouring the **187** *syn 1* configuration. The reaction is of course both diastereo- and enantio- selective.



Scheme 2. 5: Stereoselectivities of aldol reactions mediated by titanium.

These synthetic methods have been developed by Evans [17], Crimmins [13] and Heathcock, [16] and some of the key results are summarized in Scheme 2.6 and Table 2.2. Good yields and stereoselectivities were obtained in the reaction of oxazolidino- or oxazolidin-thio-propionimide with benzaldehyde or isobutyraldehyde.



Scheme 2. 6: Reactions by Evans and co-workers, Crimmins and co-workers, and Heathcock and co-workers

Crimmins and co-workers obtained a 97.6% diastereoselectivity in favour of the *syn* 1 isomer using two equivalents of $TiCl_4$ and diisopropylethylamine (DIEA, Hunig's base) (Entry 1). They also noticed an interesting inversion of stereoselectivity when sparteine replaced DIEA (Entry 2).

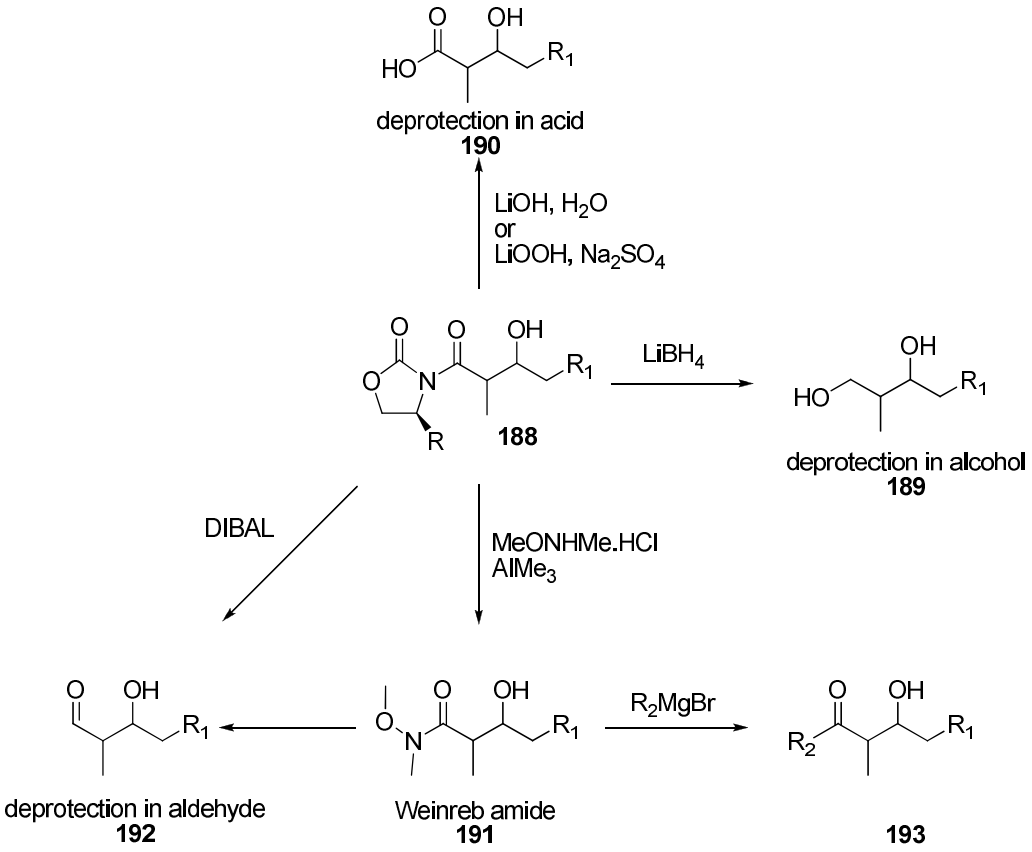
Entry	R_1	Base	Lewis acid	Temp	yield	selectivity
1	Ph	DIEA	2eq $TiCl_4$	-78 ^oC	88%	97.6% *syn* 2
2	Ph	(-)sparteine	2eq $TiCl_4$	0 ^oC	89%	97.3% *syn* 1
3	Ph	DIEA	1eq Bu_2BOTf	-78 ^oC	81%	92.4% *syn* 1
4	i-Pr	DIEA	1.2eq Bu_2BOTf 1eq $TiCl_4$	-78 ^oC	77%	89% *syn* 2
5	i-Pr	DIEA	1.2eq Cy_2BOTf 0.5eq $SnCl_4$	-78 ^oC	51%	95% *anti* 1
6	i-Pr	DIEA	1.2eq Cy_2BOTf 2eq Et_2AlCl	-78 ^oC	63%	95% *anti* 1

Table 2. 2: Aldol reactions by Evans and co-workers, Crimmins and co-workers and Heathcock and co-workers.

Sparteine not only reversed the diastereoselectivity, but also increased the rate of the reaction and permitted retention of the excellent diastereoselectivity even at 0 ^oC. The association of boron and titanium (Entry 4) proved the least selective method, whereas the combination of boron and tin (Entry 5) or aluminium (Entry 6) led to excellent diastereoselectivities, but only moderate yields. As tin and aluminium have a similar mode of binding as boron, their associations led to alcohol products with an *anti* configuration.

2.1.2.2) Deprotection of the auxiliary:

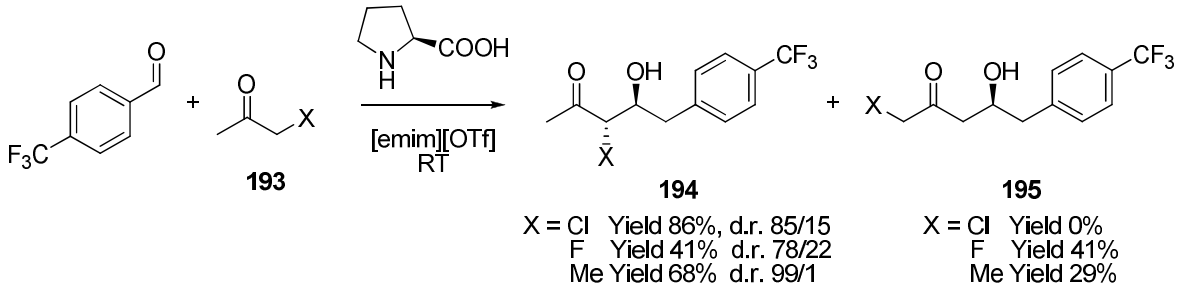
Another attractive feature of oxazolidinones as chiral auxiliaries is that several methods exist to remove the auxiliary (Scheme 2.7). This can be achieved with lithium borohydride [19] to obtain an alcohol such as **189**, and with lithium hydroxide [5] to release a carboxylic acid **190**. In that case, racemisation is sometimes observed, but this problem can be circumvented by using lithium hydroperoxide [20]. The formation of a Weinreb amide **191** permits an aldehyde **192** or a ketone **193** to be released [21], but suppresses over reaction with a nucleophile such as a Grignard reagent. Treatment of the oxazolidino-imide with DIBAL can also generate an aldehyde **192** in one step [22], but it can also competitively reduce the auxiliary, and in this case, erode the conversion to the aldehyde.



Scheme 2. 7: Different methods of auxiliary removal.

2.1.2.3) Asymmetric aldol reactions with fluorine:

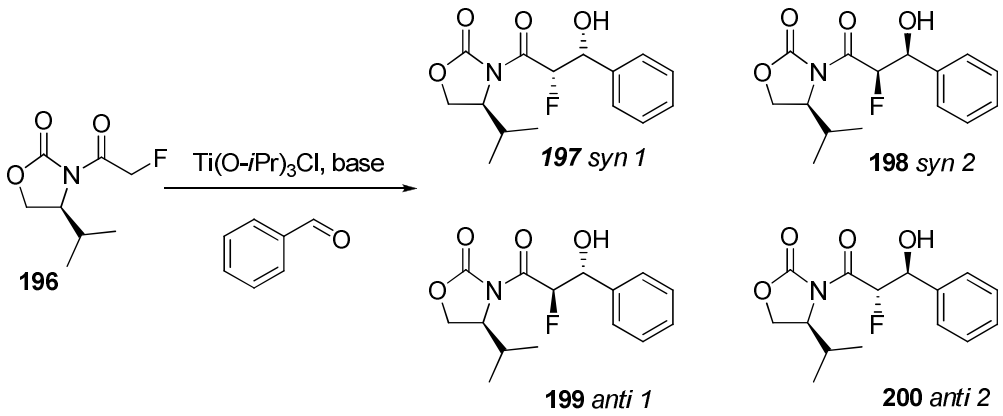
Examples of organocatalytic aldol reactions with α-fluoroenolates are quite rare. In this regard, aldol reactions catalysed by proline and involving an α-fluoroketone have been described by Kitazume and co-workers [23] (Scheme 2.8). They performed the addition of fluoroacetone **193** among other ketones, to 4-trifluoromethyl benzaldehyde, catalysed by L-proline in ionic liquid media. Better diastereoisomeric ratios were obtained when chlorine or a methyl group was the substituent.



Scheme 2. 8: Aldol reactions catalysed by proline by Kitazume and co-workers.

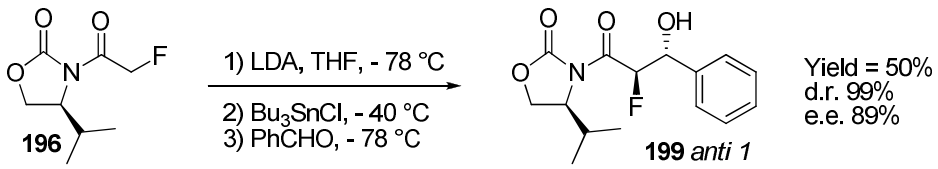
Kitazume and co-workers [23] also observed an influence of the substituent α to the ketone on the regioselectivity and stereoselectivity of the reaction. With chlorine the reaction was highly regioselective and stereoselective with complete formation of the α-chloroenolate **194** in a 85:15 diastereoisomeric ratio. Fluorine as substituent was expected to align *gauche* to the iminium prolinate intermediate, and thus to also afford a highly stereoselective reaction. But fluorine afforded aldol reaction products **194** with only a moderate dr of 78:22. Fluorine also afforded reactions with a poor regioselectivity, as **195** was present in 41% yield, showing no clear preference for aldol reactions in α and α' position. Methyl was a more selective substituent with an α' aldol product **195** limited to 29%, and an α aldol product **194** obtained in 68% yield and 99:1 dr.

By comparison to Kitazume study, aldol reactions with α-halogenated acyl groups bound to the chiral auxiliary have been achieved by Pridgen and co-workers [14] (Scheme 2.9). They first reacted halo-acetyl chlorides with oxazolidinones to generate the corresponding halo-acetimides, and then performed aldol reactions mediated by lithium, boron, titanium, tin[II and IV] and zinc.



Scheme 2. 9: Aldol reactions with α-halogenated acyl groups bound to the chiral auxiliary by Pridgen and co-workers.

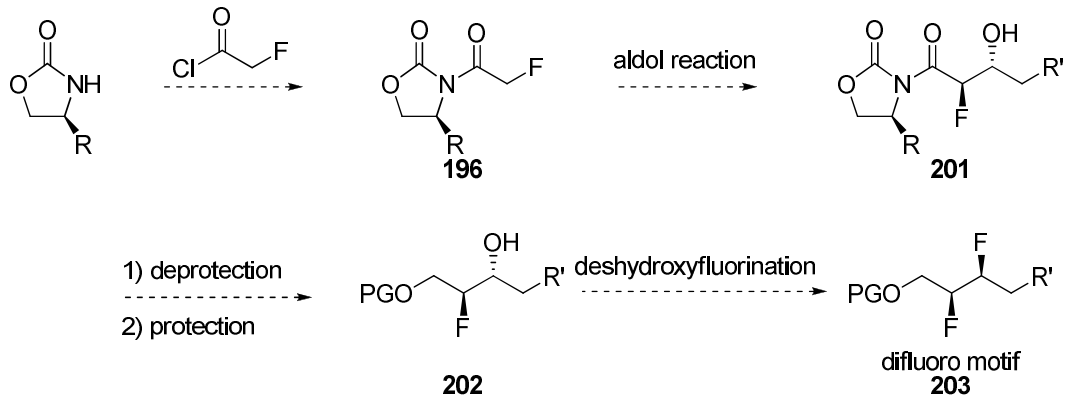
Considering the fluoro-oxazolidino-acetimide **196**, they observed that titanium (IV) favoured *syn* adducts. Indeed when Ti(O-iPr)$_3$Cl was used, a mixture of diastereoisomers was obtained in 75% yield, showing a *syn* / *anti* ratio of 90:10 with a preference for the **197** *syn 1* adduct (81% **197** *syn 1* and 9% **198** *syn 2*). They also observed that in a reaction mediated by tin (IV) the *anti* diastereoisomers were favoured. First the enolate was formed by deprotonation of the fluoro-oxazolidino-imide **196** by LDA at -78 °C (Scheme 2.10). This was followed by addition of Bu$_3$SnCl to perform a transmetallation from lithium to tin at -40 °C, and then benzaldehyde was added. α-Fluoro-alcohols were obtained in a moderate yield (50%), but with an excellent diastereoselectivity (*anti 1* + *anti 2* 99%; presence of *syn* adducts was not observed) and with a clear preference for the **199** *anti 1* diastereoisomer (89% ee).



Scheme 2. 10: Aldol reaction by Pridgen and co-workers.

2.2) Aims and objectives:

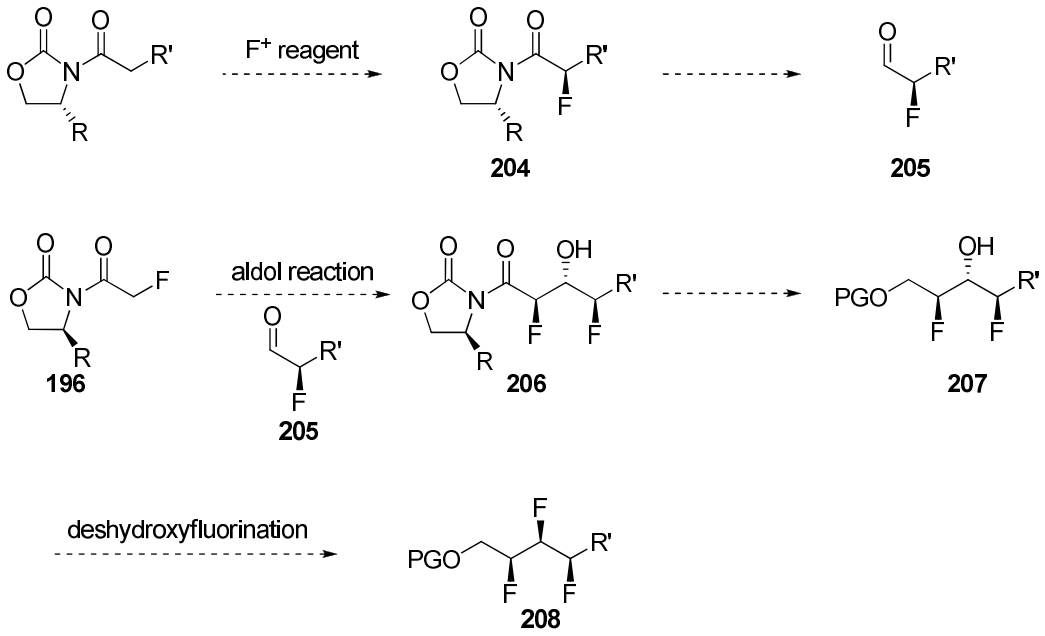
Encouraged by the results of Pridgen and co-workers [14] (see Scheme 2.10) we envisaged an approach to vicinal difluoro compounds *via* a chiral oxazolidinone strategy. The key objective of this strategy is to prepare by aldol reaction, an α-fluoro alcohol such as **201** with an *anti* configuration (Scheme 2.11). This fluoro alcohol could then be converted into its corresponding vicinal difluoro compound **203** by a deshydroxyfluorination reaction using e.g. DAST or Deoxo-Fluor®.



Scheme 2. 11: Envisaged formation of difluoro motifs by aldol reaction and deshydroxyfluorination.

In parallel, an α-fluoro aldehyde **205** could be prepared by electrophilic fluorination of an oxazolidino-imide followed by removal of the auxiliary (Scheme 2.12). This α-fluoro aldehyde could then be subjected to an aldol reaction with an oxazolidino-fluoroacetimide

196. After removal of the auxiliary and protection of the primary alcohol, a deshydroxyfluorination reaction would provide access to a trifluoro motif **208**.



Scheme 2. 12: Potential strategy to a vicinal trifluoro compounds.

Schemes 2.11 and 2.12 show the synthetic route to all-*syn* vicinal fluorines if the aldol reaction envisaged favours an *anti* fluoro alcohol product. However an aldol reaction with a different stereochemical outcome could lead to other diastereoisomers of the target vicinal trifluoro motif. The auxiliaries chosen at the outset were the 4-(*S*)-4-isopropyl oxazolidinone **209** and the 4-(*S*)-4-isopropyl-5,5-diphenyl-2-oxazolidinone **210** (Figure 2.1). The phenyl groups at the 5-position of **210** should protect the auxiliary from possible nucleophilic attack on the carbamate. It should also have advantage of being useful for the crystallisation of future aldol products in order to enhance and determine absolute stereochemistry by X-ray structure analysis.

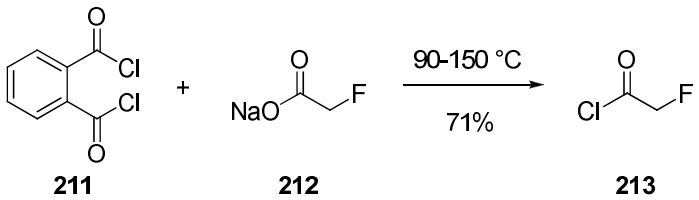
Figure 2. 1

2.3) Results and discussion:

2.3.1) Aldol reactions with chiral oxazolidino-2-fluoroacetimide:

2.3.1.1) Preparation of chiral oxazolidino-2-fluoroacetimide:

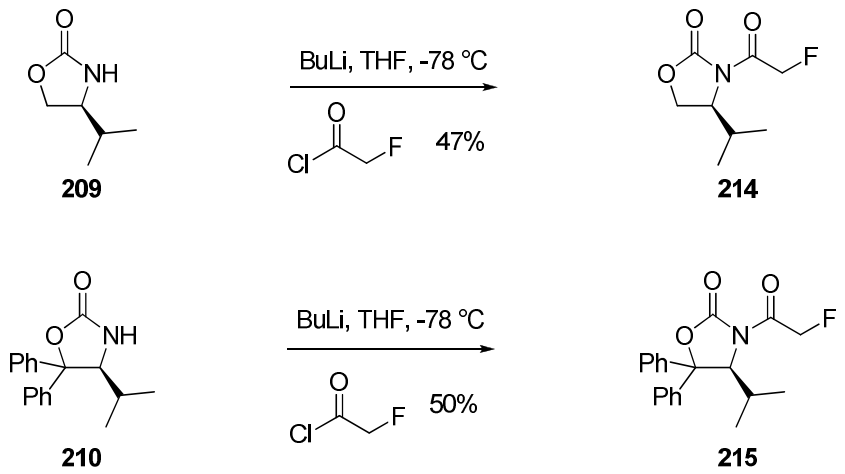
Fluoroacetate **212** (warning toxic) was heated with phthaloyl dichloride **211** from 90 °C to 150 °C and the resultant fluoroacetyl chloride **213** was recovered by distillation in 71% yield (Scheme 2.13). Due to the high toxicity of fluoroacetate and fluoroacetyl chloride, this reaction must be carried out with great care.



Scheme 2. 13: Preparation of fluoroacetyl chloride.

Freshly prepared fluoroacetyl chloride **213** was then reacted with 4-(*S*)-4-isopropyl oxazolidinone **209** and 4-(*S*)-4-isopropyl-5,5-diphenyl-2-oxazolidinone **210** which has

previously been treated with BuLi at low temperature, and the corresponding 2-fluoroacetimides **214** and **215** were recovered in 47% and 50% yield, respectively (Scheme 2.14).

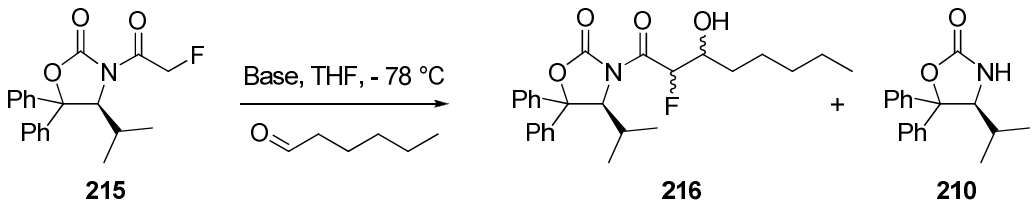


Scheme 2. 14: Preparation of 2-fluoroacetimides **214** and **215**.

These 2-fluoroacetimides **214** and **215** were then used to explore suitable conditions for the target aldol reactions.

2.3.1.2) Exploration of oxazolidino-2-fluoroacetimide:

The first step of the strategy was to find a selective method for the preparation of fluoro-alcohols with an *anti* configuration. The methods elaborated by Pridgen and co-workers [14] offered a good starting point. An aldol reaction using LDA was carried out initially to re-establish the synthesis of the *syn* fluoro-alcohol as the major product. This result could then be compared to those obtained by the Pridgen and co-workers who developed methods that generate the *anti* fluoro-alcohols. Accordingly aldol reactions were carried out using LDA to deprotonate *N*-fluoroacetyl oxazolidinone **215** at -78 ^{o}C followed by the addition of hexanal (Scheme 2.15).



Scheme 2. 15: Aldol reaction using LDA or BuLi on the acetimide **215**.

Analysis of ^{1}H-NMR and ^{19}F-NMR spectra of the crude reaction mixture showed not only a very poor conversion of 6% to a possible fluoro-alcohol product **216**, but also the presence of the free auxiliary **210** in a 70% range (presence of **210** was also observed on TLC during the monitoring of the reaction). Our attempts to improve that reaction were unsuccessful and conversions were always low with presence of oxazolidinone **210**. BuLi was then used instead of LDA to mediate the deprotonation of **215**, and this resulted in a better overall conversion. The ^{19}F-NMR spectrum of the crude reaction mixture (Figure 2.2) showed the presence of ~ 20% of **215** (signal at -230 ppm) but also the presence of several products (between -195 and -215 ppm) with the dd expected pattern or more complex patterns. The selectivity of the reaction was then low and the free oxazolidinone **210** was still persistent (~ 30% in ^{1}H-NMR).

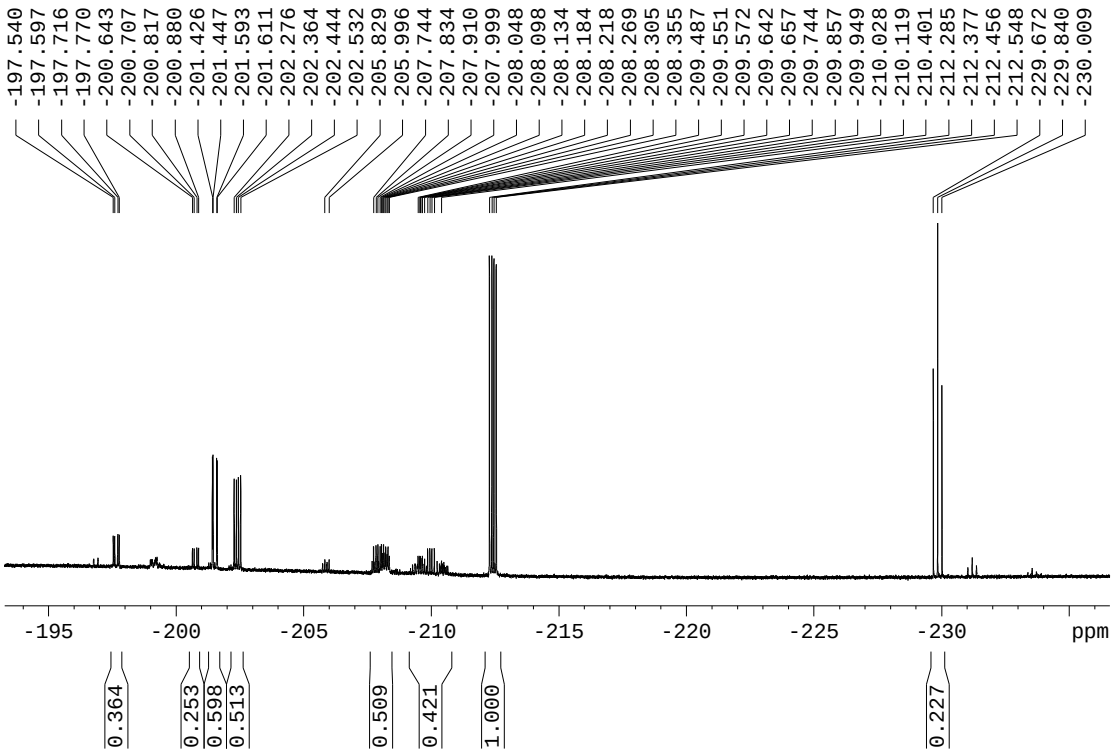
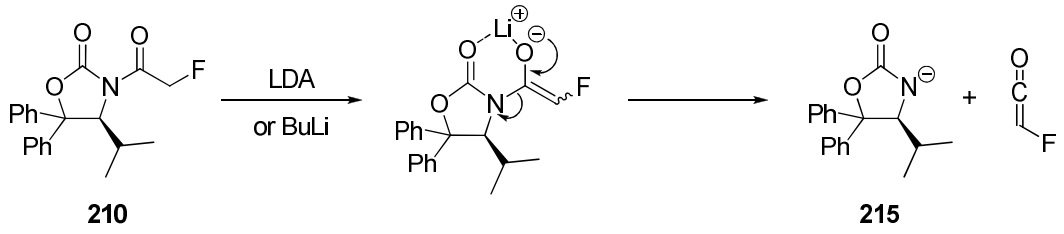


Figure 2. 2: ^{19}FNMR spectrum of the aldol reaction of **215** with hexanal and BuLi.

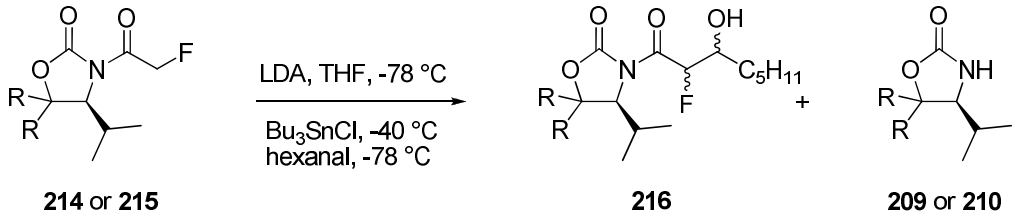
The presence of **210** either in reaction with BuLi or LDA, seemed to indicate that after deprotonation of **215**, lithium was not a sufficient counter ion to stabilise the enolate, and thus an elimination reaction occurred (proposed pathway: Scheme 2.16).



Scheme 2. 16: Proposed pathway for the elimination reaction.

To circumvent the problem of elimination, the method of Pridgen and co-workers [14], with tin, offered a solution in which the transmetallation from lithium to tin may stabilise the enolate. Thus the enolate was prepared at -78 ^{o}C using LDA or BuLi, and then

transmetallation with tributyltin was performed warming up the solution to -40 ^{o}C for 30 min (Scheme 2.17). Then, the solution was cooled again to -78 ^{o}C to carry out the aldol reaction with hexanal or benzaldehyde. The reaction was followed by ^{1}H-NMR, ^{19}F-NMR and ^{19}F{^{1}H}-NMR.



Scheme 2. 17: aldol reaction of **214** or **215** with hexanal and LDA/Bu_3SnCl.

Unfortunately the results of Pridgen (*anti* fluoro-alcohols 99% de 94% ee) could not be replicated. When **215** was reacted with hexanal, The conversion was good (> 90%) as calculated by comparison between the signal of starting material **215** at -230 ppm and other signals in ^{19}F-NMR (Figure 2.3). Analysis of the ^{1}H-NMR spectrum showed the presence of the free oxazolidinone **210** in about 10%. But the products of the reaction (around -200 ppm) were difficult to analyse by ^{19}F-NMR. Some of the them showed couplings in ^{19}F{^{1}H}-NMR (J = 5-11 Hz) that could correspond to $^{3}J_{F\text{-}F}$ coupling constants vicinal products. This could result from a possible dimerisation of the fluoroacetimide **214** and **215**. Signals on the high side of the spectrum (> -230 ppm) were also impossible to assign.

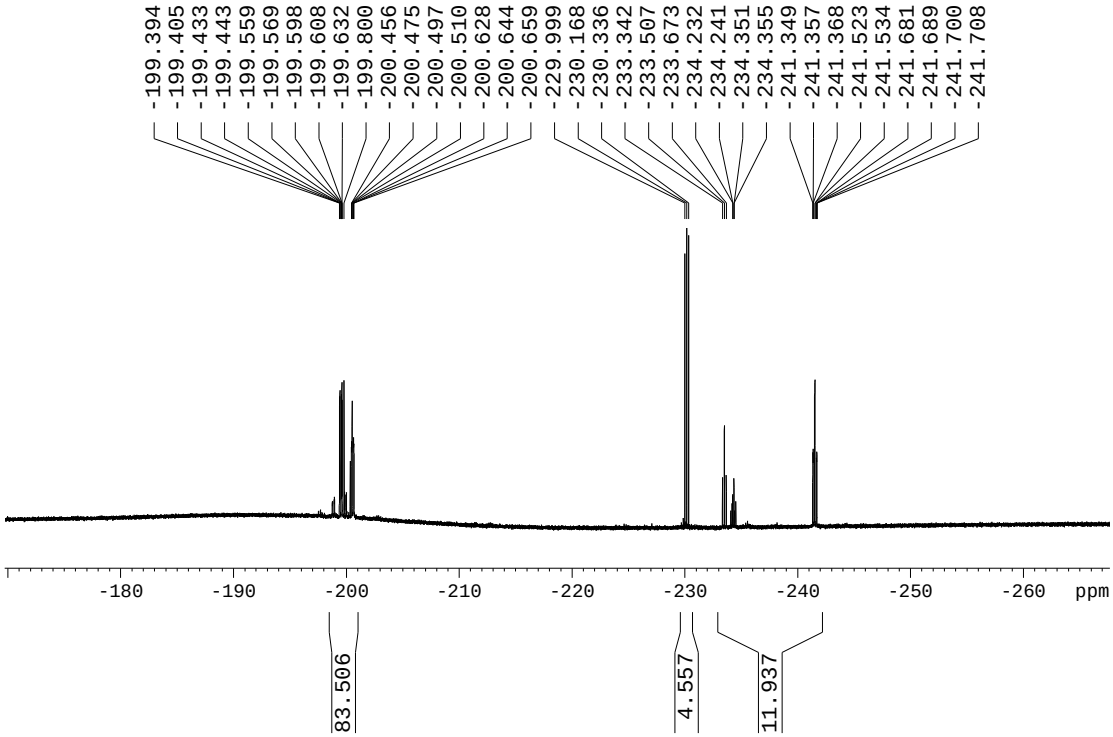
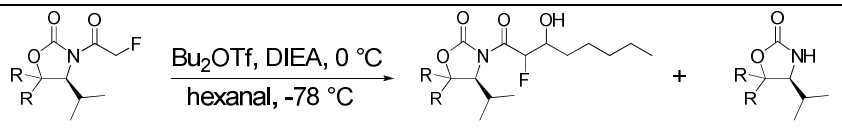


Figure 2. 3: ^{19}F-NMR spectrum of the aldol reaction of **215** with hexanal and LDA/Bu_3SnCl.

To replicate strictly the conditions of Pridgen and to analyse a possible effect of the hexanal, the reaction was carried out with benzaldehyde. Again, a series of signals was apparent in the ^{19}F-NMR and was very difficult to rationalise the origin of these signals.

An alternative approach was explored, using dibutylboron triflate as a Lewis acid and DIEA as the base. The enolate was prepared with dibutylboron triflate and DIEA at 0 ^{o}C. Then, the solution was cooled to -78 ^{o}C to explore the aldol reaction with hexanal. The product was again analysed by ^{1}H-NMR, ^{19}F-NMR and ^{19}F{^{1}H}-NMR of the crude material (Table 2.3).



Entry	R	Products
1	Ph (**215**)	50% of **210** + 50% of **215**
2	H (**214**)	no reaction

Table 2. 3: Results of aldol reactions mediated by dibutylboron triflate.

In the event only NMR signals of the triflate and the oxazolidino-imides **214** and **215** were observed in ^{19}F-NMR after reaction. An elimination of the fluoroacetyl group was again observed when fluoroacetimide **215** was used (Entry 1), and no reaction occurred at all with fluoroacetimide **214**. The persistent presence of free oxazolidinone **210** in the crude reaction mixture, seemed to correspond to a lack of stability of the enolate when stabilised by boron or lithium. We then investigated aldol reactions in presence of $TiCl_4$ expecting a better coordination of the the auxiliary by titanium, and therefore a better stability of the enolate intermediate. Fluoroacetimide **215** was then reacted with $TiCl_4$ and DIEA at -78 ^{o}C in DCM, followed by addition of hexanal (Scheme 2.18).

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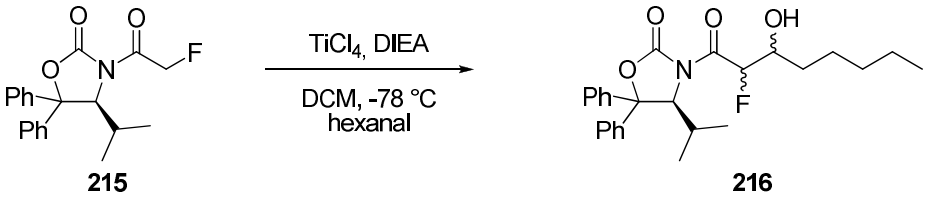


Scheme 2. 18: Aldol reaction of **215** with hexanal, mediated by $TiCl_4$ and DIEA.

A very good conversion (96%) to a fluoroalcohol product was observed as judged from the ^{19}F-NMR of the crude mixture (signal of **215** is at - 230 ppm) (Figure 2.4). The fluoroalcohol

was generated as a mixture of 4 diastereoisomers (seen between -195 ppm and -215 ppm) showing the expected dd pattern. Despite this low selectivity, the reaction was clean and oxazolidinone **210** was not formed as a by-product. No NMR signals other than **215** (^{19}FNMR signal at -230 ppm) and the four diastereoisomers of **216** were observed by ^{19}F-NMR and ^{1}H-NMR. But unfortunately the aldol products did not show signs of a possible separation over silica.

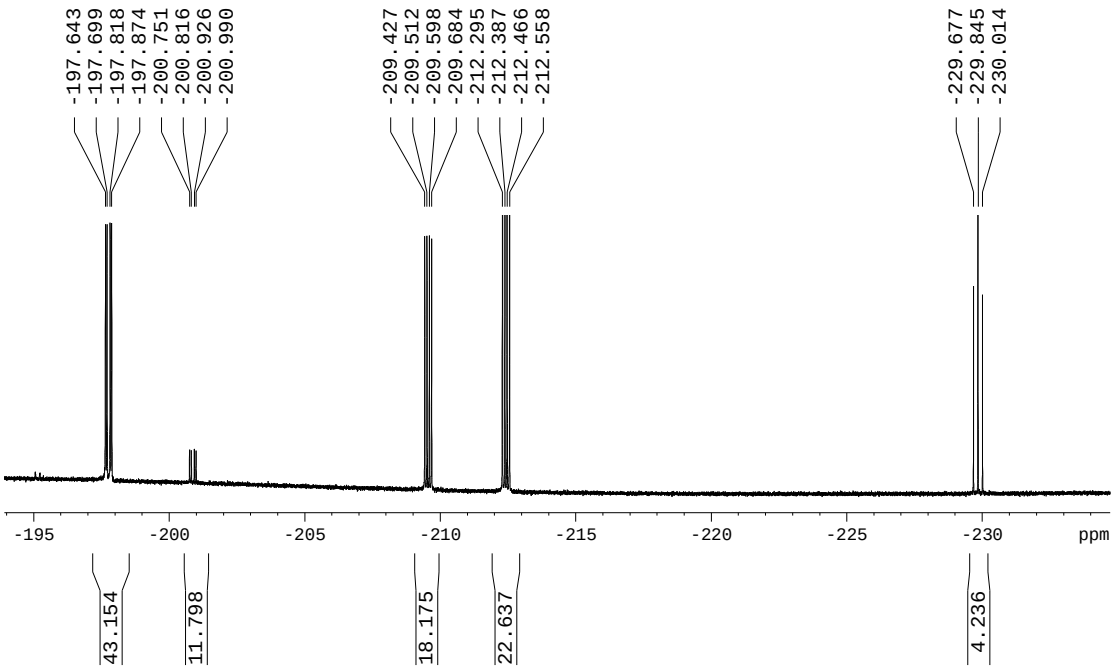
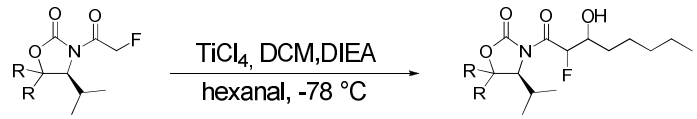


Figure 2. 4: ^{19}F-NMR of the crude mixture of the aldol reaction of **215** mediated by $TiCl_4$.

This method, using $TiCl_4$, was also explored with the fluoroacetimide **214** using one or two equivalents of Lewis acid. The results are detailed in Table 2.4.



214 or **215** → **216**

Entry	R	$TiCl_4$	Conversion	Selectivity
1	Ph (**215**)	1eq	96%	4 signals (ppm) : -212 (23%); -209 (18%); -200 (12%); -197 (43%)
2	Ph (**215**)	2eq	93%	4 signals (ppm) : -212 (6%); -209 (10%); -200 (69%); -197 (8%)
3	H (**214**)	1eq	62%	5 signals (ppm) : -212 (18%); -211 (26%); -198 (10%) -195 (4%) -194 (4%)
4	H (**214**)	2eq	92%	6 signals (ppm) : -212 (12%); -211 (23%); -209 (4%); -200 (18%); -197 (12%); -195 (23%)

Table 2. 4: Results for aldol reactions using $TiCl_4$ and the fluoroacetimides **214** and **215**.

The conversions to fluoroalcohols were good (>90%) except when the aldol reaction was carried out with the fluoroacetimide **214** (Entry 3) and two equivalents of $TiCl_4$. When compound **215** was used with two equivalents of $TiCl_4$, a major diastereoisomer (69%) was observed (Entry 2). Surprisingly a more complex product mixture was observed by ^{19}F-NMR when the fluoroacetimide **214** was used (Entries 3 and 4). No significant improvements in the selectivity were observed when two equivalents of Lewis acid were used with **214** (comparison of the Entries 3 and 4).

Thus $TiCl_4$ and DIEA proved the most efficient method to mediate these aldol reactions, with good conversions to the fluoroalcohols (>90%), but with low stereoselectivities.

2.3.2) How to improve the stereoselectivity:

In the reactions with $TiCl_4$ the obtention of 4 aldol products (or more) seems to indicate that both complexation of the Lewis acid to the oxazolidinone, and formation of the enolate are not selective. Therefore both *anti* and both *syn* products could be formed. When we elaborated our strategy we assumed that the formation of an (*E)*-enolate **217** would be favoured upon the formation of an (*Z)*-enolate **218** by a 1,3 dipolar relaxation between the atoms of oxygen and fluorine (Figure 2.5). Our study tends to prove that the preference for an (*E*)-enolate **217** does not seem to be sufficiently significant.

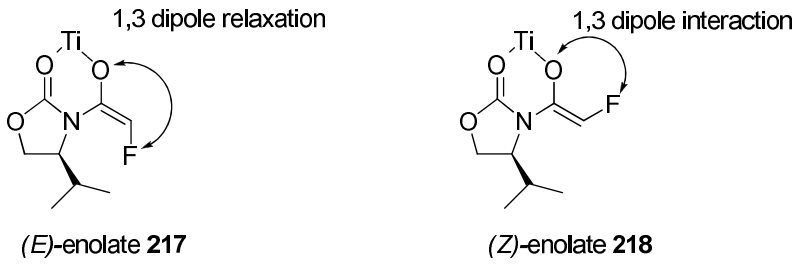
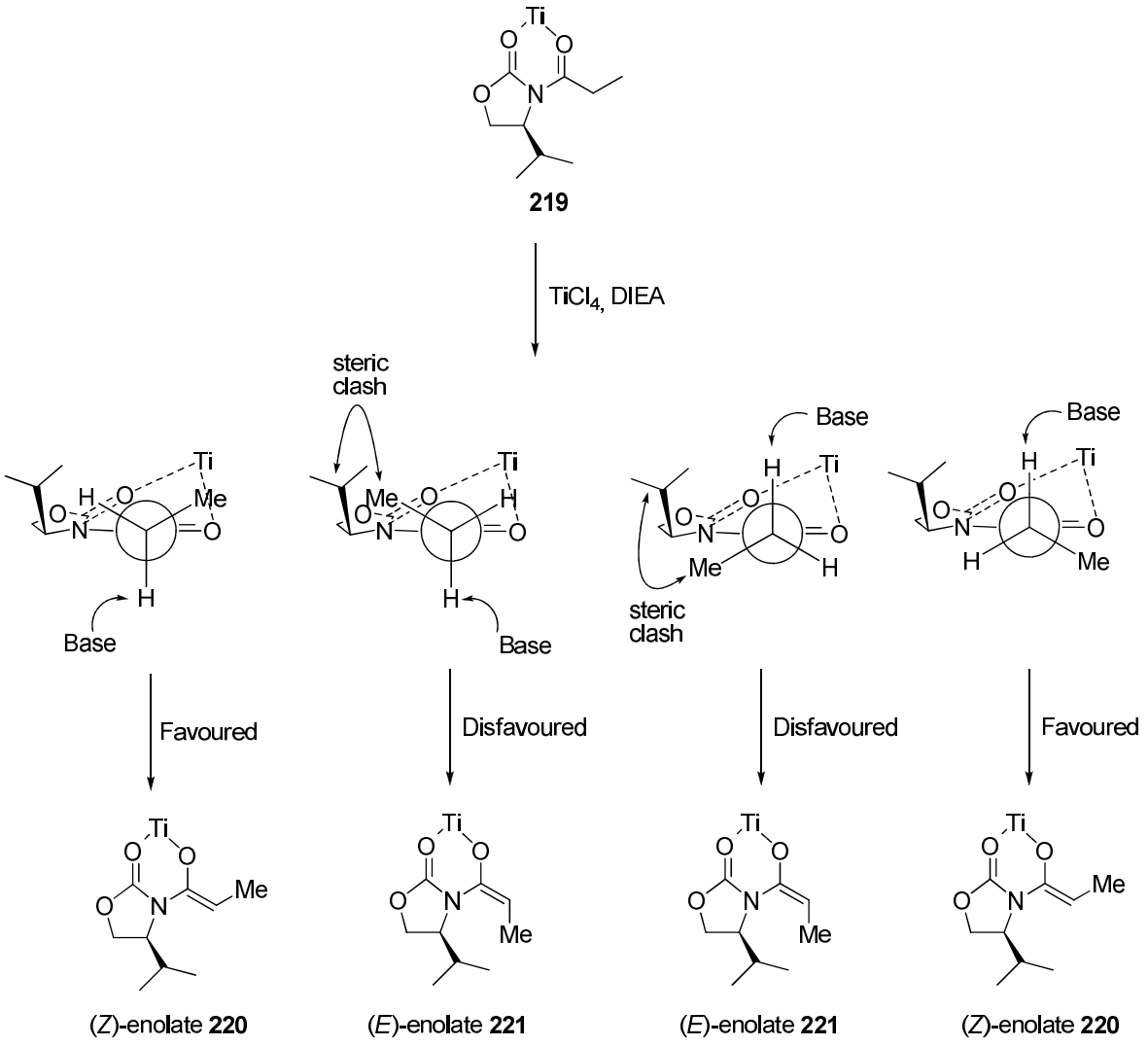


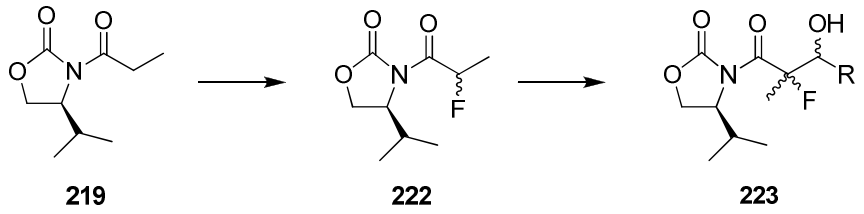
Figure 2. 5: Possible (*E*)- and (*Z)*-enolate of the fluoroacetimide **214**.

In contrast propionyl imide **219** is known to favour the formation of (*Z*)-enolate **220**. As illustrated in Scheme 2.19, when then enolate of **219** are formed, the steric hindrance of the methyl and isopropyl groups disfavours the formation of an (*E*)-enolate **221**. Considering that a fluorine atom is much smaller than a methyl group, and that it seems not to have a significant stereoelectronic impact on the enolate formation, both the (*Z)*- and (*E)*-enolates could be formed during aldol reactions with **215** and **214**, leading to only poor stereoselective aldol reactions.



Scheme 2. 19: Formation of the enolates of the propionylimide **219**.

A solution therefore to improve the selectivity could be to insert a methyl group α to the imide and trust its steric impact on the enolate formation. This would introduce a new problem however. The carbon α to the imide becomes a stereogenic centre and thus two diastereoisomers of fluoropropionylimide oxazolidinone **222** can be formed (Scheme 2.20). Would the configuration of this new asymmetric carbon influence the formation of (*E*)- or (*Z*)- enolate and thus the selectivity of the aldol reaction?

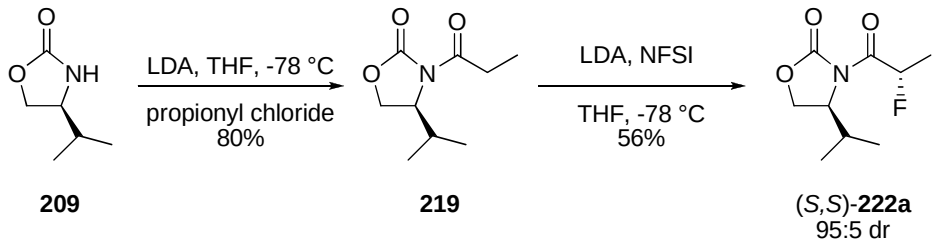


Scheme 2. 20: Fluoropropionylimide oxazolidinone **222** in aldol reaction.

The aldol products such as **223** generated from reaction of **222** with an aldehyde would be protected from epimerisation or elimination due to the presence of the α-methyl group. The subsequent manipulations of these potentially more stable products present an advantage. Accordingly, aldol reactions of the individual diastereoisomers of **222** were explored in reactions with hexanal and benzaldehyde. This required a suitable preparation of each of the diastereoisomers of **222**.

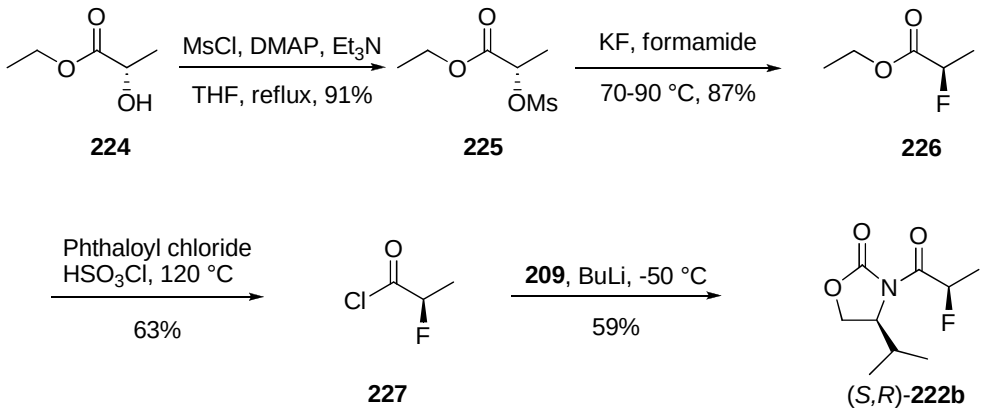
2.3.3) Aldol reactions with chiral oxazolidino-2-fluoropropionimide 222 and low temperature NMR study:

In order to explore these aldol reactions, several methods were investigated for the preparation of diastereoisomers of **222**. To this end the (*S*,*S*) diastereoisomer **222a** was prepared (Scheme 2.21). First, the oxazolidinone **209** was treated with LDA at -78 C followed by addition of propionyl chloride to generate **219** in 80% yield. An electrophilic fluorination reaction was then explored with NFSI. In the event, (*S*,*S*)-**222a** was obtained in a moderate yield (56%) and ^{19}F-NMR analysis revealed a diastereoisomeric ratio of 89:11. This ratio could be improved to 95:5 (by ^{19}F-NMR) after chromatography over silica gel.



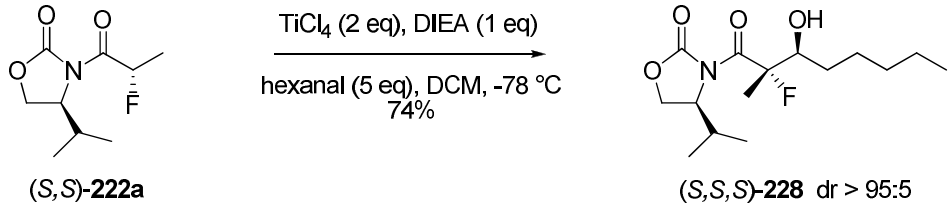
Scheme 2. 21: Preparation of fluoropropionimide (*S*,*S*)-**222a**.

The (*S*,*R*) diastereoisomer **222b** was prepared by a less straight forward protocol. It started with mesylation of ethyl (*S*)-lactate **224** (Scheme 2.22). The mesylate **225** was then treated with potassium fluoride to generate the α-fluoro ester **226** [24]. The hygroscopic character of potassium fluoride rendered that reaction's yield inconsistent. But when potassium fluoride was dried by heating under reduced pressure, prior to reaction, the displacement of the mesylate by the fluoride was achieved in 87% yield. The reaction was carried out in the highly toxic formamide. Its high polarity favoured the S_N2 pathway to take place ,and its high boiling point (210 °C) allowed the fluoro ester **226** to be purified by distillation under reduced pressure directly from the reaction mixture. Direct treatment of the ester **226** with phthaloyl chloride and chlorosulfonic acid gave the corresponding acid chloride **227** in 63% yield in one step [25,26]. (caution: chlorosulfonic acid is a highly corrosive acid which reacts violently with water, therefore it has to be handled with great care). Freshly prepared acid chloride **227** was then reacted to oxazolidinone **209** previously deprotonated with BuLi at -50 °C, to afford (*S*,*R*)-**222b** in moderate yield (59%) and with a diastereoisomeric ratio of 95:5 (by ^{19}F-NMR).



Scheme 2. 22: Preparation of fluoropropionimide (*S,R*)-**222b**.

Aldol reactions with each of the diastereoisomers were then carried out. Treatment of (*S,S*)-**222a** with $TiCl_4$ (2 eq), DIEA (1 eq) and hexanal (2 eq) at -78 ^{o}C generated (*S,S,S*)-**228** in 63% conversion (Scheme 2.23).



Scheme 2. 23: Preparation of **228** by aldol reaction of (S,S)-**222a** with $TiCl_4$ (2 eq) and hexanal.

The signal of only one aldol product was observed at -158 ppm, alongside with an unidentified signal showing no coupling constant at -164 ppm and the signals of **222a** and **222b** (-184 ppm and -186 ppm). The same stereoselectivity but with a better conversion was obtained when a larger excess of hexanal was used (5 eq), and (*S,S,S*)-**228** was isolated in 74% yield as a predominant diastereoisomer (dr > 95:5 by ^{19}F-NMR) (Figure 2.6).

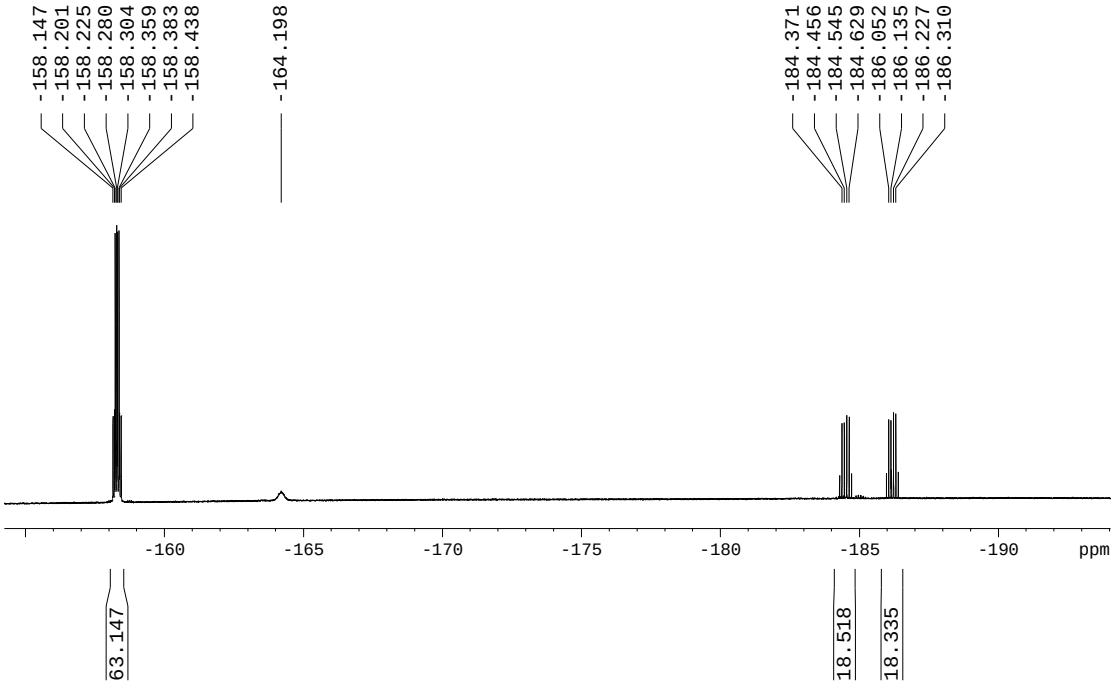
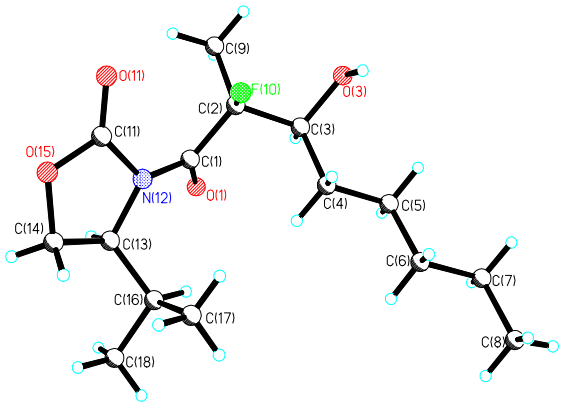
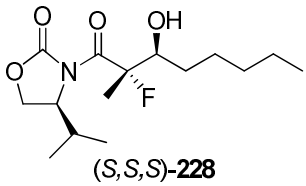


Figure 2. 6: ^{19}F-NMR spectrum of the crude mixture of the preparation of (*S*,*S*,*S*)-**228.**

X-ray structure analysis of a suitable crystal of the major aldol product **228** (Figure 2.7) revealed that the absolute and relative configuration (*S*,*S*,*S*)- of **228** as shown in Scheme 2.23 with an *anti* relationship between the fluorine and the hydroxyl group. It is notable also that in the solid state the C-F bond and the amide carbonyl are *anti* to each other, a stereoelectronic preference found more generally in α-fluoroamides.



(*S,S,S*)-**228**



(*S,S,S*)-**228**

Figure 2. 7

(*S,S*)-**222a** was also reacted with benzaldehyde (2 eq) under the same conditions ($TiCl_4$ 2 eq) (Figure 2.8). A major diastereoisomer was obtained at -159 ppm alongside with a minor product at -158 ppm and an unidentified signal at -164 ppm, and the signals of **222a** and **222b** at -184 ppm and 186 ppm. Aldol product (*S,S,S*)-**229** was isolated in 67% yield and an estimated dr of 95:5 (by ^{19}F-NMR).

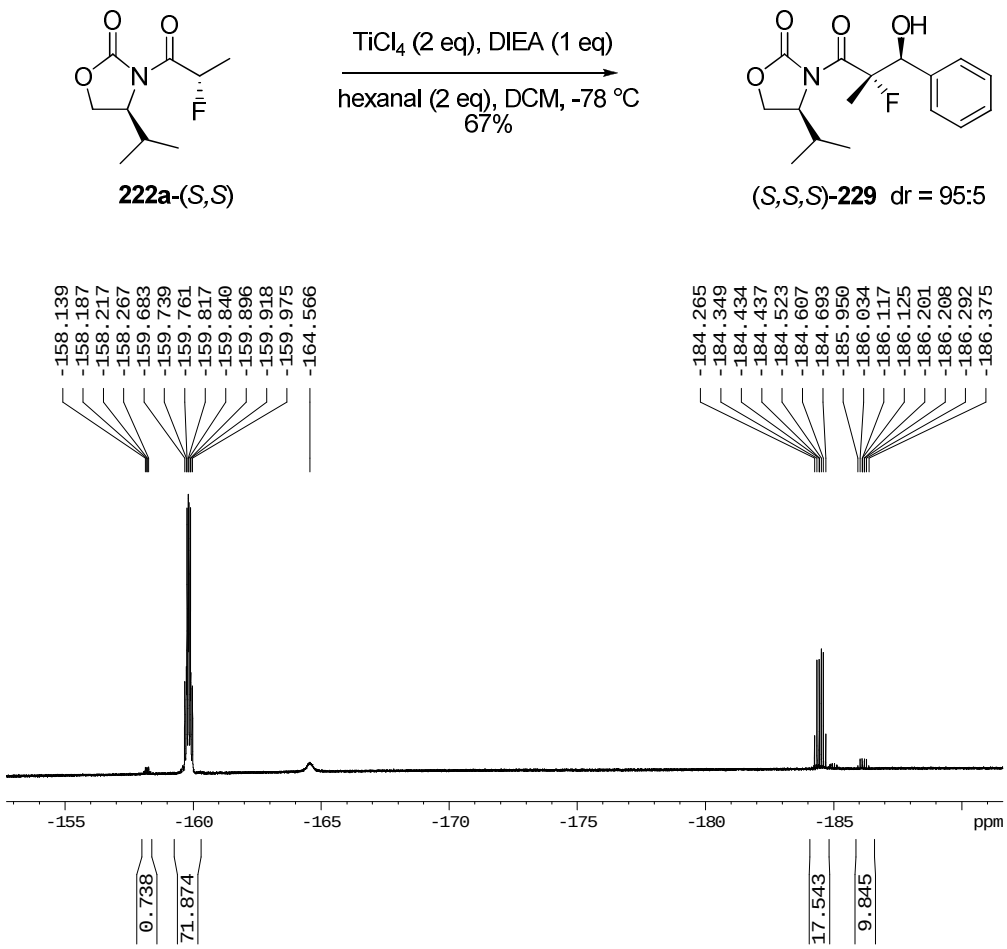
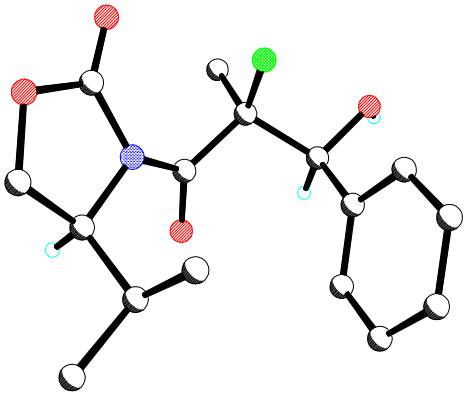
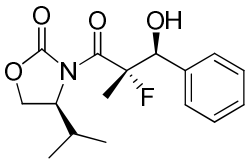


Figure 2. 8: Preparation of (*S,S,S*)-**229** by aldol reaction of (S,S)-**222a** with $TiCl_4$ (2 eq) and benzaldehyde.

A crystal structure of the aldol product **229** was also obtained (Figure 2.9). This also, confirmed absolute and relative stereochemistry (*S,S,S*)- and showed an *anti* relationship between the fluorine and the hydroxyl group.



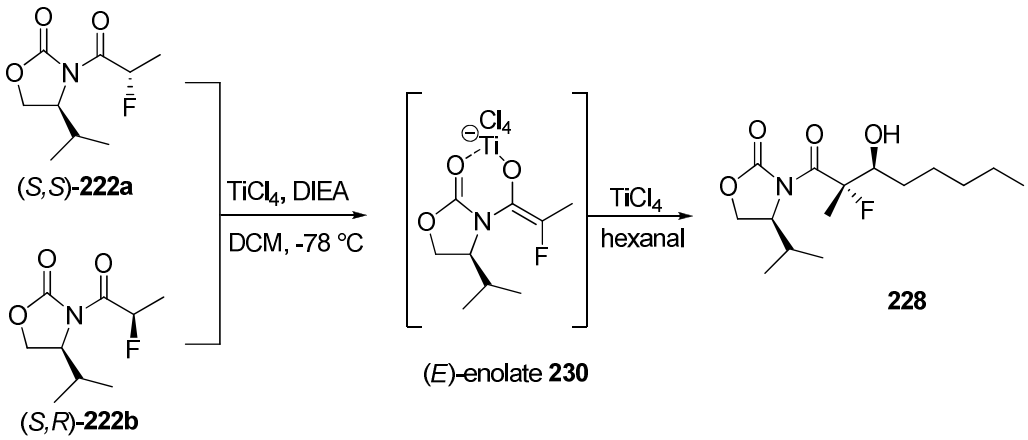
(*S,S,S*)-**229**



(*S,S,S*)-**229**

Figure 2. 9 :

^{19}F-NMR spectra of the reactions carried out with (*S,S*)-**222a** showed the presence of signals corresponding to (*S,S*)-**222a** and (*S,R*)-**222b** at -184 ppm and -186 ppm. This could signify that interconversion between these two molecules occurs in the course of the reaction with a possible similar enolate intermediate. This was confirmed when the reaction was investigated with (*S,R*)-**222b**, as the same aldol diastereoisomer (*S,S,S*)-**228** was observed (as determined by ^{19}F-NMR) with a similar dr > 95:5. It is clear that the nature of the starting diastereoisomer of (*S,S*)-**222a** or (*S,R*)-**222b** has no influence on the stereoisomer outcome of the aldol product, suggesting that the reactions proceed through a common thermodynamically favoured enolate (Scheme 2.24).



Scheme 2. 24: Aldol reaction with **222a** and **222b** through a common enolate **230**.

In order to reinforce that hypothesis, each of the two diastereoisomers of **222a** and **222b** were separately treated directly in an NMR tube, with $TiCl_4$ at -78 °C in deuteriated dichloromethane ($C^2H_2Cl_2$) and enolate formation was monitored by ^{19}F-NMR. In each case only one enolate was apparent showing a signal at -150.1 ppm by $^{19}F\{^1H\}$-NMR (Figure 2.10). The observation of a common, enolate resulting from each of the diastereoisomers of **222** is consistent with the experimental outcome, where each diastereoisomer gives the same major product. In these experiments there was no obvious presence of the second (*Z*)-enolate

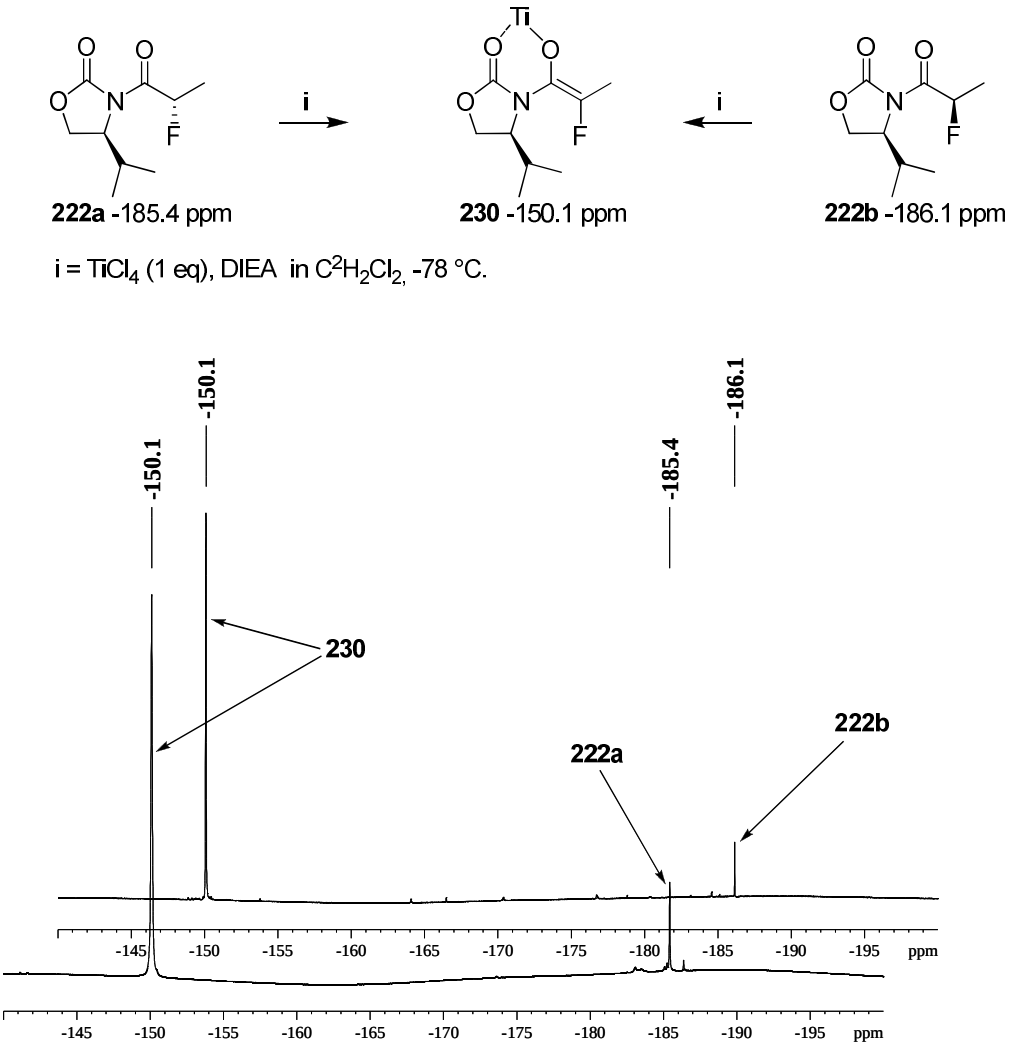


Figure 2. 10: Comparison of the $^{19}F\{^{1}H\}$-NMR spectra of the enolates generated from **222a** and **222b** after treatment with $TiCl_4$ (1 eq) and DIEA in $C^2H_2Cl_2$, -78 °C.

The $^{19}F\{^{1}H\}$-NMR spectra recorded at -78 ^{o}C in $C^2H_2Cl_2$ showed only one enolate (Figure 2.10) but when the solution was warmed up to 0 °C a second signal appeared at -148.6 ppm (Figure 2.11a). This was assumed to be the (*Z*)-enolate, representing around 4% of the overall enolate signal. When proton decoupling was turned off both signals became quartets in the ^{19}F-NMR spectrum, consistent with this analysis (Figure 2.11b). The ^{19}F-NMR signals of the (*E*)- and (*Z*)-enolates derived from **222b** after $TiCl_4$ treatment at 0 ^{o}C are shown in Figures

2.11a and 2.11b. Treatment of **222a** under the same conditions gave similar spectra with a similar *E:Z* ratio.

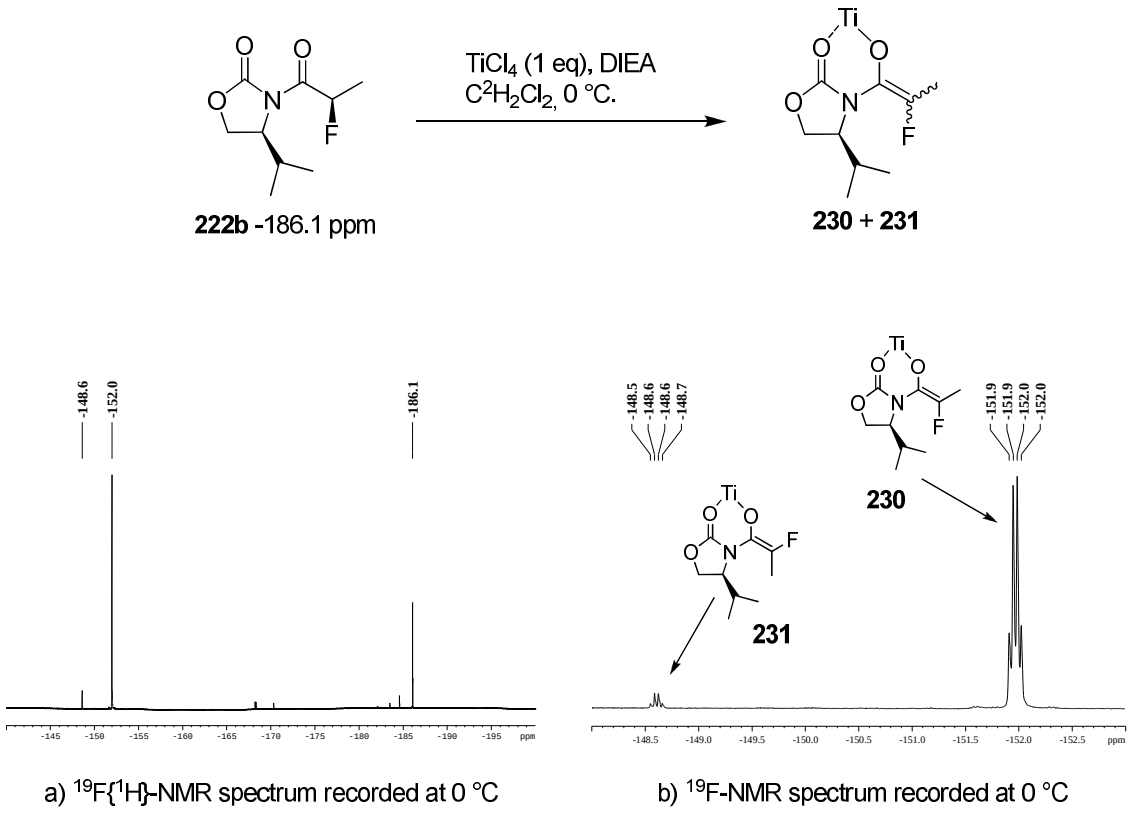
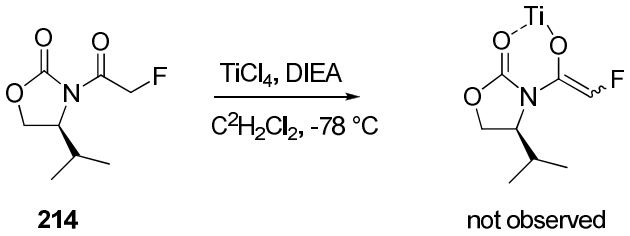


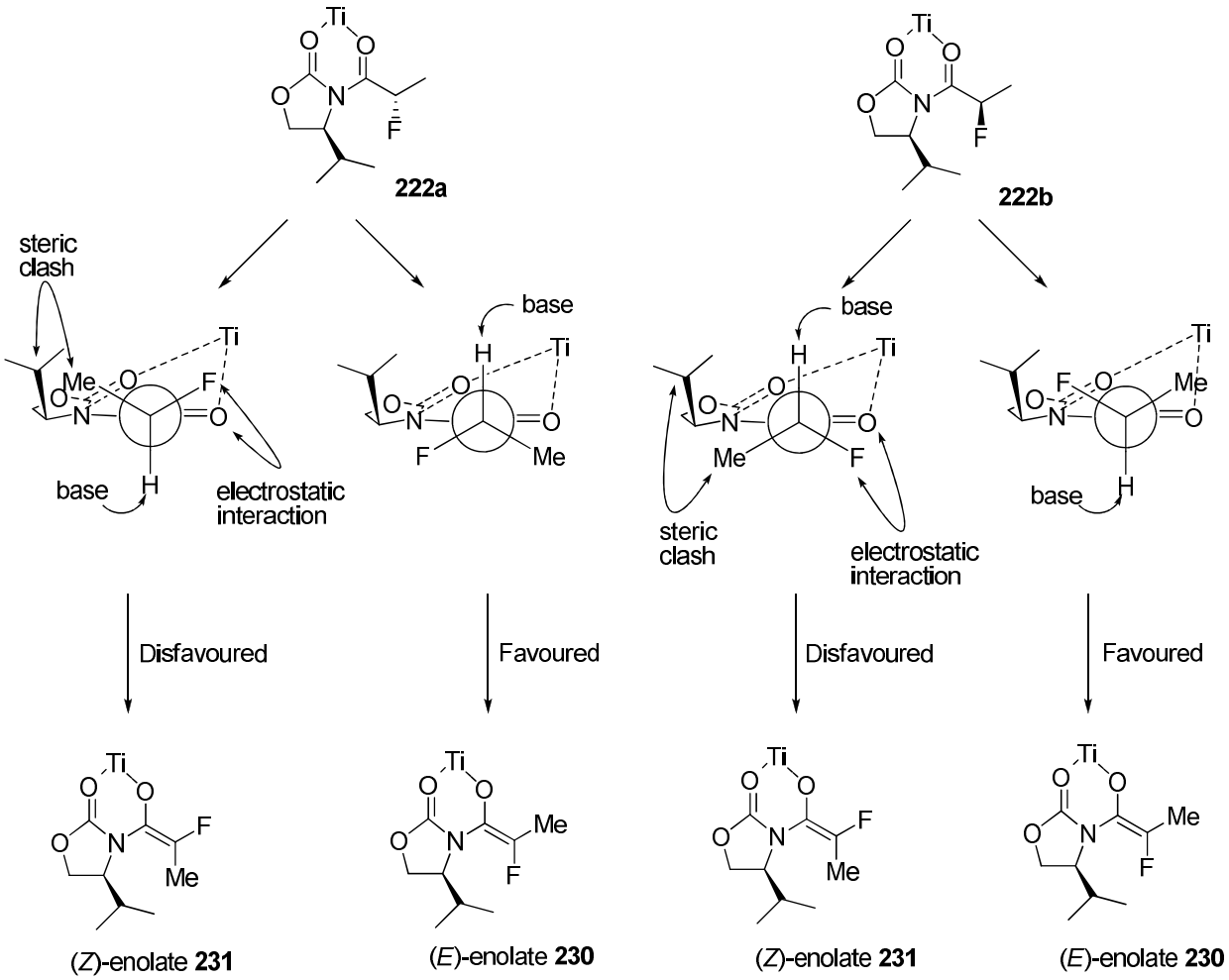
Figure 2. 11: (a) $^{19}F\{^{1}H\}$-NMR and (b) ^{19}F-NMR spectra of the (*E*)/(*Z*) enolate solution after treatment of **222b** with $TiCl_4$ and DIEA in DCM at 0 ^{o}C.

A similar low temperature experiment monitored by ^{19}F-NMR was attempted on the formation of the enolate of **214** to observe if both (*E*)- and (*Z*)-enolates were present in solution, but unfortunately this experiment failed (Scheme 2.25). After treatment with DIEA, the resulting complex of the oxazolidinone with titanium has a significative deep red colour that is usually easily observable in the reaction medium. After treatment of **214** with $TiCl_4$ and DIEA in an NMR tube, the deep red colour was observed only for few seconds, and the recorded ^{19}F-NMR spectrum showed only presence of **214**.



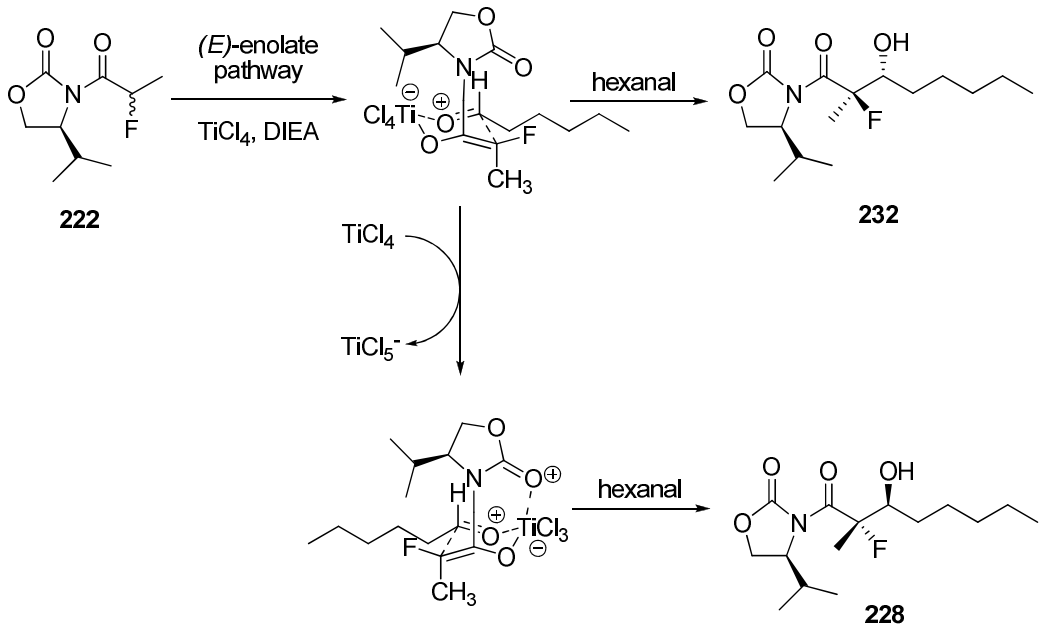
Scheme 2. 25: Treatment of **214** with $TiCl_4$ (1 eq) and DIEA in $C^2H_2Cl_2$, -78 °C.

It is assumed that at low temperature, the (*E*)-enolate **230** is the favoured enolate in solution. The (*Z*)-enolate **231** would result in a steric clash of the methyl group of the propionamide moiety with the isopropyl group of the auxiliary. The enolate formation observed by Newman projection is shown in Scheme 2.26. It appears that in both cases (**222a** and **222b**) deprotonation at an angle of 90° of the carbonyl-imide is possible with minimum steric hindrance favouring the (*E*)-enolate **230** in both cases. Also the orientation of the C-F bond *anti* to the enolate/amide C-O bond is anticipated to be stereoelectronically favoured as it will result in an electrostatic dipolar relaxation.



Scheme 2. 26: Newman projection of formation of enolates from **222a** and **222b**.

Generation of the (*E*)-enolate **230** is also consistent with the stereochemical outcome of the aldol reaction as deduced by Zimmerman/Traxler intermediates and illustrated in Scheme 2.27. Crimmins and co-workers have proposed that the second equivalent of $TiCl_4$ abstracts Cl^- from the complexed titanium allowing coordination of the oxazolidinone carbonyl to titanium to generate a highly ordered bicyclic enolate intermediate [18].



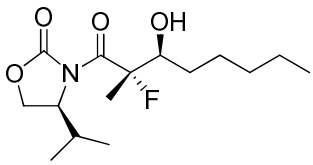
Scheme 2. 27: Zimmerman/Traxler intermediates showing the different complexation after one and two eq of $TiCl_4$, giving different stereochemical outcomes.

Attempts to prepare diastereoisomer **232** in a stereoselective manner were only partially successful. When only 1 equivalent of each of $TiCl_4$ and DIEA was added, the reaction proceeded with a poor conversion, and only a low stereoselectivity was observed. When DIEA was replaced by (-)-sparteine (1 eq at 0 °C), a diastereoisomeric ratio (80:20) in favour of the assumed isomer **232** was observed. So although we could reproduce the expected stereochemical tendancy, this did not result in a satisfactory preparative method for the fluorinated aldol product **232**.

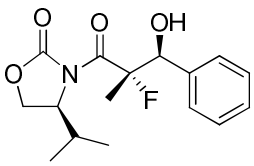
2.3.4) Strategies for vicinal difluoro preparation:

The overall objective of this study was to develop a novel stereoselective method for the introduction of the vicinal difluoromotif into organic molecules. Having developed a satisfactory stereoselective route to the *anti*-α-fluoro-α-hydroxy products **228** and **229** (Figure

2.12), the project then focused on different strategies for the introduction of the second fluorine substituent.



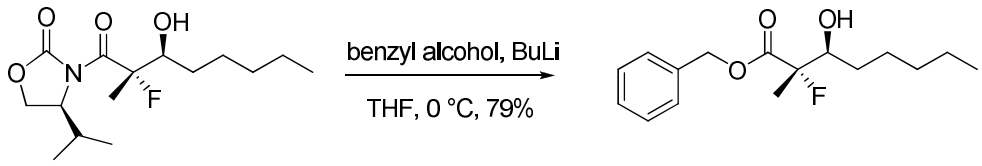
228



229

Figure 2. 12

Direct deshydroxyfluorination reactions of **228** were explored with Deoxo-Fluor®, however these were unsuccessful giving rise only to uncharacterised products. An alternative strategy was envisaged involving prior cleavage of the α-fluoro-α-hydroxyacyl group from the auxiliary. This was explored for **228** but not **229** as the hydroxyl is benzylic and vulnerable to non stereospecific substitution. Removal of the auxiliary on **228** was achieved in two ways (Scheme 2.28). Firstly, reaction of lithium phenyl methanolate with **228** generated the benzyl ester **233** in 79% yield.

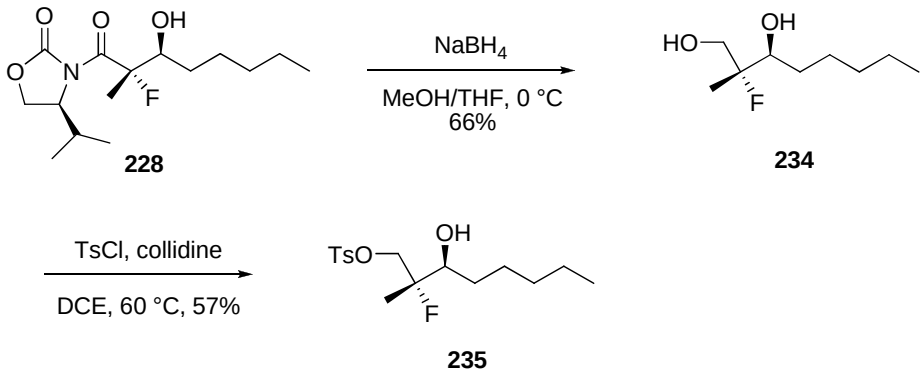


228 **233**

Scheme 2. 28 : Deprotection of the oxazolidinone auxiliary to benzyl ester

Separately, treatment with $NaBH_4$ generated diol **234** in 66% yield. This diol was selectively protected as its monotosyl derivative **235** by treatment with TsCl in dichloroethane in presence of collidine (Scheme 2.29). Recent experience in the research group had

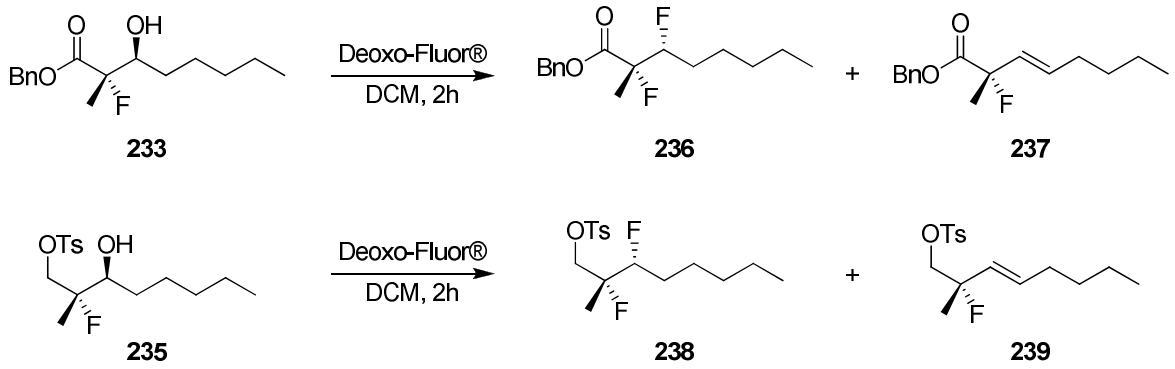
demonstrated that tosyl groups are compatible with deshydroxyfluorination reactions and in the event this proved a robust protecting group [27].



228 **234** **235**

Scheme 2. 29 : Deprotection of the oxazolidinone auxiliary to alcohol.

Reaction of **233** with Deoxo-Fluor® in DCM at 40 °C resulted in complete conversion to a mixture of **236** and olefin **237**, with poor selectivity (35:65) in favour of **237** (Table 2.5, Entry 1). Products **236** and **237** were purified in moderate yields, of 23% and 40% respectively. The selectivity was improved in favour of **236** (72:28) when the reaction was carried out at -30 °C, but with a lower conversion (55%) (Table 2.5, Entry 2).

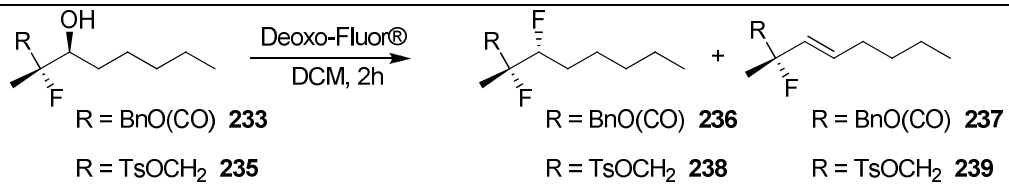


233 **236** **237**

235 **238** **239**

Scheme 2. 30 : Insertion of a second fluorine by deshydroxyfluorination reaction.

When **235** was treated with Deoxo-Fluor® in DCM at 40 °C, only the elimination product **239** was generated (Entry 3), and when the reaction was carried out at -30°C no products were formed (Entry 5). The vicinal difluoro product **238** was generated after treatment with Deoxo-Fluor® at RT but with a poor selectivity (85:11) in favour of **239** (Entry 4). Although **236** was fully characterised, attempts to purify **238** were unsuccessful due to the small scale and poor selectivity of the reaction.

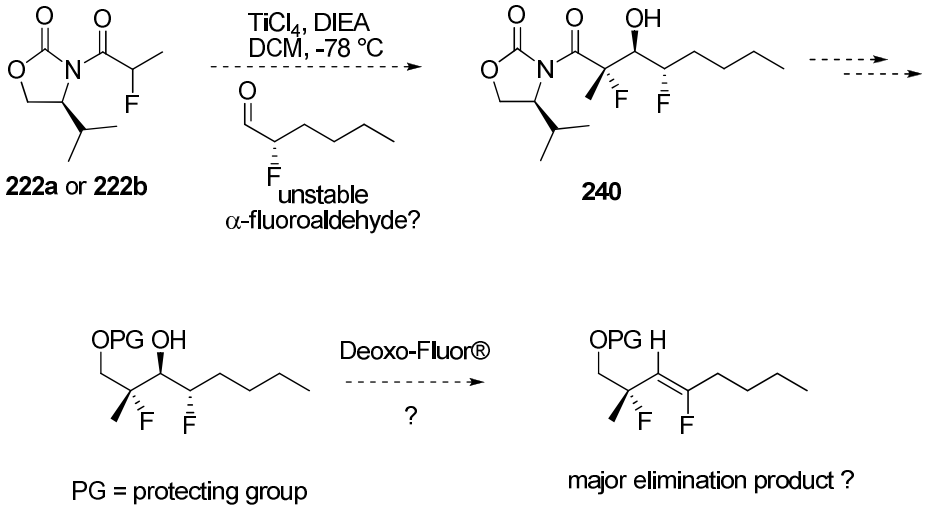


Entry	R	Temperature	Conversion	Selectivity
1	BnO(CO)	40 °C	100%	**236**/**237** = 35/65
2	BnO(CO)	-30 °C	55%	**236**/**237** = 72/28
3	$TsOCH_2$	40 °C	100%	**238**/**239** = 0/100
4	$TsOCH_2$	RT	96%	**238**/**239** = 11/85
5	$TsOCH_2$	-30 °C	no reaction	

Table 2. 5 : Different conditions explored for the insertion of a second fluorine by deshydroxyfluorination reaction.

2.4) Conclusion:

In this chapter we have explored enolate formation from the diastereoisomers of **222a** and **222b**, and have demonstrated that the common thermodynamic enolate results after treatment with $TiCl_4$. This was shown by $^{19}F\{^1H\}$-NMR analysis of the intermediate titanium enolates, and was also manifest in the product outcome where the same α-fluoro-α-hydroxyl products **228** and **229** were generated with high diastereoselectivity either of **222a** or **222b**. Subsequent manipulations of **228** to generate vicinal difluoroproducts such as **236** and **238** were only moderately successful. We then questioned the asymmetric aldol reaction strategy to prepare three vicinal fluorine motifs. If a difluoroalcohol such as **240** is obtained after a highly stereoselective aldol reaction, the risks of elimination during insertion of the third and last fluorine are still high (Scheme 2.31). This could lead to a three vicinal fluorine containing molecule, but only in low yield. Another problem also emerged: the enantio-enriched α-fluoroaldehydes have been described as impossible to isolate without erosion of the enantiopurity, and they therefore need to be transformed to hydrazone or reduced to alcohol to be easily purified [28,29,30]. Then, the preparation of vicinal trifluoro motifs by the chiral oxazolidinone strategy was not investigated any further.



Scheme 2. 31 : Possible problems in the preparation of of vicinal trifluoro motifs by the chiral oxazolidinone strategy.

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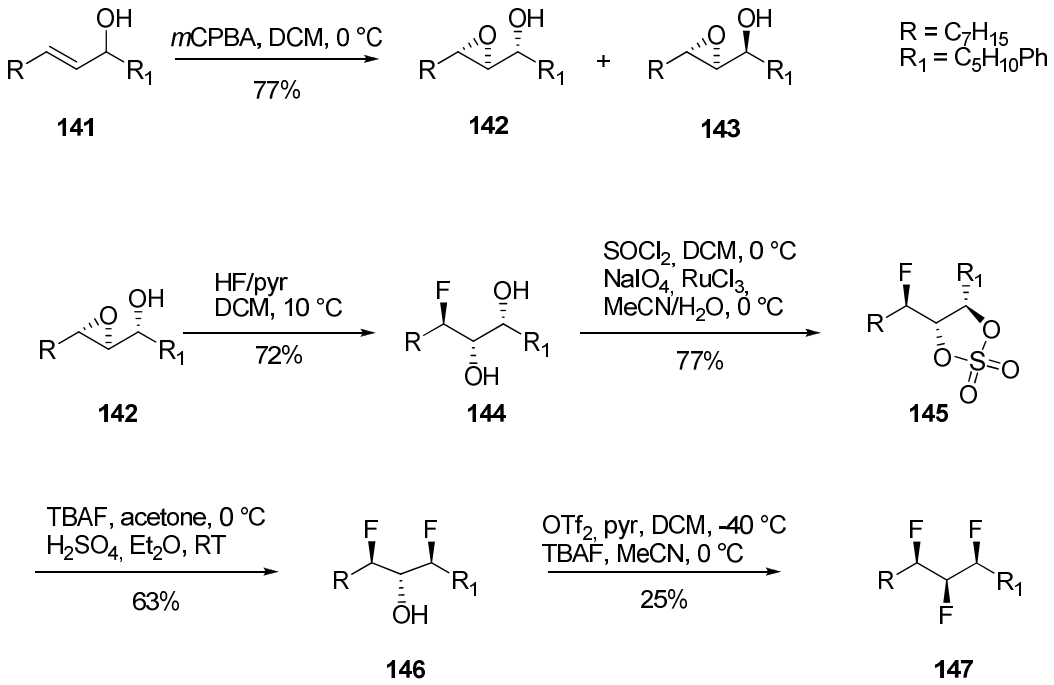
Chapter 3: Synthesis of vicinal fluoro motifs from enantio-enriched epoxy-alcohols:

3.1) Defining a new strategy:

As reported by Nicoletti and O'Hagan [1], the preparation of molecules bearing three vicinal fluorine atoms has been achieved starting from epoxy-alcohols and with a stereoselective cyclic sulphate as a key feature. This methodology proved to be highly stereoselective, and afforded enough flexibility to prepare separately two different single diastereoisomers. A summary of the synthetic pathway is shown in Scheme 3.1 for the all-*syn* diastereoisomer **147**. However this methodology had some limitations. Some steps were plagued with elimination side reactions resulting in poor yields. It also required seven steps to insert the three fluorine atoms, and with an overall yield well below 10%. It seemed essential that in the new strategy involving epoxy-alcohols, particular attention should be paid to reducing the number of steps and/or improve the yields of each individual step.



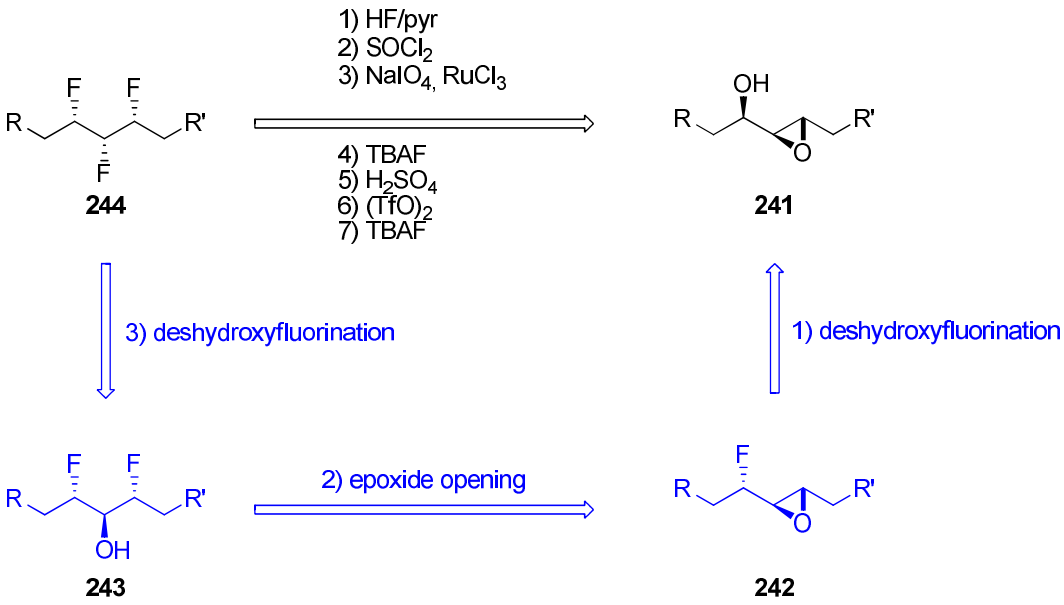
Scheme 3. 1 : Synthesis of an all-*syn* diastereoisomer of a vicinal trifluoro motif by Nicoletti and O'Hagan [1].

We tried to approach a new synthesis of the three vicinal fluorine motif with an increased diversity for the preparation of stereoisomers of the epoxy-alcohols and faster access to their fluorinated derivatives.

3.1.1) A new approach to the fluorination steps:

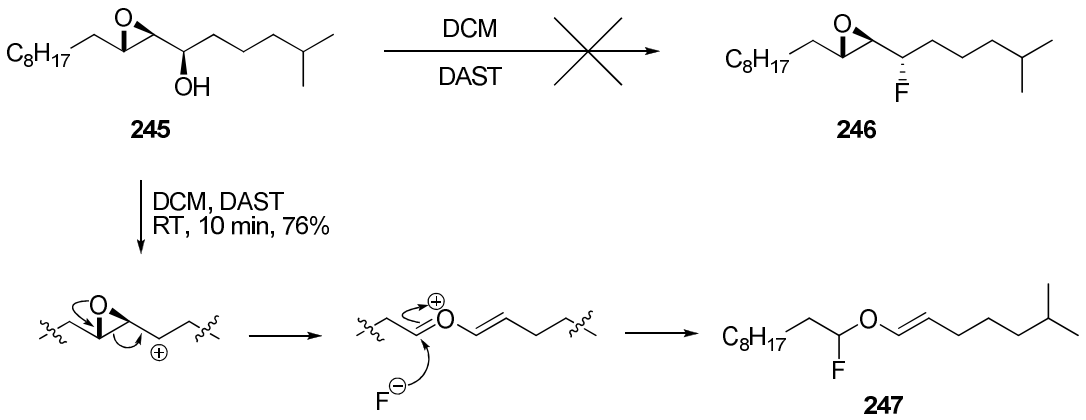
A more straightforward approach to the insertion of fluorine atoms was desirable, to consider preparing these materials on a larger scale for applications in materials chemistry. Indeed, as shown in Scheme 3.2, it was envisaged that fluorination could be achieved in three steps from an epoxy-alcohol instead of the seven steps as in the previous strategy. An epoxy-alcohol **241** clearly could be subjected to a deshydroxyfluorination reaction to form an α-fluoro-epoxide **242**, followed by epoxide ring opening with a source of HF to form **243**. Incorporation of the first fluorine should strengthen the adjacent C-O epoxide bond, allowing the HF-mediated

epoxide ring opening to be regioselective with fluorination at the β position. Epoxide ring opening with a source of HF is usually stereospecific [2,3]. Insertion of the third fluorine would then be achieved by a second deshydroxyfluorination reaction, again with a stereospecific inversion of configuration to form **244**. Such a strategy represents a very direct three step method to access the trifluoro motifs. It also avoids the use of TBAF and therefore the risk of elimination side reactions.



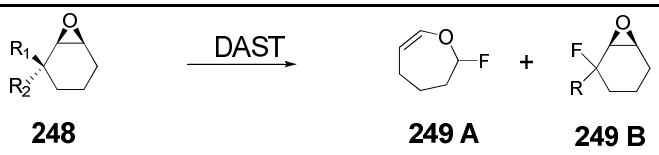
Scheme 3. 2 : Comparison between a 7 and a 3 steps retrosynthetic route to the vicinal trifluoro motif **244**.

The route appeared attractive, however there was an consideration reported by Grée and co-workers during the treatment of epoxy-alcohols with DAST [4]. As shown in Scheme 3.3, their attempt at deshydroxyfluorination of *cis*-**245** with DAST did not result in the formation of the expected fluoro analogue of dispalure **246**, but rather resulted in a rearrangement to the fluorovinyl ether **247**. This was a very efficient process, and resulted in product isolation with a yield of 76%. This process illustrates a rather unusual, but facile C-C bond cleavage.



Scheme 3. 3 : Formation of fluorovinyl ether following the mechanism proposed by Grée [4]**.**

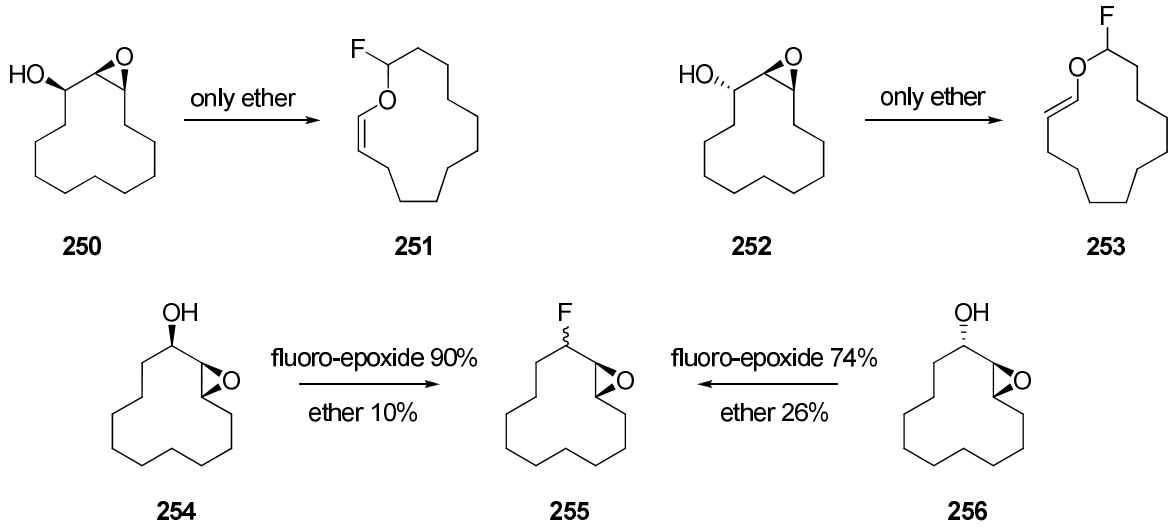
Grée and co-workers used this unusual reaction to advantage in the synthesis of oxygenated fluoroheterocycles exploiting the ring expansion strategy [5]. Some of their results are shown in Table 3.1 and Scheme 3.4. The nature of the substituent R_2 can influence the outcome of the reaction. A CF_3 substituent favoured the formation of a vinyl ether whereas a methyl group favoured the fluoro-epoxide.



248 **249 A** **249 B**

Substituents	Ratio **249 A** / **249 B**	Yield (%)
R_1 = H, R_2 = OH	63 / 37	58
R_1 = OH, R_2 = H	31 / 69	61
R_1 = OH, R_2 = Me	**249 B** only	73
R_1 = OH, R_2 = CF_3	**249 A** only	70

Table 3. 1 : Formation of fluorovinyl ether and fluoro-oxiranes by Grée [5].



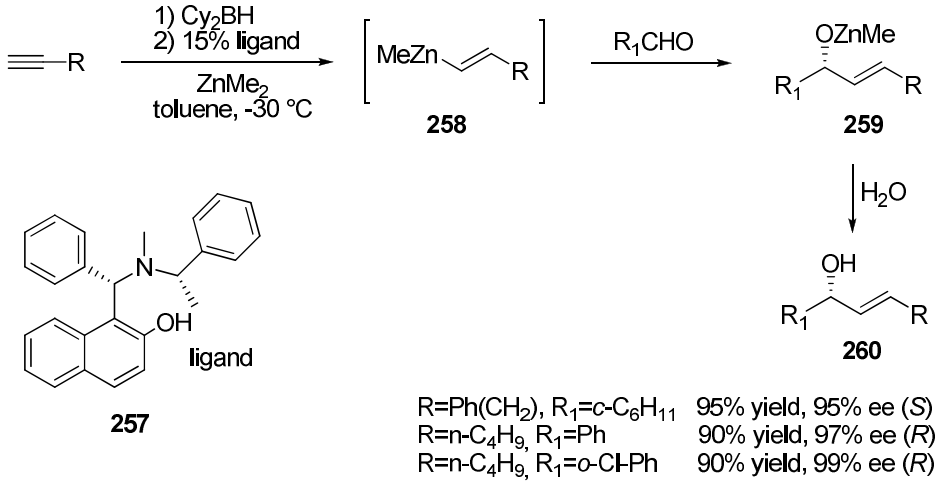
Scheme 3. 4 : Formation of fluorovinyl ether and fluoro-oxiranes by Grée [5].

The epoxide rearrangement observed by Grée seems to be persistant but substrate dependant. For instance *threo*-**250** and *erythro*-**252** epoxy-alcohols can afford a rearranged vinyl ether, whereas *threo*-**254** and *erythro*-**256** prefer to form a fluoro-oxirane. It is therefore difficult to define any absolute predictive rule concerning the reactivity of epoxy-alcohols towards the deshydroxyfluorination reaction. However, as discussed by Grée, it seems that the *threo*-epoxy-alcohols are generally more prone to undergo rearrangement than the *erythro*-isomers [4,5].

3.1.2) New approaches to the formation of enantio-enriched epoxy-alcohols:

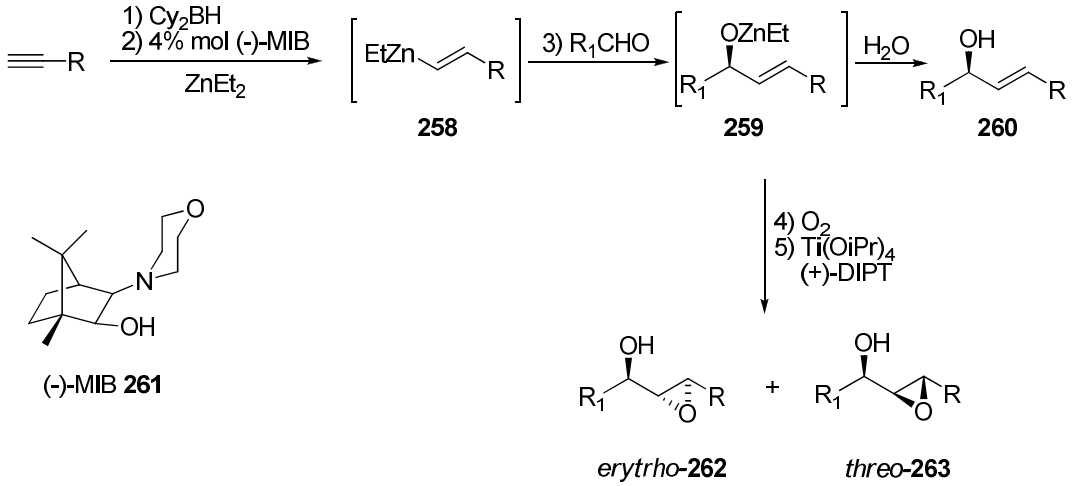
Alternative routes were also envisaged for the preparation of enantio-enriched allylic alcohols and epoxy-alcohols (Scheme 3.5). For instance, a very direct method to access allylic alcohols such as **260** involves a one-pot hydroboration of an alkyne, followed by vinyl addition to aldehydes in the presence of an alkyl zinc reagent and an amino alcohol ligand such as **257**. This has been reported by Srebnik [6], Oppolzer [7] in the early 1990's and more recently by

Chan [8] and Walsh [9,10,11]. As illustrated in Scheme 3.5, the alkyne is reduced *in situ* with dicyclohexyl borane and a transmetallation from boron to zinc is performed. After addition of a ligand **260** of a catalytic level, the vinyl zincate **258** can then undergo nucleophilic addition to an aldehyde. Asymmetric versions of this reaction have also been developed, notably by Chan and co-workers (Scheme 3.5), and Walsh and co-workers (Scheme 3.6) which provide allylic alcohols **260** in good yields and high enantioselectivities.



Scheme 3. 5 : Examples of enantioselective synthesis of allylic alcohols by Chan [8].

Walsh even extended this methodology to a one pot asymmetric synthesis of chiral epoxy-alcohols *via* a tandem catalytic asymmetric vinylation of an aldehyde, coupled to a diastereoselective epoxidation reaction (Scheme 3.6) [9,10,11]. After reaction of the vinyl zinc species **258** to the aldehyde and instead of quenching the reaction with water to obtain the allylic alcohol **260**, the nitrogen atmosphere was replaced by dioxygen. Then, addition of a titanium tartrate catalyst promoted clean and efficient formation epoxy-alcohols **262** and **263** in excellent enantioselectivities in most cases and with diastereoselectivities up to 4.5:1, in favour of the *threo*-**263** diastereoisomer.



Scheme 3. 6 : Examples of enantioselective synthesis of allylic alcohols and epoxy-alcohols by Walsh [9,10,11].

Some of the results obtained by Walsh are reported in table 3.2.

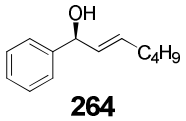
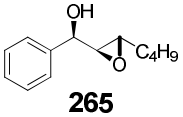
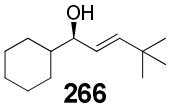
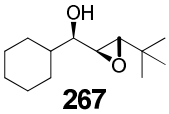
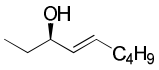
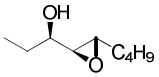
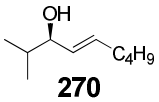
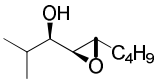
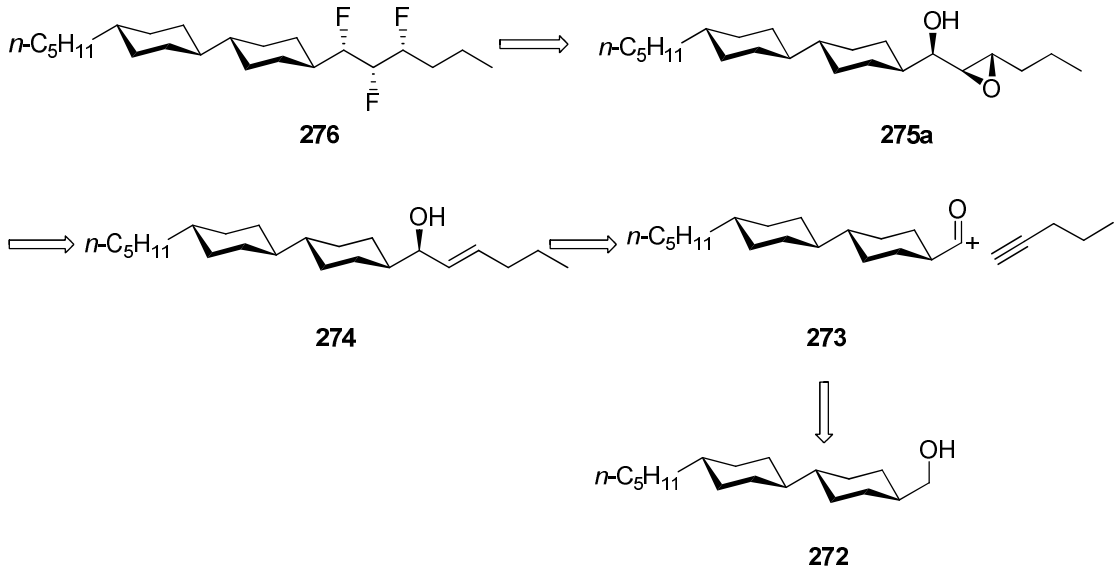
Entry	Allylic alcohol	ee (%)	Major Epoxy-alcohol	dr *threo*/*erythro*	Yield (%)
1	 **264**	94	 **265**	3.5:1	83
2	 **266**	96	 **267**	3.8:1	74
3	 **268**	79	 **269**	3.2:1	69
4	 **270**	92	 **271**	4.5:1	77

Table 3. 2 : Examples of enantioselective synthesis of allylic alcohols and epoxy-alcohols by Walsh [9,10,11].

This one pot vinylation/epoxidation reaction represents a rapid and flexible method to access a variety of enantio-enriched epoxy-alcohols with aromatic (**265**), aliphatic (**269**, **271**) or alicyclic (**267**) substituents. This could clearly be used in the preparation of vicinal fluoro-

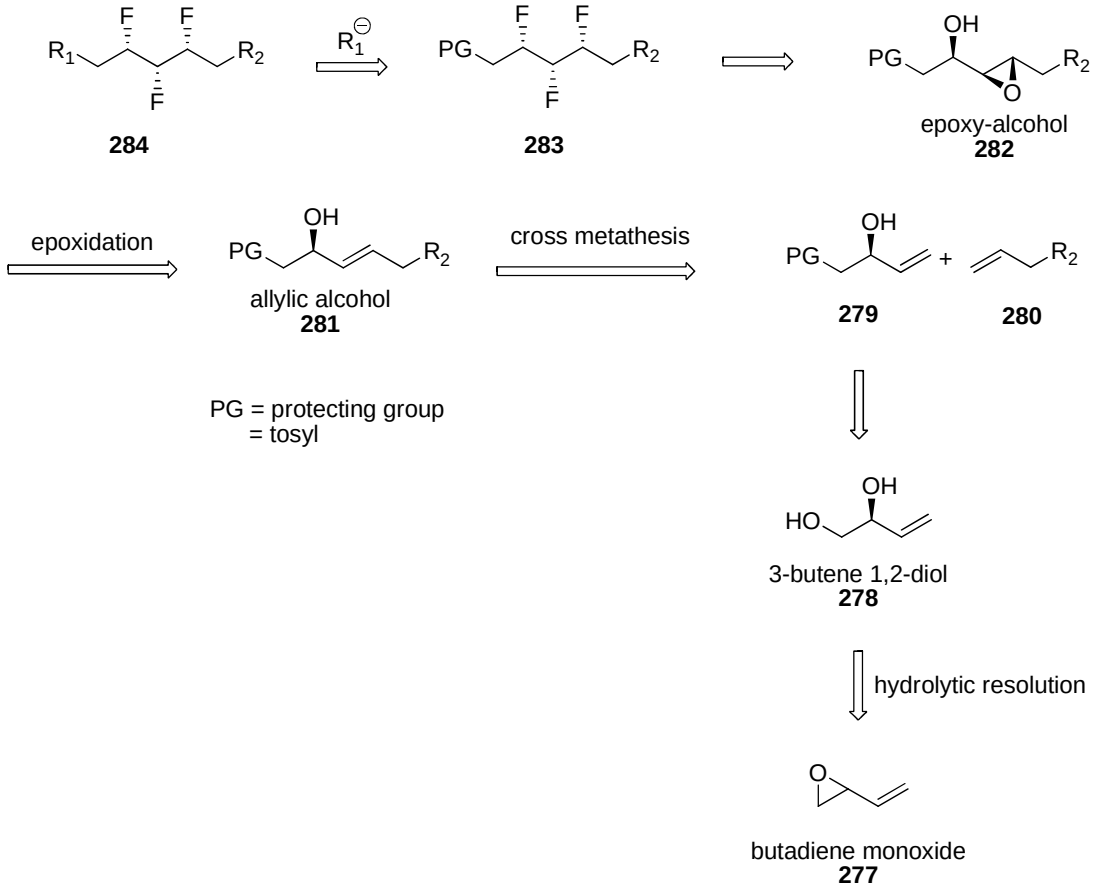
compounds bearing a liquid crystal motif. A retrosynthetic analysis of such a molecule is shown in Scheme 3.7. Alicyclic methyl alcohol **272** is a motif used by Merck in the preparation of commercial liquid crystals. After oxidation to aldehyde **273**, a reduction/vinylation could be envisaged with pentyne to access the allylic alcohol **274**. Further epoxidation of **274** or tandem vinylation/epoxidation starting from **273** would lead to the formation of *threo*-epoxy-alcohol **275a** and its diastereoisomer. Then fluorination in three steps could generate target **276**.



Scheme 3. 7 : Retrosynthetic route to an all-*syn* trifluoro liquid crystal motif **276**.

An alternative approach to the fluorination of such epoxy-alcohols was envisaged, providing increased flexibility. So far, multivicinal motifs have been prepared by fluorination of a predefined core in order to study the conformational influences of fluorine atoms situated adjacent to each other. But with a focus on finding possible applications to vicinal fluorine motifs it is essential to find easy, quick and flexible routes to their preparation. As shown in Scheme 3.8, the possibility of building a non-symmetric building block such as **284** was considered, bearing three fluorines in the middle and orthogonal end groups. For example

group R_1, could be inserted by nucleophilic substitution after the fluorination steps, whereas R_2 could be incorporated earlier in the synthesis, during the formation of an allylic alcohol **281** by a cross metathesis reaction. The protective group must meet certain requirements. It has to be resistant to HF, and also it must not interfere in the metathesis reaction. The tosyl group was attractive as it was shown to survive the desydroxyfluorination reaction in previous reactions in our research group [12]. Allylic alcohol **279** could be easily prepared by ring opening of butadiene monoxide **277** followed by regioselective protection at the primary alcohol. This route looked interesting for two reasons: first the well established chemical reactions involved. Secondly, an enantio-enriched 3-butene-1,2-diol **278** can readily be obtained after kinetic resolution of butadiene monoxide hydrolysis as it has been demonstrated by Jacobsen and co-workers [13].



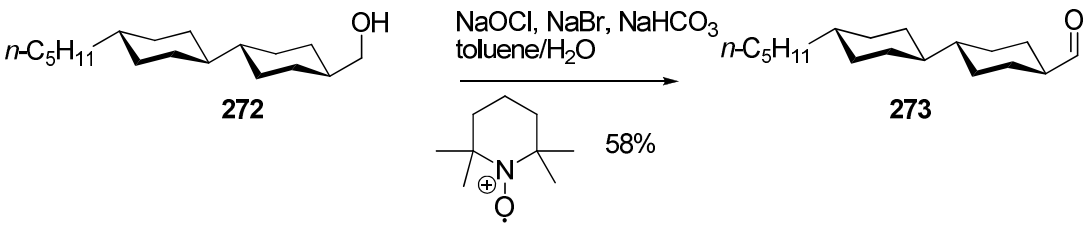
Scheme 3. 8 : Retrosynthetic route to vicinal fluorine by fluorination of an epoxy-alcohol formed *via* cross metathesis/epoxidation strategy.

3.2) Attempts at the preparation of three vicinal fluorine liquid crystal motifs:

3.2.1) Preparation of the *threo*- and *erythro*- epoxy-alcohols:

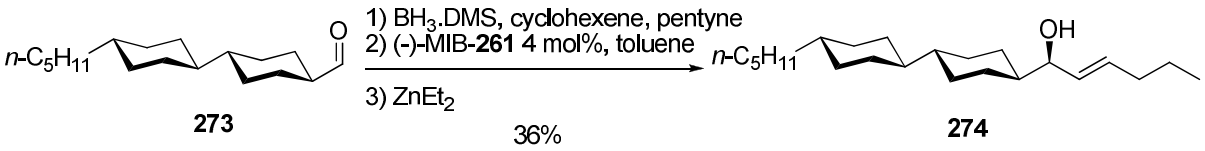
The methyl alcohol liquid crystal building block **272** provided by Merck Company was used as starting material. First, it was oxidised to aldehyde **273**. This was not straightforward as compound **273** proved to be difficult to purify over silica gel. Oxidation of alcohol **272** was first attempted with PCC in DCM at room temperature. TLC analysis showed that the reaction

did not go to completion, even with an excess of PCC. As compound **273** was not very stable over silica, only a poor yield was obtained. A better conversion to aldehyde **273** was obtained using NaOCl in the presence of a catalytic amount of TEMPO, sodium bicarbonate and potassium bromide in a toluene/water biphasic system [14] (Scheme 3.9). Although TLC analysis showed a nearly complete conversion, aldehyde **273** was obtained in only 58% yield after purification over silica.



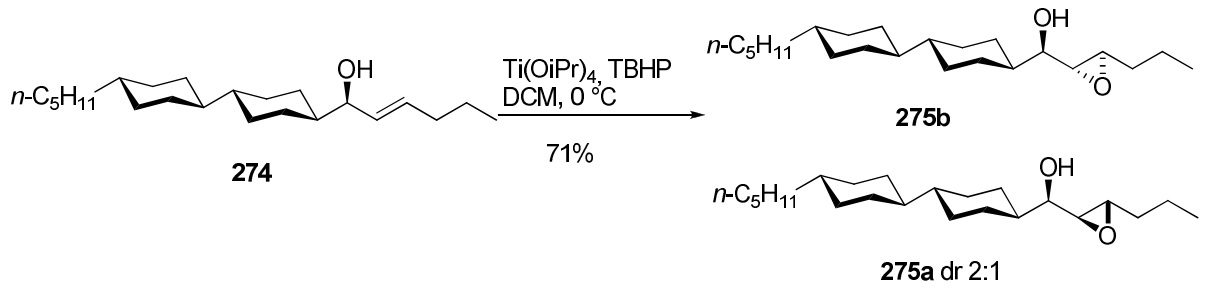
Scheme 3. 9 : Oxidation of **272** by tempo.

Aldehyde **273** was then used as an electrophile in a vinylation reaction following Walsh's method [9,10,11] (Scheme 3.10). Commercial ligand (-)-MIB-**261** was recrystallised from hexane prior to use. Dicyclohexyl borane was prepared by reacting cyclohexene with borane/dimethyl sulfide at 0 °C. Then pentyne was added at 0 °C and the reaction was stirred at RT to allow formation of the vinyl borane species. The reaction mixture was cooled to -78 °C, and diethylzinc in hexane was added followed by (-)-MIB-**261** dissolved in toluene. A solution of aldehyde **273** in toluene was added and the reaction was stirred for two days at -10 °C. Walsh showed that this reduction/vinylation reaction is versatile and affords allylic alcohols in good yield (>80%). Unfortunately, in our hands, the yield of the vinylation reaction did not exceed 36%, even when a large excess of diethylzinc was used or with 10 mol% of (-)-MIB-**261**.



Scheme 3. 10 : Preparation of allylic alcohol **274** by vinylation raction:

Purification of allylic alcohol **274** over silica was not straightforward as TLC analysis of the crude mixture showed the the presence of a range of products, therefore the one pot vinylation-epoxidation was not attempted. However after several columns, allylic alcohol **274** was successfully purified. Epoxidation of **274** with *tert*-butyl hydroperoxide (TBHP) in presence of Ti(O*i*-Pr)$_4$ in DCM at 0 °C, provided epoxy-alcohol **275a** and **275b** in 71% yield. The diastereoisomeric ratio of **275a** / **275b** was 2:1 in favour of the *threo* diastereoisomer **275a**. In this case, diastereoisomers **275a** and **275b** were easily separated by silica gel chromatography.



Scheme 3. 11 : Formation of both *threo*-**275a** and *erythro*-**275b** diastereoisomers.

3.2.2) Evaluation of the enantioselectivity of the vinylation reaction:

Evaluation of the enantiopurity of **274** was attempted by separate reactions with both (*S*)- and (*R*)- Mosher acids and analysis of the ester products by ^{19}F-NMR. Thus, **274** was reacted with an excess of (*S*)- and (*R*)- Mosher acids in DCM at RT and in the presence of an excess of DCC, and a catalytic amount of DMAP. Analysis of the ^{19}F{^{1}H}-NMR spectra of the two

Mosher esters showed the presence of a major diastereoisomer at -71.9 ppm and a minor diastereoisomer at -71.7 ppm with the (*S*)-Mosher ester (Figure 3.1 (a)). The signals were inverted for the (*R*)-Mosher ester (Figure 3.1(b)). However it was difficult to determine clearly the enantiopurity of allylic alcohol **274**, not only because of the presence of uncharacterised signals at -72.0 and -72.1 ppm, but also because analysis of ^{1}H-NMR spectra showed that reaction with Mosher acids had not gone to completion. Around 19% of unreacted allylic alcohol **274** was still present in the reaction with the (*S*)-Mosher acid and, this was even greater with the (*R*)-Mosher acid (~ 38%). However it was clear that the ee was high and close to 90%.

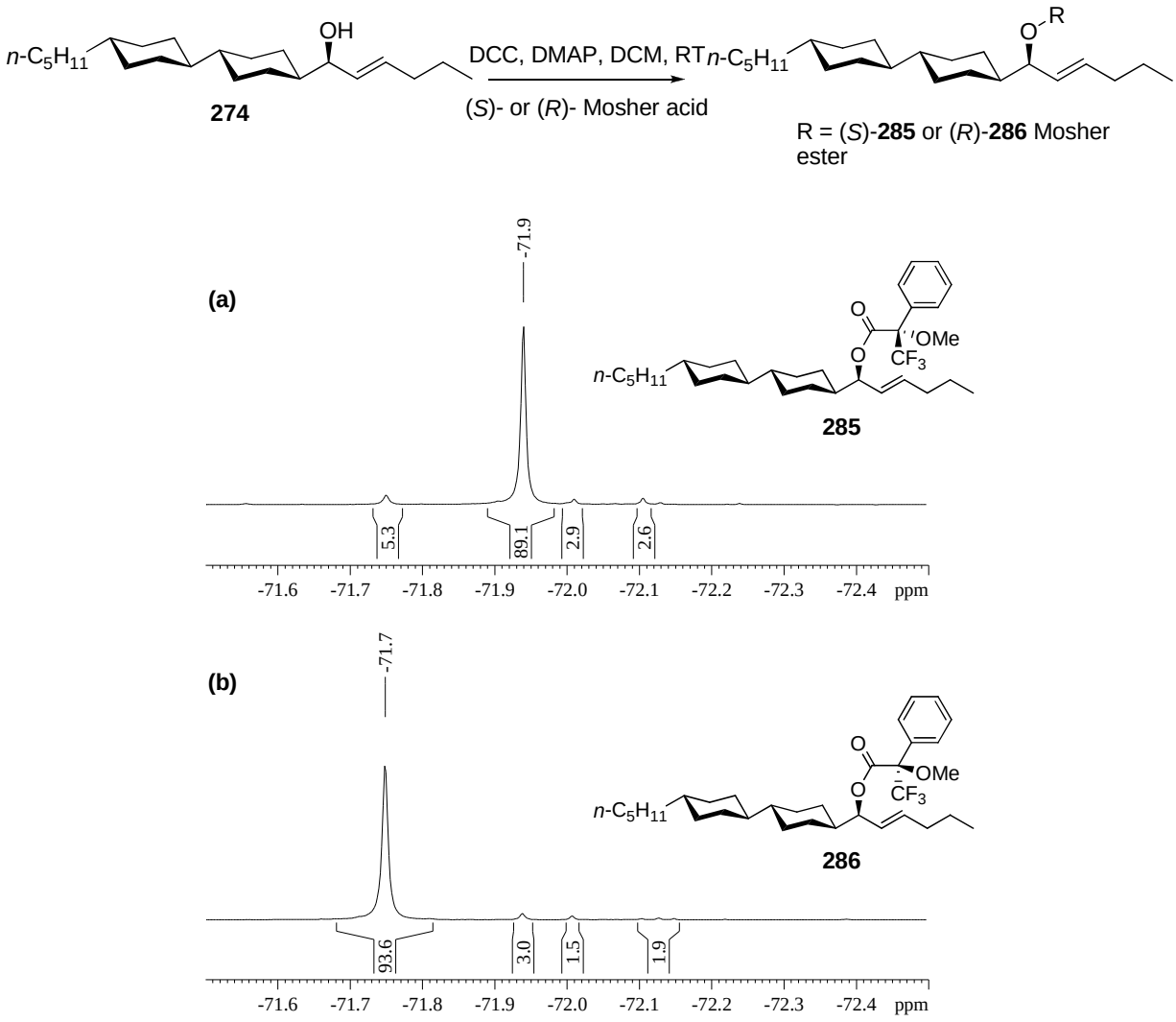


Figure 3. 1 : ^{19}F{^{1}H}-NMR spectra after: (a) reaction with (*S*)-Mosher acid. (b) reaction with (*R*)-Mosher acid.

3.2.3) Fluorination attempts of the *threo*- and *erythro*- epoxy-alcohols:

With the epoxy-alcohols **275a** and **275b** in hand, the fluorination steps were then explored. Accordingly, **275b** was subjected to a deshydroxyfluorination with Deoxo-Fluor® at 40 °C (Figure 3.2). This reaction showed an unexpected cationic character as it appeared to be poorly stereoselective. The supposed fluoro-epoxide **287** was obtained as a major diastereoisomer (^{19}F-NMR -191 ppm) but in a 7:1 ratio. The ^{19}F-NMR signal of the minor diastereoisomer is showed at -198 ppm. Another by-product **289** was also observed (broad signal at -159 ppm) which could not be separated from **287** by silica gel chromatography (For the structure of **289**, see Scheme 3.12). The NMR spectrum showed in Figure 3.2 was recorded after purification over silica gel.

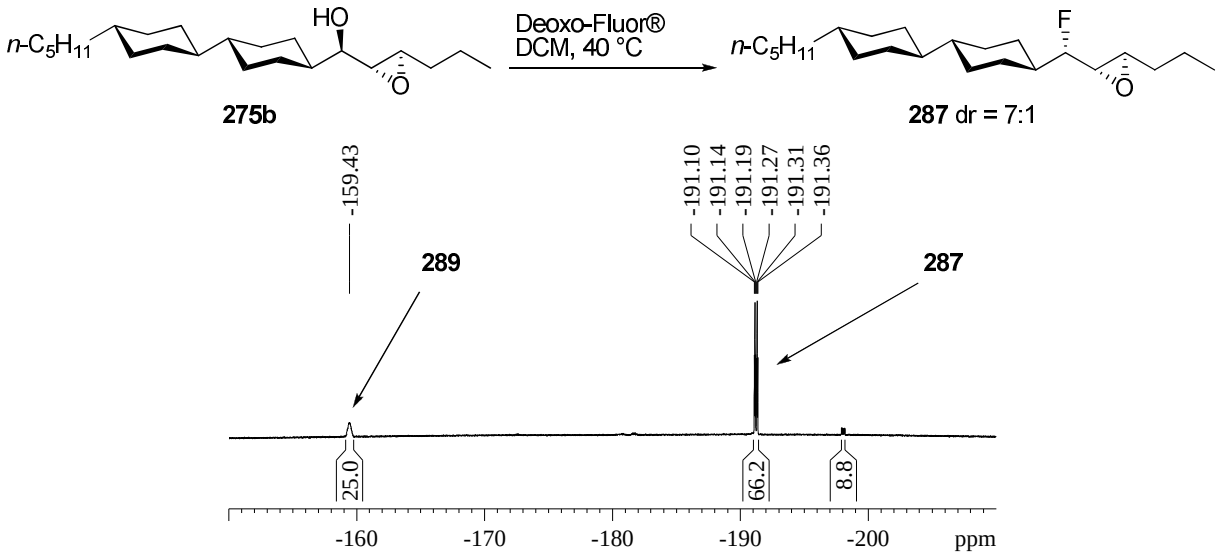


Figure 3. 2 : ^{19}F-NMR spectrum of product mix.

When the other stereoisomer **275a** was treated with Deoxo-Fluor®, the resultant fluoro-epoxide **288** was obtained as a mixture of diastereoisomers in a 2:1 ratio (^{19}F-NMR -191 and

-198 ppm). The ^{19}F-NMR spectrum is shown in Figure 3.3. The undetermined by-product **289** (^{19}F-NMR -159 ppm) was still present, but this time as a major product. Traces of another by-product were also observed (^{19}F-NMR -176.9 ppm). This could be the result of a fluoro-epoxide rearrangement into an aldehyde, ^{1}H-NMR spectrum showed traces of an aldehyde (9.75 ppm). These compounds could not be separated by chromatography (the NMR spectrum showed in Figure 3.3 was recorded after purification attempt). Deshydroxyfluorination was also attempted at low temperature (-78 °C) to explore a possible influence of the temperature on the outcome of the reaction. Unfortunately, despite the reaction being slower at -78 °C, no significant improvements were noticed in either diastereoisomeric ratio of **287** and **288**, nor the ratio between the fluoro-epoxides and by-products **289**.

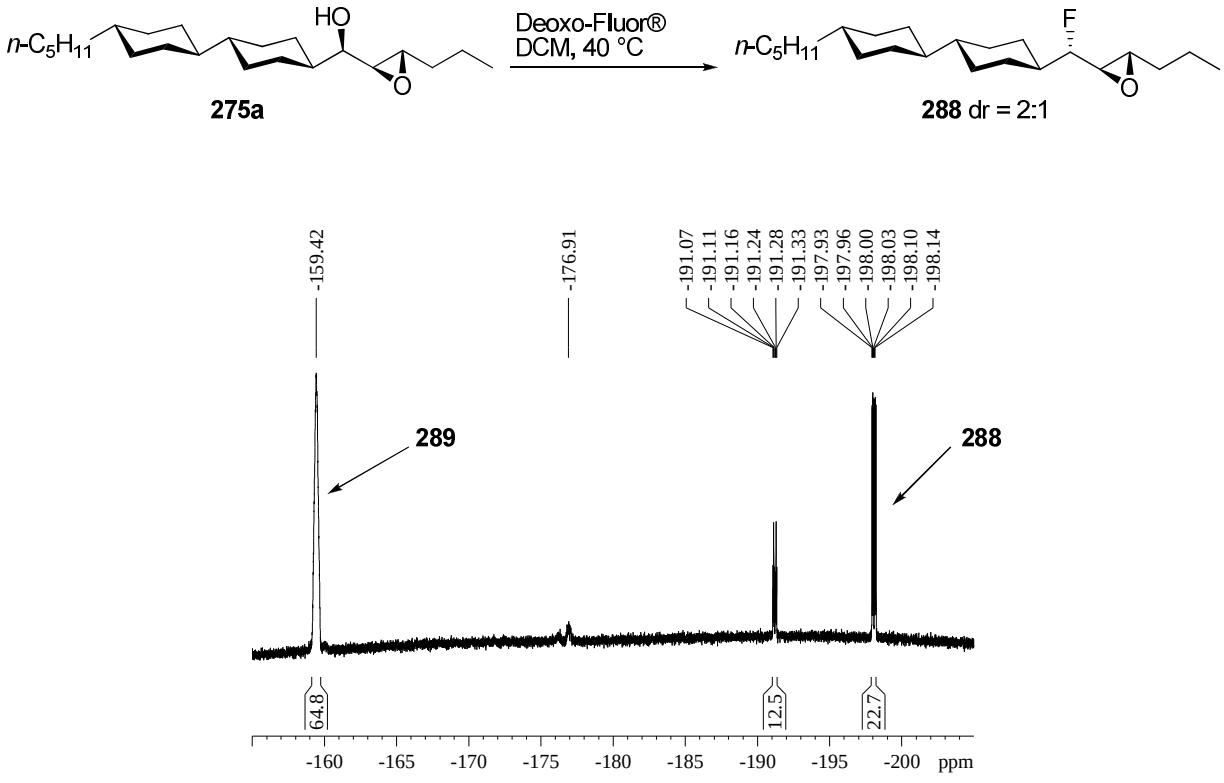
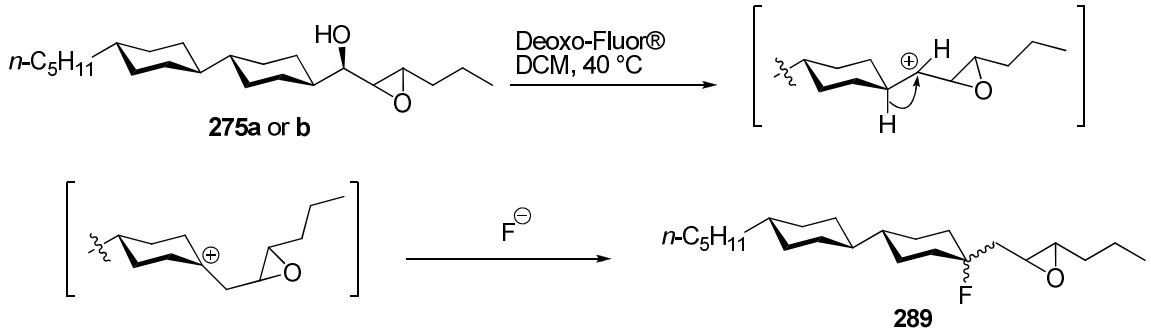


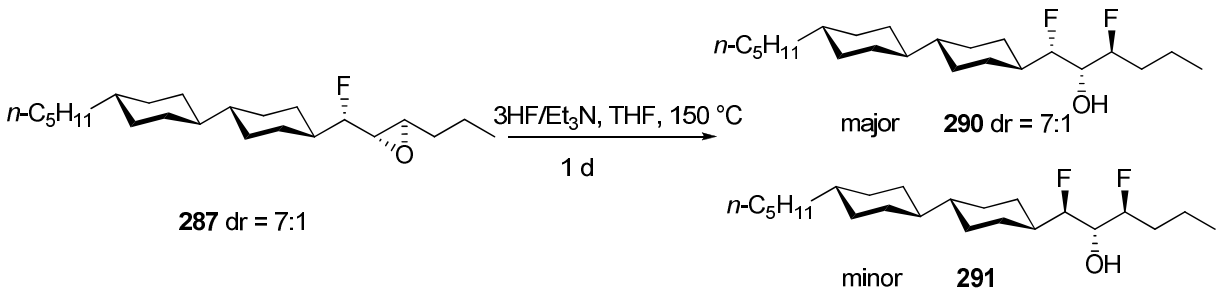
Figure 3. 3 : Putative quaternary fluorine product indicated in the ^{19}F-NMR spectrum at -159.4 ppm.

The chemical shift of this broad signal in the quaternary C-F region of the ^{19}F-NMR spectrum, reinforced by the absence of a dominant product with a $^{2}J_{F\text{-}H}$ coupling in the ^{1}H-NMR spectrum, suggested that this major product **289** had fluorine bound to a quaternary carbon. This may be the result of a rearrangement after formation of a carbocation, followed by migration of an hydrogen atom, as illustrated in Scheme 3.12.



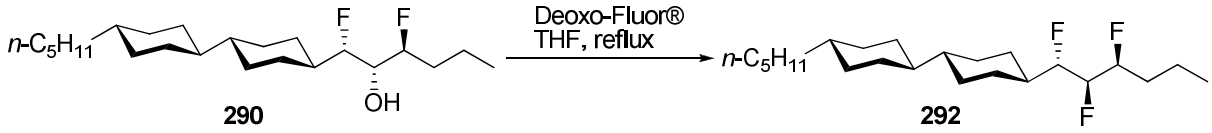
Scheme 3. 12 : Possible rearrangement of **275a** or **275b** to **289**.

Fluoro-epoxide **287**, as a mixture of stereoisomers (dr = 7:1), was then subjected to epoxide ring opening with 3HF/Et_3N. The reaction with 3HF/Et_3N can require high temperatures, sometimes higher than the boiling points of the usual solvents. It has been noticed in our laboratory that HF reactions requiring high temperature conditions can be carried out in a sealed bomb with a Teflon inner layer without any loss of solvent, even over several days. Such conditions were used for the reaction of fluoro-epoxide **287** with 3HF/Et_3N in THF at 150 °C. The reaction was carried out on a 7:1 mixture of stereoisomers and analysis of the ^{19}F-NMR of the crude reaction showed the presence of two difluoro compounds **290** and **291** in the same ratio (7:1). Separation of **290** from **291** by chromatography was not easy. A small pure fraction of **290** was isolated but in a disappointing 12% over two steps.



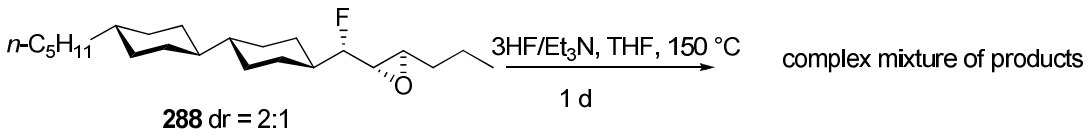
Scheme 3. 13 : Epoxide ring opening of **287** with 3HF/Et_3N.

The insertion of the third fluorine proved to be more problematic than expected. When difluoroalcohol **290** was treated with Deoxo-Fluor® in refluxing DCM, TLC analysis supported by ^{19}F-NMR of the reaction mixture, showed only a poor conversion. Therefore the reaction was carried out in refluxing THF. After one day ^{19}F-NMR of the crude products showed the presence of **290** with a new trifluoro compound in a ~ 1:1 ratio. Unfortunately a significant number of elimination by-products were also observed. Attempts to obtain a pure fraction of trifluoro alkane **292** by silica gel chromatography, failed.



Scheme 3. 14 : Attempt at the deshydroxyfluorination of **290**.

Epoxide ring opening was also attempted on fluoroepoxide **288**, using 3HF/Et_3N/THF. Fluoroepoxide **288** was used as a 2:1 mixture of diastereoisomers, but this made the crude product mixture difficult to analyse by ^{19}F-NMR as several difluoro compounds were present. It was not possible to obtain a clean fraction of these products by chromatography.



Scheme 3. 15 : Epoxide ring opening of **288** with 3HF/Et_3N.

It is probable that some of the isomers shown in Figure 3.4 were formed, however they were not appropriately characterised.

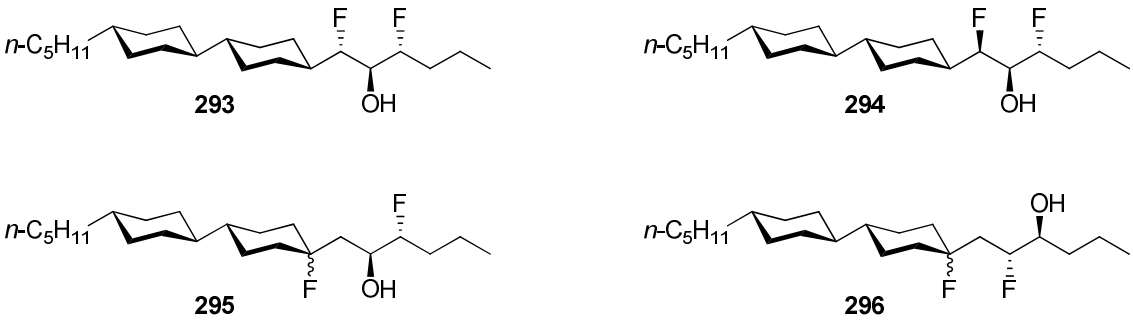


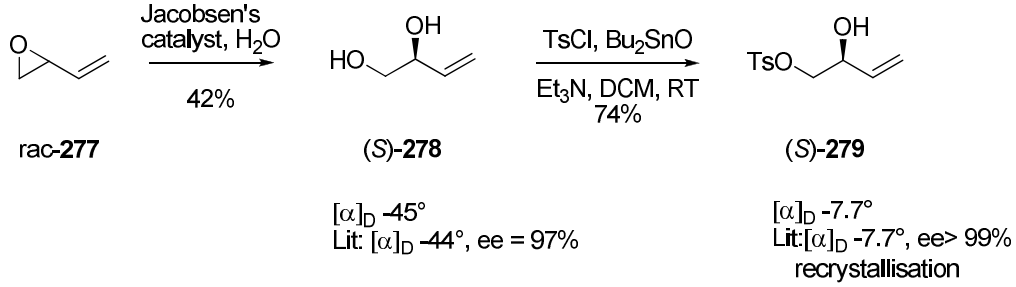
Figure 3. 4 : Possible by-products in the epoxide ring opening of **288** with 3HF/Et_3N.

In order to take a different approach, the preparation of vicinal trifluoro motifs by a cross metathesis / epoxidation / fluorination strategy was then explored.

3.3) Preparation of vicinal trifluoro motifs by cross metathesis / epoxidation:

3.3.1) Formation of erythro- epoxy-alcohols:

Allylic alcohol **279** emerged as an attractive starting material. Compound **279** is commercially available, and can be purchased from Sigma-Aldrich. However, due to its cost (160£/g), it was prepared in the lab by the route shown in Scheme 3.16. Diol **278** was obtained in 42% yield after a hydrolytic resolution of butene dioxide following the procedure of Jacobsen with a colbat-Salen catalyst [13]. The enantiomeric excess of diol **278** was estimated to be 97% by comparison of the optical rotation of diol **278** in the literature [13]. Diol **278** was then reacted with tosyl chloride in the presence of Et_3N, and a catalytic amount of dibutyl tin oxide following the procedure of Marinelli and co-workers [15] to give tosyl alcohol **279** in 74% yield. The reaction was completely regioselective, and showed no signs of tosylation of the secondary alcohol. Regioselective tosylation was also attempted with TsCl and collidine, in the absence of a catalyst, but under these conditions the reaction was sluggish and led to allylic alcohol **279**, but in lower yield (66%). After recrystallisation from toluene, the optical rotation of **279** was recorded ($[\alpha]_D$ -7.7°), and its value proved to be identical to the commercial product **279** [16].



Scheme 3. 16 : Preparation of **279** by hydrolytic resolution of **277** followed by regioselective tosylation.

Allylic alcohol **279** was then explored in cross metathesis reactions. Reactions were performed using 2-3 mol% of Grubbs' second generation catalyst in refluxing DCM and with an excess of alkene (5 eq), to favour the cross metathesis reaction. As shown in Figure 3.5, allylic alcohol **279** was reacted either with hexene or allyl benzene to form allylic alcohols **297** and **298**. The products were obtained in good yields (81% and 80% respectively), and as a mixture of (*E*)- and (*Z*)- diastereoisomers. The (*E*)- and (*Z*)- ratio for **297** and **298**, was determined by analysis of the ^{1}H-NMR. It was not possible to separate (*E*)- and (*Z*)-diastereoisomers by chromatography at that stage, however they could be separated after the subsequent epoxidation step.

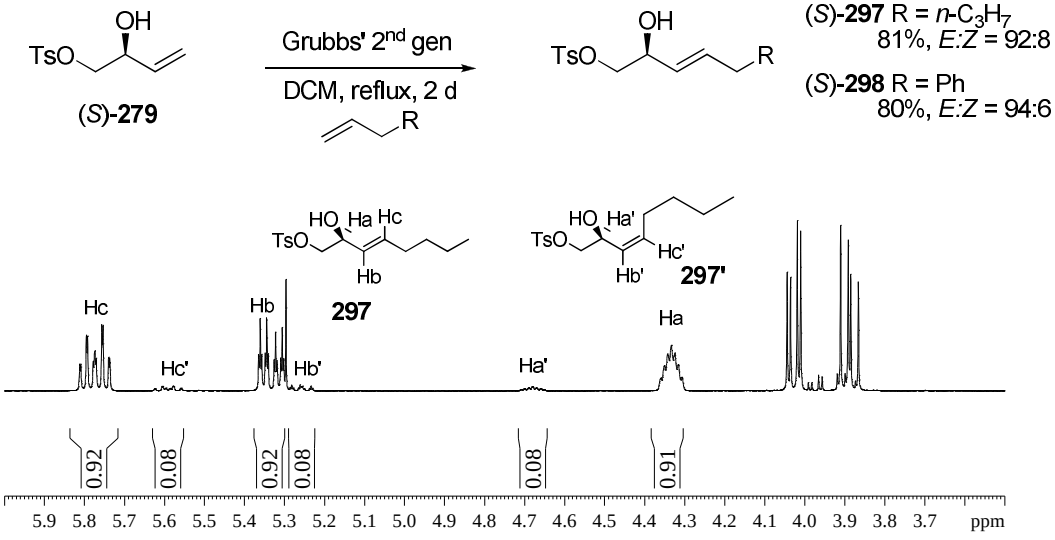
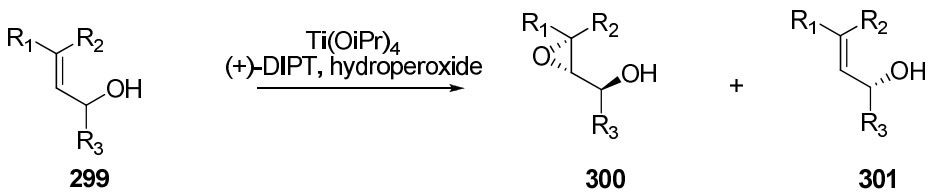


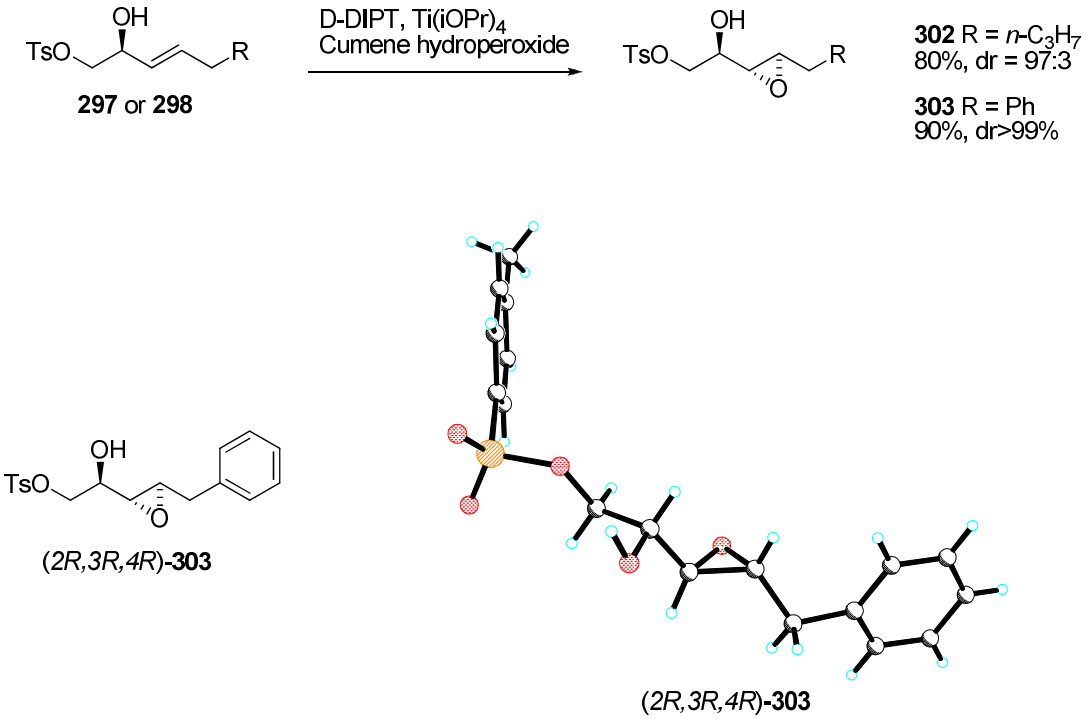
Figure 3. 5 : ^{1}H-NMR spectrum of **297** showing the presence of (*E*)-isomer **297** (92%) and (*Z*)-isomer **297'** (8%).

Compound **297** and **298** were then subjected to epoxidation following Sharpless' classical methodology. Sharpless asymmetric epoxidation is usually applied to the kinetic resolution of prochiral allylic alcohols such as **299** (Scheme 3.17). Despite the enduring success of this method for preparing enantio-enriched epoxy-alcohols **300** and allylic alcohols **301**, some significant limitations remain. For instance, if the desired product is the epoxy-alcohol **300**, the kinetic resolution must be quenched at low conversion to ensure a product with a high ee. Alternatively the resolved allylic alcohol **301** is often isolated and epoxidised in a separate step. In addition the maximum yield of a kinetic resolution cannot exceed 50%. In our study, as substrates **297** and **298** are enantio-enriched, and then a kinetic resolution is not necessary, therefore yields were expected to be higher than 50% and with good ee's.



Scheme 3. 17 : Sharpless asymmetric kinetic resolution of an allylic alcohol **299**.

Accordingly **297** and **298** were reacted with $Ti(iOPr)_4$ and D-DIPT to favour the formation of the *erytho*-epoxy-alcohol. In the case of **297**, epoxide **302** was obtained in 80% yield and in 97:3 dr (^{1}H-NMR analysis showed the presence of 3% of another diastereoisomer). In the case of allylic alcohol **298,** the resulting epoxide **303** was present as the only one diastereoisomer as deduced by ^{1}H-NMR. Epoxide **303** was recrystallised from diethyl ether to afford crystals suitable for X-ray analysis. Subsequent structure analysis demonstrated that the relative and absolute configuration of epoxy-alcohol **303** is (2*R*,3*R*,4*R*), and is therefore the 3,4-*erythro*-isomer.

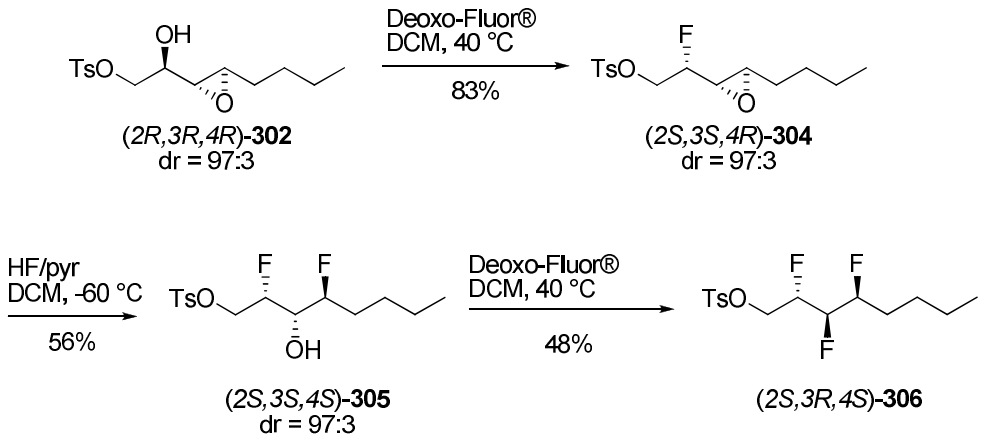


Scheme 3. 18 : Epoxidation of **297** and **298** and crystal structure of **303**.

3.3.2) Fluorination of the *erythro*- epoxy-alcohols 302 and 303:

Epoxides **302** and **303** were then explored in deshydroxyfluorination reactions with Deoxo-Fluor®. Epoxy-alcohol **302** reacted smoothly with Deoxo-Fluor® at 40 °C (Scheme 3.19). After one hour, TLC analysis showed a complete a conversion of the starting material. Purification over silica gave (*2S,3S,4R*)-**304** in 83% yield, and with a 97:3 diastereoisomeric ratio as determined by ^{19}F-NMR. Epoxide ring opening of **304** was then attempted with HF/pyridine and this step proved to be both regio- and stereo-selective. When the reaction was carried out at 0 °C the resultant difluoro **305** was obtained in 36% yield, whereas the yield was improved to 47% at -35 °C and 56% at -60°C. Epoxide ring opening was stereoselective, and the (2*S*,3*S*,4*S*)-difluoro alcohol **305** was obtained in a 97:3 ratio. The third and final fluorine atom was then inserted by a deshydroxyfluorination reaction with Deoxo-

Fluor® using our standard conditions (DCM, 40 °C). After one hour, TLC analysis showed complete conversion of the starting material, and the desired (*2S,3R,4S*)-**306** was obtained after purification over silica in a moderate 48% yield.



Scheme 3. 19 : Fluorination steps towards **306**.

The ^{19}F-NMR of the product **306** prior to purification shown in Figure 3.6, shows traces of elimination derived side products, but not in a significant enough amount to explain the moderate yield. The conversion to products looks good but it may be that **306** is volatile, and that there were some losses during work up. It was not easy to accurately estimate the diastereoisomeric ratio of **306**. Figure 3.6 shows the ^{19}F{^{1}H}-NMR spectrum to the three fluorine signals at -190, -201 and -214 ppm, some elimination products were present, but it was difficult to identify any signals of a second trifluoro vicinal diastereoisomer.

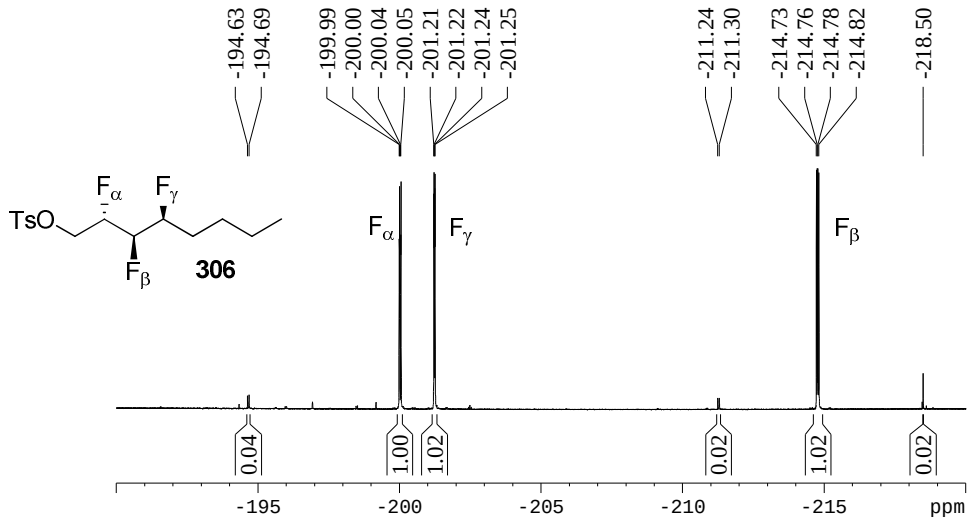
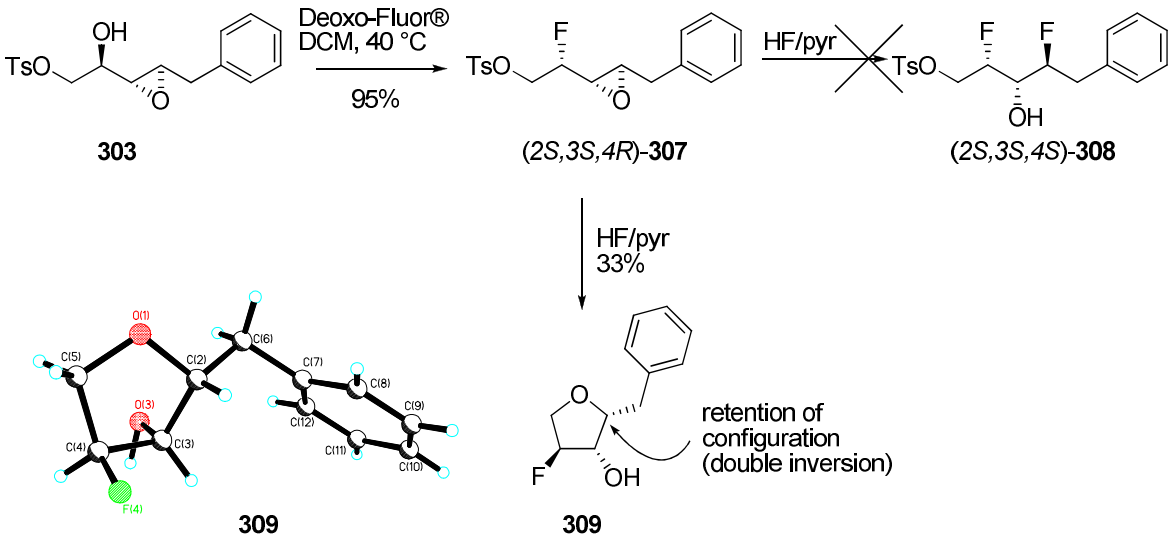


Figure 3. 6 : $^{19}F\{^{1}H\}$-NMR spectrum of **306**.

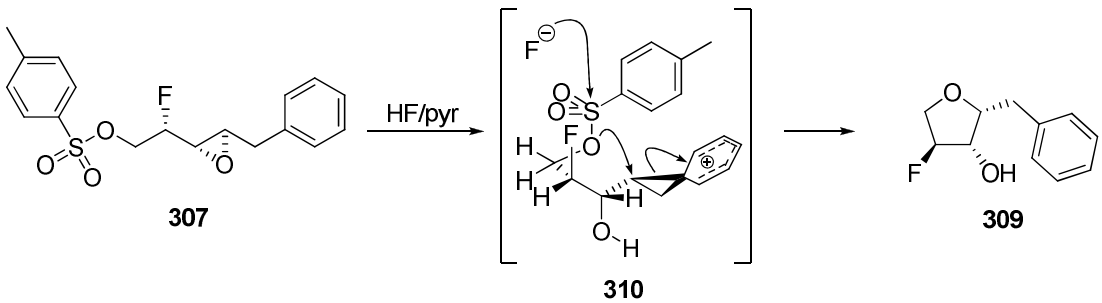
A direct route to the vicinal trifluoro motif was achieved. Fluorination of the *erythro*- epoxy-alcohol **302** in three steps proved straightforward and was accomplished in 21% yield, over the three steps. Unfortunately product **306** was not crystalline, and it was then not possible to obtain a crystal structure.

Fluorination of epoxy-alcohol **303** was now investigated. Reaction of **303** with Deoxo-Fluor® proceeded smoothly resulting in the (*2S,3S,4R*) fluoro epoxide **307** in a very good yield (95%) (Scheme 3.20). Analysis of ^{1}H- and ^{19}F-NMR spectra indicated a single stereoisomer. With fluoro-epoxide **307** in hand, introduction of the second fluorine was then investigated. Accordingly, when **307** was treated with HF/pyridine, there was no evidence that difluoro compound **308** was formed. Frustratingly, the fluoro cyclic ether **309** was isolated in 33%. This furan was crystalline and its relative and absolute configuration was established by X-ray analysis as shown in Figure 3.20.



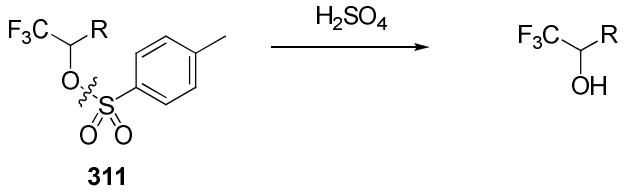
Scheme 3. 20 : Deshydoxyfluorination of **303** and formation of furan **309**.

This side reaction was surprising not only because there were no traces of the analogous cyclisation product during treatment of **304** with HF/pyridine, but also because formation of compound **309** occurred with a retention of configuration at the C4 position. An explanation for this stereochemical outcome is proposed in Scheme 3.21. In acidic media, the epoxide could perhaps be opened with the assistance of the phenyl ring, to form a bicyclic phenoxonium intermediate **310**. Then, substitution by fluoride ion on the sulfur of the tosylate would result in activation of the adjacent oxygen followed by a 5-*exo* cyclisation.



Scheme 3. 21 : Proposed mechanism for the formation of **309**.

Such a reaction would be triggered by fluoride cleavage of the tosyl ester. An unusual fluoride mediated cleavage has been reported in the literature [17] during the hydrolysis of compound **311** with concentrated sulfuric acid (Scheme 3.22). The electron withdrawing influence of the CF_3 group at the α position, clearly influences the cleavage of the S-O bond over C-O bond.

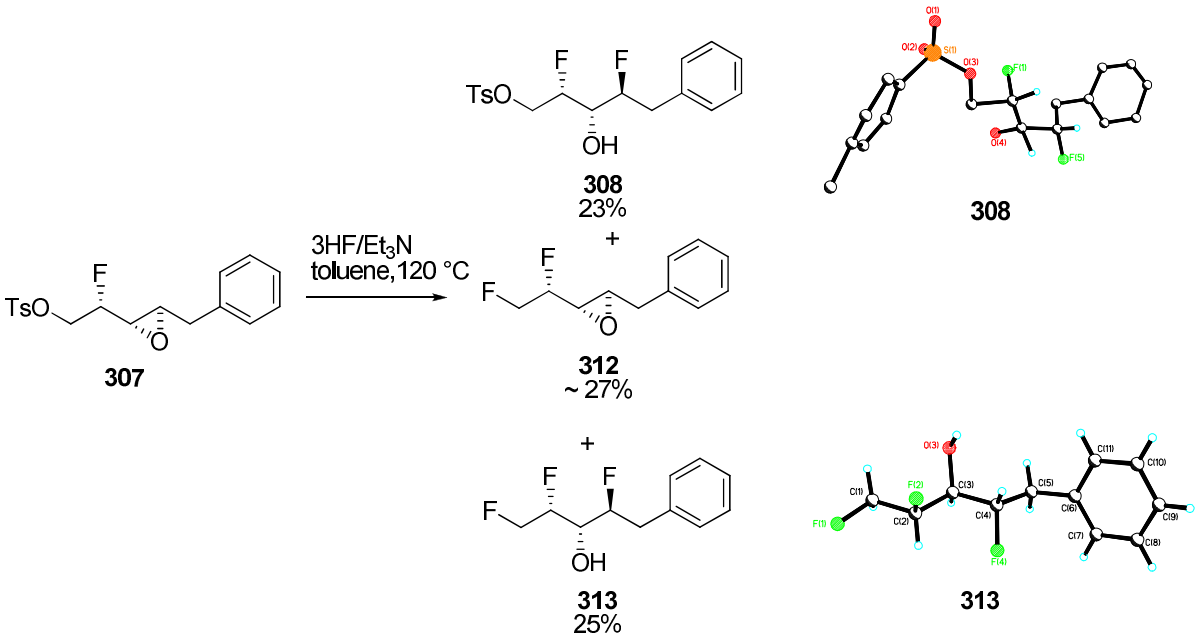


311

Scheme 3. 22 : Example of cleavage of a tosyl group α to a CF_3 group, by sulfuric acid.

In the case of the formation of furan **309**, the role of pyridine is not clear because when **307** was treated with 3HF/Et_3N instead of HF/pyridine, cyclisation did not occur. Perhaps pyridine could stabilise the phenoxonium intermediate by a π-stacking interaction.

Epoxide ring opening of compound **307** with 3HF/Et_3N in toluene at 120 °C resulted in the formation of three new fluorinated products testifying to a competition between epoxide ring opening and nucleophilic substitution by fluoride ion of the tosylate.



Scheme 3. 23 : Treatment of **307** with 3HF/Et_3N.

This reaction was explored more fully. Compounds **308** and **313** were isolated in 23 % and 25% yields respectively, and their stereochemistries were established by X-ray structure analysis. The X-ray derived structure of **308** not only shows that ring opening occurred in a regio- and stereo- selective manner with inversion of configuration, but also that the deshydroxyfluorination of the previous step had occurred stereospecifically, and also with an inversion of configuration. It is noticeable that **308** did not recrystallise nicely, and therefore several recystallisation attempts of **308** were attempted. Each of the crystal structures obtained confirmed a (*2S,3S,4S*)- configuration for **308**, and two different preferred conformations were observed in the solid state (Figure 3.7). Surprisingly, the structure **308 A** shows the two 1,3 fluorine atoms pointing in opposite directions whereas structure **308 B** shows, somewhat unexpectedly the two fluorine atoms in the same plane.

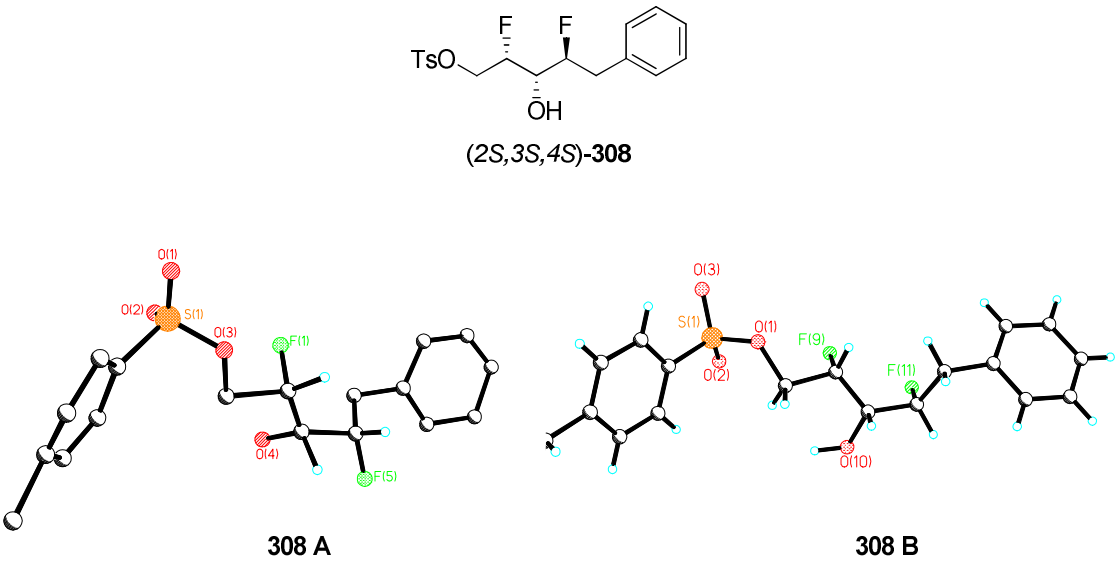


Figure 3. 7 : Different X-ray structures of **308 A** and **308 B**.

Influences of temperature and solvent were investigated in the epoxide ring opening of **307**, and the results are summarised in Table 3.3. Reactions were carried out on a 10 mg scale, with 10 equivalents of 3HF/Et_3N (~30 eq of HF), and the ratio of products was evaluated by $^{19}F\{^{1}H\}$-NMR analysis of the product mixture. First toluene was replaced for THF to promote a less "naked" fluoride ion to decrease the nucleophilic preference for the tosylate. At 70 °C no reaction occurred whereas at 100 °C a 35% conversion to difluoro alcohol **308** and 5% to **312** were observed. Poorer conversions were obtained when acetonitrile or dioxane was used at 100 °C. Temperature is clearly a factor in the conversion and the regioselectivity of the epoxide ring opening. This can be seen when dioxane was used at 120 °C, as all three products were formed. DCM afforded good regioselectivity, but the reaction was slow. Taking all of the conditions that were explored, it appears that the best conversion and selectivity was obtained using chloroform.

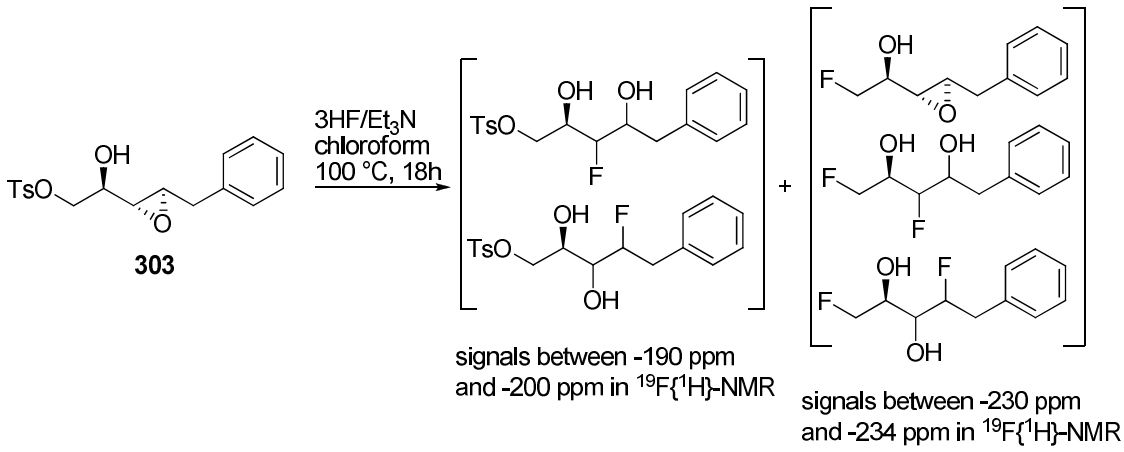
solvent	temperature	conversion	**308**	**312**	**313**
THF	70 °C, 12h	No reaction	-	-	-
THF	100 °C, 18h	40%	35%	5%	-
MeCN	100 °C, 12h	22%	18%	4%	-
Dioxane	100 °C, 12h	27%	22%	5%	-
Dioxane	120 °C, 12h	72%	39%	16%	17%
DCM	100 °C, 12h	31%	27%	4%	-
Chloroform	100 °C, 18h	65%	56%	2%	4%

Table 3. 3 : Conditions explored for the reaction of epoxide **307** with $3HF.Et_3N$.

Epoxide ring opening of **307** in chloroform was attempted on a larger scale, and it proved to be slow as it required three days at 100 °C to reach a 60% conversion. Although this reaction was regioselective with a very large excess of $3HF/Et_3N$, it was not possible to force it to completion, even with extended reaction times.

To make a comparison, epoxide ring opening was also carried out with epoxy-alcohol **303**, under the same conditions ($3HF.Et_3N$, chloroform, 100 °C) and the ratio between products was evaluated by analysis of the $^{19}F\{^1H\}$-NMR spectrum of the product mixture (Scheme 3.24). The reaction of $3HF/Et_3N$ on the epoxy alcohol **303** proved to be less regio- and stereo-selective than with the fluoro-epoxide **307**, as many signals were observed by $^{19}F\{^1H\}$-NMR. Considering the number of fluorinated products it looked like a non-regioselective epoxide ring opening was occuring, and in a non-stereoselective manner. Integration of signals between -190 ppm and -200 ppm, and those between -230 ppm and -235 ppm give some indication of the ratio between ring opening and substitution of the tosyl group. Surprisingly this ratio appeared to be roughly 1:1, indicating a strong electronic effect of the fluorine in compound **307**. By strengthening the adjacent bonds, fluorine makes it more difficult relative

to OH, to open the ring at the α position and also to displace the tosyl group in α', and therefore favouring epoxide ring opening at the β position.



Scheme 3. 24 : Epoxide ring opening of **303** with 3HF.Et_3N.

The difluoro alcohol **308** was then treated with Deoxo-Fluor® under our standard conditions (Figure 3.8). Alcohol **308** reacted smoothly towards deshydroxyfluorination and after 1 hour TLC analysis showed a complete conversion to trifluoroalkane **314**. After purification over silica gel, trifluoro product (*2S,3R,4S*)-**314** was isolated in 78% yield.

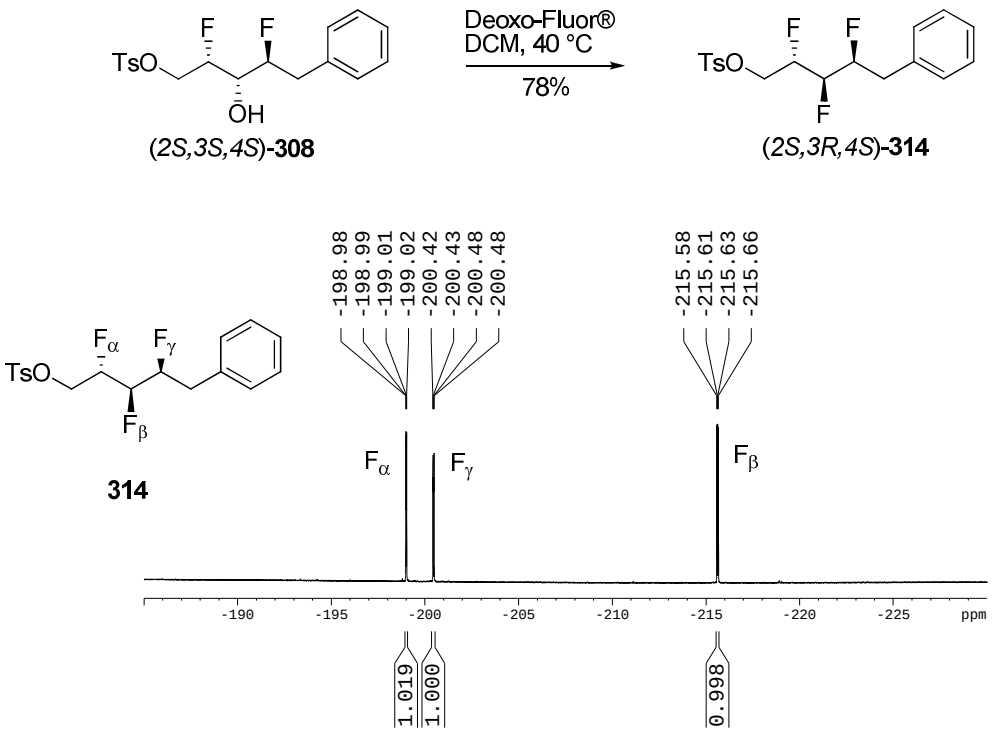


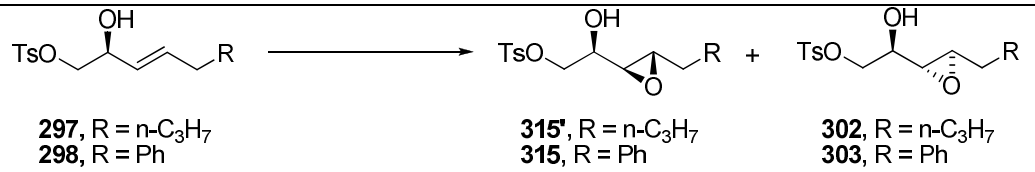
Figure 3. 8 : $^{19}F\{^{1}H\}$-NMR spectrum of **314**.

Fluorination of the epoxy-alcohol **303** in three steps proved relatively straightforward, and was achieved in an overall yield of 43%. Similar to **306**, **314** was not a crystalline compound and it was then not possible to obtain a crystal structure to explore the relative orientations of the C-F bonds.

3.3.3) Preparation of *threo*- epoxy-alcohols:

Having successfully generated the trifluoro motif from the *erythro*-epoxy-alcohol, the *threo*-epoxy-alcohol was now considered. This should generate the all-*syn* diastereoisomer of a trifluoro motif. The epoxidation of allylic alcohols **297** and **298** was first attempted under Sharpless' conditions with L-diisopropyl tartrate to favour formation of the *threo* isomer (Table 3.4). These reactions showed surprisingly poor stereoselectivity and the resultant

epoxy-alcohols were obtained in only moderate yields. The diastereoisomeric ratios are summarised in Table 3.4. Epoxidation reaction were also carried out with *m*-CPBA and $Ti(OiPr)_4$ in the absence of tartrate.



297, R = n-C_3H_7
298, R = Ph

315', R = n-C_3H_7
315, R = Ph

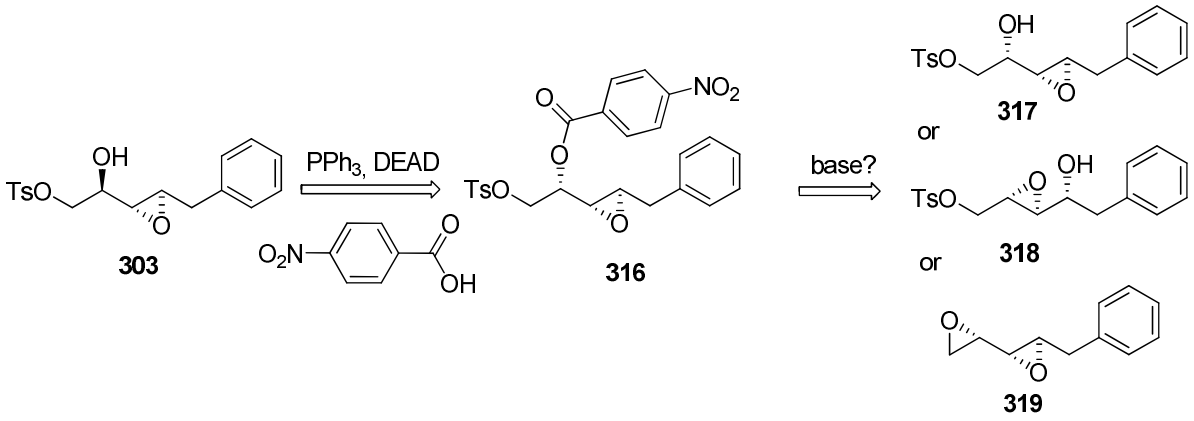
302, R = n-C_3H_7
303, R = Ph

R	Conditions	*threo* : *erythro*
n-C_3H_7	$Ti(OiPr)_4$, L-DIPT, CHP, DCM, -35°C, 55%	76 : 24
Ph	$Ti(OiPr)_4$, L-DIPT, CHP, DCM, -35°C, 61%	68 : 32
n-C_3H_7	*m*-CPBA, DCM, 0 °C	67 : 33
n-C_3H_7	*m*-CPBA, DCM, -30 °C	68 : 32
Ph	*m*-CPBA, DCM, 0 °C, 59%	57 : 43
n-C_3H_7	$Ti(OiPr)_4$, CHP, DCM, -35°C	62 : 38
Ph	$Ti(OiPr)_4$, TBHP, DCM, -35°C, 79%	52 : 48

Table 3. 4: Different condition tested in the epoxidation of **297** and **298**.

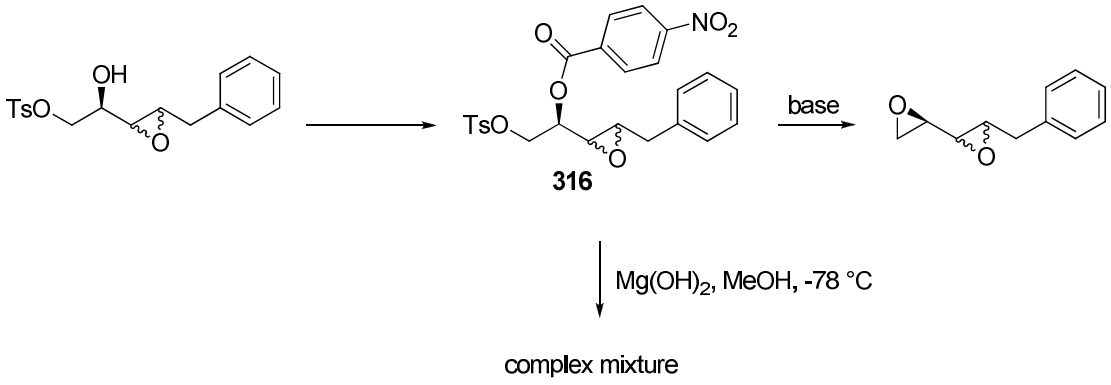
The lack of selectivity during the formation of the *threo* epoxy-alcohol was problematic, because it was impossible to separate the two diastereoisomers by chromatography. In an effort to obtain a clean *threo* epoxy-alcohol an approach was investigated including an inversion of configuration at the C-OH stereogenic centre of an *erythro* isomer. This involved a Mitsunobu inversion reaction (Scheme 3.25). Under standard conditions, The Mitsunobu reaction results in the formation of an ester such as **316** [18]. But a potential problem emerges with the hydrolysis of such an ester. Clearly, treatment of ester **316** with a base could result in

either loss of the tosyl group by formation of an epoxide **318**, or formation of a regioisomer epoxy-alcohol **319** by Payne rearrangement.



Scheme 3. 25 : Possible formation of a *threo*-epoxy-alcohol **317** by Mitsunobu reaction of **307**.

None-the-less ester **316** was prepared by reaction of epoxy-alcohol **303** (~7:3 dr), with *p*-nitrobenzoyl chloride in DCM and in the presence of Et_3N (Scheme 3.26). The two diastereoisomers of **316** could not be separated by chromatography. Hydrolysis of the *p*-nitrobenzyl ester was attempted with sodium carbonate in a mix of DCM and methanol at 0 °C, but this resulted in the immediate loss of the tosylate group by an intramolecular substitution, as indicated by ^{1}H-NMR analysis of the crude product mixture. Hydrolysis of the ester was also attempted by treatment with magnesium methoxide as this reagent is known to be selective for deprotection of *p*-nitrobenzyl esters, even in presence of esters (acetate, benzoate, pivaloate) [19,20]. It is notable that tosyl esters can also be deprotected by magnesium methoxide [21], thus we treated ester **316** with magnesium methoxide at -78 °C but this resulted in a complex mixture of products which proved difficult to analyse (Scheme 3.26).



Scheme 3. 26 : Attempts at the hydrolysis of ester **316**.

It was eventually noticed that the *threo* isomer of epoxy-alcohol **315** crystallised faster than *erythro* isomer **303**, from diethyl ether. To exploit this, a purification of the *threo* isomer by recrystallisation was attempted, starting from a ~1:1 mixture of isomers **315** and **303**. This ratio was evaluated by integration of the protons α to the tosyl groups in the ^{1}H-NMR spectra (Figure 3.9). First recrystallisation afforded the *threo* isomer **315** in a ~ 2:1 ratio, which was improved to a ~12:1 ratio through four successive recrystallisations. This ratio was satisfactory in order to attempt the subsequent fluorination step, but it resulted in a significant loss in material as only 21 mg of the *threo* **315** were obtained with a 12:1 dr, starting from more than 700 mg of 1:1 dr mixture.

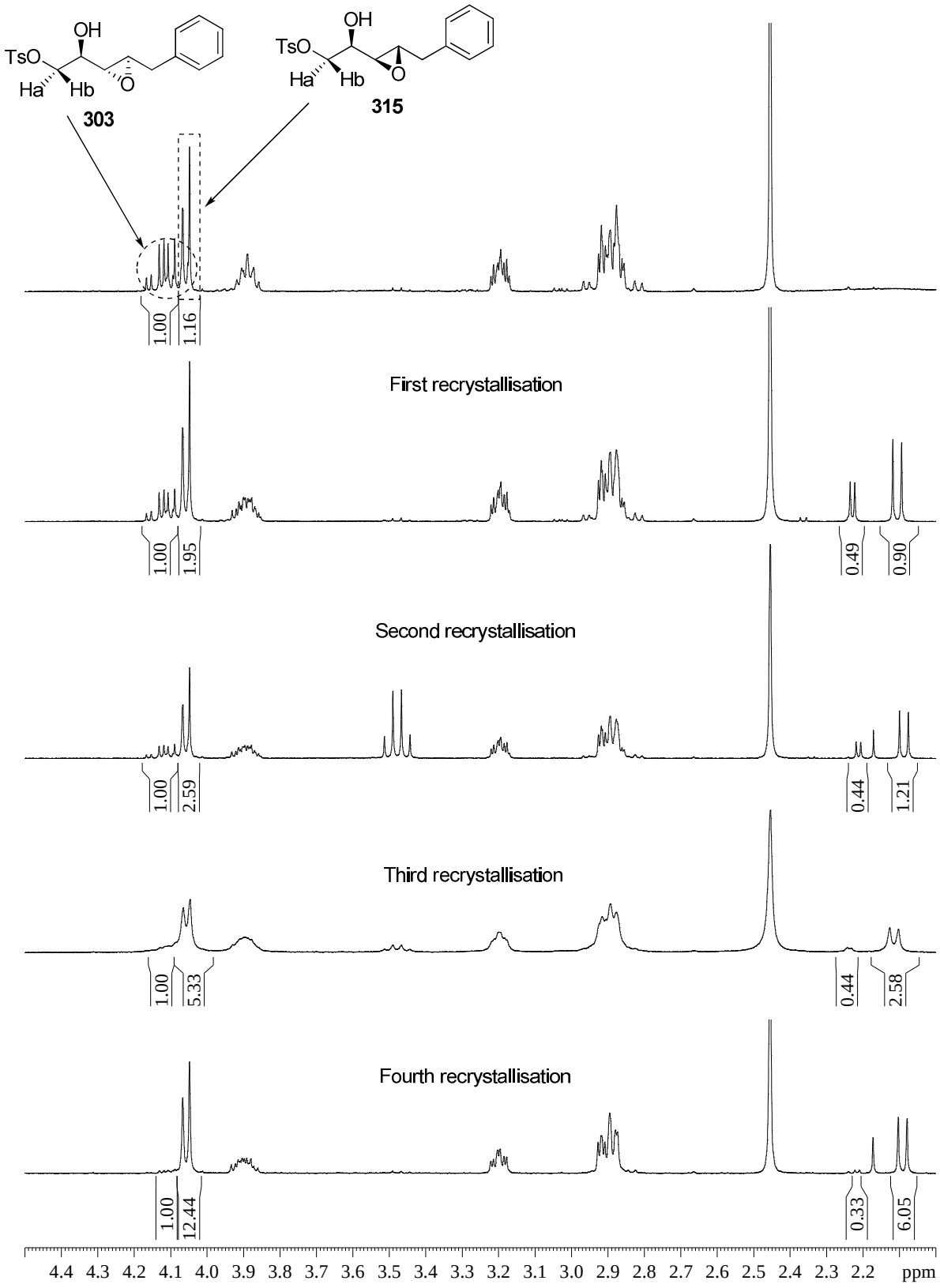


Figure 3. 9 : ^{1}H-NMR spectra of the consecutives crystallisations of *threo* epoxy-alcohol **315**.

Crystals of *threo* epoxy-alcohol **315** were then subjected to X-ray structure analysis, and the (*2R,3S,4S*)- configuration of **315** was confirmed. The structure is shown in Figure 3.10.

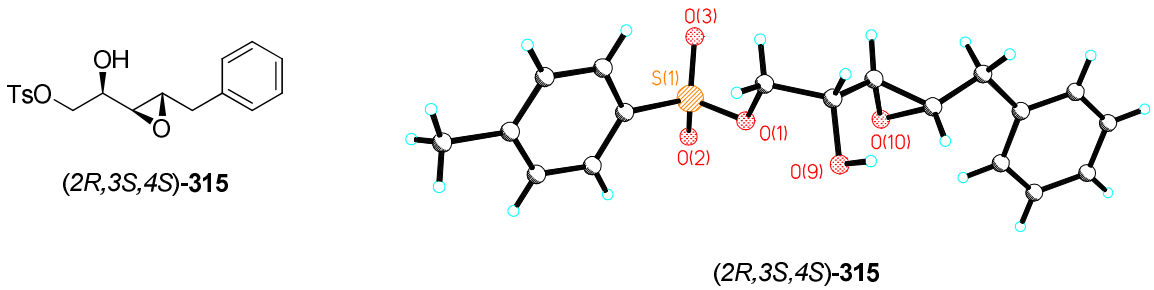


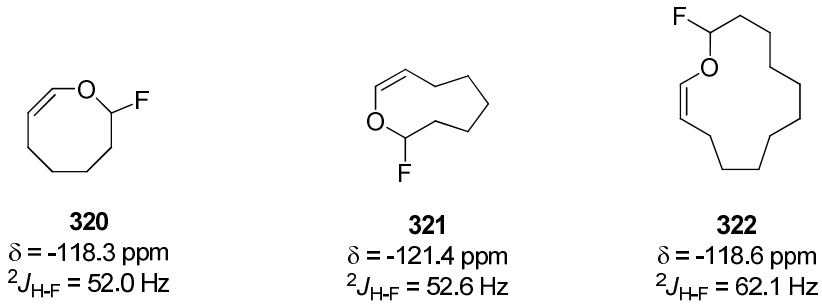
Figure 3. 10 : Crystal structure of **315**.

Unfortunately, ^{1}H-NMR analysis of the product over time showed a degradation of epoxy-alcohol **315**, before fluorination reactions could be attempted. This instability of the *threo* isomer at room temperature over a few days contrasts greatly with the stability of the *erythro* isomer which did not show any signs of degradation even after several months stored at RT with no particular precautions taken.

3.3.4) Formation of an all-*syn* vicinal trifluoro motif:

In the view of the lack of stability of the epoxy-alcohol **315**, it was decided to carry out a deshydroxyfluorinaton reaction on a mixture of both *threo*-**315** and *erythro*-**303** diastereoisomers. Grée and co-workers had shown that the *threo* epoxy-alcohols are more prone to rearrangement [5], but treatment of *erythro* epoxy-alcohol **303** with Deoxo-Fluor® resulted in a highly stereoselective and efficient (95% yield) formation to fluoro-epoxide **307**. Therefore it was anticipated that any formation of by-products might result only from the *threo* stereoisomer with an efficient conversion of the *erythro*. The fluoroethers such as **320**-

322 (Figure 3.11) characterised by Grée showed characteristic chemical shifts in the ^{19}F-NMR spectrum around -120 ppm, and also characteristic H-F coupling constants ($^{2}J_{H\text{-}F}$ ~50-60 Hz). Thus, these compounds should be easily visible when analysing the ^{19}F-NMR spectra of product mixture.



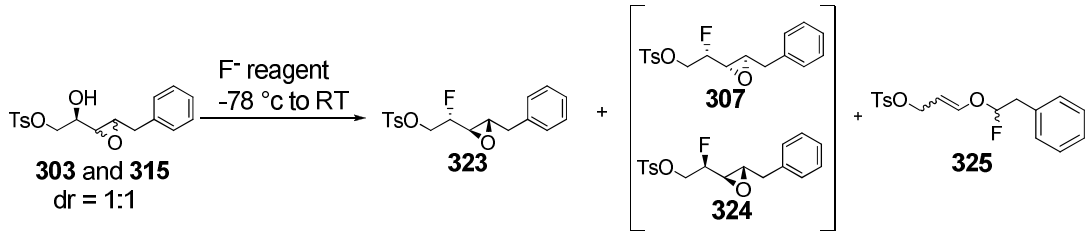
320
δ = -118.3 ppm
$^{2}J_{H\text{-}F}$ = 52.0 Hz

321
δ = -121.4 ppm
$^{2}J_{H\text{-}F}$ = 52.6 Hz

322
δ = -118.6 ppm
$^{2}J_{H\text{-}F}$ = 62.1 Hz

Figure 3. 11 : Characteristic chemical shift and coupling constants of fluorovinyl ethers.

Accordingly, deshydroxyfluorination reactions were then carried out on a 10 mg scale on a 1:1 mixture of diastereoisomers **303** and **315**, and crude product mixtures were analysed by ^{19}F-NMR. In the mechanism proposed by Grée [4,5] for the rearrangement of epoxy-alcohols to fluoroethers, significant cationic character for the deshydroxyfluorination reaction is implied. It was therefore suspected that deshydroxyfluorination reactions carried out on *threo*-epoxy-alcohol **315** may result in the formation of **323** and also in the formation of **324** (the enantiomer product of **307**). Fluorinating reagents were added at -78 °C, and the temperature was allowed to rise to room temperature and the reaction was monitored till TLC analysis showed complete conversion of the starting material (Table 3.5). When Deoxo-Fluor® was used as the fluorinating reagent either in DCM or toluene products **323**, **307**/**324** and **325** were obtained in a mixture. DAST proved to be less selective and in the end, Deoxo-Fluor® in THF provided the best results with compounds **323**, **307**/**324** and **325** obtained in a 1:1.29:0.44 ratio.



	Products ratios (by ^{19}F-NMR)		
Conditions	**323**	**307/324**	**325**
Deoxo-Fluor®, DCM	1	1.43	0.56
Deoxo-Fluor®, toluene	1	1.41	0.53
DAST, DCM	1	1.64	0.66
Deoxo-Fluor®, THF	1	1.29	0.44

Table 3. 5 : Reaction of **303** and **315** under various conditions.

Epoxy-alcohols, **303** and **315** taken as a 1:1 mixture were then treated with Deoxo-Fluor® in THF on a lager scale and the ^{19}F-NMR spectrum of the crude reaction mixture is shown in Figure 3.12. Four individual fluoroethers **325** were tentatively assigned to the signals between -118 ppm and 130 ppm, as they all had characteristic $^{2}J_{H\text{-}F}$ coupling constants greater than 60 Hz. Signals corresponding to fluoro-oxiranes **323** and **307/324** are shown between -196 ppm and -197 ppm, and **323** was assigned to the signal at -196.2 ppm by comparison with the ^{19}F-NMR spectrum of compound **307** previously prepared as a single diastereoisomer. Scaling up the reaction did not modify the product ratio between fluoro-oxiranes and fluoroethers, although some additional side products emerged. Purification over silica gel afforded a mixture of **323** and **307/324** in 47% yield, but it was not possible to separate **323** as a single diastereoisomer.

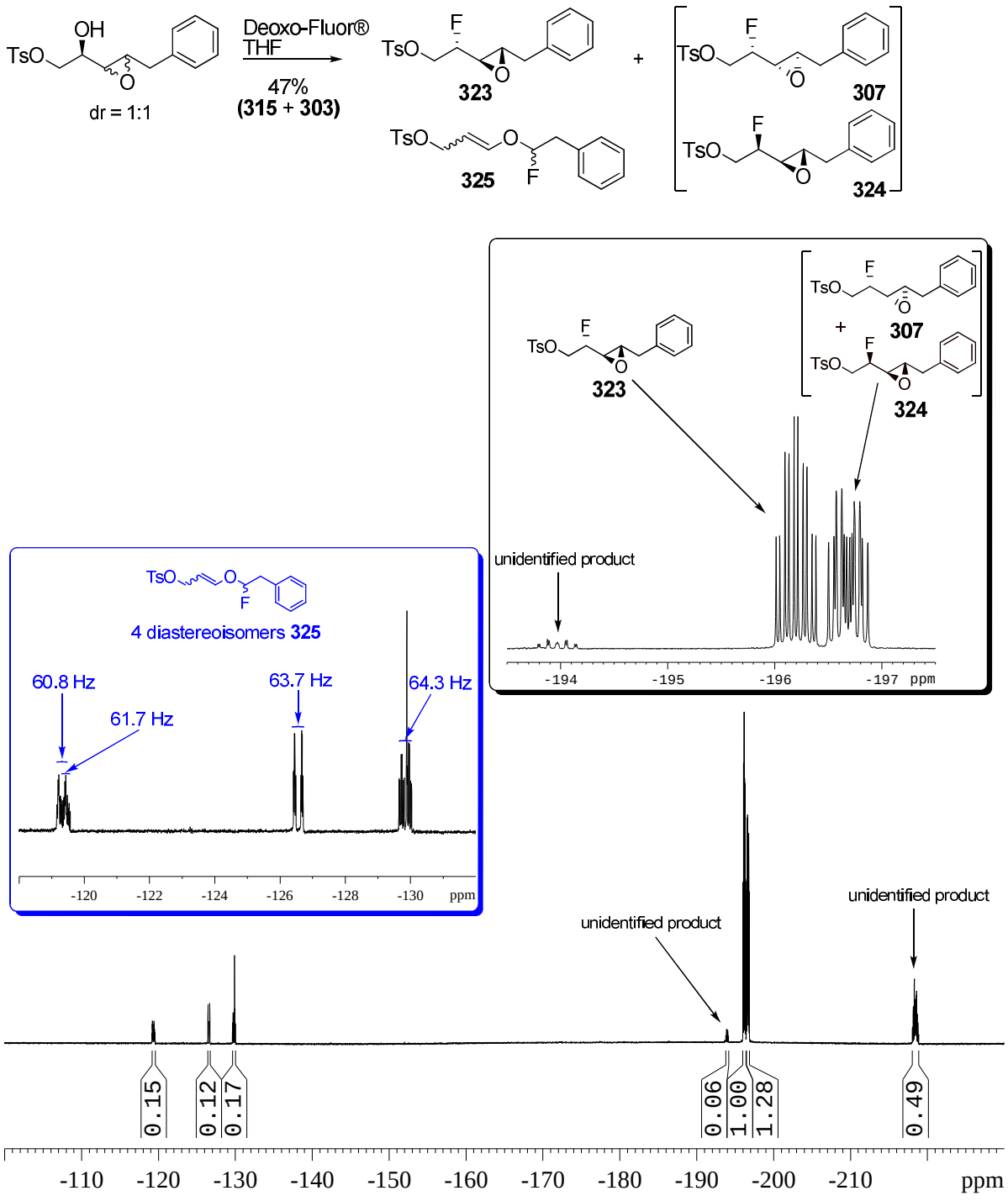
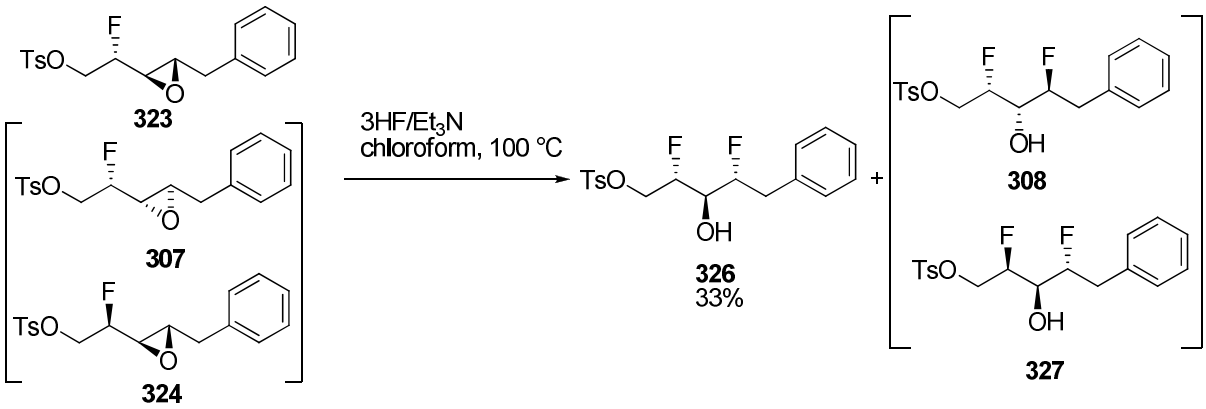


Figure 3. 12 : ^{19}F-NMR spectrum of the product mixture after deshydroxyfluorination reaction of **303** and **315**.

With this mixture of **323** and **307/324** in hand, an attempt was made to explore the introduction of the second fluorine atom. The mixture of **323** and **307/324** (1:1.3 ratio) was treated with 3HF/Et_3N in chloroform at 100 °C and after 3 days a mixture of **326** and **308/327** in a ~ 1:1 ratio was obtained.



Scheme 3. 27 : Epoxide ring opening of **323** with 3HF/Et_3N.

Separation of **326** from **308/327** by chromatography proved to be difficult, however separation of these diastereoisomers was achieved by preparative TLC and a clean fraction of (*2S,3R,4R*)-**326** was obtained in 33% yield. The optical rotation of the supposed mix of **308/327** was recorded ($[\alpha]_D$= -13.1° (C= 1, DCM), and proved to be different from the optical rotation of **308** ($[\alpha]_D$= -24.2° (C= 0.9, DCM) prepared from enantio-enriched epoxy-alcohol **303**. This shows the S_N1 character of the deshydroxyfluorination reaction on *threo*-isomer **315**. Difluoro alcohol **326** was then treated with Deoxo-Fluor® under our standard conditions to insert the third fluorine. Although TLC analysis showed a good conversion of fluorodiol **326**, the all-*syn* vicinal trifluoro motif (*2S,3S,4R*)-**328** was obtained in a moderate 57% yield.

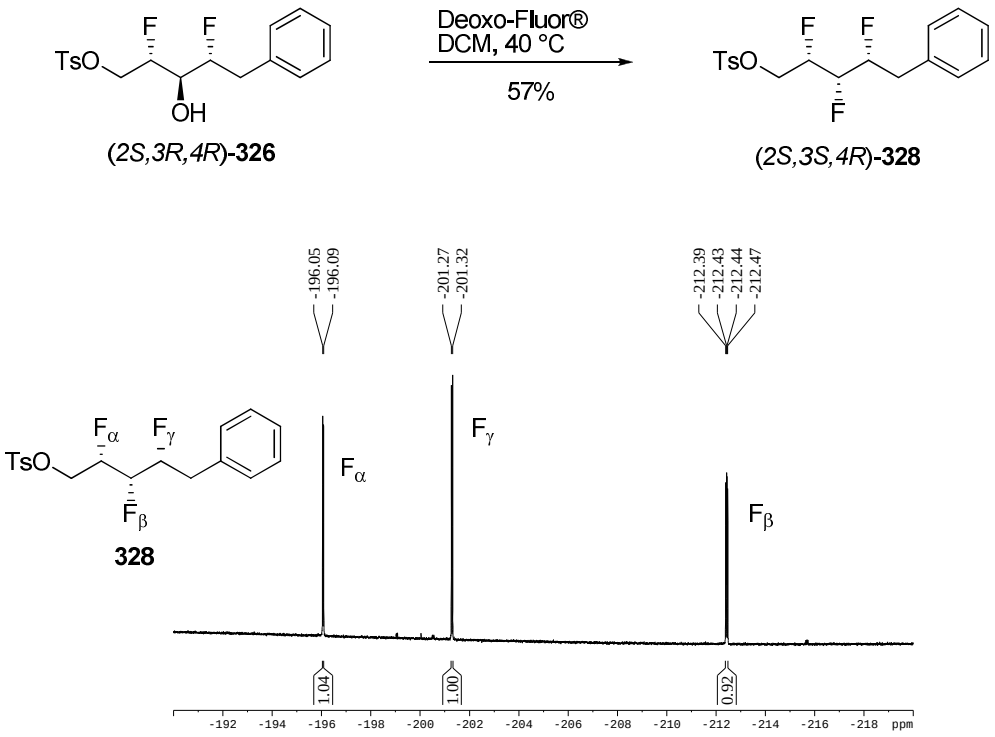


Figure 3. 13 : $^{19}F\{^{1}H\}$-NMR spectrum of the all-*syn* isomer **328**.

As shown in Table 3.6, the $^{19}F\{^{1}H\}$-NMR data recorded in this study are consistent with those previously reported in the literature by Nicoletti and O'Hagan [1].

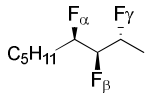
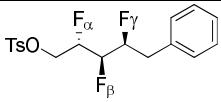
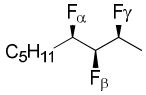
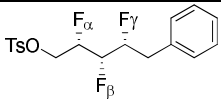
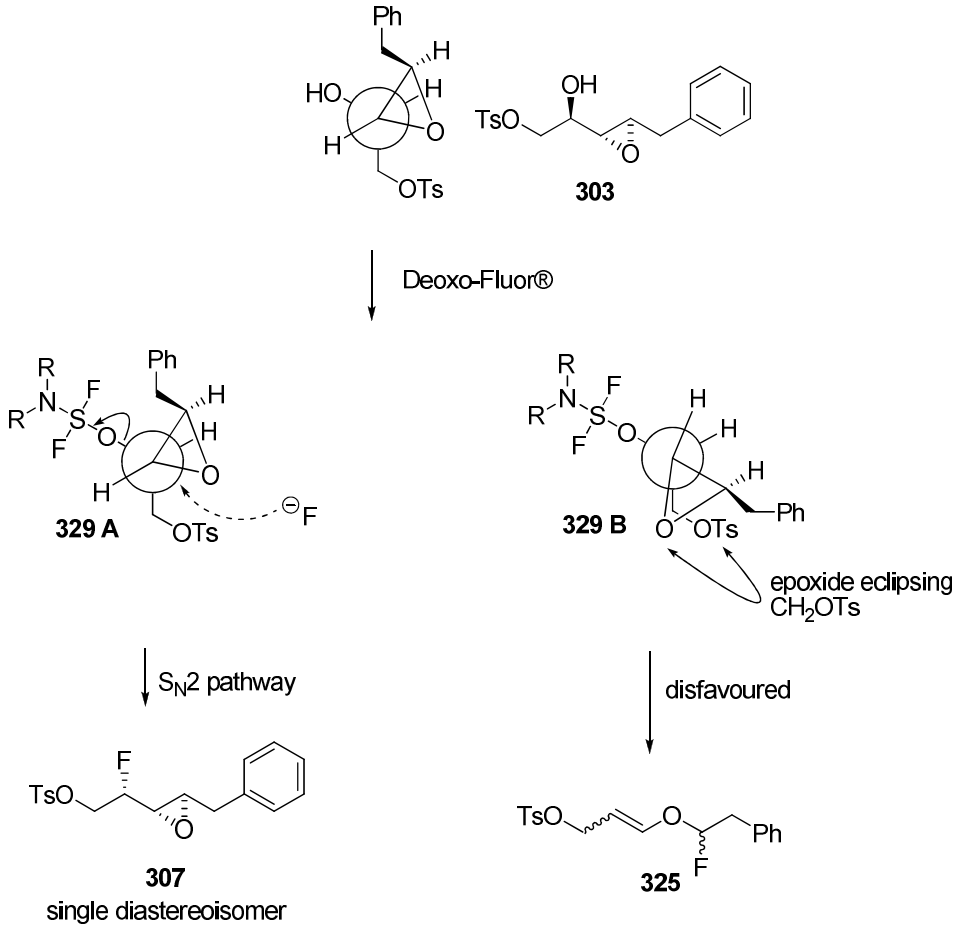
Compound	^{19}F-NMR chemical shifts (ppm)			$J_{F\text{-}F}$ (Hz)		
	F_α	F_β	F_γ	$J_{\alpha\text{-}\beta}$	$J_{\alpha\text{-}\gamma}$	$J_{\beta\text{-}\gamma}$
	-185	-199	-207	14.4	3.4	9.3
	-198	-215	-203	9.6	2.8	15.4
	-189	-199	-207	12.9	-	11.2
	-196	-201	-212	10.8	-	13.6

Table 3. 6 : ^{19}F{^{1}H}-NMR chemical shifts and coupling constants of different diastereoisomers of the vicinal trifluoro motif.

3.3.5) Attempt to rationalise the difference in reactivities of *threo* and *erythro* epoxy-alcohols:

It was interesting to observe a significant contrast in the reactivities of the two epoxy-alcohols **303** and **315**. *Erythro*- isomer **303** was easily accessible and its synthesis was pretty much straight forward. On the other hand preparation of *threo*- isomer **315** as a single diastereoisomer proved to be very challenging and could not be achieved in our hands. Both diastereoisomers of epoxy-alcohols **303** and **315** also reacted very differently in reaction with Deoxo-Fluor®. An attempt to explain this difference in reactivity is made in Schemes 3.28 and 3.29. As illustrated in Scheme 3.28, when the *erythro* isomer **303** reacts with Deoxo-Fluor®, the resulting intermediate **329 A** is formed. In **329 A** the C-O alkoxide and O-SF_2R group sit *anti* to each other and this could give this intermediate enough stability to react through a S_N2 process. As formation of a carbocation during deshydroxyfluorination reaction has not been

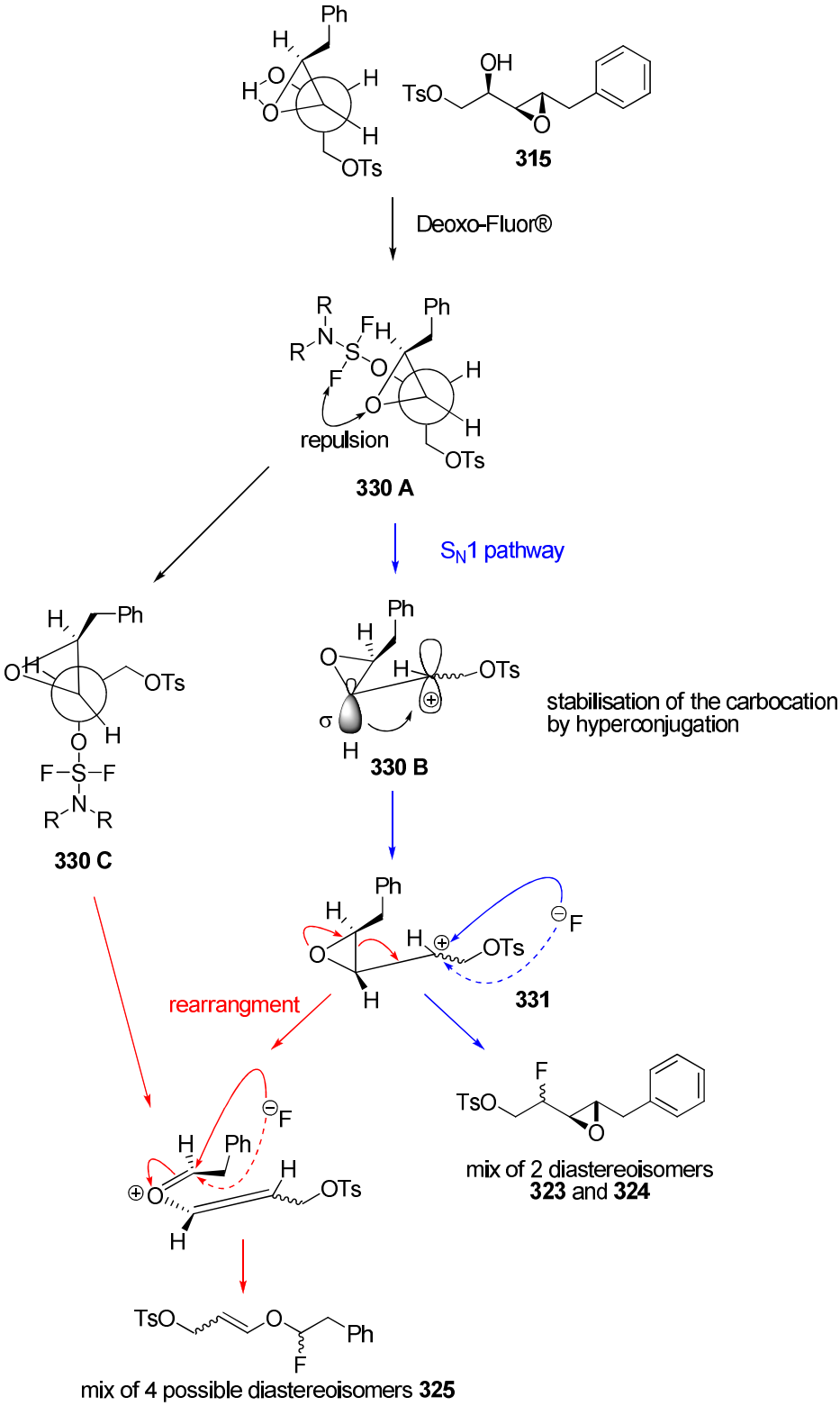
observed experimentally it means that to rationalise a possible rearrangement to fluoro ethers, the intermediate **329 B** has to be considered. In **329 B**, to bring the C-C bond to break antiperiplanar to the O-SF_2R to leave are, the oxygen of the epoxide has to eclipse the CH_2OTs group, and this is probably not sterically favoured. This could explain why the rearrangement to fluoroethers was not observed during deshydroxyfluorination reaction of epoxy-alcohol **303**.



Scheme 3. 28 : Attempt at rationalising the deshydroxyfluorination reaction of epoxy-alcohol **303**.

When the *threo* epoxy-alcohol **315** reacts with Deoxo-Fluor® it results in the formation of intermediate **330 A** (Scheme 3.29). A potential instability of **330 A** could be explained by the electrostatic repulsion between the O-SF_2R group and the epoxide sitting on the same side of the molecule. A more relaxed intermediate **330 B** could be formed by loss of the O-SF_2R

group. The resulting carbocation **330 B** could then benefit from stabilisation by hyperconjugaison with the $\sigma_{C\text{-}H}$ oribital of the adjacent carbon.

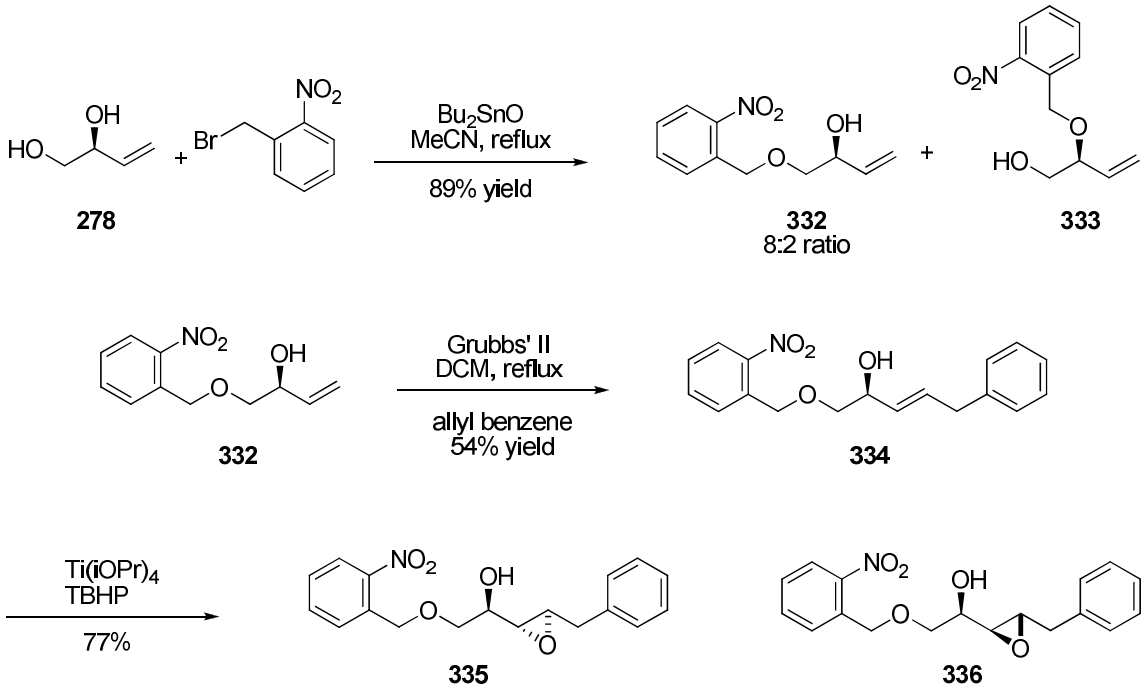


Scheme 3. 29 : Proposed mechanism for the deshydroxyfluorination reaction of epoxy-alcohol **315**.

Considering a rearrangement directly from the intermediate **330 C**, it is noticeable that in such an intermediate when the C-C bond to break is antiperiplanar to the O-SF_2R to leave, the epoxide eclipses an hydrogen. This could partially explain why the *threo*-epoxy-alcohol is more prone to rearrange to fluoroether than the *erythro*-epoxy-alcohol.

3.3.6) *o*-Nitrobenzyl group as a protecting group:

Considering the problematic preparation of the *threo*-epoxyalcohol **315** as a single diastereoisomer, other protecting groups were explored (*p*-bromobenzoyl, *p*-nitrobenzyl and *o*-nitrobenzyl group). The *o*-nitrobenzyl group proved to be effective. As illustrated in Scheme 3.30, diol **278** was reacted with *o*-nitrobenzyl bromide in the presence of dibutyltin oxide. This afforded regioisomers **332** and **333** in a 8:2 ratio and 89% yield. These two regioisomers were separated by silica gel chromatography and **332** was then subjected to a cross metathesis reaction with allyl benzene. The resultant allylic alcohol **334** was obtained in a 54% yield. Presence of ~ 8% of the *Z*- diastereoisomer was observed (^{1}H-NMR) of the product mixture, but it was readily separated from **334** by chromatography. Epoxidation of **334** was then achieved in 77% yield by reaction with TBHP in presence of titanium tetra-isopropoxide. Separation of **335** and **336** was then achieved over silica, and clean fractions of both diastereoisomers were obtained.



Scheme 3. 30 : Preparation of *erythro*-**335** and *threo*-**336** epoxy-alcohol with *o*-nitrobenzyl as protecting group.

Deshydroxyfluorination reactions on both the *threo*-**336** and *erythro*-**335** isomers were carried out, and results were analysed by $^{19}F\{^{1}H\}$-NMR of the product mixture. As illustrated in Figure 3.14, *erythro* epoxy-alcohol **335** reacted smoothly and stereoselectively with Deoxo-Fluor® and gave only one diastereoisomer of fluoroepoxide **337** (-195 ppm in $^{19}F\{^{1}H\}$-NMR), which was isolated in 85% yield.

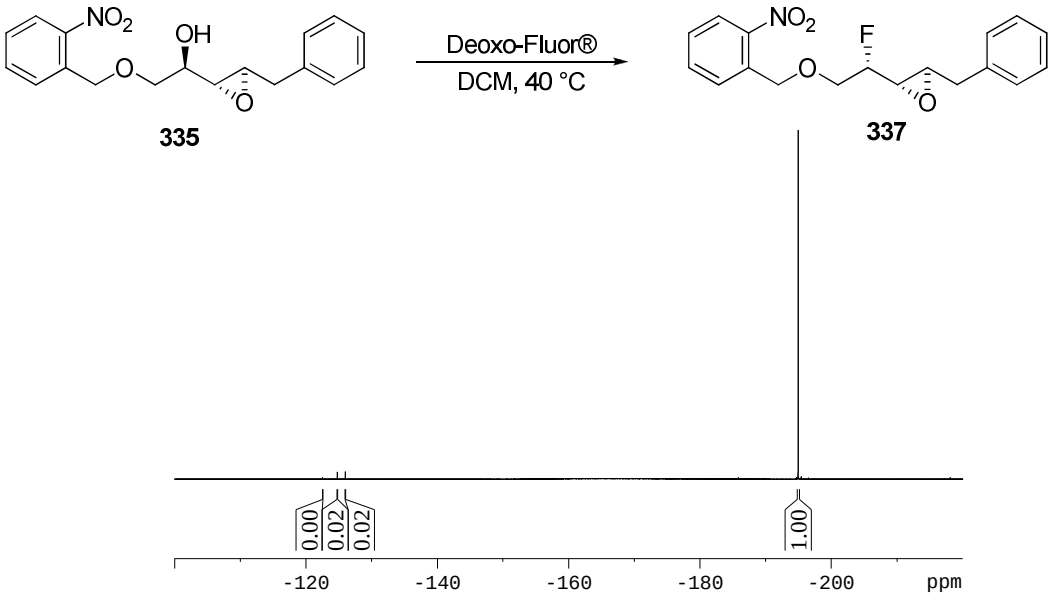
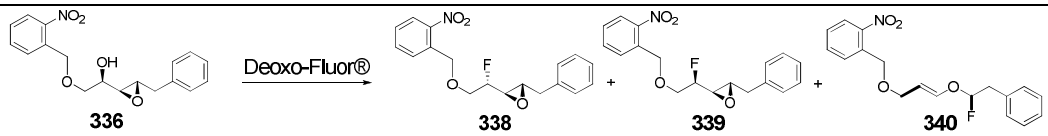


Figure 3. 14 : $^{19}F\{^{1}H\}$-NMR spectrum of the crude mixture product in the deshydroxyfluorination reaction of **335**.

When the *threo* isomer **336** was treated with Deoxo-Fluor® both diastereoisomers of the desired fluoro-epoxides were observed, as well as some rearranged fluorovinyl ethers. The presence of two fluoro-epoxides indicates significant S_N1 character of the deshydroxyfluorination reaction when carried out on the *threo*-epoxy-alcohol. Several condition rection were explored, as illustrated in Table 3.7. The temperature influenced the outcome of the reaction. Better ratios between the fluoro-epoxides **338** and **339** were obtained at 40 °C (ratio 1:0.31) compared to -78 °C (ratio 1:0.54). In both cases, the fluoroethers were present in a similar ratio (~ 0.5-0.6).



	Products ratios (by ^{19}F-NMR)		
Conditions	**338**	**339**	**340**
DCM, 40 °C	1	0.31	0.66
DCM, -78 °C	1	0.54	0.55

Table 3. 7 : Deshydroxyfluorination reaction of **336**.

Humphrey and co-workers [22], reported in 2003, the stereoselective preparation of fluoro-epoxide derivatives of unsaturated fatty acids by deshydroxyfluorination reactions of epoxy-alcohols with DAST. They noticed that improved yields were obtained by conversion of the substrates to trimethyl silyl ethers prior to reaction with DAST. The *threo* epoxy-alcohol **336** was therefore reacted with a small excess of TMSCl in the presence of Et_3N in THF at 50 °C. After one hour, TLC analysis showed a complete conversion of substrate **336** to its trimethyl silyl ether **341**. Purification and characterisation of silyl ether **341** was not attempted, instead the THF was removed under reduced pressure and replaced by Et_2O to help precipitate the triethylamine hydrogen chloride salt which was subsequently removed by filtration over a pad of silica. Silyl ether **60** was then subjected to a deshydroxyfluorination reaction with Deoxo-Fluor® in DCM at 40 °C. Analysis of the $^{19}F\{^1H\}$-NMR spectrum showed an improvement in the conversion to the fluoro-epoxide products. As shown in Figure 3.15, the fluoro-epoxides were obtained in a 1:0.27 ratio in favour of **338**, and the ratio of fluoroethers **340** was also decreased to 0.38.

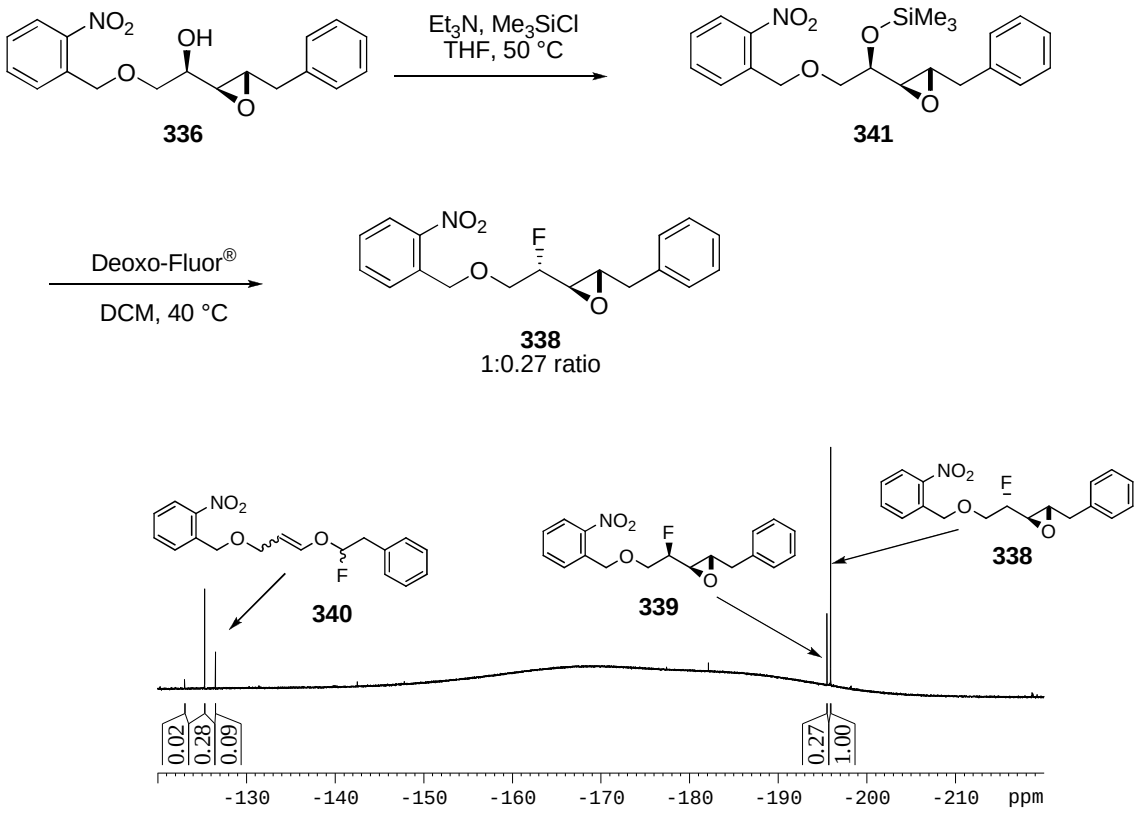
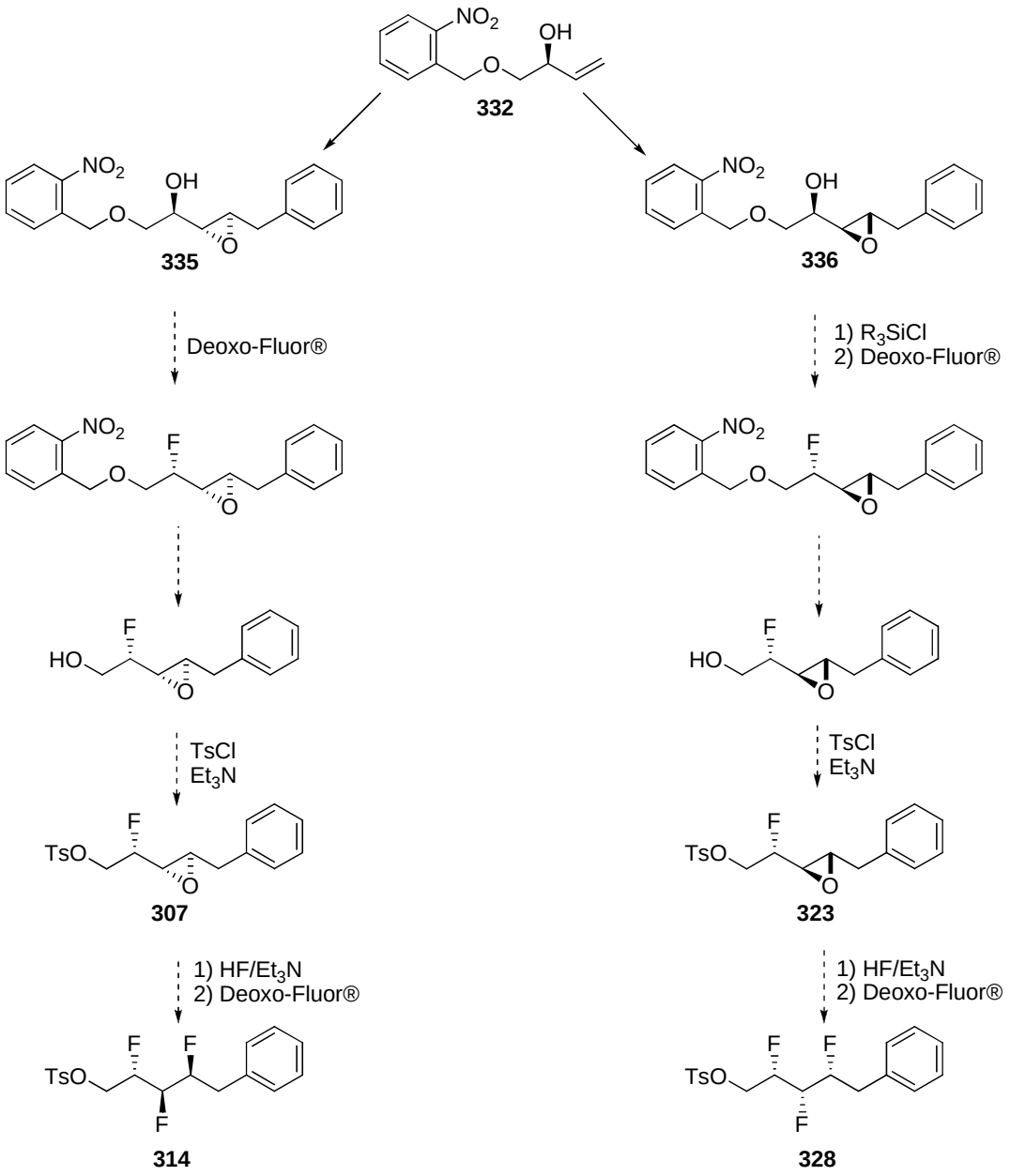


Figure 3. 15 : $^{19}F\{^{1}H\}$-NMR spectrum of the deshydroxyfluorination reaction of **341**.

The use of *o*-nitrobenzyl ether group in place of the tosyl ester, allowed to successfully separate the *threo*-**336** and *erythro*-**335** epoxy-alcohol isomers. It also allowed a better understanding of the deshydroxyfluorination reaction with the *threo*- epoxy-alcohol **336**, as it was used as a single diastereoisomer. However, with the *o*-nitrobenzyl group it was not possible to successfully prepare the corresponding vicinal trifluoro motifs, as it is not stable in HF media. Indeed, epoxide ring opening of fluoro-epoxide **337** was attempted under a wide range of temperatures (from -78 °C to 120 °C) and using several fluorinating reagents (HF/pyr, $3HF/Et_3N$, $TBAH_2F_3$, KHF_2, $BF_3.Et_2O$). The *o*-nitrobenzyl group showed signs of degradation when treated with HF/pyr, even at -78 °C. Epoxide ring opening with $HF.Et_3N$, $TBAH_2F_3$ [23], KHF_2 [24] required temperatures above 100 °C, and the *o*-nitrobenzyl group was also not stable under these conditions. The use of $BF_3.Et_2O$ was also explored in the epoxide openings [25]. It proved to be very reactive, and led to complex mixture of

fluorinated products which proved impossible to analyse, even when the reaction was carried out at -78 °C.

Nevertheless, in an attempt to prepare vicinal trifluoro motifs on a larger scale, the *o*-nitrobenzyl group could be used to initiate the synthetic route. As illustrated in Scheme 3.31, this would allow the preparation and purification of both the *erythro*-**335** and *threo*-**336** epoxy-alcohols as single diastereoisomers. Then, after deshydroxyfluorination reaction, the *o*-nitrobenzyl group could be removed and replaced by a tosyl group to carry on the synthesis described earlier in this chapter. Efficient deprotections of *o*-nitrobenzyl group have been reported in the literature by irradiation with UV light [26,27], or reduction by H_2/Pd/C followed by oxidation with DDQ [28].

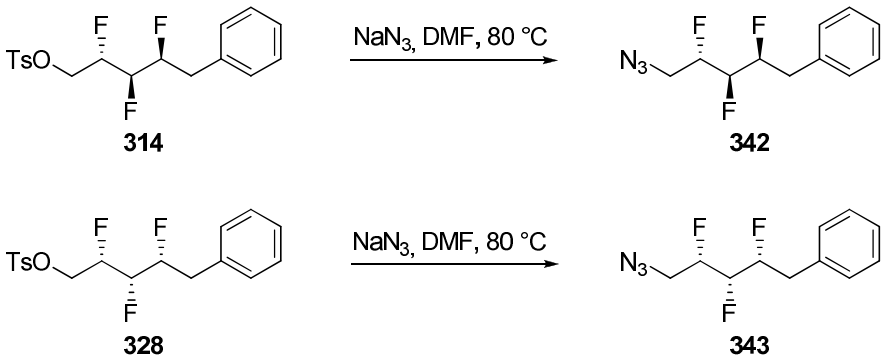


Scheme 3. 31 : Possible route to vicinal trifluoro motif starting with *o*-nitrobenzyl group as protecting groups.

3.3.7) Preparation of azido-trifluoro derivatives:

With both diastereoisomers **314** and **328** of a vicinal trifluoro motif in hand, the substitution of the tosyl group was then attempted. Compounds **314** and **328** were hardwon materials and therefore there was not much room for error in the choice of the nucleophile. A strong

nucleophilic with poor basic character was selected. Sodium azide has been shown to cleanly displace the tosyl group even with the presence of fluorine at the α position [29]. Therefore trifluoro motifs **314** and **328** were treated with NaN_3 in DMF at 80 °C on a small scale (Scheme 3.32). TLC analysis showed conversion to a major product, with an indication of minor by-products. The reaction was then stopped after three hours and purification was successfully achieved by preparative TLC, without previous work up, as instability of azides **342** and **343** was a risk. Purification of **342** and **343** was successfully achieved over preparative TLC, and **342** and **343** were obtained as clean fractions on an analytical scale, but with traces of DMF.



Scheme 3. 32 : Reaction of **314** and **328** with sodium azide.

3.4) Conclusion:

The synthesis of unique stereoisomers of vicinal trifluoro molecules has successfully been achieved (Figure 3.16).

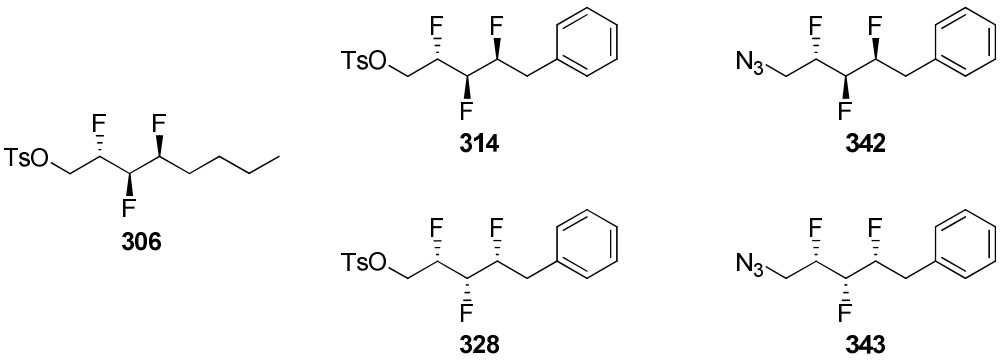


Figure 3. 16

The insertion of three fluorine atoms in three sequential steps has been achieved for **306**, **314**, **328**, **342**, **343** from enantio-enriched epoxy-alcohol motifs. Although this strategy was straightforward when applied to the *erythro*- diastereoisomer and has been achieved in up to 43% yield (considering the fluorination of **314**), it proved nonetheless, to be more challenging when applied to the *threo*- diastereoisomer. This chemistry is currently successfully applied to a variety of new targets in the laboratory.

References Chapter 3

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Chapter 4: Experimental section

4.1) General methods:

All reagents were of synthesis grade and were used without further purification unless otherwise stated. Dry diethyl ether and dry THF were distilled from sodium wire and benzophenone. Dry DCM and dry methanol were distilled from calcium hydride.

All moisture sensitive reactions were carried out under a positive pressure of N_2 in oven dried glassware (140 °C). Reaction temperatures between 0 °C and -78 °C were obtained using solid CO_2 in acetone, or isopropanol bath or by using a bath cooling apparatus LP technology RP-100-CD. Organic extracts were dried over anhydrous $MgSO_4$.

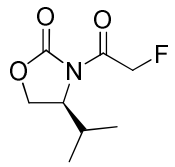
Thin layer chromatography (TLC) was performed using Macherey-Nagel polygram Sil G/UV_{254} plastic plates. Visualisation of TLC's was achieved by inspection under UV light (254 nm) or by the use of potassium permanganate strain, molybdenum-based stain, ferric chloride stain. Column chromatography were performed using silica gel 60 (40-63 micron) from Apollo Scientific Ltd. GC/Ms analysis were obtained using an Agilent 5890 gas chromatograph equipped with an Agilent 5973N mass-selective detector. High-resolution mass spectrometry spectra were performed by Mrs. C. Horsburgh on a Waters LCT or GCT time-of-flight (T. F) mass spectrometer at the University of St Andrews.

NMR spectra were recorded on either Bruker AV-300 (^{1}H at 300.06 MHz, ^{13}C at 75.45 MHz, ^{19}F at 282.34 MHz), Bruker AV-400 (^{1}H at 400.13 MHz, ^{13}C at 100.61 MHz, ^{19}F at 376.49 MHz) Bruker AV-500 (^{1}H at 499.90 MHz, ^{19}F at 470.33 MHz). Chemical shifts δ are reported in parts per million (ppm) and quoted relative to internal standards (Me_4Si, $CFCl_3$). ^{1}H, ^{13}C and ^{19}F spectroscopic data were assigned by a combination of one- and two- dimensional experiments (COSY, HSCQ, HMBC, NOESY). Melting points were measured using a GallenKamp Griffin MPA350BM2.5 melting point apparatus, and are uncorrected. Optical

rotations were determined using a A-1000 polarimeter (optical polarimeter Ltd.) or a Perkin Elmer model 341 polarimeter. $[\alpha]_D^{20}$ values are measured at 589 nm and given in 10^{-1}deg.cm^2.g^{-1}. IR spectra were recorded on a Perkin Elmer Spectrum GX FT-IR system as KBr disc or as thin film on PTFE discardable plates. Single X-ray diffraction analyses were carried out by Prof. A.M.Z. Slawin at the University of St Andrews.

4.2) Protocols:

Fluoroacetyl (*S*)-4-isopropyl-2-oxazolidinone 214:

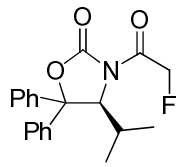


214

Fluoroacetate (1 g, 10 mmol) and phthaloyl dichloride (2 mL, 14 mmol) were stirred vigorously, and heated from 90 ^{o}C to 150 ^{o}C. Fluoroacetyl chloride was purified by distillation under atmospheric pressure, and recovered as colourless oil (680 mg, 71%). *n*-BuLi (2.5 M in hexane, 1.6 mL, 4 mmol) was added to a solution of (*S*)-4-isopropyl-2-oxazolidinone 98% **209** (0.51 g, 3.95 mmol) in THF (25 mL) at -78 ^{o}C. After 30 min fluoroacetyl chloride distilled freshly (345 mg, 3.59 mmol) as a solution in dry THF (3 mL) was added. The solution was allowed to warm to RT over 12 h, and was then quenched with a saturated solution of NH_4Cl (10 mL). The organic compounds were extracted into EtOAc (3 x 20 mL) and the organic layer was washed with water (10 mL), brine (10 mL) and dried over $MgSO_4$. **214** was purified over silica gel (cyclohexane 8 / EtOAc 2) and recovered as a colourless oil (0.35 g, 47%), that crystallised after few days at RT.

Mp = 60-61 ^{o}C (lit Mp = 61-62 °C [1]). **^{1}H-NMR** ($CDCl_3$, 300 MHz): δ (ppm)= 5.36 (d, 2 H, *J* = 47.6 Hz, FC*H*$_2$); 4.39 (m, 2 H, O-C*H*H and N-C*H*); 4.26 (dd, 1 H, *J* = 8.0, 2.0 Hz, O-CH*H*); 2.37 (m, 1 H, $(CH_3)_2$C*H*); 0.88 (d, 3 H, *J* = 7.0 Hz, C*H*$_3$); 0.83 (d, 3 H, *J* = 6.9 Hz, C*H*$_3$). **^{13}C-NMR** ($CDCl_3$, 75Mz): δ (ppm)= 167.7 (d, *J* = 20.6 Hz, H_2FC-*C*O); 154.5 (*C*O); 80.5 (d, *J* = 179.2 Hz, *C*H_2F); 65.5 (OC- *C*H_2); 58.5 (N-*C*H); 28.6 $(CH_3)_2$*C*H); 18.2 (*C*H_3); 14.9 (*C*H_3). **^{19}F-NMR** ($CDCl_3$, 282MHz): δ (ppm) = -230.3 (t, *J* = 47.6 Hz). **^{19}F{^{1}H}-NMR** ($CDCl_3$, 282MHz): δ (ppm) = -230.3.

Fluoroacetyl (*S*)-4-isopropyl-5,5-diphenyl-2-oxazolidinone 215:



215

n-BuLi (2.5 M in hexane, 3.6 mL, 9 mmol) was added to a solution of (*S*)-4-isopropyl-5,5-diphenyl-2-oxazolidinone **210** (2.38 g, 8.47 mmol) in THF (150 mL) at -78 ^{o}C, under N_2 atmosphere. After 30 min, the solution was allowed to warm to -20 °C over 30 min and then cooled again to -78 ^{o}C. Freshly distilled fluoroacetyl chloride (680 mg, 7.08 mmol) as a solution in dry THF (10 mL) was added. The solution was allowed to warm to RT over 12 h, and was then quenched with a saturated solution of NH_4Cl (20 mL). The organic compounds were extracted into EtOAc (3 x 50 mL), and the organic layer was washed with water (20 mL), brine (20 mL) and dried over $MgSO_4$. **215** was purified over silica gel (cyclohexane 8 / EtOAc 2) and recovered as white solid (1.2 g, 50%).

Mp = 171 ^{o}C. $\mathbf{[\alpha]_D^{20}}$ = -232° (C = 1; $CHCl_3$). **^{1}H-NMR** ($CDCl_3$, 300 MHz): δ (ppm)= 7.47 (m, 2 H, *H* ar); 7.34 (m, 8 H, *H* ar); 5.42 (dd, 1 H, *J* = 16.5, 47.5 Hz, FC*Ha*Hb); 5.37 (d, 1 H, *J* = 3.2 Hz, C*H*); 5.26 (dd, 1 H, *J* = 16.5, 47.5 Hz, FCHa*Hb*); 2.01 (m, 1 H, $(CH_3)_2CH$); 0.92 (d, 3 H, *J* = 7 Hz, CH_3); 0.77 (d, 3 H, *J* = 6.7 Hz, CH_3). **^{13}C-NMR** ($CDCl_3$, 75Mz): δ (ppm)= 167.7 (d, *J* = 20.4 Hz, H_2FC-*C*O); 153.3 (*C*O); 142.1 (*C* ar); 138.0 (*C* ar); 129.5 (*C* ar); 129.3 (*C* ar); 128.9 (*C* ar); 128.6 (*C* ar); 126.2 (*C* ar); 125.9 (*C* ar); 91.7 ($C(Ph)_2$); 80.2 (d, *J* = 180.2 Hz, CH_2F); 64.9 (N-*C*H); 30.4 ($(CH_3)_2CH$); 22.2 (CH_3); 16.7 (CH_3). **^{19}F-NMR** ($CDCl_3$, 282MHz): δ (ppm) = -229.9 (t, *J* = 47.5 Hz). **^{19}F{^{1}H}-NMR** ($CDCl_3$, 282MHz): δ (ppm) = -229.9. $\mathbf{\nu_{max}/cm^{-1}}$ 2360, 1777, 1723, 1365, 1208, 1150. ***m/z*** (CI^+): 342 [MH+] (5%), 298 (100%). HRMS (CI+) calc for $C_{20}H_{21}NO_3F$ = 342.1505, found = 342.1508.

General procedure for aldol reaction mediated with LDA:

LDA (2 M in THF/heptane, 80 μL 0.16 mmol) was added to a solution of (*S*)-4-isopropyl-5,5-diphenyl-3-fluoroacetyl-2-oxazolidinone **215** (50 mg, 0.146 mmol) in dry THF (1 mL) at -78 ^{o}C. After 45 min, hexanal 96% (22 μL, 0.16 mmol) was added. After 3 h, the reaction was quenched with a saturated solution of NH_4Cl (1 mL). The organic compounds were extracted into EtOAc (3 x 5 mL) and the organic layer was washed with water (3 mL), brine (3 mL) and dried over $MgSO_4$.

The reaction product was analysed by ^{1}H-NMR and ^{19}F-NMR of the crude mixture.

General procedure for aldol reaction mediated with *n*-BuLi-tributyltin chloride:

n-BuLi (2.5 M in hexane, 32 μL 0.08 mmol) was added to a solution of (*S*)-4-isopropyl-5,5-diphenyl-3-fluoroacetyl-2-oxazolidinone **215** (25 mg, 0.073 mmol) in dry THF (0.5 mL) at -78 ^{o}C. The solution was stirred for 30 min and then tributyltin chloride 96% (25 μL, 0.088 mmol) was added. The solution was allowed to warm to -40 ^{o}C over 30 min and then cooled again to -78 ^{o}C. Hexanal 96% (12 μL, 0.1 mmol) was added, and the solution stirred at -78 $^{\circ}$C for 1.5 h. The reaction was quenched with a saturated solution of NH_4Cl (0.5 mL). The organic compounds were extracted into EtOAc (3 x 5 mL), and the organic layer was washed with water (3 mL), brine (3 mL), and dried over $MgSO_4$.

The reaction product was analysed by ^{1}H-NMR and ^{19}F-NMR of the crude mixture.

General procedure for aldol reaction mediated with dibutylboron triflate-DIEA:

DIEA 99.5% (32 μL, 0.177 mmol) and dibutylboron triflate (1 M in THF, 172 μL, 0.172 mmol) were added to a solution of (*S*)-4-isopropyl-5,5-diphenyl-3-fluoroacetyl-2-oxazolidinone **215** (50 mg, 0.146 mmol) in dry DCM (1 mL) at 0 ^{o}C. After 30 min, the solution was cooled to -78 ^{o}C and hexanal 96% (22 μL, 0.18 mmol) in dry DCM (60 μL) was added. After 3 h at -78 ^{o}C, the reaction was quenched with a 5:1 mixture of MeOH/30% H_2O_2. Stirring was continued for 10 min at -78 ^{o}C, and the solution was warmed up to 0 ^{o}C and stirred for 30 extra minutes. A saturated solution of NH_4Cl (1 mL) was then added and the organic compounds were extracted into EtOAc (3 x 5 mL). The organic layer was washed with water (3 mL), brine (3 mL), and dried over $MgSO_4$.

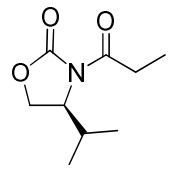
The reaction product was analysed by ^{1}H-NMR and ^{19}F-NMR of the crude mixture.

General procedure for aldol reaction mediated with titanium tetrachloride-DIEA:

$TiCl_4$ (1 M in DCM, 80 μL, 0.08 mmol) was added to a solution of (*S*)-4-isopropyl-5,5-diphenyl-3-fluoroacetyl-2-oxazolidinone **215** (25 mg, 0.07 mmol) in dry DCM (0.5 mL) at -78 ^{o}C. The solution turned yellow, and after 4-5 min DIEA (15 μL, 0.08 mmol) was added (the solution turned immediately dark red). After 1.5 h at -78 ^{o}C, hexanal 96% (18 μL, 0.15 mmol) was added. After 3 h, the reaction was quenched with a saturated solution of NH_4Cl (0.5 mL). The organic compounds were extracted into Et_2O (3 x 5 mL), and the organic layer was washed with water (3 mL), brine (3 mL), and dried over $MgSO_4$.

The reaction product was analysed by ^{1}H-NMR and ^{19}F-NMR of the crude mixture.

(*S*)-4-Isopropyl-3-propionyloxazolidin-2-one 219:

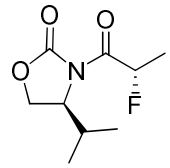


219

LDA (2 M in THF/n-heptane, 4.18 mL, 8.36 mmol) was added to a solution of 4-(*S*)-4-isopropyl-2-oxazolidinone **209** 98% (1 g, 7.59 mmol) in dry THF (15 mL) at -78 ^{o}C. After 35 min, propionyl chloride 97% (0.82 mL, 9.11 mmol) was added and the solution was stirred for 1 h at -78 ^{o}C. The reaction was then quenched with a saturated solution of NH_4Cl (5 mL). The product was extracted into Et_2O (3 x 10 mL), washed with water (10 mL), and dried over $MgSO_4$. Solvents were removed under reduced pressure. The product **219** was purified over silica (cyclohexane 8 / EtOAc 2) and recovered as a colourless oil (1.12 g, 80%).

$[\alpha]_D^{20}$ = +90.1° (C = 8.5; DCM) (lit $[\alpha]_D^{20}$ = +96.8° (C = 8.7; DCM) [2]. **^{1}H-NMR** ($CDCl_3$, 300 MHz): δ (ppm) = 4.39 (m, 1 H, N-C*H*); 4.23 (dd, 1 H, *J* = 9.0, 8.1 Hz, O-C*H*H); 4.16 (dd, 1 H, *J* = 9.0, 3.2 Hz, O-CH*H*); 2.89 (m, 2 H, CH_3-C*H*$_2$); 2.33 (m, 1 H, $(CH_3)_2$C*H*); 1.12 (t, 3 H, *J* = 7.3 Hz, CH_2-C*H*$_3$); 0.87 (d, 3 H, *J* = 7.1 Hz, C*H*$_3$); 0.83 (d, 3 H, *J* = 6.9 Hz, C*H*$_3$). **^{13}C-NMR** ($CDCl_3$, 75Mz): δ (ppm) = 174.4 (*C*O); 154.5 (*C*O); 63.8 (OC- *C*H_2); 58.8 (N-*C*H); 29.5 (O-*C*H_2); 28.7 $(CH_3)_2$*C*H); 18.3 (CH_2-*C*H_3); 15.0 (*C*H_3); 8.8 (*C*H_3).

(*S*)-3-((*S*)-2-Fluoropropanoyl)-4-isopropyloxazolidin-2-one 222a:

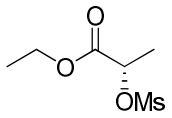


222a

LDA (2 M in THF/n-heptane, 5.6 mL, 11.2 mmol) was added to a solution of **219** (1.72 g, 9.3 mmol) in dry THF (30 mL) at -78 ^{o}C. After 1.5 h NFSI 97% (4.51 g, 13.9 mmol) was added and the solution was stirred for 2 h at -78 ^{o}C. The reaction was then quenched with a saturated solution of NH_4Cl (10 mL). The product was extracted into Et_2O (3 x 15 mL), washed with water (15 mL), and dried over $MgSO_4$. Solvents were removed under reduced pressure. The product **222a** was purified over silica (hexane/EtOAc from 9/1 to 7/3), and recovered as a brown oil (1.05 g, 56%) with a diastereoisomeric ratio of 90:10. This ratio was improved to 95:5 after a second purification over silica (hexane 95 / EtOAc 5) (0.75g, 40%).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 6.01 (qd, 1 H, *J* = 6.5, 49.0 Hz, FC*H*); 4.42 (m, 1 H, N-C*H*); 4.34 (dd, 1 H, *J* = 7.9, 8.9 Hz, *H*CH); 4.27 (dd, 1 H, *J* = 3.1, 8.9 Hz, HC*H*); 2.47 (m, 1 H, $(CH_3)_2CH$); 1.58 (dd, 3 H, *J* = 6.5, 23.9 Hz, FHC-CH_3); 0.93 (d, 3 H, *J* = 7.0 Hz, CH_3); 0.88 (d, 3 H, *J* = 6.9 Hz, CH_3). **^{13}C-NMR** ($CDCl_3$, 75Mz): δ (ppm) = 170.7 (d, *J* = 22.8 Hz, O*C*-CHF); 153.9, (*C*O); 86.2 (d, *J* = 176.5 Hz, *C*HF); 64.5 (CH_2); 59.0 (N-*C*H); 28.4 ($(CH_3)_2CH$); 18.6 (d, *J* = 23.3 Hz, FHC-*C*H_3); 18.3 (*C*H_3); 14.8 (*C*H_3). **^{19}F-NMR** ($CDCl_3$, 282MHz): δ (ppm) = -184.5 (qd, *J* = 23.9, 49.0 Hz). **^{19}F{^{1}H}-NMR** ($CDCl_3$, 282MHz): δ (ppm) = -184.5. **ν_{max}/cm^{-1}** 2962, 1777, 1713, 1388, 1201, 1133, 1044. ***m/z*** (CI^+): [MH+] 204 (100%); HRMS (CI) calc for $C_9H_{15}NO_3F$ = 204.1036 found = 204.1029.

Ethyl (*S*)-2-(methylsulfonyloxy)-propanoate 225:

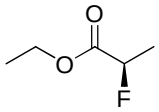


225

(*S*)-(-)-Ethyl lactate **224** 98% (10 mL. 85.8 mmol) was added to a solution of triethylamine (15 mL, 107.6 mmol), DMAP (0.2 g, 1.64 mmol) in dry THF (50 mL) at RT. The solution was cooled to -20 °C, and methyl sulfonyl chloride (8.5 mL, 109.82 mmol) was added. The reaction was then warmed to 60 °C, and stirred for 6 h. The solution was filtered through celite, washed with Et_2O (3 x 50 mL), and solvents were removed under reduced pressure. **225** was recovered as a brown oil (15.4 g, 91%) and used without further purification.

$[\alpha]_D^{20}$= -44.4° (C = 1.05, DCM) **(lit -52.9°, C = 4.32, $CHCl_3$ [3])**. **^{1}H-NMR** ($CDCl_3$, 300 MHz): δ (ppm) = 5.07 (q, 1 H, *J* = 7.0 Hz, C*H*CH_3); 4.21 (q, 2 H, *J* = 7.1 Hz, C$H_2$$CH_3$); 3.11 (s, 3 H, SO_2C*H*$_3$); 1.57 (d, 3 H, *J* = 7.0 Hz, CHC*H*$_3$); 1.27 (t, 3 H, *J* = 7.1 Hz, CH_2C*H*$_3$). **^{13}C-NMR** ($CDCl_3$, 75Mz): δ (ppm) = 169.8 (*C*O); 74.7 (SO_2*C*H_3); 62.5 (*C*H_2); 39.49 (O*C*H); 18.7 (*C*H_3); 14.4 (*C*H_3).

Ethyl 2-(*R*)-fluoropropanoate 226:

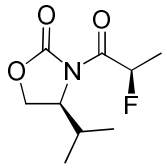


226

(*S*)-Ethyl 2-(methylsulfonyloxy)-propanoate **225** (15 g, 76.5 mmol) was added to a solution of potassium fluoride (17.7 g, 305 mmol) in formamide (60 mL). The solution was heated from 70 °C to 90 °C over 4 h, and **226** was then distilled from the reaction mixture under reduced pressure. The title compound **226** was recovered as a colourless oil (8.1g, 87%).

$[\alpha]_D^{20}$= +3.9 ° (C = 1.05, DCM) **(lit $[\alpha]_D$= +6.4 ° (C= 1.4, $CHCl_3$) [4]**. **^{1}H-NMR** ($CDCl_3$, 300 MHz): δ (ppm) = 4.97 (qd, 1 H, *J* = 6.9, 48.7 Hz, *H*CF); 4.23 (q, 2 H, *J* = 7.1 Hz, C*H*$_2$CH$_3$); 1.55 (dd, 3 H, *J* = 6.9, 23.6 Hz, FHC-C*H*$_3$); 1.28 (t, 3 H, *J* = 7.1 Hz, CH$_2$C*H*$_3$). **^{13}C-NMR** ($CDCl_3$, 100 MHz): δ (ppm) = 170.4 (d, *J* = 23.4 Hz, *C*O); 85.6 (d, *J* = 181.4 Hz, *C*F); 61.5 (*C*H$_2$); 22.5 (d, *J*= 18.3 Hz, *C*H$_3$); 14.11 (*C*H$_3$). **^{19}F-NMR** ($CDCl_3$, 282MHz): δ (ppm) = -185.05 (dq, *J* = 23.6, 48.7 Hz).

Preparation of (*S*)-3-((*R*)-2-Fluoropropanoyl)-4-isopropyloxazolidin-2-one 222b:



222b

Preparation of (*R*)-2-fluoropropanoyl chloride **227**:

Chlorosulfonic acid (3.3 mL, 50 mmol) was added to a solution of phthaloyl dichloride (7.2 mL, 50 mmol) and ethyl-2-(*R*)-fluoropropanoate **226** (3g, 25 mmol) at RT. The solution was heated at 120 °C for 4 h. 2-(*R*)-Fluoropropanoyl chloride **227** was distilled from the reaction mixture under reduced pressure and recovered as a colourless oil (1.73g, 63%).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 5.15 (dq, 1 H, *J* = 6.9, 48.6 Hz, *H*CF-CH_3); 1.71 (dd, 3 H, *J* = 6.9, 22.8 Hz, HCF-C*H*$_3$). **^{19}F-NMR** ($CDCl_3$, 282MHz): δ (ppm) = -171.4 (dq, *J* = 22.8, 48.6 Hz).

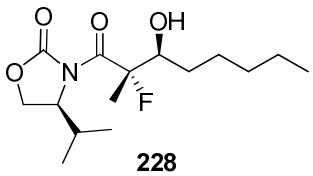
Preparation of (*S*)-3-((*R*)-2-fluoropropanoyl)-4-isopropyloxazolidin-2-one **222b**:

n-BuLi (2.5 M in hexane, 7.5 mL, 18.7 mmol) was added to a solution of 4-(*S*)-4-isopropyl-2-oxazolidinone **209** (2.2 g, 1.7 mmol) in dry THF (20 mL) at -50 ^{o}C. After 30 min, freshly prepared (*R*)-2-fluoropropanoyl chloride **227** (1.7 mL, 1.5 mmol) was added, and the solution was stirred for 4 h at -50 ^{o}C. The reaction was then quenched with a saturated solution of NH_4Cl (5 mL). The organic compounds were extracted into Et_2O (3 x 10 mL), washed with water (10 mL) and dried over $MgSO_4$. Solvents were removed under reduced pressure. The

product **222b** was purified over silica (hexane 8 / EtOAc 2), and recovered as a brown oil (1.85 g, 59%) with a diastereoisomeric ratio of 95:5 (by ^{19}F-NMR).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 6.0 (qd, 1 H, *J* = 6.7, 49.5 Hz, FC*H*); 4.5 (m, 1 H, N-C*H*); 4.4 (dd, 1 H, *J* = 8.4, 9.2 Hz, *H*CH); 4.3 (dd, 1 H, *J* = 3.2, 9.2 Hz, HC*H*); 2.35 (m, 1 H, $(CH_3)_2$C*H*); 1.64 (dd, 3 H, *J* = 6.7, 23.6 Hz, FHC-CH_3); 0.92 (d, 3 H, *J* = 7.0 Hz, CH_3); 0.87 (d, 3 H, *J* = 6.9 Hz, CH_3). **^{13}C-NMR** ($CDCl_3$, 75Mz): δ (ppm) = 173.7 (d, *J* = 2.6 Hz, O*C*-CHF); 161.3 (*C*O); 85.3 (d, *J* = 180.6 Hz, *C*HF); 68.8 (*C*H_2); 58.4 (N-*C*H); 32.5 ((CH_3)$_2$*C*H); 18.2 (d, *J* = 22.4 Hz, FHC-*C*H_3); 17.8 (*C*H_3); 17.5 (*C*H_3). **^{19}F-NMR** ($CDCl_3$, 282 MHz): δ (ppm) = -186.2 (qd, *J* = 23.6, 49.5 Hz). **ν_{max}/cm^{-1}** 2975, 1790, 1720, 1201, 1133, 1040. ***m/z*** (CI+): [MH+] 204 (100). HRMS (CI) calc for $C_9H_{15}NO_3F$ = 204.1036 found = 204.1031.

(*S*)-3-((2*S*,3*S*)-2-Fluoro-3-hydroxy-2-methyloctanoyl)-4-isopropyloxazolidin-2-one 228:

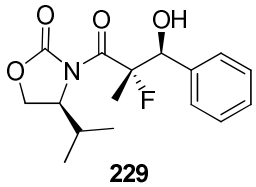


228

$TiCl_4$ (1 M in DCM, 1.5 mL, 1.5 mmol) was added to a solution of **222a** (0.3 g, 1.5 mmol) in dry DCM (5 mL) at -78 °C. After 5 min DIEA 99.5% (310 µL, 1.8 mmol) was added, and the solution was stirred for 2 h at -78 °C. $TiCl_4$ (1 M in DCM, 3 mL, 3 mmol) was added, followed by hexanal 96% (0.9 mL, 7.5 mmol). The solution was stirred for 4 h at -78 °C and the reaction was then quenched with a saturated solution of NH_4Cl (2 mL). The organic products were extracted into Et_2O (3 x 10 mL), washed with water (10 mL) and dried over $MgSO_4$. Solvents were removed under reduced pressure and the product was purified over silica gel (hexane 8 / EtOAc 2). The title compound **228** was recovered as a white solid (0.332 g, 74%).

Mp = 122 °C. $\mathbf{[\alpha]_D^{20}}$ = +45° (C= 0.82, DCM). **^{1}H-NMR** ($CDCl_3$, 300 MHz): δ (ppm) = 4.46 (m, 1 H, N-C*H*); 4.32 (dd, 1 H, *J* = 9.0, 8.0 Hz, *O*-C*H*H); 4.23 (dd, 1 H, *J* = 3.6, 9.0 Hz, O-CH*H*); 4.1 (m, 1 H, HOC*H*); 3.26 (1 H, *J* = 5.3 Hz, *H*OCH); 2.38 (m, 1 H, $(CH_3)_2CH$); 1.7 (d, 3 H, *J* = 22.2 Hz, FC-CH_3); 1.47-1.29 (m, 8 H, 4 x CH_2); 0.90 (m, 9 H, 3 x CH_3). **^{13}C-NMR** ($CDCl_3$, 75Mz): δ (ppm) = 172.8 (d, *J* = 27.9 Hz, O*C*-CF); 153.0 (*C*O); 101.7 (d, *J* = 190.2 Hz, *C*F); 75.2 (d, *J* = 23.5 Hz, HO*C*H); 64.1 (O-*C*H_2); 60.8 (N-*C*H); 32.0 (*C*H_2); 31.5 (d, *J* = 4.5 Hz, *C*H_2); 28.7 $(CH_3)_2CH$); 26.0 (*C*H_2); 22.9 (*C*H_2); 19.6 (d, *J* = 23.6 Hz, FC-*C*H_3); 18.4 (*C*H_3); 15.1 (*C*H_3); 14.4 (*C*H_3). **^{19}F-NMR** ($CDCl_3$, 282 MHz): δ (ppm) = -158.3 (qd, *J* = 22.2, 15.5 Hz). $^{19}F\{^1H\}$-NMR ($CDCl_3$, 282 MHz): δ (ppm)= -158.3. $\mathbf{\nu_{max}/cm^{-1}}$ 3329, 2953, 1803, 1692, 1365, 1208, 1150, 1125. ***m/z*** = 304 (MH^+, 100%); HRMS (CI+) calc for $C_{15}H_{27}NO_4F$ = 304.1924, found = 304.1929.

(*S*)-3-((2*S*,3*S*)-2-Fluoro-3-hydroxy-2-methyl-3-phenylpropanoyl)-4-isopropyloxazolidin-2-one 229:

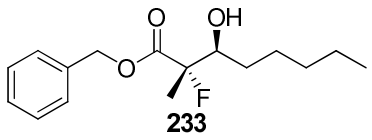


229

$TiCl_4$ (1 M in DCM, 0.5 mL, 0.5 mmol) was added to a solution of **222a** (0.1 g, 0.5 mmol) in dry DCM (2 mL) at -78 °C. After 5 min DIEA 99.5% (105 µL, 0.6 mmol) was added and the solution was stirred for 2 h at -78 °C. $TiCl_4$ (1 M in DCM, 0.5 mL, 0.5 mmol) and benzaldehyde 99.5% (90 µL, 0.9 mmol) were then added. The solution was stirred for 4 h at -78 °C. The reaction was quenched with a saturated solution of NH_4Cl (0.5 mL). The products were extracted into Et_2O (3 x 5 mL), washed with water (5 mL) and dried over $MgSO_4$. Solvents were removed under reduced pressure and the product was purified over silica gel (hexane 7 / EtOAc 3). The aldol product **229** was recovered as a white solid (0.093 g, 67%).

Mp = 102-104 °C. $\mathbf{[\alpha]_D^{20}}$ = +43.5° (C= 1, DCM). **^{1}H-NMR** ($CDCl_3$, 300 MHz): δ (ppm) = 7.38 (m, 2 H, H ar); 7.30 (m, 3 H, H ar); 5.35 (d, 1 H, *J* = 15.9 Hz, *H*C-OH); 4.29 (m, 1 H, N-C*H*); 4.17 (m, 2 H, O-CH_2); 3.70 (br s, 1 H, O*H*); 2.16 (m, 1 H, $(CH_3)_2$C*H*); 1.67 (d, 3 H, *J* = 22.3 Hz, FC-CH_3); 0.85 (d, 3 H, *J* = 7.0 Hz, (CH_3)$_2$CH); 0.75 (d, 3 H, *J* = 6.9 Hz, (CH_3)$_2$CH). **^{13}C-NMR** ($CDCl_3$, 75Mz): δ (ppm) = 171.5 (d, *J* = 27.5 Hz, O*C*-CF); 152.7 (*C*O); 138.1 (*C* ar); 128.5 (*C* ar); 128.2 (*C* ar); 127.8 (ar); 99.4 (d, *J* = 194.0 Hz, *C*F); 76.3 (d, *J* = 23.1 Hz, HO*C*H); 63.7 (O-*C*H_2); 60.3 (N-*C*H); 28.4 (CH_3)$_2$*C*H); 19.6 (d, *J* = 23.3 Hz, FC-*C*H_3); 17.9 (*C*H_3); 14.5 (*C*H_3). **^{19}F-NMR** ($CDCl_3$, 282 MHz): δ (ppm) = -159.2 (dq, *J* = 22.3, 15.9 Hz). **^{19}F{^{1}H}-NMR** ($CDCl_3$, 282 MHz): δ (ppm)= -159.2. $\mathbf{\nu_{max}/cm^{-1}}$ 3490, 2965, 1787, 1701, 1454, 1387, 1366, 1305, 1201, 1112, 1054, 704. ***m/z*** (ES+) = 332.14 (MNa^+, 100%); HRMS (ES+) calc for $C_{16}H_{20}NO_4FNa$ = 332.1274, found = 332.1280.

(2*S*,3*S*)-Benzyl 2-fluoro-3-hydroxy-2-methyloctanoate 233:

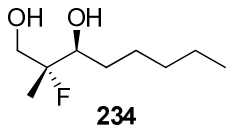


233

n-BuLi (0.2 mL, 0.5 mmol) was added to benzyl alcohol (70 µL, 0.7 mmol) in THF (2 mL) at 0°C. After 30 min, a solution of **228** (0.1 g, 0.3 mmol) in THF (2 mL) (previously cooled to 0 °C) was added and the solution was stirred at 0 °C for 2 h. The reaction was then quenched with a saturated solution of NH_4Cl (1 mL). Organic residues were extracted into Et_2O (3 x 5 mL), washed with water (5 mL) and dried over $MgSO_4$. Solvents were removed under reduced pressure. The title compound **233** was purified over silica (hexane 8 / EtOAc 2), and recovered as a white solid (73 mg, 79%).

Mp = 36-38 °C. $\mathbf{[\alpha]_D^{20}}$ = -25.4 ° (C= 1.1, DCM). **^{1}H-NMR** ($CDCl_3$, 300 MHz): δ (ppm) = 7.36 (m, 5 H, *H* ar); 5.23 (m, 2 H, PhCH_2); 3.77 (ddd, 1 H, *J* = 2.3, 10.0, 17.8 Hz, HOC*H*); 2.05 (br s, 1 H, O*H*), 1.60 (d, 3 H, *J* = 22.1 Hz, FCCH_3); 1.53-1.12 (m, 8 H, 4 x CH_2); 0.87 (t, 3 H, *J* = 6.8 Hz, CH_3). **^{13}C-NMR** ($CDCl_3$, 75Mz): δ (ppm) = 171.2 (d, *J* = 25.0 Hz, *C*O); 144.4 (*C* ar); 129.1 (*C* ar); 129.0 (*C* ar); 128.8 (*C* ar); 97.3 (d, *J* = 187.3 Hz, *C*F); 75.0 (d, *J* = 22.7 Hz, COH); 67.7 (Ph*C*H_2); 31.9 (*C*H_2); 31.5 (d, *J* = 3.4 Hz, *C*H_2); 26.0 (*C*H_2); 22.9 (*C*H_2); 20.2 (d, *J* = 23.9 Hz, *C*H_3CF); 14.4 (*C*H_3). **^{19}F-NMR** ($CDCl_3$, 282MHz): δ (ppm) = -167.4 (dq, *J* = 17.8, 22.1 Hz). $\mathbf{\nu_{max}/cm^{-1}}$ 3443, 2954, 2859, 1739, 1456, 1283, 1114, 1082, 956, 751, 697. ***m/z*** (ES+) = 305.16 (MNa^+, 100%); HRMS (ES+) calc for $C_{16}H_{23}O_3FNa$ = 305.1529, found = 305.1534.

(2*R*,3*S*)-2-Fluoro-2-methyloctane-1,3-diol 237:

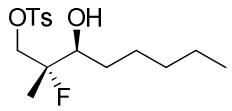


234

$NaBH_4$ (70 mg, 1.84 mmol) was added portion wise to a solution of **228** (138 mg, 0.455 mmol) in a mixture of THF (4 mL) and methanol (0.5 mL) at 0 °C. The solution was stirred for 2.5 h at 0 °C, and then HCl 2N was added dropwise till pH 3-4. Water was added, and the organic product was extracted into EtOAc (3 x 5 mL). Organic layers were dried over $MgSO_4$, and the solvent was removed under reduced pressure. The title compound **234** was purified over silica (cyclohexane/EtOAc 60/40) and recovered as a white solid (53 mg, 66%).

Mp = 58-59 °C. $\mathbf{[\alpha]_D^{20}}$ = -28° (C = 0.98, DCM). $^{\mathbf{1}}$**H-NMR** ($CDCl_3$, 300 MHz): δ (ppm) = 3.83 (dd, 1 H, *J* = 12.4, 25.1 Hz, *Ha*Hb); 3.79 (m, 1 H, *H*COH); 3.65 (dd, 1 H, *J* = 12.4, 17.5 Hz, Ha*Hb*); 2.96 (br s, 2 H, O*H*); 1.61-1.23 (m, 8 H, 4 x CH_2); 1.24 (d, 3 H, *J* = 22.4 Hz, CH_3); 0.89 (t, 3 H, *J* = 6.6 Hz, CH_3). $^{\mathbf{13}}$**C-NMR** ($CDCl_3$, 75Mz): δ (ppm) = 97.6 (d, *J* = 170.1 Hz, *C*F); 74.0 (d, *J* = 26.3 Hz, H*C*OH); 66.1 (d, *J* = 23.6 Hz, H_2*C*OH); 31.7 (*C*H_2); 30.8 (d, *J* = 2.8 Hz, *C*H_2); 26.0 (*C*H_2); 22.5 (*C*H_2); 17.4 (d, *J* = 23.2 Hz, *C*H_3); 14.0 (*C*H_3). $^{\mathbf{19}}$**F-NMR** ($CDCl_3$, 282MHz): δ (ppm) = -162.1 (dddq, *J*= 25.1, 22.4, 17.5, 7.7 Hz). $\mathbf{\nu_{max}/cm^{-1}}$ 3320, 2923, 2853, 1463, 1378, 1057. ***m/z*** (ES+) = 201.04 (MNa^+, 100%); HRMS (ES+) calc for $C_9H_{19}O_2FNa$ = 201.1267 found = 201.1276.

(2*R*,3*S*)-2-Fluoro-3-hydroxy-2-methyloctyl-4'-ethylbenzenesulfonate 235:

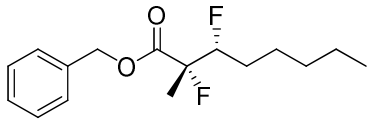


235

Tosyl chloride 98% (65 mg, 0.3 mmol) was added to a solution of **234** (49 mg, 0.3 mmol) and 2,4,6-trimethyl pyridine (73 µL, 0.5 mmol) in DCM (3 mL). The solution was heated at 60 °C for 3 d. EtOAc (10 mL) was added and the reaction mixture was washed with a saturated solution of $CuSO_4$ (3 x 2 mL) and water (2 x 2 mL). The organic layers were dried over $MgSO_4$ and solvents were removed under reduced pressure. The product **235** was purified over silica (cyclohexane 8 / EtOAc 2) and recovered as a colourless oil (52 mg, 57%).

$\mathbf{[\alpha]_D^{20}}$ = -10.4 ° (C= 0.8, DCM). **^{1}H-NMR** ($CDCl_3$, 300 MHz): δ (ppm) = 7.80 (d, 2 H, *J* = 8.3 Hz, H ar); 7.35 (d, 2 H, *J* = 8.3 Hz, H ar); 4.25 (dd, 1 H, *J* = 11.1, 21.0 Hz, TsOC*Ha*Hb); 4.03 (dd, 1 H, *J* = 11.1, 20.4 Hz, TsOCHa*Hb*); 3.78-3.70 (m, 1 H, HOC*H*); 2.45 (s, 3 H, CH_3); 2.18 (d, 1 H, *J*= 5.04 Hz, O*H*); 1.56-1.23 (m, 8 H, 4 x CH_2); 1.27 (d, 3 H, *J* = 22.0 Hz, CH_3); 0.88 (t, 3 H, *J* = 6.7 Hz, CH_3). **^{13}C-NMR** ($CDCl_3$, 75Mz): δ (ppm) = 145.6 (*C* ar); 132.9 (*C* ar); 130.3 (*C* ar); 128.4 (*C* ar); 96.5 (d, *J* = 175.8 Hz, *C*F); 73.0 (d, *J* = 26.3 Hz, HO*C*HCF); 71.6 (d, *J* = 24.1 Hz, *C*H_2CF); 32.1 (*C*H_2); 30.7 (d, *J* = 2.2 Hz, *C*H_2); 26.4 (*C*H_2); 23.0 (*C*H_2); 22.1 (*C*H_3); 17.2 (d, *J* = 23.2 Hz, *C*H_3CF); 14.4 (*C*H_3). **^{19}F-NMR** ($CDCl_3$, 282MHz): δ (ppm) = -160.7 (*J*= 22.3, 20.8, 28.1, 8.1 Hz). $\mathbf{\nu_{max}/cm^{-1}}$ 2360, 117, 799, 668. ***m/z*** (CI+) = 333.15 (MH^+, <10%) ; HRMS (CI+) calc for $C_{16}H_{26}O_4SF$ = 333.1536 found = 333.1528.

(2*R*,3*R*)-Benzyl 2,3-difluoro-2-methyloctanoate 236:

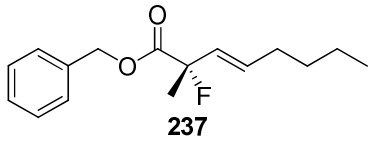


236

Deoxo-Fluor® (50% in THF, 200 µL, 0.5 mmol) was added to **233** (30 mg, 0.1 mmol) in DCM (2 mL) at RT. The solution was then heated under reflux for 2 h and the reaction mixture was cooled to RT and quenched with silica. ^{19}F-NMR analysis indicated complete conversion of the starting material to products **236** and **237** with a ratio 35/65. These two products were purified over silica (hexane 95 / EtOAc 5) and recovered as colourless oils (**236**, 7 mg, 23%) (**237**, 11 mg, 40%).

$[\alpha]_D^{20}$ = +5.0° (C= 0.7, $CDCl_3$). **^{1}H-NMR** ($CDCl_3$, 300 MHz): δ (ppm) = 7.4-7.3 (m, 5 H, *H* ar); 5.2 (2 x d, 2 H, *J* = 12.2 Hz, PhC*H*$_2$); 4.6 (dddd, 1 H, *J* = 1.9, 10.0, 19.8, 46.5 Hz, FC-CF*H*); 1.7-1.8 (m, 1 H, FC-C*H*H); 1.6-1.5 (m, 1 H, FC-CH*H*); 1.5 (dd, 3 H, *J* = 21.2, 1.2 Hz, C*H*$_3$-CF-CF); 1.4-1.2 (m, 6 H, 3 x C*H*$_2$); 7.0 (t, 3 H, *J* = 7.0 Hz). **^{13}C-NMR** ($CDCl_3$, 75Mz): δ (ppm) = 128.6 (*C* ar); 128.5 (*C* ar); 128.2 (*C* ar); 94.7 (dd, *J* = 179.5, 23.4 Hz, HC*F*); 67.5 (Ph*C*H$_2$); 31.4 (*C*H$_2$); 28.2 (dd, *J* = 21.5, 3.5 Hz, FC*C*H$_2$); 24.8 (*C*H$_2$); 22.4 (*C*H$_2$); 19.5 (dd, *J* = 24.0, 5.1 Hz, FC*C*H$_3$); 14.0 (*C*H$_3$); (the signals of the three quaternary carbons were not observed). **^{19}F-NMR** ($CDCl_3$, 282MHz): δ (ppm) = -170.2 (m, 1 F); -191.2 (m, 1 F). **^{19}F{^{1}H}-NMR** ($CDCl_3$, 282 MHz): δ (ppm)= -170.2 (d, *J* = 11.1 Hz, CH$_3$-C*F*); -191.2 (d, *J* = 11.1 Hz, HC*F*). **ν_{max}/cm^{-1}** 2958 , 1768, 1652, 1456, 1381, 1282, 1136, 1104. ***m/z*** (ES+) = 307.17 (MNa$^+$, 100%); HRMS (ES+) calc for $C_{16}H_{22}O_2F_2Na$ = 307.1486, found = 307.1479.

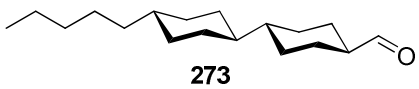
(*S*,*E*)-Benzyl 2-fluoro-2-methyloct-3-enoate 237:



237

$[\alpha]_D^{20}$ = -15.7 ° (C = 1.1, $CDCl_3$). **^{1}H-NMR** ($CDCl_3$, 300 MHz): δ (ppm) = 7.35 (m, 5 H, *H* ar); 5.8 (ddt, 1 H, *J* = 6.9, 15.7, 1.7 Hz, FC-CH=C*H*); 5.6 (ddt, 1 H, *J* = 1.4, 15.7, 15.9 Hz, FC-C*H*=CH); 5.2 (s, 2 H, PhCH_2); 2.0 (m, 2 H, CH=CH-CH_2); 1.6 (d, 3 H, *J* = 21.4 Hz, FCCH_3); 1.3 (m, 4 H, 2 x CH_2); 0.9 (t, 3 H, *J* = 7.1 Hz, CH_3). **^{13}C-NMR** ($CDCl_3$, 75Mz): δ (ppm) = 171.0 (d, *J* = 27.1 Hz, CO); 135.3 (*C* ar); 133.4 (d, *J* = 9.8 Hz, FC-C=*C*); 128.6 (*C* ar); 128.4 (*C* ar); 128.1 (*C* ar); 127.1 (d, *J* = 21.1 Hz, (FC-*C*=C); 92.3 (d, *J* = 183.9 Hz, *C*F); 67.1 (ph*C*H_2); 31.8 (*C*H_2); 30.8 (*C*H_2); 23.9 (d, *J* = 25.4 Hz, *C*H_3CF); 22.1 (*C*H_2); 13.9 (*C*H_3). **^{19}F-NMR** ($CDCl_3$, 282MHz): δ (ppm) = -150.6 (dq, *J* = 15.9, 21.4 Hz). **ν_{max}/cm^{-1}** 2958, 2930, 2873, 1761, 1740, 1456, 1378, 1269, 1118, 971, 696. ***m/z*** (ES+) = 287.15 (MNa^+, 100%); HRMS (ES+) calc for $C_{16}H_{21}O_2FNa$ = 287.1423, found = 287.1426.

4'-Pentylbi(cyclohexane)-4-carbaldehyde 273 :



273

TEMPO (0.1 g, 0.64 mmol) was added to a mixture of Merck motif **272** (3 g, 11.29 mmol) in toluene (50 mL). Then NaBr (500 mg, 4.86 mmol) and a saturated solution of $NaHCO_3$ (20 mL) were added, followed by bleach (10-13% in water, 10 mL, ~ 13.5 mmol). The biphasic mixture was stirred vigorously overnight and organic compounds were then extracted into EtOAc (3 x 50 mL), and washed with water (2 x 20 mL). Organic layer was dried over $MgSO_4$ and solvents were removed under reduced pressure. Aldehyde **273** was purified over silica (hexane 5 / Et_2O 5) and recovered as white solid (1.728 g, 58%).

Mp = 43-45 °C. **^{1}H-NMR** ($CDCl_3$, 300 MHz): δ (ppm) 9.59 (d, 1 H, *J* = 1.6 Hz, *H*CO); 2.13 (ttd, 1 H, *J* = 12.1, 3.5, 1.6 Hz, *H*C-CHO); 2.0-1.96 (m, 2 H, CH_2); 1.84 (m, 6 H, 3 x CH_2); 1.32-0.81 (m, 22 H, 3 x C*H*, 8 x CH_2, CH_3). **^{13}C-NMR** ($CDCl_3$, 75Mz): 205.4 (*C*O); 51.1 (*C*H); 43.6 (*C*H); 43.2 (*C*H); 38.3 (*C*H); 37.8 (*C*H_2); 34.0 (2 x *C*H_2); 32.6 (*C*H_2); 30.4 (2 x *C*H_2); 29.2 (2 x *C*H_2); 27.1 (*C*H_2); 26.7 (2 x *C*H_2); 23.1 (*C*H_2); 14.5 (*C*H_3). **ν_{max}/cm^{-1}** 2909, 2848, 1717, 1204, 1150, 749, 764. ***m/z*** (CI+) = 265.25 (MH^+, 40%). HRMS (CI+) found 265.2528 for $C_{18}H_{33}O$, requires 265.2531.

(*R*,*E*)-1-((1*R*,4*R*,4'*R*)-4'-Pentylbi(cyclohexan)-4-yl)hex-2-en-1-ol 274:

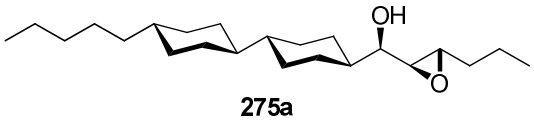
274

Cyclohexene (1.21 mL, 12 mmol) was added to BH_3.DMS (1 M in DCM, 6 mL, 6 mmol) at 0 °C, and the solution was stirred at that temperature for 2 h. Pentyne (0.59 mL, 6 mmol) was then added, and the solution stirred at RT for 1 h. The solution was then cooled to - 78 °C and diethyl zinc (1 M in hexane, 10 mL, 10 mmol) was added, followed by (-)-MIB **261** (0.1 g, 0.4 mmol) dissolved in 1 mL toluene. After 30 minutes, the reaction mixture was warmed to -40 °C and aldehyde **273** (1 g, 3.7 mmol) dissolved in 5 mL toluene was added. The reaction mixture was stirred at -10 °C for 2 days, and then quenched by addition of a saturated solution of NH_4Cl (10 mL). The organic compounds were extracted into DCM (3 x 10 mL) and washed with water (10 mL). The organic layer was dried over $MgSO_4$, and the solvents were removed under reduced pressure. Allylic alcohol **274** was purified over silica (hexane 7 / Et_2O 3) and recovered as a white solid (0.454 g, 36%).

Mp = 59-60 °C. $\mathbf{[\alpha]_D^{20}}$ **=** +5.0 ° (C= 0.8, $CHCl_3$). **^{1}H-NMR** ($CDCl_3$, 300 MHz): δ (ppm) 5.59 (dt, 1 H, *J* = 15.4, 6.6 Hz, HC=C*H*); 5.44 (ddt, 1 H, *J* = 7.3, 15.4, 1.1 Hz, *H*C=CH); 3.75 (ddd, 1 H, *J* = 6.6, 3.6, 1.1 Hz, *H*COH); 2.01 (dt, 2 H, *J* = 7.3, 6.1 Hz, HC=CH-CH_2); 1.91-1.67 (m, 8 H, 4 x CH_2); 1.43-0.85 (m, 28 H, 9 x CH_2, 2 x CH_3, 4 x C*H*). **^{13}C-NMR** ($CDCl_3$, 75Mz): 133.2 (H*C*=CH); 132.1 (HC=*C*H); 78.2 (H*C*OH); 44.3 (*C*H); 43.8 (*C*H); 43.7 (*C*H); 38.3 (*C*H); 37.9 (*C*H_2); 34.7 (*C*H_2); 34.1 (2 x *C*H_2); 32.7 (*C*H_2); 30.5 (2 x *C*H_2); 30.1 (*C*H_2); 30.0 (*C*H_2); 29.4 (*C*H_2); 27.1 (*C*H_2); 23.1 (*C*H_2); 14.5 (*C*H_3); 14.1 (*C*H_3). $\mathbf{\nu_{max}/cm^{-1}}$ 2913, 2848, 1275, 1268, 1183, 764, 749. ***m/z*** (ES+) = 357.27 (MNa^+, 100%); HRMS (ES+) found 357.3138 for $C_{23}H_{42}ONa$, requires 357.3133.

(*R*)-((1*R*,4*R*,4'*R*)-4'-Pentylbi(cyclohexan)-4-yl)((2*S*,3*S*)-3-propyloxiran-2-yl)methanol

275a:



275a

TBHP (5.5 M in decane, 0.325 mL, 1.78 mmol) was added dropwise to a solution allylic alcohol **274** (414 mg, 1.24 mmol) and titanium tetraisopropoxide (0.44 mL, 1.36 mmol) in DCM (10 mL) at -20 °C. The solution was stirred for 10 h and then quenched by addition of $Na_2S_2O_3$ 10% (5 mL). Organic compounds were extracted into DCM (“ x 10 mL), washed with water (10 mL), and the organic layer was dried over $MgSO_4$. Solvent was removed under reduced pressure and compound **275a** and **275b** were purified over silica (DCM 80 / hexane 15 / Et_2O 5) and recovered as white solids (**275b** 0.107 g, **275a** 0.202 g, 71%).

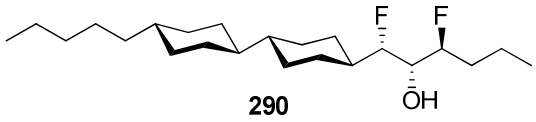
Mp = 90-93 °C. $\mathbf{[\alpha]_D^{20}}$ = -15.3° (C = 0.75, $CHCl_3$). **^{1}H-NMR** ($CDCl_3$, 300 MHz): δ (ppm) 3.15 (dd, 1 H, *J* = 5.3, 6.6 Hz, *H*COH); 2.88 (dt, 1 H, *J* = 2.3, 4.7 Hz, *H*CO-CH_2); 2.78 (dd, 1 H, *J* = 2.3, 5.3 Hz, *H*CO); 1.99-1.96 (m, 2 H, C*H*$_2$); 1.78-1.67 (m, 6 H, 3 x C*H*$_2$); 1.57-1.40 (m, 5 H, 2 x C*H*$_2$, 1 x C*H*); 1.30-0.81 (m, 24 H, 2 x C*H*$_3$, 8 x C*H*$_2$, 3 x C*H*). **^{13}C-NMR** ($CDCl_3$, 75Mz): 76.0 (H*C*OH); 60.8 (H*C*O); 57.4 (H*C*O); 43.8 (*C*H); 43.6 (*C*H); 42.8 (*C*H); 38.3 (*C*H); 37.9 (*C*H_2); 34.1 (*C*H_2); 34.0 (2 x *C*H_2); 32.6 (*C*H_2); 30.4 (2 x *C*H_2); 29.9 (*C*H_2); 29.3 (2 x *C*H_2); 27.1 (*C*H_2); 23.1 (*C*H_2); 19.7 (*C*H_2); 14.5 (*C*H_3); 14.3 (*C*H_3). $\mathbf{\nu_{max}/cm^{-1}}$ 2906, 2847, 2360, 1276, 1275, 1184, 760, 749. ***m/z*** (ES+) = 373.24 (MNa^+, 100%); HRMS (ES+) found 373.3078 for $C_{23}H_{42}O_2Na$, requires 373.3083.

(*R*)-((1*R*,4*R*,4'*R*)-4'-Pentylbi(cyclohexan)-4-yl)((2*R*,3*R*)-3-propyloxiran-2-yl)methanol 275b:

275b

Mp = 80-84 °C. **$[\alpha]_D^{20}$** = -2.7° (C = 0.3, $CHCl_3$). **^{1}H-NMR** ($CDCl_3$, 300 MHz): δ (ppm) 3.58 (m, 1 H, *H*COH); 3.00 (dt, 1 H, *J* = 2.6, 5.6 Hz, *H*CO-CH_2); 2.82 (dd, 1 H, *J* = 2.9, 2.6 Hz, *H*CO); 1.90-1.86 (m, 2 H, C*H*$_2$); 1.80-1.67 (m, 6 H, 3 x C*H*$_2$); 1.56-1.42 (m, 5 H, 2 x C*H*$_2$, 1 x C*H*); 1.32-0.81 (m, 24 H, 2 x C*H*$_3$, 8 x C*H*$_2$, 3 x C*H*). **^{13}C-NMR** ($CDCl_3$, 75Mz): 72.7 (H*C*OH); 60.0 (H*C*O); 55.2 (H*C*O); 43.7 (*C*H); 43.6 (*C*H); 42.2 (*C*H); 38.3 (*C*H); 37.9 (*C*H_2); 34.0 (2 x *C*H_2); 32.6 (*C*H_2); 30.5 (*C*H_2); 30.1 (*C*H_2); 29.3 (*C*H_2); 28.9 (*C*H_2); 27.1 (*C*H_2); 23.1 (*C*H_2); 19.8 (*C*H_2); 14.5 (*C*H_3); 14.4 (*C*H_3). **ν_{max}/cm^{-1}** 2905, 2849, 2360, 1268, 1275, 1181, 764, 749. ***m/z*** (ES+) = 373.22 (MNa^+, 100%); HRMS (ES+) found 373.3075 for $C_{23}H_{42}O_2Na$, requires 373.3083.

(1*S*,2*S*,3*S*)-1,3-Difluoro-1-((1*S*,4*R*,4'*S*)-4'-pentylbi(cyclohexan)-4-yl)hexan-2-ol 290:

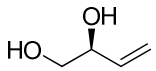


290

3HF.Et_3N (1 mL, 6.13 mmol) was added to a solution of fluoro epoxide **287** (7:1 dr) (75 mg, 0.021 mmol) in THF (3 mL) in a sealed bomb with a Teflon inner layer. The reaction mixture was stirred at 150 °C for 1 day, and then quenched by addition of aqueous solution of $NaHCO_3$ 5% (5 mL). Organic compounds were extracted into DCM (3 x 5 mL), and washed with a solution of $NaHCO_3$ 5% (5 mL), and water. Organic layers were dried over $MgSO_4$ and solvents were removed under reduced pressure. **290** was purified over silica gel (hexane 9 / Et_2O 1) and recovered as a white paste (10 mg, 12%).

$[\alpha]_D^{20}$ = -2.0° (C = 1, $CHCl_3$). **^{1}H-NMR** ($CDCl_3$, 300 MHz): δ (ppm) 4.47 (ddt, 1 H, *J* = 2.2, 8.7, 48.2 Hz, *H*CF-CH_2); 4.36 (br dd, 1 H, *J* = 47.3, 8.8 Hz, *H*CF); 3.71-3.54 (m, 1 H, *H*COH); 2.06-0.8 (m, 39 H). **^{13}C-NMR** ($CDCl_3$, 75Mz): 95.8 (d, *J* = 169.6 Hz, *C*F); 92.0 (d, *J* = 168.7 Hz, *C*F); 71.0 (dd, *J* = 24.9, 20.0 Hz, HO*C*H); 43.1 (d, *J* = 25.1 Hz); 39.9 (*C*H); 37.9 (CH_2); 33.6 (CH_2); 32.3 (CH_2); 29.9 (d, *J* = 23.1 Hz CH_2); 29.6 (*C*H); 29.4 (*C*H); 29.2 (CH_2); 29.0 (CH_2); 28.4 (d, *J* = 6.9 Hz CH_2); 26.7 (CH_2); 22.8 (CH_2); 18.1 (CH_2); 14.1 (CH_3); 13.9 (CH_3).**^{19}F-NMR** ($CDCl_3$, 282MHz): [-191.1]-[-191.5] (m, HC*F*); [-207.3]-[-207.6] (m, HC*F*). **^{19}F{^{1}H}-NMR** ($CDCl_3$, 282MHz): -191.3 (d, *J* = 4.1 Hz, HC*F*); - 207.4 (d, *J* = 4.1 Hz, HC*F*). **ν_{max}/cm^{-1}** 2919, 2849, 1275, 1267, 1206, 1150, 764, 749. ***m/z*** (ES+) = 395.22 (MNa^+, 100%); HRMS (ES+) found 395.3101 for $C_{23}H_{42}OF_2Na$, requires 395.3101.

(*S*)-But-3-ene-1,2-diol 278 :

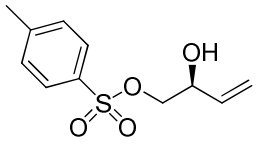


278

Butadiene monoxide **277** 98% (15 mL, 0.182 mol) was added to Jacobsen's catalyst Co^{III} acetate prepared following a literature procedure [5] (0.55 g, 0.091 mmol), and the mixture was cooled to 0 °C. Water (1.48 mL, 82 mmol) was then added dropwise and the mixture allowed to rise to RT. After 12 h the excess of water and butadiene monoxide were distilled off under reduced pressure at 30 °C, and the title compound **278** was distilled off under reduced pressure at 60 °C and recovered as a colourless oil (6.91g, 42%).

$[\alpha]_D^{20}$ = -45° (C = 2.5, iPrOH) (literature $[\alpha]_D$ -44°, [5]). **^{1}H-NMR** ($CDCl_3$, 300 MHz): δ (ppm) 5.86 (ddd, 1 H, *J* = 5.6, 10.5, 17.3 Hz, *H*C=CHH); 5.37 (ddd, 1 H, *J* = 1.4, 17.3, 1.4 Hz, HC=C*H*H); 5.24 (ddd, 1 H, *J* = 10.6, 1.4, 1.4 Hz, HC=CH*H*); 4.29-4.23 (m, 1H, *H*COH); 3.67 (dd, 1 H, *J* = 11.2, 3.5 Hz, HOC*H*H); 3.50 (dd, 1 H, *J* = 11.2, 7.2 Hz, HOCH*H*); 2.13 (s, 2 H, OH). **^{13}C-NMR** ($CDCl_3$, 75Mz): δ (ppm) = 136.7 (H*C*=CH_2), 116.7 (HC=*C*H_2), 73.3 (H*C*OH), 66.2 (H_2*C*OH).

(*S*)-2-Hydroxybut-3-enyl 4-methylbenzenesulfonate 279 :

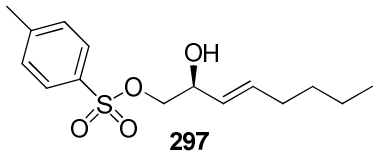


279

Dibutyltin oxide 98% (0.17 g, 0.67 mmol) was added to a solution of diol **278** (1 g, 11.33 mmol) in MeCN (20 mL), and the mixture was heated under reflux till complete dissolution of dibutyltin oxide. The solution was then cooled to RT and Et_3N (1.8 mL, 12.94 mmol) was added, followed by TsCl (2.43 g, 12.49 mmol). After 1 h at RT, MeCN was removed under reduced pressure and compound **279** was purified over silica gel (DCM 95 / Et_2O 5) and recovered as a white solid (2.03 g, 74%). **279** was recrystallised from toluene at 4 °C (~ 1.5 mL Toluene/g of **279**).

Mp = 58-60 °C. **$[\alpha]_D^{20}$** = -7.8 ° (C= 1, MeOH) (literature $[\alpha]_D$ -7.7 °) [6]. **^{1}H-NMR** ($CDCl_3$, 300 MHz): δ (ppm) 7.8 (d, 2 H, *J* = 8.3 Hz, *H* ar) ; 7.36 (d, 2 H, *J* = 8.3 Hz, *H* ar) ; 5.75 (ddd, 1 H, *J* = 5.4, 10.5, 17.2 Hz, *H*C=CH_2); 5.37 (ddd, 1 H, *J* = 1.4, 17.2, 1.4 Hz, HC=C*H*H) ; 5.25 (ddd, 1 H, *J* = 10.5, 1.4, 1.4 Hz, HC=CH*H*) ; 4.43-4.37 (m, 1 H, *H*COH) ; 4.07 (dd, 1 H, *J* = 10.2, 3.3 Hz, TsOC*Ha*Hb) ; 3.91 (dd, 1 H, *J* = 10.2, 7.4 Hz, TsOCHa*Hb*) ; 2.45 (s, 3 H, C*H*$_3$) ; 2.15 (brs, 1 H, OH). **^{13}C-NMR** ($CDCl_3$, 75Mz): δ (ppm) = 145.1 (*C* ar); 134.6 (H*C*=CH_2); 132.6 (*C* ar); 130.0 (*C*H ar); 128.0 (*C*H ar); 118.1 (HC=*C*H_2); 73.0 (TsO-*C*H_2); 70.4 (HO-*C*H); 21.7 (CH_3).

(*S*,*E*)-2-Hydroxyoct-3-enyl 4-methylbenzenesulfonate 297:



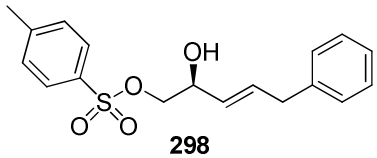
297

Grubbs' 2nd generation catalyst (105 mg, 0.124 mmol) was added to a solution of **279** (1.5 g, 6.2 mmol) and 1-hexene (7.75 mL, 62.2 mmol) in DCM (15 mL). The solution was heated under reflux for 9 h. Then DCM was removed under reduced pressure and **297** was purified over silica (DCM 95 / Et_2O 5). The title compound was recovered as a brown oil (1.20 g, 81%), in a 92:8 *E:Z* ratio.

$[\alpha]_D^{20}$ = +22.1° (C = 1, DCM). **^{1}H-NMR** ($CDCl_3$, 300 MHz): δ (ppm) 7.80 (d, 2 H, *J* = 8.4 Hz, H ar); 7.35 (d, 2 H, *J* = 8.4 Hz, H ar); 5.77 (dtd, 1 H, *J* = 15.4, 6.7, 1.1 Hz, HC=C*H*CH_2); 5.33 (ddt, 1 H, *J* = 15.4, 6.5, 1.5 Hz, *H*C=CHCH_2); 4.33 (m, 1 H, HOC*H*); 4.02 (dd, 1 H, *J* = 10.1, 3.4 Hz, O_2SOC*H*H); 3.88 (dd, 1 H, *J* = 10.1, 7.7 Hz, O_2SOCH*H*); 2.45 (s, 3 H, CH_3); 2.04-1.97 (m, 2 H, CH_2); 1.34-1.23 (m, 4 H, 2 x CH_2); 0.87 (t, 3 H, *J* = 7.1 Hz, CH_3). **^{13}C-NMR** ($CDCl_3$, 75Mz): 145.0 (*C* ar); 135.6 (H*C*=CH); 132.7 (*C* ar); 129.9 (*C*H ar); 128.0 (*C*H ar); 126.2 (HC=*C*H); 73.4 (O_2SO*C*H_2); 70.3 (HO*C*H); 31.9 (*C*H_2); 30.9 (*C*H_2); 22.1 (*C*H_2); 21.6 (*C*H_3); 13.9 (*C*H_3). **ν_{max}/cm^{-1}** 2360, 1205, 1149, 758, 764, 749. ***m/z*** (ES+) = 321.02 (MNa^+, 100%); HRMS (ES+) calc for $C_{15}H_{22}O_4NaS$ = 321.1137 found = 321.1128.

(Selected assignment of Z-isomer: 5.59 (dtd, 1 H, *J* = 11.0, 7.5, 1.1 Hz, HC=C*H*CH_2); 4.68 (m, 1 H, HOC*H*)).

(*S*,*E*)-2-Hydroxy-5-phenylpent-3-enyl 4-methylbenzenesulfonate 298:



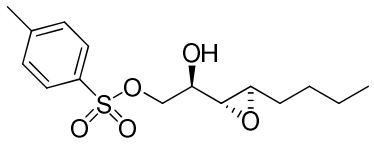
298

Grubbs' 2nd generation catalyst (79 mg, 0.09 mmol) was added to a solution of **279** (2 g, 8.26 mmol) and allyl benzene (5.47 mL, 41.30 mmol) in DCM (20 mL). The solution was heated under reflux for 2 days. Then DCM was removed under reduced pressure and **298** purified over silica (DCM 95 / Et_2O 5). The title compound was recovered as a brown oil (2.20 g, 80% yield), in a 94:6 *E*:*Z* ratio.

$[\alpha]_D^{20}$ = +16.2 ° (C = 1, DCM). **^{1}H-NMR** ($CDCl_3$, 300 MHz): δ (ppm) 7.79 (d, 2 H, *J* = 8.3 Hz, *H* ar); 7.34 (d, 2 H, *J* = 8.3 Hz, *H* ar); 7.32-7.12 (m, 5 H, *H* ar); 5.95 (ddt, 1 H, *J* 1.2, 6.7, 15.4 Hz, *H*C=CH); 5.41 (ddt, 1 H, *J* = 1.5, 6.4, 15.4 Hz, HC=C*H*); 4.41-4.35 (m, 1 H, HOC*H*), 4.05 (dd, 1 H, *J* = 3.4, 10.2 Hz, SO_2OC*H*H), 3.91 (dd, 1 H, *J* = 7.5, 10.2 Hz, SO_2OCH*H*); 3.36 (d, 2 H, *J* = 6.7 Hz, CH_2); 2.45 (s, 3 H, CH_3), 2.11 (s, 1 H, O*H*). **^{13}C-NMR** ($CDCl_3$, 75Mz): δ (ppm) = 145.5 (*C* ar); 139 (*C* ar); 134.1 (H*C*=CH); 133.1 (*C* ar); 130.41 (HC=*C*H); 129.0 (*C*H ar); 128.9 (*C*H ar); 128.4 (*C*H ar); 128.2 (*C*H ar); 126.7 (*C*H ar); 73.7 (SO_3-*C*H_2); 70.4 (HO-*C*H); 39.0 (*C*H_2); 22.1 (*C*H_3). **ν_{max}/cm^{-1}** 3025, 1355, 1189, 1175, 1148, 967, 750. ***m/z*** (ES+) = 355.06 (MNa^+, 100%); HRMS (ES+) found 355.0969 for $C_{18}H_{20}O_4NaS$, requires 355.0980.

Selected assignment for *Z*-isomer: 5.80 (ddt, 1 H, *J* = 1.2, 7.7, 10.9 Hz, *H*C=CH); 4.83-4.79 (m, 1 H, HOC*H*).

(*R*)-2-((2*R*,3*R*)-3-Butyloxiran-2-yl)-2-hydroxyethyl 4-methylbenzenesulfonate 302:

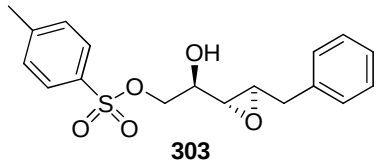


302

(-)-D-diisopropyl tartrate 98% (0.16 mL, 0.738 mmol) was added to a solution of titanium tetraisopropoxide 99.99% (0.2 mL, 0.682 mmol) in DCM (7 mL) with molecular sieves 4Å at -30 °C, and the solution was stirred for 30 min at -30 °C. Then **297** (0.195 g, 0.625 mmol) dissolve in DCM (3 mL) was added dropwise, followed by CHP 88% (0.22 mL, 1.25 mmol). The reaction mixture was stirred for 40 h at -30 °C and then quenched by addition of a 10% solution of $Na_2S_2O_3$. Organic compounds were extracted into DCM (3 x 20 mL) and washed with HCl 1N (5 mL), and water (10 mL). Organic layer was dried over $MgSO_4$, and solvent was removed under reduced pressure. **302** was purified twice over silica gel (hexane 7 / EtOAc 3 and DCM 9 / Et_2O 1) and recovered as a colourless oil (162 mg, 80%).

$[\alpha]_D^{20}$ = +16.3 ° (C = 1, DCM). **^{1}H-NMR** ($CDCl_3$, 300 MHz): δ (ppm) 7.80 (d, 2 H, *J* = 8.4 Hz, H ar); 7.36 (d, 2 H, *J* = 8.4 Hz, H ar); 4.16 (dd, 1 H, *J* = 10.5, 3.9 Hz, O_2SOCHH); 4.09 (dd, 1 H, *J* = 10.5, 5.5 Hz, O_2SOCHH); 3.87 (m, 1 H, HO*CH*); 2.94 (td, 1 H, *J* = 5.6, 2.2 Hz, O*CH*CH_2); 2.79 (dd, 1 H, *J* = 4.5, 2.2 Hz, O*CH*); 2.45 (s, 3 H, CH_3); 2.31 (d, 1 H, *J* = 3.74 Hz, O*H*); 1.57-1.50 (m, 2 H, CH_2); 1.42-1.30 (m, 4 H, 2 x CH_2); 0.89 (t, 3 H, *J* = 7.1 Hz, CH_3). **^{13}C-NMR** ($CDCl_3$, 75 MHz): 145.6 (*C* ar); 132.8 (*C* ar); 130.4 (*C*H ar); 128.4 (*C*H ar); 71.2 (O_2SOCH_2); 68.5 (HO*C*H); 57.6 (*C*-O); 56.7 (*C*-O); 31.4 (CH_2); 28.3 (CH_2); 22.8 (CH_2); 22.1 (CH_3); 14.3 (CH_3). **ν_{max}/cm^{-1}** 2925, 2360, 1354, 1123, 972, 902, 749. ***m/z*** (CI+) = 315.13 (MH^+, 10%), 297.12 (M - H_2O, 10%), HRMS (CI) calc for $C_{15}H_{23}O_5S$ = 315.1266 found = 315.1274.

(*R*)-2-((2*R*,3*R*)-3-Benzyloxiran-2-yl)-2-hydroxyethyl 4-methylbenzenesulfonate 303:

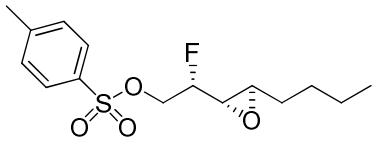


303

Titanium tetraisopropoxide 99.99% (0.53 mL, 1.81 mmol) was added to (-)-D-diisopropyl tartrate 98% (0.39 mL, 1.81 mmol) in DCM (15 mL) at -30 °C with molecular sieves 4 Å. After 45 minutes, allylic alcohol **298** (0.5 g, 1.51 mmol) in DCM (5 mL) and precooled to -30 °C, was slowly canulated. Then CHP 88% (0.5 mL, 3.01 mmol) was added dropwise. The reaction mixture was stirred at -30 °C for 42 hours. Then a solution of sodium bisulfite (10 mL) was added and the solution warmed to RT. Organic compounds were extracted into DCM (3 x 10 mL), washed with water (10 mL) and dried over $MgSO_4$. After solvent was removed under reduced pressure, **303** was purified over silica (DCM 92/ Et_2O 8) and recovered as colourless oil (0.468 g, 90%), that slowly crystallised.

Mp = 64-66 °C. $\mathbf{[\alpha]_D^{20}}$ = + 24.7 ° (C = 1.05, DCM). $^{\mathbf{1}}$**H-NMR** ($CDCl_3$, 300 MHz): δ (ppm) 7.78 (d, 2 H, *J* = 8.3 Hz, H ar); 7.51 (d, 2 H, *J* = 8.3 Hz, H ar); 7.37-7.21 (m, 5 H, *H* ar); 4.14 (dd, 1 H, *J* = 3.9, 10.6 Hz, SO_3CHaHb); 4.08 (dd, 1 H, *J* = 5.5, 10.6 Hz, SO_3CHa*Hb*); 3.90-3.85 (m, 1 H, HOC*H*); 3.19 (ddd, 1 H, *J* = 2.2, 4.6, 6.0 Hz, *H*C-O); 2.93 (dd, 1 H, *J* = 4.6, 14.7 Hz, PhCHa*Hb*); 2.87 (dd, 1 H, *J* = 2.2, 4.4 Hz, *H*C-O); 2.84 (dd, 1 H, *J* = 6.0, 14.7 Hz, PhC*H*H); 2.45 (s, 3 H, CH_3); 2.19 (1 H, d, *J* = 3.7 Hz, O*H*). $^{\mathbf{13}}$**C-NMR** ($CDCl_3$, 75Mz): 145.2 (*C* ar); 136.6 (*C* ar); 132.5 (*C* ar); 130.0 (*C*H ar); 129.0 (*C*H ar); 128.6 (*C*H ar); 128.0 (*C*H ar); 126.8 (*C*H ar); 70.6 (SO_3-CH_2); 68.1 (HO-*C*H); 56.9 (H*C*O); 56.2 (H*C*O); 37.6 (CH_2); 21.7 (CH_3). $\mathbf{\nu_{max}/cm^{-1}}$ 2922, 1597, 1495, 1357, 1175, 977, 749. ***m/z*** (ES+) = 370.97 (MNa^+, 100%); HRMS (ES+) found 371.0939 for $C_{18}H_{20}O_5NaS$, requires 371.0929.

(*S*)-2-((2*S*,3*R*)-3-Butyloxiran-2-yl)-2-fluoroethyl 4-methylbenzenesulfonate 304:

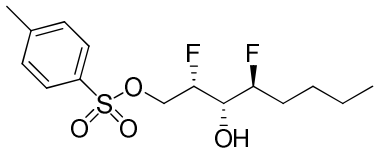


304

Deoxo-Fluor® (1.8 mL of solution 50% in THF, 4.48 mmol) to a solution of epoxy-alcohol **302** (0.33 g, 1.05 mmol) in DCM (7 mL) and the solution was heated at 40 °C for 1 h. The reaction was then cooled to RT and quenched by addition of silica. DCM was removed under reduced pressure and **304** was purified over silica gel (hexane 7 / EtOAc 3) and was recovered as a colourless oil (0.28 g, 83%).

$[\alpha]_D^{20}$ = -2.5° (C= 0.9, $CHCl_3$). **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ (ppm) 7.80 (d, 2 H, *J* = 8.4 Hz, C*H* ar); 7.36 (d, 2 H, *J* = 8.4 Hz, C*H* ar); 4.48 (dddd, 1 H, *J* = 47.7, 6.16, 4.86, 3.99 Hz, FC*H*); 4.16 (ddd, 1H, *J* = 21.38, 11.35, 3.99 Hz, O_2SOCH*H*); 4.11 (ddd, 1 H, *J* = 17.98, 11.35, 6.16 Hz, O_2SOC*H*H); 2.86 (ddd, 1 H, *J* = 5.62, 2.19, 0.99 Hz, OC*H*); 2.84 (ddd, 1 H, *J* = 14.41, 4.86, 2.19 Hz, OC*H*); 2.46 (s, 3 H, CH_3); 1.58-1.52 (m, 2 H, CH_2); 1.44-1.30 (m, 4 H, 2 x CH_2); 0.90 (t, 3 H, *J* = 7.1 Hz, CH_3). **^{13}C-NMR** ($CDCl_3$, 100 MHz): 145.4 (*C* ar); 132.3 (*C* ar); 130.0 (*C*-H ar); 128.0 (*C*-H ar); 89.1 (d, *J* = 180.3 Hz, *C*-F); 68.1 (d, *J* = 27.2, H_2C-CF); 55.8 (d, *J* = 22.7 Hz, O*C*-CF); 55.2 (d, *J* = 7.9 Hz, O*C*-C-CF); 31.0 (*C*H_2); 27.8 (*C*H_2); 22.4 (*C*H_2); 21.7 (*C*H_3); 13.9 (*C*H_3). **^{19}F-NMR** ($CDCl_3$, 376 MHz): -196.1 (ddddd, 1 F, *J* = 47.70, 21.39, 17.98, 14.41, 0.99 Hz). **ν_{max}/cm^{-1}** 2957, 2931, 2862, 1598, 1456, 1363, 1190, 1177, 944, 815, 554. ***m/z*** (ES+) = 339.05 (MNa^+, 100%); HRMS (ES+) calc for $C_{15}H_{21}O_4NaSF$ = 339.1042 found = 339.1034.

(2*S*,3*S*,4*S*)-2,4-Difluoro-3-hydroxyoctyl 4-methylbenzenesulfonate 305 :

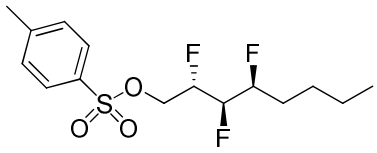


305

HF.pyridine 70/30 (0.75 mL) was added to a solution of **304** (0.13 g, 0.42 mmol) in DCM (5 mL) at -60 °C. After 20 h at -60 °C, starting **304** was still visible on TLC. HF.pyridine (0.25 mL) was added leading to a complete conversion of **304** after 8 hours. The reaction was then quenched by pouring into a solution of 5% $NaHCO_3$ (5 mL), and organic compounds extracted into DCM (3 x 5 mL). The organic layer was washed with solution of 5% $NaHCO_3$ (5 mL),water (5 mL), and dried over $MgSO_4$. Solvents were removed under reduced pressure and **305** was purified over silica (hexane 8 / EtOAc 2) and recovered as a colourless oil (80 mg, 56%).

$[\alpha]_D^{20}$ = -13.3° (C = 0.9, DCM). **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ (ppm) 7.80 (d, 2 H, *J* = 8.4 Hz, C*H* ar); 7.30 (d, 2 H, *J* = 8.4 Hz, C*H* ar); 4.88 (m, 1 H, *J* = 47.1 Hz, FC*H*); 4.45 (ddt, 1 H, *J* = 48.0, 2.7, 8.4 Hz, FC*H*); 4.31-4.25 (m, 2 H, O_2SOCH_2); 3.68-3.56 (m, 1 H, HOC*H*); 2.45 (s, 3 H, CH_3); 2.15 (dd, 1 H, *J* = 1.1, 8.7 Hz, O*H*); 1.88-1.31 (m, 6 H, 3xCH_2); 0.91 (t, 3 H, *J* = 7.4 Hz, CH_3). **^{13}C-NMR** ($CDCl_3$, 100 MHz): 145.4 (*C* ar); 132.3 (*C* ar); 130 (*C*H ar); 128.0 (*CH* ar); 91.6 (dd, *J* = 172.8, 3.2 Hz, *C*F); 88.6 (dd, *J* = 177.9, 3.4 Hz, *C*F); 70.9 (dd, *J* = 25.6, 18.3 Hz, *C*OH); 68.0 (d, *J* = 27.2 Hz, *C*-COH); 31.1 (d, *J* = 20.3 Hz, FC-*C*H_2); 26.8 (d, *J* = 2.3 Hz, FC-C-*C*H_2); 22.4 (*C*H_2); 21.7 (*C*H_3); 13.9 (*C*H_3). **^{19}F-NMR** ($CDCl_3$, 376 MHz): [-191.37]-[-191.67] (m, 1 F); [-208.82]-[-209.12] (m, 1 F). **ν_{max}/cm^{-1}** 1268, 1275, 1179, 1125, 920, 749. ***m/z*** (ES+) = 359.05 (MNa^+, 100%); HRMS (ES+) found 359.1100 for $C_{15}H_{22}O_4NaSF_2$, requires 359.1105.

(2*S*,3*R*,4*S*)-2,3,4-Trifluorooctyl 4-methylbenzenesulfonate 306 :

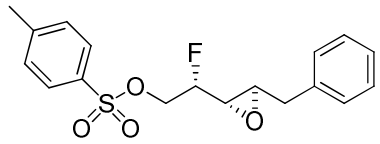


306

Deoxo-Fluor® (55 µL of solution 50% in THF, 0.15 mmol) was added to a solution of **305** (25 mg, 0.07 mmol) in DCM (3 mL), and the solution was heated at 40 °C for 1 h. The reaction was then cooled to RT and quenched by addition of silica. DCM was then removed under reduced pressure and **306** was purified over silica (hexane 8 / EtOAc 2) and was recovered as a colourless oil (12 mg, 48%).

$[\alpha]_D^{20}$ = -2.7° (C = 1, $CHCl_3$). **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ (ppm) 7.81 (d, 2 H, *J* = 8.3 Hz, C*H* ar); 7.36 (d, 2 H, *J* = 8.3 Hz, C*H* ar); 4.86 (m, 1 H, *J* = 45.5 Hz, FC*H*); 4.74-4.37 (m, 3H, 2xFC*H* + O_2SOC*Ha*Hb); 4.27 (dddd, 1 H, *J* = 2.6, 4.2, 11.9, 29.6 Hz, O_2SOCHa*Hb*); 2.46 (s, 3 H, CH_3); 1.94-1.84 (m, 1 H, CHa*Hb*); 1.70-1.58 (m, 1 H, C*Ha*Hb); 1.49-1.33 (m, 4 H, 2xCH_2); 0.92 (t, 3 H, *J* = 7.4 Hz, CH_3). **^{13}C-NMR** ($CDCl_3$, 100 MHz): 145.3 (*C* ar); 132.3 (*C* ar); 130.0 (*CH* ar); 128.0 (*C*H ar); 89.8 (ddd, *J* = 178.3, 18.7, 1.9 Hz, *C*F); 88.3 (ddd, *J* = 181.7, 18.6, 29.1 Hz, *C*F); 85.7 (ddd, *J* = 179.0, 30.4, 5.6 Hz, *C*F); 67.4 (d, *J* = 19.8 Hz, *C*-CH_2); 29.6 (dd, *J* = 21.1, 4.6 Hz, *C*H_2); 27.0 (d, *J* = 5.0 Hz, *C*H_2); 22.3 (*C*H_2); 21.6 (*C*H_3); 13.8 (*C*H_3). **^{19}F-NMR** ($CDCl_3$, 376 MHz): [-199.82]-[-200.12] (m, 1 F); [-201.04]-[-201.38] (m, 1 F), [-214.61]-[-214.89] (m, 1 F). **^{19}F-{^{1}H}-NMR** ($CDCl_3$, 376 MHz): -199.9 (dd, 1 F, *J* = 15.9, 3.2 Hz); -201.2 (dd, 1 F, *J* = 9.5, 3.2 Hz); -214.7 (dd, 1 F, *J* = 9.5, 15.9 Hz). **ν_{max}/cm^{-1}** 1363, 1275, 1179, 897, 758, 749. ***m/z*** (ES+) = 361.01 (MNa^+, 100%); HRMS (ES+) found 361.1047 for $C_{15}H_{22}O_4NaSF_2$, requires 361.1061.

(*S*)-2-((2*S*,3*R*)-3-Benzyloxiran-2-yl)-2-fluoroethyl 4-methylbenzenesulfonate 307 :

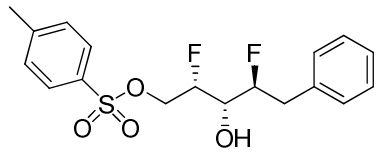


307

Deoxo-Fluor® (50% in THF, 0.92 mL, 2.47 mmol) was added to a solution of epoxy-alcohol **303** (0.29 g, 0.83 mmol) in DCM (10 mL) at RT. The reaction mixture was then heated at 40 °C for 1 h and the reaction quenched by addition of silica. Solvents were removed under reduced pressure and fluoro-epoxide **307** was purified over silica (hexane 4 / DCM 4 / Et_2O 1). Title compound was recovered as a colourless oil (0.27 g, 95 %).

$[\alpha]_D^{20}$ = +2.4 ° (C= 0.99, DCM). **^{1}H-NMR** ($CDCl_3$, 300 MHz): δ (ppm) 7.77 (d, 2 H, *J* = 8.4 Hz, C*H* ar); 7.37-7.20 (m, 7 H, C*H* ar); 4.58 (dddd, 1 H, *J* = 47.6, 6.2, 4.6, 3.9 Hz, *H*CF); 4.19 (ddd, 1 H, *J* = 21.9, 11.4, 3.9 Hz, SO_3C*Ha*Hb); 4.16 (ddd, 1 H, *J* = 18.2, 11.4, 6.2 Hz, SO_3CHa*Hb*); 3.19 (tdd, 1 H, *J* = 5.2, 2.2, 0.8 Hz, *H*CO); 2.97 (ddd, 1 H, *J* = 14.8, 4.6, 2.2, *H*CO); 2.91 (d, 2 H, *J* = 5.2 Hz, CH_2Ph); 2.46 (s, 3 H, CH_3). **^{13}C-NMR** ($CDCl_3$, 75Mz): δ (ppm) 145.4 (*C* ar); 136.2 (*C* ar); 132.3 (*C* ar); 130.1 (*C*H ar); 129.0 (*C*H ar); 128.7 (*C*H ar); 128.0 (*C*H ar); 127.0 (*C*H ar); 88.9 (d, *J* = 181.2 Hz, *C*F); 68.2 (d, *J* = 26.6 Hz, *C*H_2CF); 55.5 (d, *J* = 22.9 Hz, *C*HCF); 55.2 (d, *J* = 8.0 Hz, FC-CH-*C*H); 37.4 (*C*H_2); 21.7 (*C*H_3). **^{19}F-NMR** ($CDCl_3$, 282MHz): -196.61 (ddddd, 1 F, *J* = 47.6, 21.9, 18.2, 14.8, 0.8 Hz). **ν_{max}/cm^{-1}** 1362, 1276, 1268, 1177, 993, 749. ***m/z*** (ES+) = 373.06 (MNa^+, 100%); HRMS (ES+) found 373.0883 for $C_{18}H_{19}O_4NaSF$, requires 373.0886.

(2*S*,3*S*,4*S*)-2,4-Difluoro-3-hydroxy-5-phenylpentyl 4-methylbenzenesulfonate 308:

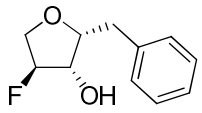


308

3HF.Et_3N (1 mL, 6.13 mmol) was added to a solution of fluoro epoxide **307** (0.14 g, 0.40 mmol) in chloroform (5 mL) in a sealed bomb with a Teflon inner layer. The reaction mixture was stirred at 100 °C for 3 days, and then quenched by addition of aqueous $NaHCO_3$ 5% (5 mL). Organic compounds were extracted into DCM (3 x 5 mL) and washed with $NaHCO_3$ 5% (5 mL), and water (5 mL). Organic layers were dried over $MgSO_4$ and solvents were removed under reduced pressure. **308** was purified over silica gel (hexane 5 / DCM 3 / Et_2O 2) and recovered as a white solid (86 mg, 58%).

Mp = 66-68 °C. **$[\alpha]_D^{20}$ =** -24.2 ° (C= 0.9, DCM). **^{1}H-NMR** ($CDCl_3$, 300 MHz): δ (ppm) 7.79 (d, 2 H, *J* = 8.3 Hz, C*H* ar); 7.35 (d, 2 H, *J*= 8.3 Hz, C*H* ar); 7.32-7.24 (m, 5 H, C*H* ar); 4.89 (m, 1 H, *J* = 47.2 Hz, *H*CF); 4.69 (ddt, 1 H, *J* = 3.1, 8.0, 47.1 Hz, *H*CF); 4.31-4.21 (m, 2 H, SO_3C*HaHb*); 3.68-3.58 (m, 1 H, *H*COH); 3.20 (ddd, 1 H, *J* = 3.0, 14.8, 31.7 Hz, C*Ha*HbPh); 2.97 (ddd, 1 H, *J* = 7.2, 14.8, 26.1 Hz, CHa*Hb*Ph); 2.45 (s, 3 H, CH_3), 2.24 (m, 1 H, O*H*). **^{13}C-NMR** ($CDCl_3$, 75Mz): 145.4 (*C* ar); 136.0 (*C* ar); 132.3 (*C* ar); 130.0 (2 *C*H ar); 129.7 (*C*H ar); 128.6 (*C*H ar); 128.0 (*C*H ar); 126.9 (*C*H ar); 91.2 (dd, *J* = 176.0, 3.7 Hz, H*C*-CF); 88.5 (dd, *J* = 177.9, 3.0 Hz, H*C*-CF); 70.1 (dd, *J* = 25.7, 18.3 Hz, HO*C*H); 67.9 (d, *J* = 27.1 Hz, *C*H_2-CF); 37.6 (d, *J* = 20.0 Hz, *C*H_2-CF); 21.7 (*C*H_3). **^{19}F-NMR** ($CDCl_3$, 282MHz): [-189.82]-[-190.20] (m, HC*F*); [-209.30]-[-209.71] (m, HC*F*). **^{19}F{^{1}H}-NMR** ($CDCl_3$, 282MHz): - 189.6 (d, *J* = 3.5 Hz, HC*F*); - 209.0 (d, *J* = 3.5 Hz, HC*F*). **ν_{max}/cm^{-1}** 1267, 1261, 1209, 1151, 758, 749. ***m/z*** (ES+) = 393.01 (MNa^+, 100%); HRMS (ES+) found 393.0942 for $C_{18}H_{20}O_4NaSF_2$, requires 393.0948.

(2*R*,3*S*,4*S*)-2-Benzyl-4-fluorotetrahydrofuran-3-ol 309:

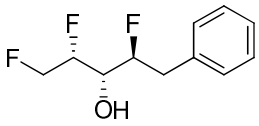


309

HF.pyridine 70/30 (0.75 mL) was added to a solution of **307** (0.115 g, 0.33 mmol) in DCM (5 mL) at 0 °C. After 6 h, the reaction was quenched by pouring into a solution of 5% $NaHCO_3$ (5 mL), and organic compounds extracted into DCM (3 x 5 mL). The organic layer was washed with solution of 5% $NaHCO_3$ (5 mL), water (5 mL), and dried over $MgSO_4$. Solvents were removed under reduced pressure and **309** was purified over silica gel (hexane 6 / DCM 2 / Et_2O 2) and recovered as a white solid (23 mg, 33%).

Mp = 86-88 °C. $\mathbf{[\alpha]_D^{20}}$ = -12.9° (C = 1, $CHCl_3$). **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ (ppm) 7.34-7.24 (m, 5 H, *H* ar), 5.01 (dd, 1 H, *J* = 3.7, 52.2 Hz, *H*CF); 4.27 (ddd, 1 H, *J* = 4.0, 11.4, 38.5 Hz, *H*COH); 4.24-4.12 (m, 2 H, OC*H*$_2$); 3.91 (dd, 1 H, *J* = 11.5, 31.6 Hz, *H*CO); 3.07-2.95 (m, 2 H, C*H*$_2$Ph); 1.84 (d, 1 H, *J* = 6.3 Hz, O*H*). **^{13}C-NMR** ($CDCl_3$, 100Mz): 137.8 (*C* ar); 129.1 (*C*H ar); 128.6 (*C*H ar); 126.6 (*C*H ar); 96.8 (d, *J* = 181.6 Hz, *C*-F); 81.6 (O-*C*H-CH_2Ph); 74.5 (d, *J* = 25.4 Hz, HO-*C*); 71.4 (d, *J* = 23.6 Hz, *C*H_2O); 34.3 (*C*H_2Ph). **^{19}F-NMR** ($CDCl_3$, 376MHz): [-180.3]-[-184.9] (m, 1 F). **ν_{max}/cm^{-1}** 3329, 1276, 1180,1055, 764, 750. ***m/z*** (ES+) = 219.01 (MNa^+, 100%); HRMS (ES+) found 219.0794 for $C_{11}H_{13}O_2NaF$, requires 219.0797.

(2*R*,3*S*,4*S*)-1,2,4-Trifluoro-5-phenylpentan-3-ol 313:

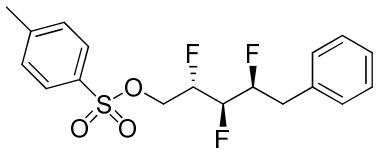


313

3HF.Et_3N (1 mL, 6.13 mmol) was added to a solution of fluoro epoxide **307** (0.05 g, 0.14 mmol) in toluene (1 mL) in a sealed bomb with a Teflon inner layer. The reaction mixture was stirred at 120 °C for 18 h and then quenched by addition of aqueous $NaHCO_3$ 5% (2 mL). Organic compounds were extracted into DCM (3 x 5 mL), and washed with $NaHCO_3$ 5% (5 mL) and water (5mL). Organic layers were dried over $MgSO_4$ and solvents were removed under reduced pressure. **313** was purified over silica gel (hexane 5 / DCM 3 / Et_2O 1) and recovered as a white solid (7 mg, 23%). From the same reaction difluoroalcohol **308** was also recovered (11mg).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) 7.35-7.26 (m, 5 H, *H* ar); 4.93 (ddm, 1 H, *J* = 18.4, 47.7 Hz, FCH_2-C*H*F); 4.85-4.51 (m, 3 H, FC*H*$_2$ + HOC-C*H*F); 3.71 (m, 1 H, *J* = 23.8 Hz, *H*C-OH); 3.24 (ddd, 1 H, *J* = 3.2, 15.0, 31.3 Hz, C*Ha*HbPh); 3.01 (ddd, 1 H, *J* = 7.6, 15.0, 26.8 Hz, CHa*Hb*Ph); 2.10 (dt, 1 H, *J* = 8.3, 1.8 Hz, O*H*). **^{13}C-NMR** ($CDCl_3$, 75Mz): 136.0 (*C* ar); 129.7 (*C*H ar); 128.6 (*C*H ar); 126.9 (*C*H ar); 91.3 (dd, *J* = 2.9, 175.8 Hz, *C*-F); 89.6 (ddd, *J* = 3.1, 20.2, 175.9 Hz, *C*-F); 82.4 (ddd, *J* = 2.1, 24.8, 171.6 Hz, *C*H_2F); 70.2 (ddd, *J* = 6.1, 18.8, 26.1 Hz, *C*OH); 37.5 (d, *J* = 20.4 Hz, *C*H_2Ph). **^{19}F-NMR** ($CDCl_3$, 282MHz): [-189.7]-[-190.1] (m, HC*F*); [-210.9]-[-211.4] (m, HC*F*); [-232.7]-[-233.2] (m, CH_2*F*). **^{19}F{^{1}H}-NMR** ($CDCl_3$, 282MHz): -189.9 (d, *J* = 3.0 Hz, HC*F*); -211.1 (dd, *J* = 3.0, 14.8 Hz, HC*F*); -232.9 (d, *J* = 14.8 Hz, CH_2*F*). ***m/z*** (ES+) = 241.03 (MNa^+, 100%); HRMS (ES+) found 241.0813 for $C_{11}H_{13}ONaF_3$, requires 241.0816.

(2*S*,3*R*,4*S*)-2,3,4-Trifluoro-5-phenylpentyl 4-methylbenzenesulfonate 314:

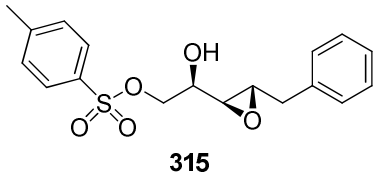


314

Deoxo-Fluor® (50% in THF, 175 μL, 0.47 mmol) was added to a solution of **308** (58 g, 0.16 mmol) in DCM (3 mL) at RT. The reaction mixture was then heated at 40 °C for 1 h, and the reaction quenched by addition of silica. Solvents were removed under reduced pressure, and **314** purified over silica (hexane 5 / DCM / 3 / Et_2O 1). Title compound was recovered as a colourless oil (45 mg, 78 %).

$[\alpha]_D^{20}$ = -2.8° (C= 0.7, $CDCl_3$). **^{1}H-NMR** ($CDCl_3$, 300 MHz): δ (ppm) 7.78 (d, 2 H, *J* = 8.4 Hz, C*H* ar); 7.35 (d, 2 H, *J* = 8.4 Hz, C*H* ar); 7.31-7.21 (m, 5 H, C*H* ar); 4.88 (m, 1 H, *J* = 45.9 Hz, *H*CF); 4.73-4.38 (m, 2 H, 2 x *H*CF); 4.42 (ddd, 1 H, *J* = 1.9, 12.1, 23.4 Hz, SO_3C*Ha*Hb); 4.26 (ddd, 1 H, *J* = 4.5, 12.1, 28.9 Hz, SO_3CHa*Hb*); 3.21 (ddd, 1 H, *J* = 7.5, 13.8, 22.2 Hz, C*Ha*HbPh); 3.01 (ddd, 1 H, *J* = 6.8, 13.8, 21.1 Hz, CHa*Hb*Ph); 2.46 (s, 3 H, CH_3). **^{13}C-NMR** ($CDCl_3$, 75Mz): 145.2 (*C* ar); 135.1 (*C* ar); 132.3 (*C* ar); 129.9 (2 *C*H ar); 129.3 (*C*H ar); 128.9 (*C*H ar); 128.0 (*C*H ar); 127.2 (*C*H ar); 90.1 (ddd, *J* = 181.8, 20.0, 2.3 Hz, *C*F); 87.0 (ddd, *J* = 183.0, 29.7, 18.1 Hz, *C*F); 86.0 (ddd, *J* = 179.5, 30.7, 5.5 Hz, *C*F); 67.4 (d, *J*= 19.7 Hz, *C*H_2); 36.3 (dd, *J*= 22.5, 5.2 Hz, *C*H_2); 21.7 (*C*H_3). **^{19}F-NMR** ($CDCl_3$, 376 MHz): [-198.80]-[-199.23] (m, 1 F); [-200.27]-[-200.69] (m, 1 F), [-215.48]-[-215.78] (m, 1 F). **^{19}F{^{1}H}-NMR** ($CDCl_3$, 376 MHz): -198.61 (dd, 1 F, *J* = 9.6, 2.8 Hz); -200.03 (dd, 1 F, *J*= 15.4, 2.8 Hz); -215.18 (dd, 1 F, *J*= 9.6, 15.4 Hz). **ν_{max}/cm^{-1}** 1365, 1261, 1267, 1208, 1190, 1177, 1151, 749. ***m/z*** (ES+) = 394.95 (MNa^+, 100%); HRMS (ES+) found 395.0906 for $C_{18}H_{19}O_3NaSF_3$, requires 395.0905.

(*R*)-2-((2*S*,3*S*)-3-Benzyloxiran-2-yl)-2-hydroxyethyl 4-methylbenzenesulfonate 315:

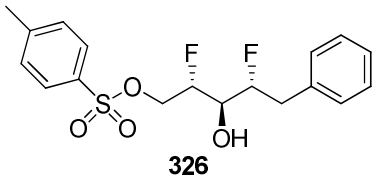


315

Epoxy-alcohol **315** was obtained after several consecutive recrystallisations of a ~ 1:1 mixture with epoxy-alcohol **303**. Epoxide **315** underwent degradation before full characterisation was achieved.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) 7.8 (d, 2 H, *J* = 8.1 Hz, H ar); 7.35 (d, 2 H, *J* = 8.1 Hz, H ar); 7.31-7.20 (m, 5 H, H ar); 4.07 (brs, 1 H, SO_3C*Ha*Hb); 4.05 (brs, 1 H, SO_3CHa*Hb*); 3.93-3.86 (m, 1 H, HOC*H*); 3.20 (ddd, 1 H, *J* = 2.2, 5.6, 5.4 Hz, *H*C-O); 2.93-2.87 (m, 3 H, PhCH_2 + *H*C-O); 2.45 (s, 3 H, CH_3); 2.19 (1 H, d, *J* = 7.2 Hz, O*H*). ***m/z*** (ES+) = 371.05 (MNa^+, 100%); HRMS (ES+) found 371.0939 for $C_{18}H_{20}O_5NaS$, requires 371.0929.

(2*S*,3*R*,4*R*)-2,4-Difluoro-3-hydroxy-5-phenylpentyl 4-methylbenzenesulfonate 326:



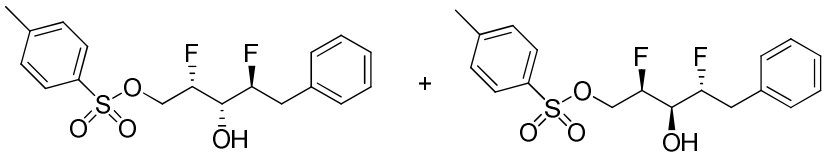
326

Deoxo-Fluor® (50% in THF, 0.24 mL, 0.6 mmol) was added to a solution of epoxy-alcohol **315** and **303** in a ~ 1:1 ratio (148 mg, 0.42 mmol) in DCM (5 mL) at RT. The reaction mixture was then heated at 40 °C for 1 h, and the reaction quenched by addition of silica. Solvents were removed under reduced pressure and fluoro-epoxide **323** and **324**/**307** were purified over silica gel (hexane 6 / DCM 3 / Et_2O 1) and recovered as a colourless oil (70 mg, 47%).

$^{19}F\{^1H\}$-NMR ($CDCl_3$, 282MHz) [-195.9] and [-197.0] in a 1:1.3 ratio.

3HF.Et_3N (0.5 mL, 3 mmol) was added to a solution of fluoro epoxide **323** and **324**/**307** (34 mg, 0.10 mmol) in chloroform (3 mL) in a sealed bomb with a Teflon inner layer. The reaction mixture was stirred at 100 °C for 3 days and then quenched by addition of aqueous $NaHCO_3$ 5% (5 mL),. Organic compounds were extracted into DCM (3 x 5 mL), and washed with $NaHCO_3$ 5% (5 mL), and water (5 mL),. Organic layers were dried over $MgSO_4$ and solvents were removed under reduced pressure. Compounds **326** and **327**/**308** were purified first over silica gel (hexane 5 / DCM 3 / Et_2O 2). A second purification by preparative TLC (hexane 5 / Et_2O 5) allowed purification of **326** as a single diastereoisomer. **326** was recovered as an oil (6 mg, 33%)

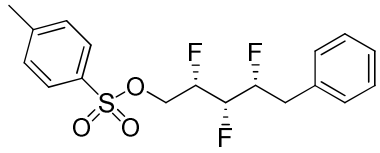
$[\alpha]_D^{20}$ = +1.4° (C= 1, DCM). **^{1}H-NMR** ($CDCl_3$, 300 MHz): δ (ppm) 7.80 (d, 2 H, *J* = 8.2 Hz, C*H* ar); 7.36 (d, 2 H, *J* = 8.2 Hz, C*H* ar); 7.32-7.22 (m, 5 H, *H* ar); 4.77 (m, 1 H, *J* = 46.1 Hz, *H*CF); 4.73 (m, 1 H, *J* = 47.1 Hz, *H*CF); 4.41-4.39 (m, 1 H, SO_3C*Ha*Hb); 4.33-4.31 (m, 1 H, SO_3CHa*Hb*); 4.10-3.99 (m, 1 H, *H*COH); 2.97 (m, 2 H, CH_2Ph); 2.45 (s, 3 H, CH_3). **^{13}C-NMR** ($CDCl_3$, 75Mz): 145.3 (*C* ar); 136.2 (*C* ar); 132.5 (*C* ar); 130.0 (*C*H ar); 129.4 (*C*H ar); 128.6 (*C*H ar); 128.0 (*C*H ar); 126.9 (*C*H ar); 93.4 (dd, *J*= 174.0, 4.2 Hz, *C*F); 89.6 (dd, *J* = 178.2, 5.2 Hz, *C*F); 70.1 (t, *J* = 23.6 Hz, HO*C*H); 68.1 (dd, *J* = 21.6, 3.0 Hz, *C*H_2); 36.5 (d, *J* = 21.0 Hz, *C*H_2); 29.7 (*C*H_3). **^{19}F-NMR** ($CDCl_3$, 282MHz): [-192.54]-[-192.94] (m, HC*F*); [-198.50]-[-198.88] (m, HC*F*). **^{19}F{^{1}H}-NMR** ($CDCl_3$, 282MHz): - 192.73 (s, HC*F*); - 198.69 (s, HC*F*). **ν_{max}/cm^{-1}** 2921, 1360,1190, 1176, 1146, 983, 913, 743. ***m/z*** (ES+) = 392.95 (MNa^+, 100%); HRMS (ES+) found 393.0946 for $C_{18}H_{20}O_4NaSF_2$, requires 393.0948.



308 **327**

The spectroscopic data of the mixture of **308** + **327** were identical to those of **308** except for the optical rotation: **$[\alpha]_D^{20}$** = -13.1° (C= 1, DCM). **m/z** (ES+) = 392.95 (MNa^+, 100%); HRMS (ES+) found 393.0942 for $C_{18}H_{20}O_4NaSF_2$, requires 393.0948.

(2*S*,3*S*,4*R*)-2,3,4-Trifluoro-5-phenylpentyl 4-methylbenzenesulfonate 328:

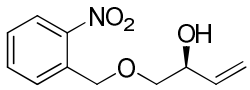


328

Deoxo-Fluor® (50% in THF, 15 μL, 0.05 mmol) was added to a solution of **326** (7 g, 0.02 mmol) in DCM (1 mL) at RT. The reaction mixture was then heated at 40 °C for 1 h and the reaction quenched by addition of silica. Solvents were removed under reduced pressure and **328** purified by preparative TLC (hexane 7 / Et_2O 3). Title compound was recovered as a colourless oil (4 mg, 57 %).

$[\alpha]_D^{20}$ = +1.75 ° (C = 0.4, $CDCl_3$). **^{1}H-NMR** ($CDCl_3$, 300 MHz): δ (ppm) 7.74 (d, 2 H, *J* = 8.3 Hz, *H* ar); 7.37-7.22 (m, 7 H, *H* ar); 5.06-4.43 (m, 3 H, 3 x *H*CF); 4.73-4.38 (m, 2 H, 2 x *H*CF); 4.35 (brd, 1 H, *J* = 3.8 Hz, SO_3CHaHb); 4.27 (brd, 1 H, *J* = 3.8 Hz, SO_3CHaHb); 3.15-2.97 (m, 2 H, CH_2Ph); 2.45 (s, 3 H, CH_3). **^{13}C-NMR** ($CDCl_3$, 75Mz): 130.1 (*C*H ar); 129.3 (*C*H ar); 128.9 (*C*H ar); 128.0 (*C*H ar); 127.3 (*C*H ar); 21.7 (CH_3). Quaternary carbons and carbons coupled bound to fluorine were not observed, even with an extended number of scans (12000 scans). **^{19}F-NMR** ($CDCl_3$, 376 MHz): [-195.84]-[-196.29] (m, 1 F); [-201.07]-[-201.51] (m, 1 F), [-212.23]-[-212.63] (m, 1 F). **^{19}F{^{1}H}-NMR** ($CDCl_3$, 376 MHz): -196.1 (d, 1 F, *J* = 10.8 Hz); -201.29 (d, 1 F, *J* = 13.6 Hz); -212.43 (dd, 1 F, *J* = 10.8, 13.6 Hz). **ν_{max}/cm^{-1}** 1360, 1269, 1208, 1190, 1146, 983, 910, 740. ***m/z*** (ES+) = 394.96 (MNa^+, 100%); HRMS (ES+) found 395.0903 for $C_{18}H_{19}O_3NaSF_3$, requires 395.0905.

(*S*)-1-(2-Nitrobenzyloxy)but-3-en-2-ol 332 :

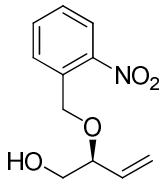


332

Dibutyltin oxide (8.4 g, 33.06 mmol) was added to a solution of diol **278** (2.57 g, 29.16 mmol) in MeCN (100 mL) followed by 2-nitrobenzyl bromide (7.71 g, 34.99 mmol). The reaction mixture was heated under reflux for 24 h, and the solvent was removed under reduced pressure. Regioisomers **332** and **333** were purified over silica gel (DCM 9 / Et_2O 1) and obtained as a yellow oil (5.81 g, 89% yield and 86% regioselectivity). Regioisomers **332** and **333** were then separated over silica gel (hexane 5 / Et_2O 5). **332** was obtained as a yellow solid (3.51 g) and **333** as a yellow oil (0.38 g), plus 1.12 g of mixed fractions.

Mp = 36-38 °C. $\mathbf{[\alpha]_D^{20}}$ **=** -2.4 ° (C = 1, DCM). **^{1}H-NMR** ($CDCl_3$, 300 MHz): δ (ppm) 8.03 (dd, 1 H, *J* = 1.2, 8.3 Hz, *H* ar); 7.76 (dd, 1 H, *J* = 0.9, 7.7 Hz, *H* ar); 7.63 (ddd, 1 H, *J* = 1.2, 7.7, 7.5 Hz, *H* ar); 7.43 (ddd, 1 H, *J* = 8.3, 7.5, 0.9 Hz, *H* ar); 5.86 (ddd, 1 H, *J*= 5.6, 10.6, 17.4 Hz,); 5.37 (ddd, 1 H, *J*= 17.4, 1.5, 1.6 Hz,); 5.21 (ddd, 1 H, *J*= 10.6, 1.5, 1.4 Hz,); 4.9 (s, 2 H); 4.4 (m, 1 H,); 3.63 (dd, 1 H, *J* = 3.5, 9.7 Hz,); 3.50 (dd, 1 H, *J* = 7.5, 9.7 Hz,), 2.53 (br s, 1 H, O*H*). **^{13}C-NMR** ($CDCl_3$, 75Mz): 147.7 (*C* ar), 136.9 (*C* ar), 135.0 (*C*H ar), 134.1 (*C*H ar), 129.1 (*C*H ar), 128.6 (*C*H ar), 125.1 (H*C*=CH_2), 117.1 (HC=*C*H_2), 75.4 (Ph*C*H_2), 71.9 (H*C*OH), 70.3 (O*C*H_2). $\mathbf{\nu_{max}/cm^{-1}}$ 3420, 2900, 2863, 1612, 1524, 1341, 1114, 993, 790, 729. ***m/z*** (ES+) = 246.07 (MNa^+, 100%); HRMS (ES+) found 246.0746 for $C_{11}H_{13}NO_4Na$, requires 246.0742.

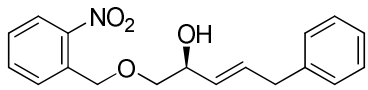
(*S*)-2-(2-Nitrobenzyloxy)but-3-en-1-ol 333 :



333

$[\alpha]_D^{20}$ = -8.5° (C = 1, DCM). **^{1}H-NMR** ($CDCl_3$, 300 MHz): δ (ppm) 8.03 (dd, 1 H, *J* = 1.2, 8.2 Hz, *H* ar); 7.78 (dd, 1 H, *J* = 0.8, 7.9 Hz, *H* ar); 7.63 (ddd, 1 H, *J* = 1.2, 7.9, 7.6 Hz, *H* ar); 7.44 (ddd, 1 H, *J* = 8.2, 7.6, 0.8 Hz, *H* ar), 5.75 (dd, 1 H, *J* = 7.4, 10.4, 17.4 Hz, *H*C=CH_2); 5.39 (ddd, 1 H, *J* = 1.0, 1.5, 17.4 Hz, HC=C*H*H); 5.35 (ddd, 1 H, *J* = 1.5, 10.4, 1.6 Hz, HC=CH*H*); 4.95 (d, 1 H, *J* = 14.6 Hz PhC*Ha*Hb); 4.82 (d, 1 H, *J* = 14.6 Hz PhCHa*Hb*); 4.1 (m, 1 H, OC*H*); 3.67 (br dd, 2 H, *J* = 6.4, 5.4 Hz, HOCH_2); 2.03 (br s, 1 H, O*H*). **^{13}C-NMR** ($CDCl_3$, 75Mz): 147.9 (*C* ar), 135.0 (*C* ar); 134.8 (*C*H ar); 133.9 (*C*H ar); 129.5 (*C*H ar); 128.6 (*C*H ar); 125.1 (H*C*=CH_2); 120.3 (HC=*C*H_2); 82.6 (O*C*H); 67.6 (Ph*C*H_2); 65.7 (*C*H_2OH). **ν_{max}/cm^{-1}** 3420, 2910, 2863, 1615, 1524, 1342, 1110, 993, 790, 729 ***m/z*** (ES+) = 246.08 (MNa^+, 100%); HRMS (ES+) found 246.0741 for $C_{11}H_{13}NO_4Na$, requires 246.0742.

(*S*,*E*)-1-(2-Nitrobenzyloxy)-5-phenylpent-3-en-2-ol 334:

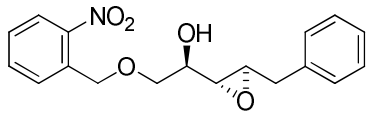


334

Grubbs' 2nd generation catalyst (79 mg, 0.09 mmol) was added to a solution of allylic acohol **332** (3.14 g, 14.08 mmol) and allyl benzene (10 mL, 75.40 mmol) in DCM (20 mL). The solution was heated under reflux for 12 h. Then DCM was removed under reduced pressure, and allylic alcohol **334** was purified over silica gel (from hexane 3 / Et_2O 1 to hexane 1 / Et_2O 4). The title compound was recovered as a yellow solid (2.38 g, Yield 54%).

Mp = 40-41 °C. $\mathbf{[\alpha]_D^{20}}$ = +13.2° (C = 1.5, $CHCl_3$). **^{1}H-NMR** ($CDCl_3$, 300 MHz): δ (ppm) 8.06 (dd, 1 H, *J* = 1.3, 8.2 Hz, *H* ar); 7.76 (dd, 1 H, *J* = 0.9, 7.8 Hz, *H* ar); 7.64 (ddd, 1 H, *J* = 1.3, 7.8, 7.5 Hz, *H* ar); 7.45 (ddd, 1 H, *J* = 8.2, 7.5, 0.9 Hz, *H* ar); 7.32-7.17 (m, 5 H, *H* ar); 5.98 (ddt, 1 H, *J*= 1.3, 6.8, 15.5 Hz, HC=C*H*-CH_2); 5.55 (ddt, 1 H, *J*= 1.5, 6.4, 15.5 Hz, *H*C=CH-CH_2); 4.98 (d, 1 H, *J* = 15.2 Hz, PhC*H*HO); 4.92 (d, 1 H, *J* = 15.2 Hz, PhCH*H*O); 4.40 (m, 1 H, OC*H*); 3.63 (dd, 1 H, *J* = 3.5, 9.7 Hz, OC*H*H); 3.52 (dd, 1 H, *J* = 7.7, 9.7 Hz, OCH*H*); 3.46 (br dd, 2 H, *J* = 1.5, 6.8 Hz, H_2Ph); 2.39 (d, 1 H, *J* = 3.4 Hz, O*H*). **^{13}C-NMR** ($CDCl_3$, 75Mz): 147.3 (*C* ar); 139.8 (*C* ar); 134.7 (*C* ar); 133.7 (*C*H ar); 132.5 (*C*H ar); 129.6 (*C*H ar); 128.7 (*C*H ar); 128.6 (*C*H=CH); 128.5 (CH=*C*H); 128.2 (*C*H ar); 126.2 (*C*H ar); 124.8 (*C*H ar); 75.2 (CH_2); 71.2 (O*C*H); 69.9 (CH_2); 38.7 (CH_2). $\mathbf{\nu_{max}/cm^{-1}}$ 2852, 2358, 1521, 1339, 1199, 1146, 696, 772. ***m/z*** (ES+) = 336.02 (MNa^+, 100%); HRMS (ES+) found 336.1216 for $C_{18}H_{19}NO_4Na$, requires 336.1212.

(*R*)-1-((2*R*,3*R*)-3-Benzyloxiran-2-yl)-2-(2-nitrobenzyloxy)ethanol 335:

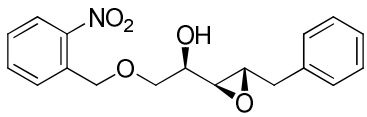


335

Titanium tetraisopropoxide 99.99% (1.03 mL, 3.51 mmol) was added to allylic alcohol **334** (1 g, 3.19 mmol) in DCM (50 mL) at -20 °C. Then TBHP (5.5 M in decane, 0.87 mL, 4.79 mmol) was added dropwise. The reaction mixture was stirred at -20 °C for 15 hours. Then a solution of sodium bisulfite (10 mL) was added, and the solution warmed to RT. The organic compounds were extracted into DCM (3 x 20 mL), washed with water (20 mL), and brine (10 mL), and dried over $MgSO_4$. Solvent was removed under reduced pressure, and **335** and **336** were purified over silica gel (Hexane 5 / DCM 3 / Et_2O 2) and recovered as yellow oils: **335** (247 mg) plus **336** (409 mg) plus 156 mg of mixed fractions. Overall yield = 77%.

$[\alpha]_D^{20}$ = -17.0° (C = 1, DCM). **^{1}H-NMR** ($CDCl_3$, 300 MHz): δ (ppm) 8.06 (dd, 1 H, *J* = 1.3, 8.3 Hz, *H* ar); 7.72 (br d, 1 H, *J* = 7.9 Hz, *H* ar); 7.64 (ddd, 1 H, *J* = 1.3, 7.9, 7.5 Hz, *H* ar); 7.45 (ddd, 1 H, *J* = 8.3, 7.5, 0.9 Hz, *H* ar); 7.34-7.19 (m, 5 H, *H* ar); 4.98 (s, 2 H, PhCH_2O); 3.93-3.88 (m, 1 H, *H*COH); 3.70 (br s, 1 H, BnOC*Ha*Hb); 3.68 (br d, 1 H, *J* = 2.0 Hz, BnOCHa*Hb*); 3.26 (dt, 1 H, *J* = 2.1, 5.6 Hz, *H*CO); 2.98 (dd, 1 H, *J* = 2.1, 4.5 Hz, *H*CO); 2.92 (br s, 1 H, C*Ha*HbPh); 2.91 (br s, 1 H, CHa*Hb*Ph); 2.44 (br s, O*H*). **^{13}C-NMR** ($CDCl_3$, 75Mz): 147.3 (*C* ar); 136.9 (*C* ar); 134.4 (*C* ar); 133.7 (*C*H ar); 129.6 (*C*H ar); 129.0 (*C*H ar); 128.7 (*C*H ar); 128.6 (*C*H ar); 128.2; (*C*H ar); 126.7 (*C*H ar); 72.3 (CH_2); 70.1(CH_2); 69.1 (H*C*O); 58.1; (H*C*O) 56.1; (H*C*O); 37.9 (CH_2). **ν_{max}/cm^{-1}** 2990, 2856, 1521, 1339, 1276, 1120, 763, 759. ***m/z*** (ES+) = 352.04 (MNa^+, 100%); HRMS (ES+) found 352.1156 for $C_{18}H_{19}NO_5Na$, requires 352.1161.

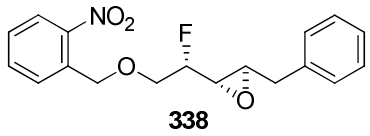
(*R*)-1-((2*S*,3*S*)-3-Benzyloxiran-2-yl)-2-(2-nitrobenzyloxy)ethanol 336:



336

$[\alpha]_D^{20}$ = +9.5° (C = 1.2, DCM). **^{1}H-NMR** ($CDCl_3$, 300 MHz): δ (ppm) 8.08 (dd, 1 H, *J* = 1.3, 8.3 Hz, *H* ar); 7.74 (br d, 1 H, *J* = 7.9 Hz, *H* ar); 7.65 (ddd, 1 H, *J* = 1.3, 7.9, 7.5 Hz, *H* ar); 7.45 (ddd, 1 H, *J* = 8.3, 7.5, 0.9 Hz, *H* ar); 7.34-7.19 (m, 5 H, *H* ar); 4.93 (s, 2 H, PhCH_2O); 3.91-3.83 (m, 1 H, *H*COH); 3.70 (dd, 1 H, *J* = 4.8, 9.8 Hz, BnOC*Ha*Hb); 3.66 (dd, 1 H, *J* = 5.8, 9.8 Hz, BnOCHa*Hb*); 3.26 (dt, 1 H, *J* = 2.3, 5.6 Hz, *H*CO); 3.03 (dd, 1 H, *J* = 2.3, 3.9 Hz, *H*CO); 2.96 (dd, 1 H, *J* = 5.9, 14.6 Hz, C*Ha*HbPh); 2.88 (dd, 1 H, *J* = 5.4, 14.6 Hz, CHa*Hb*Ph); 2.36 (d, *J* = 6.5 Hz, O*H*). **^{13}C-NMR** ($CDCl_3$, 75Mz): 147.7 (*C* ar); 137.3 (*C* ar); 134.9 (*C* ar); 134.15 (*C*H ar); 129.4 (*C*H ar); 129.0 (*C*H ar); 128.9 (*C*H ar); 128.6 (*C*H ar); 127.2; (*C*H ar); 125.14 (*C*H ar); 73.2 (CH_2); 70.5(CH_2); 69.5 (H*C*O); 59.3; (H*C*O) 56.1; (H*C*O); 38.5 (CH_2). **ν_{max}/cm^{-1}** 2862, 2357, 1521, 1339, 1204, 1148, 764, 749. ***m/z*** (ES+) = 351.99 (MNa^+, 100%); HRMS (ES+) found 352.1167 for $C_{18}H_{19}NO_5Na$, requires 352.1161.

(2*R*,3*S*)-2-Benzyl-3-((*S*)-1-fluoro-2-(2-nitrobenzyloxy)ethyl)oxirane 337 :

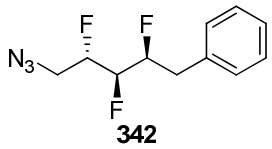


338

Deoxo-Fluor® (50% in THF, 0.17 mL, 0.45 mmol) was added to a solution of epoxy-alcohol **335** (0.1 g, 0.30 mmol) in DCM (10 mL) at RT. The reaction mixture was then heated at 40 °C for 1 h, and the reaction quenched by addition of silica. Solvents were removed under reduced pressure and fluoro-epoxide was **338** purified over silica gel (hexane 4 / DCM 4 / Et_2O 1). Title compound was recovered as a colourless oil (86 mg, 85 %).

$[\alpha]_D^{20}$ = +1.3 ° (C = 0.3, $CHCl_3$). **^{1}H-NMR** ($CDCl_3$, 300 MHz): δ (ppm) 8.08 (dd, 1 H, *J* = 1.3, 8.3 Hz, *H* ar); 7.73 (br d, 1 H, *J* = 7.9 Hz, *H* ar); 7.65 (ddd, 1 H, *J* = 1.3, 7.9, 7.5 Hz, *H* ar); 7.45 (ddd, 1 H, *J* = 8.3, 7.5, 0.9 Hz, *H* ar); 7.30-7.19 (m, 5 H, *H* ar); 4.90 (s, 2 H, PhCH_2O) 4.58 (dddd, 1 H, *J* = 47.8, 5.3, 4.5, 6.6 Hz, *H*CF); 3.82 (ddd, 1 H, *J* = 27.4, 10.8, 4.3 Hz, BnOC*Ha*Hb); 3.75 (ddd, 1 H, *J* = 18.2, 10.8, 3.2 Hz, BnOC*Ha*Hb); 3.21 (tdd, 1 H, *J* = 5.6, 2.2, 1.1 Hz, *H*CO); 3.12 (ddd, 1 H, *J*= 13.6, 5.6, 2.3, *H*CO); 2.96 (dd, 1 H, *J* = 5.5, 0.9 Hz, C$H_a$$H_b$Ph); 2.85 (dd, 1 H, *J* = 5.5, 14.8 Hz, C$H_a$$H_b$Ph). **^{13}C-NMR** ($CDCl_3$, 75Mz): 144.9 (*C* ar); 136.5 (*C* ar); 134.6 (*C* ar); 133.8 (*C*H ar); 128.9 (*C*H ar); 128.6 (*C*H ar); 128.5 (*C*H ar); 128.2 (*C*H ar); 126.8; (*C*H ar); 124.7 (*C*H ar); 91.2 (d, *J* = 177.7 Hz, *C*F); 70.6 (d, *J* = 24.9 Hz, *C*H_2CF); 70.2 (*C*H_2); 56.7 (d, *J* = 23.4 Hz, *C*HCF); 55.2 (d, *J* = 8.1 Hz, FC-CH-*C*H); 37.8 (*C*H_2). **^{19}F{^{1}H}-NMR** ($CDCl_3$, 282 MHz): -195.5. **ν_{max}/cm^{-1}** 2360, 1275, 1219, 1149, 770, 638. ***m/z*** (ES+) = 354.05 (MNa^+, 100%); HRMS (ES+) found 354.1107 for $C_{18}H_{19}NO_5Na$, requires 354.1118.

((2*S*,3*R*,4*S*)-5-Azido-2,3,4-trifluoropentyl)benzene 342 :



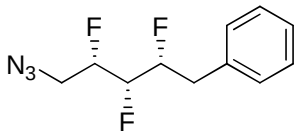
342

Sodium azide (5 mg, 0.07 mmol) was added to a solution of **314** (5 mg, 0.01 mmol) in anhydrous DMF (0.3 mL). The solution was heated at 80 °C for 3 h. Then 1 mL of Et_2O was added and **342** was purified by preparative TLC (hexane 95 / Et_2O 5). Title compound was recovered as an oil (3 mg but with some DMF).

^{1}H-NMR ($CDCl_3$, 500 MHz): δ (ppm) 7.36-7.33 (m, 2 H, C*H* ar); 7.30-7.15 (m, 3 H, C*H* ar); 4.91 (2 m overlapped: [m, 1 H, *J* = 45.9 Hz, *H*CF] + [dddd, 1 H, *J* = 2.6, 7.5, 45.9, 27-30 Hz, *H*CF] last *J* was estimated due to overlapping); 4.53 (dddd, 1 H, *J* = 5.1, 8.3, 27.4, 45.2 Hz, *H*CF); 3.73 (ddd, 1 H, *J* = 2.0, 13.9, 24.4 Hz, N_3C*Ha*Hb); 3.58 (ddd, 1 H, *J* = 4.8, 13.9, 29.6 Hz, N_3CHa*Hb*); 3.24 (ddd, 1 H, *J* = 7.6, 14.0, 21.2 Hz, C*Ha*HbPh); 3.06 (ddd, 1 H, *J* = 7.1, 14.0, 23.1 Hz, CHa*Hb*Ph). **^{13}C-NMR** ($CDCl_3$, 125 Mz): 129.3 (*C*H ar); 128.9 (*C*H ar); 127.2 (*C*H ar); signals of other carbons were not seen even after extended acquisition time. **^{19}F-NMR** ($CDCl_3$, 470 MHz): [-198.63]-[-198.61] (m, 2 F); [-215.02]-[-215.18] (m, 1 F). **^{19}F{^{1}H}-NMR** ($CDCl_3$, 470 MHz): -198.17 (br d, 1 F, *J* = 15.0 Hz); -198.26 (b rd, 1 F, *J* = 9.5 Hz); -214.85 (dd, 1 F, *J* = 9.5, 15.0 Hz).

m/z (CI+) = 244.12 (MH^+, <10%); 196.10 (M - N_2 - F, 40%); 195 (M - N_2 - HF, 30%).

((2*R*,3*S*,4*S*)-5-Azido-2,3,4-trifluoropentyl)benzene 343 :



343

Sodium azide (5 mg, 0.07 mmol) was added to a solution of **328** (5 mg, 0.01 mmol) in anhydrous DMF (0.3 mL). The solution was heated at 80 °C for 3 h. Then 1 mL of Et_2O was added and **343** was purified by preparative TLC (hexane 95 / Et_2O 5). Title compound was recovered as an oil (2 mg but with some DMF).

^{1}H-NMR ($CDCl_3$, 500 MHz): δ (ppm) 7.36-7.33 (m, 2 H, C*H* ar); 7.30-7.25 (m, 3 H, C*H* ar); 4.98-4.74 (m, 2 H, 2 x *H*CF]; 4.63 (ddddd, 1 H, *J* = 2.7, 5.4, 17.2, 25.1, 46.8 Hz, *H*CF); 3.68 (br ddd, 1 H, *J* = 13.6, 2.5, 22.4 Hz, N_3C*Ha*Hb); 3.61 (brddd, 1 H, *J* = 5.0; 13.6, 26.0 Hz, N_3CHa*Hb*); 3.18 (ddd, 1 H, *J* = 8.0, 14.2, 30.3 Hz, C*Ha*HbPh); 3.11 (ddd, 1 H, *J* = 5.6, 14.2, 26.8 Hz, CHa*Hb*Ph). **^{13}C-NMR** ($CDCl_3$, 125 Mz): carbons were not seen even after extended acquisition time. **^{19}F-NMR** ($CDCl_3$, 470 MHz): [-195.76]-[-196.03] (m, 1 F); [-198.19]-[-198.46] (m, 1 F); [-211.32]-[-211.55] (m, 1 F). **^{19}F{^{1}H}-NMR** ($CDCl_3$, 470 MHz): -195.64 (d, 1 F, *J* = 10.9 Hz); -198.07 (d, 1 F, *J* = 13.4 Hz); -211.19 (dd, 1 F, *J* = 10.9, 13.4 Hz). **m/z** (CI+) = 244.12 (MH^+, <10%); 196.09 (M - N_2 - F, 70%); 195.08 (M - N_2 - HF, 40%).

4.3) References Chapter 4:

[1] L. N. Pridgen, A. M. Ahmed, I. Lantos, S. Shilcrat and D. S. Eggleston, *J. Org. Chem.*, 1993, **58**, 5107-5117.

[2] D. A. Evans, J. Bartoli and T. L. Shih, *J. Am. Chem. Soc.*, 1981, **103**, 2127-2129.

[3] L. R. Hillis and R. C. Ronald, *J. Org. Chem.*, 1981, **46**, 3348-3349.

[4] S. Colonna, A. Re, G. Gelbard and E. Cesarotti, *J. Chem. Soc. Perkin Trans 1*, 1979, **9**, 2248-2252.

[5] S. E. Schaus, B. D. Brandes, J. F. Larrow, M. Tokunaga, K. B. Hansen, A. E. Gould, M. E. Furrow and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2002, **124**, 7, 1307-1315.

[6] Sigma-Aldrich, CAS number 133095-74-6,

4.4) Crystallographic data:

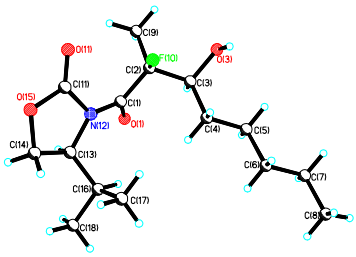


Table 1. Crystal data and structure refinement for VBDH1: 228

Identification code	vbdh1	
Empirical formula	C15 H26 F N O4	
Formula weight	303.37	
Temperature	93(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 12.609(3) Å	α= 90°.
	b = 5.1419(12) Å	β= 113.707(10)°.
	c = 13.677(4) Å	γ = 90°.
Volume	811.9(4) $Å^3$	
Z	2	
Density (calculated)	1.241 Mg/m^3	
Absorption coefficient	0.096 mm^{-1}	
F(000)	328	
Crystal size	0.280 x 0.100 x 0.010 mm^3	
Theta range for data collection	3.01 to 25.35°.	
Index ranges	-10<=h<=14, -4<=k<=6, -14<=l<=15	
Reflections collected	4763	
Independent reflections	2604 [R(int) = 0.0340]	
Completeness to theta = 25.35°	94.0 %	
Absorption correction	Multiscan	
Max. and min. transmission	1.0000 and 0.6853	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2604 / 2 / 196	
Goodness-of-fit on F^2	1.072	
Final R indices [I>2sigma(I)]	R1 = 0.0422, wR2 = 0.0998	
R indices (all data)	R1 = 0.0476, wR2 = 0.1029	
Absolute structure parameter	0.9(9)	
Extinction coefficient	0.014(6)	
Largest diff. peak and hole	0.224 and -0.250 $e.Å^{-3}$	

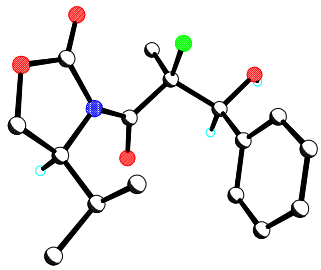


Table 1. Crystal data and structure refinement for vbdh2: 229

Identification code	vbdh2	
Empirical formula	C17.50 H23.50 F N O4	
Formula weight	330.87	
Temperature	173(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 17.1631(16) Å	α= 90°.
	b = 5.3978(6) Å	β= 109.026(3)°.
	c = 21.617(2) Å	γ = 90°.
Volume	1893.2(3) $Å^3$	
Z	4	
Density (calculated)	1.161 Mg/m^3	
Absorption coefficient	0.734 mm^{-1}	
F(000)	706	
Crystal size	0.300 x 0.300 x 0.010 mm^3	
Theta range for data collection	2.16 to 67.80°.	
Index ranges	-20<=h<=20, -5<=k<=5, -25<=l<=25	
Reflections collected	24736	
Independent reflections	5814 [R(int) = 0.1400]	
Completeness to theta = 67.00°	93.3 %	
Absorption correction	Multiscan	
Max. and min. transmission	1.0000 and 0.8284	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5814 / 6 / 423	
Goodness-of-fit on F^2	1.081	
Final R indices [I>2sigma(I)]	R1 = 0.1209, wR2 = 0.3007	
R indices (all data)	R1 = 0.1546, wR2 = 0.3273	
Absolute structure parameter	0.2(5)	
Extinction coefficient	0.0017(8)	
Largest diff. peak and hole	0.705 and -0.315 $e.Å^{-3}$	

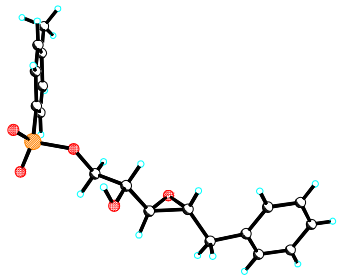


Table 1. Crystal data and structure refinement for vbdh3: 303

Identification code	vbdh3	
Empirical formula	C18 H20 O5 S	
Formula weight	348.40	
Temperature	93(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 6.0029(9) Å	α= 90°.
	b = 8.6118(13) Å	β= 90°.
	c = 32.445(5) Å	γ = 90°.
Volume	1677.3(4) $Å^3$	
Z	4	
Density (calculated)	1.380 Mg/m^3	
Absorption coefficient	0.218 mm^{-1}	
F(000)	736	
Crystal size	0.2000 x 0.1000 x 0.0100 mm^3	
Theta range for data collection	2.45 to 25.34°.	
Index ranges	-5<=h<=7, -10<=k<=9, -38<=l<=24	
Reflections collected	10153	
Independent reflections	2993 [R(int) = 0.0355]	
Completeness to theta = 25.00°	98.5 %	
Absorption correction	Multiscan	
Max. and min. transmission	1.0000 and 0.6932	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2993 / 1 / 223	
Goodness-of-fit on F^2	1.041	
Final R indices [I>2sigma(I)]	R1 = 0.0386, wR2 = 0.0746	
R indices (all data)	R1 = 0.0466, wR2 = 0.0787	
Absolute structure parameter	-0.05(7)	
Largest diff. peak and hole	0.188 and -0.339 $e.Å^{-3}$	

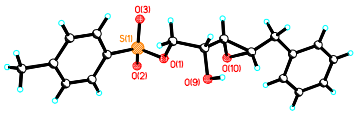


Table 1. Crystal data and structure refinement for vbdh15: 315

Identification code	vbdh15	
Empirical formula	C18 H20 O5 S	
Formula weight	348.40	
Temperature	93(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 9.164(4) Å	α= 90°.
	b = 6.088(3) Å	β= 100.702(19)°.
	c = 15.126(6) Å	γ = 90°.
Volume	829.1(6) $Å^3$	
Z	2	
Density (calculated)	1.396 Mg/m^3	
Absorption coefficient	0.220 mm^{-1}	
F(000)	368	
Crystal size	0.300 x 0.100 x 0.010 mm^3	
Theta range for data collection	3.62 to 25.34°.	
Index ranges	-6<=h<=10, -7<=k<=7, -17<=l<=14	
Reflections collected	4374	
Independent reflections	2647 [R(int) = 0.0676]	
Completeness to theta = 25.00°	98.6 %	
Absorption correction	Multiscan	
Max. and min. transmission	1.0000 and 0.8783	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2647 / 2 / 223	
Goodness-of-fit on F^2	1.077	
Final R indices [I>2sigma(I)]	R1 = 0.0738, wR2 = 0.1489	
R indices (all data)	R1 = 0.1028, wR2 = 0.1626	
Absolute structure parameter	0.08(18)	
Largest diff. peak and hole	0.239 and -0.240 $e.Å^{-3}$	

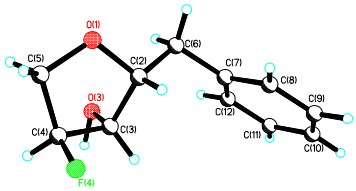


Table 1. Crystal data and structure refinement for vbdh4: 309

Identification code	vbdh4	
Empirical formula	C11 H13 F O2	
Formula weight	196.21	
Temperature	93(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 5.450(3) Å	α= 90°.
	b = 8.242(5) Å	β= 90.809(14)°.
	c = 11.274(6) Å	γ = 90°.
Volume	506.3(5) $Å^3$	
Z	2	
Density (calculated)	1.287 Mg/m^3	
Absorption coefficient	0.099 mm^{-1}	
F(000)	208	
Crystal size	0.1000 x 0.1000 x 0.1000 mm^3	
Theta range for data collection	1.81 to 25.32°.	
Index ranges	-5<=h<=6, -9<=k<=9, -13<=l<=12	
Reflections collected	3158	
Independent reflections	1672 [R(int) = 0.0554]	
Completeness to theta = 25.00°	97.7 %	
Absorption correction	Multiscan	
Max. and min. transmission	1.0000 and 0.2946	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1672 / 2 / 133	
Goodness-of-fit on F^2	1.061	
Final R indices [I>2sigma(I)]	R1 = 0.0640, wR2 = 0.1622	
R indices (all data)	R1 = 0.0648, wR2 = 0.1637	
Absolute structure parameter	-1.0(13)	
Extinction coefficient	0.04(3)	
Largest diff. peak and hole	0.369 and -0.412 e.$Å^{-3}$	

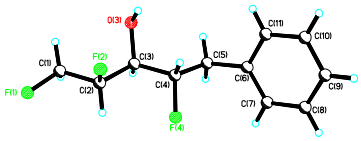


Table 1. Crystal data and structure refinement for vbdh20: 313

Identification code	vbdh20	
Empirical formula	C11 H13 F3 O	
Formula weight	218.21	
Temperature	93(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 8.6198(16) Å	α= 90°.
	b = 4.8446(8) Å	β= 90.142(10)°.
	c = 12.696(2) Å	γ = 90°.
Volume	530.19(16) $Å^3$	
Z	2	
Density (calculated)	1.367 Mg/m^3	
Absorption coefficient	0.121 mm^{-1}	
F(000)	228	
Crystal size	0.3000 x 0.1000 x 0.0100 mm^3	
Theta range for data collection	2.36 to 25.33°.	
Index ranges	-8<=h<=10, -5<=k<=5, -15<=l<=14	
Reflections collected	4858	
Independent reflections	1883 [R(int) = 0.0387]	
Completeness to theta = 25.00°	96.8 %	
Absorption correction	Multiscan	
Max. and min. transmission	1.0000 and 0.8114	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1883 / 2 / 141	
Goodness-of-fit on F^2	1.047	
Final R indices [I>2sigma(I)]	R1 = 0.0415, wR2 = 0.1053	
R indices (all data)	R1 = 0.0474, wR2 = 0.1117	
Absolute structure parameter	1.0(8)	
Largest diff. peak and hole	0.168 and -0.176 $e.Å^{-3}$	

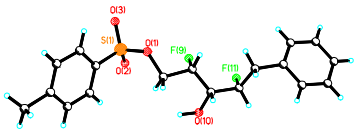


Table 1. Crystal data and structure refinement for vbdh14: 308

Identification code	vbdh14	
Empirical formula	C18 H20 F2 O4 S	
Formula weight	370.40	
Temperature	173(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 5.1792(17) Å	α= 90°.
	b = 18.645(7) Å	β= 92.307(14)°.
	c = 18.365(6) Å	γ = 90°.
Volume	1771.9(11) $Å^3$	
Z	4	
Density (calculated)	1.388 Mg/m^3	
Absorption coefficient	1.990 mm^{-1}	
F(000)	776	
Crystal size	0.100 x 0.100 x 0.010 mm^3	
Theta range for data collection	3.38 to 44.69°.	
Index ranges	-4<=h<=4, -16<=k<=16, -16<=l<=16	
Reflections collected	8450	
Independent reflections	2780 [R(int) = 0.1443]	
Completeness to theta = 44.69°	99.5 %	
Absorption correction	Multiscan	
Max. and min. transmission	1.0000 and 0.8053	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2780 / 2 / 155	
Goodness-of-fit on F^2	1.074	
Final R indices [I>2sigma(I)]	R1 = 0.1476, wR2 = 0.3374	
R indices (all data)	R1 = 0.1977, wR2 = 0.3765	
Absolute structure parameter	0.07(12)	
Extinction coefficient	0.0015(7)	
Largest diff. peak and hole	1.080 and -0.559 $e.Å^{-3}$	

4.5) Appendix:

List of publications

- V. A. Brunet, D. O'Hagan, A. M. Z. Slawin, Titanium mediated asymmetric aldol reaction with α-fluoropropionimide enolates, *J. Fluorine Chem.*, **2007**, 128, 1271-1279.
- V. A. Brunet, D. O'Hagan, Asymmetric fluorination comes of age, *Angew. Chem. Int. Ed.*, **2008**, 47, 1179-1182.
- V. A. Brunet, D. O'Hagan, A. M. Z. Slawin, Improved synthesis of single stereoisomers of the vicinal trifluoroalkane motif, **2009**, *in preparation*.

Oral presentations :

- 3rd National Organic Symposium Trust, conference for research scholars at Guru Nanak Dev University, Amritsar, India (2007).
- 7th RSC fluorine meeting, University of Leicester (2007).
- 4th Organic Chemistry Postgraduate Symposium, University of St Andrews (2007).

Poster presentations :

- 15th European Symposium on Fluorine Chemistry, Institute of Chemical Technology of Prague, Czech Republic (2007).
- 3rd Organic Chemistry Postgraduate Symposium, University of St Andrews (2006).

Conferences attended:

- 37th Scottish organic division Meeting, Glasgow University (UK), 2007.
- 36th Scottish organic division Meeting, Herriot Watt University (UK), 2006.
- 6th RSC fluorine meeting, University of Manchester (UK), 2006.
- 35th Scottish organic division Meeting, Strathclyde University (UK), 2005.
- 5th RSC fluorine meeting, University of Oxford (UK), 2005.