NEW APPROACHES FOR C-F BOND FORMATION IN ORGANIC CHEMISTRY

Guillaume Launay

A Thesis Submitted for the Degree of PhD
at the
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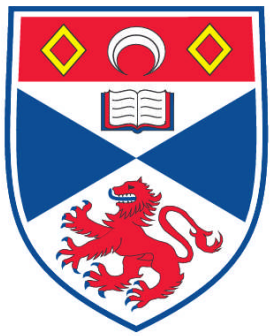

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New Approaches

for C-F Bond Formation

in Organic Chemistry

A thesis presented for the degree of Doctor of Philosophy to
the School of Chemistry, University of St. Andrews

2009

Guillaume Launay

Declarations

I, Guillaume Launay, hereby certify that this thesis, which is approximately 38900 words in length, has been written by me, that it is the record of work carried out by me and that it has not been submitted in any previous application for a higher degree.

I was admitted as a research student in February 2005 and as a candidate for the degree of Doctor in Philosophy in December 2005 the higher study for which this is a record was carried out in the University of St Andrews between 2005 and 2009.

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Abbreviations

DBH: 1,3-dibromo-5,5-dimethylhydantoin

DEAD: diethyl azodicarboxylate

DIBAL-H: diisobutylaluminium hydride

DMF: dimethylformamide

HRMS: high resolution mass spectrometry

LDA: lithium diisopropylamide

LRMS: low resolution mass spectrometry

MTBE: methyl-*tert*-butyl ether

NBS: *N*-bromosuccinimide

NFSI: *N*-fluorobenzenesulfonimide

NIS: *N*-iodosuccinimide

PMA: phosphomolybdic acid

RedAl: sodium bis(2-methoxyethoxy)aluminium hydride

r.t.: room temperature

Selectfluor: *N*-Chloromethyl-*N*′-fluorotriethylenediammonium bis(tetrafluoroborate)

TBAF: tetrabutylammonium fluoride

Tf: trifluoromethanesulfonyl

TFA: trifluoroacetic acid

THF: tetrahydrofuran

TMSCl: trimethylsilyl chloride

TMSOTf: trimethylsilyl trifluoromethanesulfonate

Ts: *p*-toluenesulfonyl

TsCl: *p*-toluenesulfonyl chloride

Abstract

The importance of fluorinated organic molecules has grown over the last 50 years, particularly in the pharmaceutical and agrochemical industries. Therefore the development of new methods for fluorination is a very attractive research area.

In **Chapter 1**, the properties and impact of the fluorine atom on organic molecules are overviewed. Existing electrophilic and nucleophilic fluorination methods are reviewed, and new developments in asymmetric fluorination are discussed.

The emergence of the Prins fluorination reaction as a side product in $BF_3.OEt_2$ catalysed processes has been investigated as a synthesis method in **Chapter 2**. Indeed, it is possible to form 4-fluorotetrahydropyrans with some diastereoselectivity from an allylic alcohol and an aldehyde with a stoichiometric amount of $BF_3.OEt_2$. During this study, formation of 4-fluoropiperidines from *N*-tosyl-4-butenylamine was achieved. Optimisation of reaction conditions was investigated such as the solvent, the reaction temperature and the influence of substituents on the alcohol and the aldehyde reagents. A ring-opening reaction of 4-fluoro-2-phenyltetrahydropyran was successfully performed. Both oxa-Prins and aza-Prins fluorination reactions were investigated under microwave conditions, allowing reduced reaction times, a process that had a minimum impact on the diastereoselectivity.

Attempt to form γ-hydroxy-α-vinylfluorides by the reduction-fluorination of propargylic alcohols with aluminium hydride, or by Horner-Emmons reaction with diethyl (fluoromethyl)phosphonate are reported in **Chapter 3**. Unfortunately these approaches were unsuccessful in the preparation of γ-hydroxy-α-vinylfluorides. Attempts to fluorinate epoxides by α-lithiation and then treatment with electrophilic fluorination reagents gave encouraging results, but the products could not be purified and characterised due to an apparent instability.

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Chapter 1: Fluorine in organic chemistry

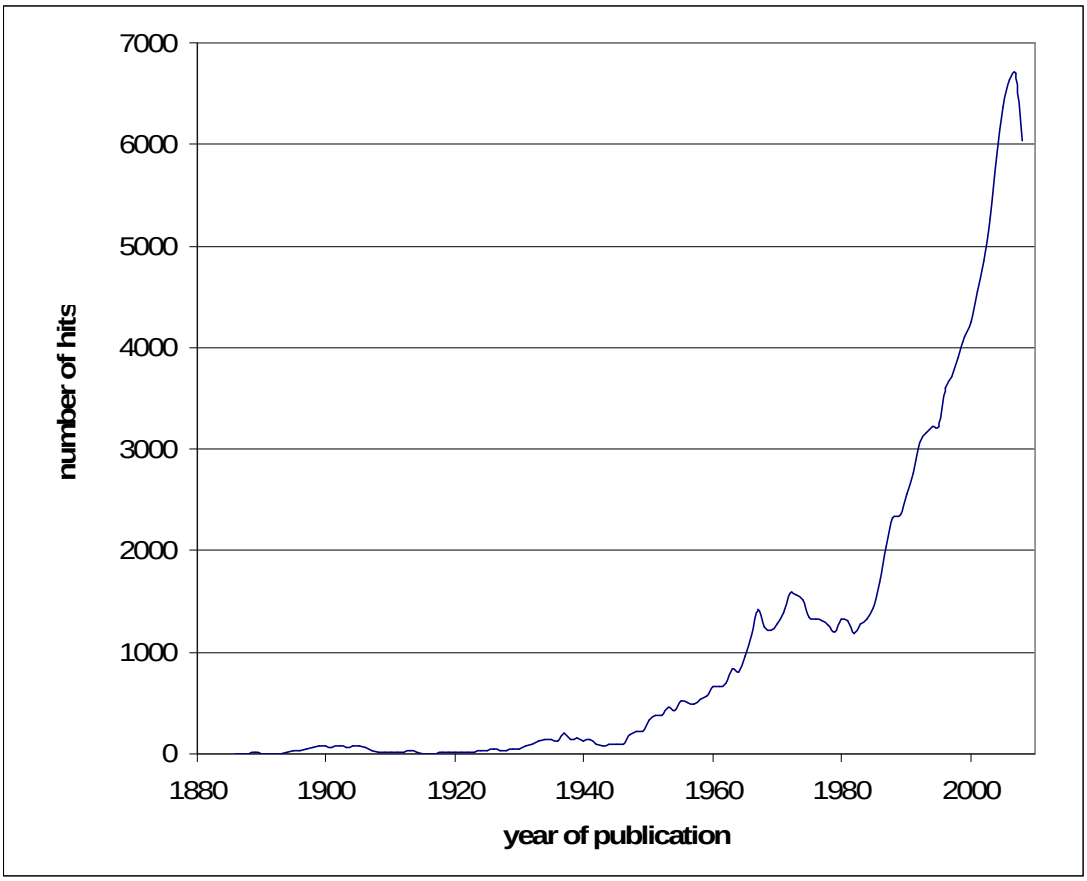
1 Properties of fluorine

1.1 Introduction

Throughout time, humans have tried to improve their knowledge to increase their well-being, making their way from the Stone Age to modern times. The way has been marked by numerous major discoveries from the domestication of fire in the early stage of the human story, to the elucidation of DNA in 1953, *via* the steam engine and electricity in the 1800's. The sciences have experienced huge development during the last 300 years, with an incredible acceleration within the last century. One factor in this knowledge expansion is the desire to discover or to improve what has already been invented, to achieve the best result possible for improvements in daily life, with progress such as electronics and the miniaturisation of equipment, or the discovery and development of new drugs to treat all kinds of illnesses.

But to reach these objectives, it has been essential to test and explore the fundamental properties of matter and to create new material. Or, in the fields of biology and medicine, to understand enzymes and proteins and then the processes and pathways involved in cells and, on a larger scale, in whole organisms.

In order to do so, the element fluorine has been prominent. Since the discovery and isolation of elemental fluorine by Henri Moissan in 1886, fluorine has interested the scientific community because of the very particular properties of the fluorine atom (small size, strong electronegativity, low polarisability). The presence of one (or more) fluorine atom(s) in an organic compound confers properties and reactivity, which are significantly different from those of the non-fluorinated counterpart, without significant modification of sterics, because the length of the CF bond is almost the same as the length as the CH bond (1.39 and 1.09 Å respectively). The study of fluorinated organic materials currently constitutes a field of research which continues to grow as revealed by a straightforward request on Scifinder using the word 'fluorine' (Graphic 1-1).



Graphic 1-1: The evolution of publications involving 'fluorine' as revealed in a Scifinder search (June 2009).

This development can be explained by the unique properties of the fluorine atom and its resulting applications and potential. Today, molecules containing at least one fluorine atom are widespread. They are used in various fields but particularly in agrochemicals, electronics, and medicine, or in the process to separate ^{235}U from ^{238}U for nuclear power stations. One example of a fluorinated compound that is used in everyday life is the polymer Teflon© which is the coating used in non-stick pans. However, the field that has seen the most important expansion of fluorinated compounds is medicinal chemistry. Before 1957 (the synthesis of 5-fluorouracil[1] **1**, an anti-tumour drug), there were no drugs containing a fluorine that had been developed, but since the synthesis of 5-fluorouracil, the situation changed dramatically (Table 1-1)[2] and now over 150 fluorinated drugs have been released on the market; now representing ~20 % of all pharmaceuticals, with even higher proportions for agrochemicals.[3] Nowadays pharmaceutical research involving fluorinated molecules is conducted on a routine basis[4] and some fluorinated drugs are among the best sellers, such as the anti-depressant fluoxetine (Prozac) **2**, the anti-cholesterol atorvastatin (Lipitor) **3** or the anti-bacterial ciprofloxacin (Ciprobay) **4** (Figure 1-1). According to the World Drug Index (WDI), there are 128 fluorinated compounds with US trade names. Of the 31 new chemical entities approved in 2002, nine compounds contained a fluorine atom (NCBI).[5]

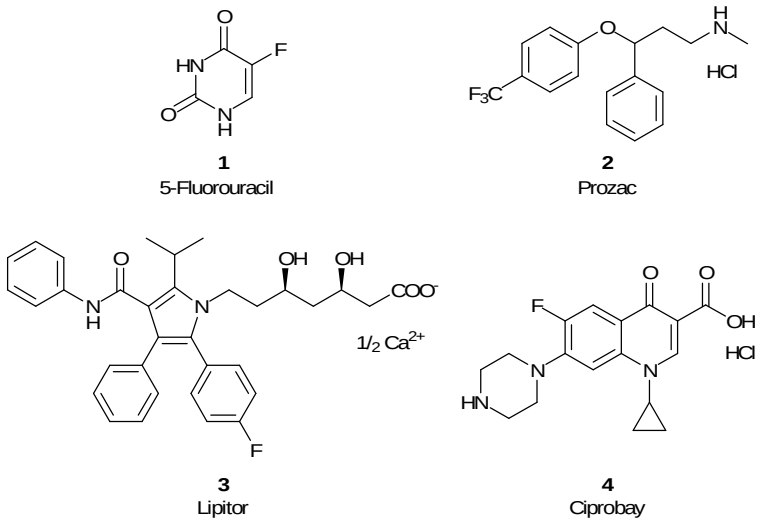


Figure 1-1: Examples of drugs containing a fluorine atom.

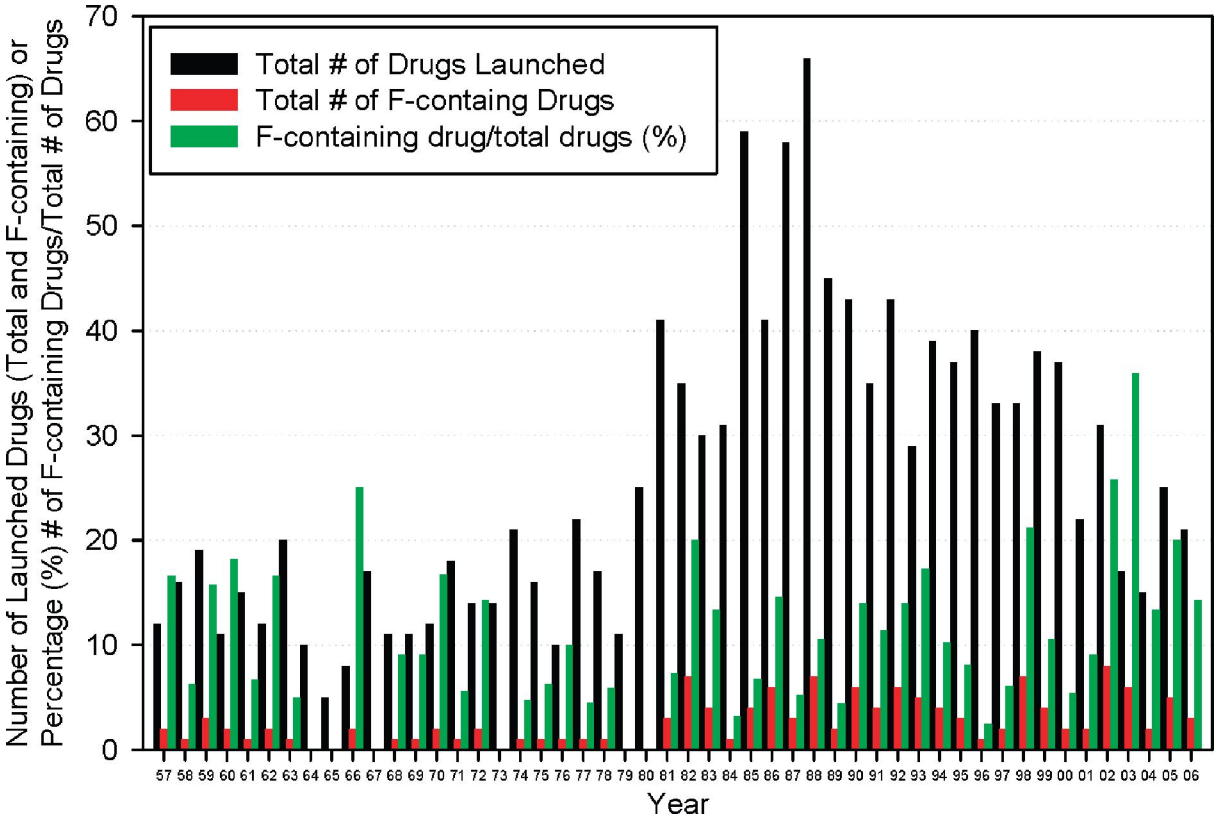


Table 1-1: Drugs emerging successfully from clinical trials which contain a fluorine atom, between the years 1957-2006.[2]

1.2 Electronic effect of fluorine

Fluoride is abundant (0.065%) in the earth's crust and it is the most abundant of all the halogens. However, as an element, fluorine is extremely reactive and difficult to prepare. It was first isolated in 1886 by the French chemist Henry Moissan. This was such a significant event that he was awarded the Nobel Prize in 1906 for its successful isolation. Pure elemental fluorine is a highly reactive diatomic gas under standard conditions. The element contains the most electronegative atom at 4.0 on the Pauling scale, implying a low polarisability and a high ionisation potential. For comparison, carbon is 2.5 and hydrogen is 2.1 on the Pauling scale. The origin of the high electronegativity of fluorine is due to the positive charge of the nucleus (+9) which strongly attracts the electrons of the outer 2p shell.

The C-F bond is the strongest single bond in organic chemistry (Table 1-2).[4, 6] This can be explained by the high electronegativity of the fluorine atom which strongly attracts the covalent electron density, rendering the C-F bond highly polarised, with the electron density displaced towards the fluorine. Thus, the high strength of the bond can be understood to be due to an electrostatic attraction between $C^{\delta+}$ and $F^{\delta-}$ rather than a normal covalent bond with electron sharing.

Bond	Dissociation energy (kcal.mol^{-1})
C-F	105.4
C-H	98.8
C-O	84.0
C-C	83.1
C-Cl	78.5
C-N	69.7

Table 1-2: Dissociation energy of various C-X bonds.[6]

1.3 Steric influence of fluorine

The fluorine atom is small with a Van der Waals radius of 1.47 Å.[7] Its size lies between hydrogen and oxygen with atomic radii of 1.20 and 1.52 Å respectively (Table 1-3). Although fluorine is closer to oxygen in term of size, it has been found to be a good substituent to replace hydrogen on organic molecules.

Atom	Van der Waals radii (Å)
H	1.20
F	1.47
O	1.52
N	1.55
Cl	1.75

Table 1-3: Van der Waals radii of various atoms.[7]

Indeed, the substitution of fluorine for hydrogen is the most conservative on steric hindrance,[8] and does not significantly change the geometry of the molecule. Analysis by scanning tunnelling microscopy (STM) of monofluorinated stearic acids deposited onto graphite reveals an increase of only 1% in the area demanded of an individual molecule in the two dimensional packing arrangement.[8] In solid state X-ray structures, hydrogen and fluorine are often interchangeable.[9] It has also been established that enzymes will generally bind the fluorinated analogue of a natural compound. Thus, despite the difference in size, fluorine is a good hydrogen mimic and has been widely used in this regard in medicinal chemistry.[4, 10, 11] However, there is some evidence that replacing a hydrogen atom with fluorine can induce a

change in the geometry of the molecule. For example, Seebach[12] has shown that the α-fluoro substituent of a *β*hAla(α-F) residue in a β-heptapeptide was oriented antiperiplanar to the C=O, with the consequence of significantly modifying the geometry of the peptide relative to the non fluorinated analogue. Instead of adopting a helical structure like the natural peptide, the overall structure possesses two quasi helical termini, with a central turn in the middle.[12] This is an electronic, rather than steric effect where the C-F bond orientates anti to the C=O of the amide, and results in the new geometry.

There are many more examples where replacement of C-F for C-H allows modification of the electronic environment of a biological molecule without introducing a significant steric perturbation. For example the pK_a's of adjacent functional groups can be influenced by fluorine (Tables 1-4 and 1-5).

Compound	$CH_3CH_2NH_2$	$CH_2FCH_2NH_2$	$CHF_2CH_2NH_2$	$CF_3CH_2NH_2$
pK_a	10.58	9.19	7.45	5.40

Table 1-4: pK_a of ethylamines at 25 °C in water.[13]

Compound	CH_3COOH	CH_2FCOOH	CHF_2COOH	CF_3COOH
pK_a	4.76	2.60	1.40	0.51

Table 1-5: pK_a of acetic acids at 30 °C in water.[14]

Replacement of oxygen by fluorine is a more neutral change, as the electronegativity is similar (oxygen possesses the second highest electronegativity behind fluorine with a value

of 3.44 on the Pauling Scale). The Van der Waals radii of F and O are very close (1.52 Å for oxygen atom, 1.47 Å for fluorine) and their bond lengths are comparable (Table 1-6).

Bond	Bond length (Å)
C-H	1.09
C-F	1.39
C-O (OH)	1.43
C-Cl	1.77

Table 1-6: length of various C-X bonds.

However, this substitution is not perfect as the change of a C-OH to a C-F bond is accompanied by loss of the acidic hydrogen and this clearly affects the hydrogen bond donor capacity. This property has been helpful in understanding the role of C-OH in biological systems; to determine whether the polar nature of the C-OH bond or hydrogen bonding is dominant in specific biological systems. One example is collagen: collagen is a protein showing a tight triple helical conformation, which is very stable. The sequence of the polypeptide chain is a repeat of the following sequence: X-Y-Gly. Gly represent glycine, X is often a proline (Pro) and Y 4-(*R*)-hydroxyproline (Hyp) residues. Investigations have been made by Holmgren *et al.*[15] and Jenkins *et al.*,[16] comparing the thermal stability between $(ProProGly)_{10}$ and $(ProHypGly)_{10}$. The collagen formed from $(ProHypGly)_{10}$ exhibited an enhanced thermal stability compare to $(ProProGly)_{10}$, due to the presence of the hydroxyl groups of the Hyp residues. In order to distinguish whether the helical stability was due to

hydrogen bonding or alternatively due to the polar nature of the hydroxyl groups, $(ProFlpGly)_{10}$ peptides were synthesised where Flp is (4*R*)-fluoroproline residue. It emerged that $(ProFlpGly)_{10}$ was the most stable of the three triple helical peptides tested. As the fluorine is a poor hydrogen bond donor, the thermal stability enhancement of the collagen triple helical structure in $(ProHypGly)_{10}$ is more likely to be due to the polar nature of the C-OH bond of hydroxyproline residues rather than hydrogen bonding. It was subsequently concluded that the polar nature of the C-F bond influenced the 5-membered ring conformation, and the *cis/trans* proline/amide rotation, and that this lead to the enhanced stability, not intermolecular hydrogen bonding.

Replacement of a C=O group with a C-F or CF_2 is not ideal and involves a significant change in the geometry at carbon (from sp^2 to sp^3) and generally involves an unsatisfactory change in molecular shape.

The substitution of a hydrogen atom for a fluorine atom in the α-position of a phosphonate has been explored as a phosphate mimic. Phosphonates are susceptible to hydrolysis by phosphatase enzymes in biological environment. In order to synthesise phosphatase resistant mimics, replacing the bridging oxygen by a carbon appeared to be a solution. However such modification considerably alters the pK_a. Indeed, the pK_a of second deprotonation of α-dihyrogenophosphonate is higher compare to a phosphate (pK_a of 6.5), while the α-monofluorophosphonate is isoacidic, and the difluorophosphonate is more acidic. But this higher acidity is generally accepted to be not too prejudicial as it is assumed that the phosphate group will be completely ionised during the protein binding. However the presence of fluorines on the phosphonate has consequences on the geometry of the molecule. In the case of a monofluorinated phosphonate, the angle widens from 112.1° to 113.3°. However, when difluorinated, the angle increases even more to 116.5° and gets closer to the angle of a phosphate (118°). Thus, with the closer geometry to the phosphate group, and with the pKa

closer to the natural phosphonate, the α,α-difluorophosphonate possesses good arguments to be a good phosphonate mimic. On the other hand, the change of an oxygen to a CF_2 will have an increased steric impact, the fluorine atoms occupying the space where the lone pairs of the oxygen would be in the case of phosphate.

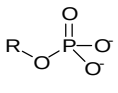
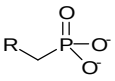
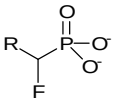
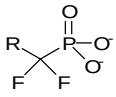
				
Angle C-X-P	118.7	112.1°	113.3°	116.5°
pKa of second deprotonation	6.4	7.5-8	6.5	5.5-6

Table 1-7: Geometry of phosphonate analogues.[17]

The CF_3 group is not a good CH_3 mimic. Indeed, CF_3 is far bigger than CH_3 and the experimental evidence indicates that it is actually closer to an isopropyl, and sometimes acts more like a *tert*-butyl in terms of steric impact (Table 1-8).[18-21]

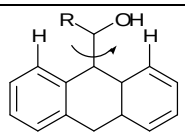
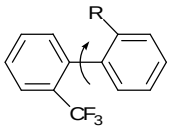
			
Energy barriers of the single bond rotation		Energy barriers of the single bond rotation	
R= ^{i}Pr	14.0 kcal/mol	R= ^{i}Pr	109.8 kcal/mol
R=CF_3	14.5 kcal/mol	R=CF_3	109.2 kcal/mol

Table 1-8: Rotation energy barriers.[22]

1.4 C-F Bond energy

One of the interesting aspects of incorporating an atom of fluorine into a biologically active molecule is the strength of the C-F bond. As indicated previously the C-F bond is the strongest single bond in organic chemistry, often making fluorinated compounds resistant to metabolic degradation.

1.5 Hydrogen bonding to fluorine

One important feature of molecules in biological systems is the presence of hydrogen bonds. A hydrogen bond is defined as a contact between a partially positively charged hydrogen and an electron rich atom, with a distance smaller than the sum of the Van der Waals radii. Therefore in the case of fluorine, this C-F····H-X distance should be shorter than 2.35 Å, where X is an electronegative atom such as O or N. The high electronegativity of fluorine as well as the fact that the C-F bond is highly polarised, with the presence of three lone pairs, suggests that C-F should be a good hydrogen bond acceptor. However, studies evaluating structures deposited in the Cambridge Structural Database show that true H····F contacts are rare.[23] Moreover, fluoro-organic compounds form only weak hydrogen bonds. Calculations give 2.0 - 3.2 kcal. mol^{-1} for a $C(sp^3)$-F····H-O, compared to 5.0 – 10.0 kcal. mol^{-1} for a C-O····H-O contact - less than half the strength of a typical hydrogen bond.[23-25] According to Dunitz, "organic fluorine hardly ever accepts hydrogen bonds, that is, it does so only in the absence of a better acceptor"[26]. This reluctance to enter into hydrogen bonding can be explained by the high electronegativity of the fluorine atom and the strong electrostatic character of the C-F bond which compresses the lone pairs around the fluorine atom, reducing

dramatically the capacity of organic fluorine to act as a hydrogen bonding acceptor. However, even if interactions are weaker than C=O···H-X (X= N or O), they do play a role in crystal packing.[27]

Several studies of crystal structures of small molecules from the Cambridge Structural Database (CSD) and protein-ligand complexes from the Protein Data Base (PDB), have shown evidence of dipole-dipole interactions between C-F (aliphatic and aromatic) and polarised functional groups such as carbonyl, carbonyl derivatives, nitriles and even the nitro group.[28-30] Analysis of the orientation of C-F bonds in fluorinated molecules established that these interactions possess a structural similarity with nucleophile attack to a carbonyl group described by Bürgi and Dunitz. The Bürgi-Dunitz angle characterises the angle of attack of a nucleophile to a carbonyl group along its π-plane below the Van der Waals contact distance (Figure 1-2).[31-33] But in contrast with the attack of a nucleophile, which involves partial transfer of electron density from the nucleophile to the carbonyl, associated with a change of hybridation of the carbonyl, the C-F···C=O interactions observed in the crystallographic data bases are more a multipolar interaction without noticeable changes in the structure of the carbonyl.[29]

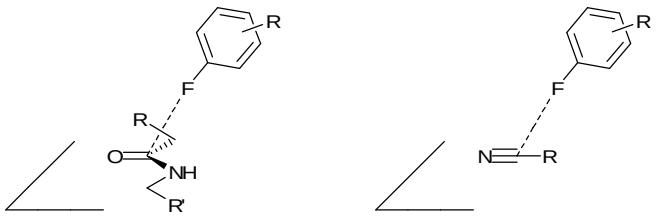


Figure 1-2: dipole-dipole interaction between a fluorine atom and $C^{\delta+}$ from carbonyls or cyanides.

Recognising that these weak interactions occur can now be used to improve and refine protein-ligand binding interactions for optimal orientation of a molecule onto a biding site.

1.6 Fluorine and lipophilicity

Lipophilicity is an important property, particularly in a medicinal chemistry. To cross lipid membranes, a drug needs to be sufficiently lipophilic. In order to obtain good binding affinity to a molecular target, lipophilic interactions are important. However, a drug must not be too lipophilic as this would reduce its water solubility and its bioavailability. Selective fluorination emerges as a good method in which to tune the lipophilicity of a molecule, as the introduction of one or more fluorine atoms can increase the lipophilicity in an incremental manner. However, it can be difficult to predict precisely what the effect of the introduction of a fluorine atom will be, but some general rules have been established. In the case of aromatic molecules, the presence of a fluorine atom will usually increase the lipophilicity.[34] On the other hand, with aliphatic molecules, the situation is a bit more complicated and it is important to go back to the definition of lipophilicity, which is the logarithmic coefficient of a compound's distribution between octanol and water at a given pH. Usually when the lipophilicity increases, the hydrophobicity increases, and *vice versa*. However, with the introduction of fluorine, lipophilicity can decrease but the hydrophobicity can increase at the same time. As the solubility of the fluorinated molecule decreases more in water than in octanol, there is an apparent overall lipophilicity increase, however, this just reflects the lack of affinity for both solvents. When molecules become highly fluorinated, or even perfluorinated, they are no longer lipophiles or hydrophiles, but they now form a third layer on their own, known as the 'fluorous' phase.

2 Fluorine in organic chemistry

2.1 The chemical properties of fluorine

The fluorine atom is a strong electron withdrawing group by the inductive effect, due to its high electronegativity. However, similar to N and O, its lone pairs can donate electrons by the mesomeric effect to stabilise adjacent carbocations counterbalancing the inductive effect. Thus fluorine will stabilise an adjacent carbocation, or on an aromatic ring it will induce *ortho/para* substitution in electrophilic aromatic substitution reactions. On the other hand, β-carbocations are destabilised by the negative fluorine inductive effect (Figure 1-3).

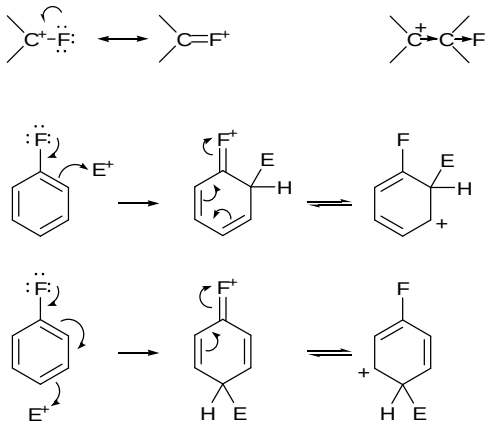


Figure 1-3: Fluorine stabilises α carbocations and destabilises β carbocations.

β-Carbanions are generally stabilised by the inductive effect and also by negative hyperconjugation (displacement of electron density from a π orbital to a σ^*), while a carbanion positioned α- to a fluorine atom is generally destabilised due to a repulsive n-π interaction (Figure 1-4).

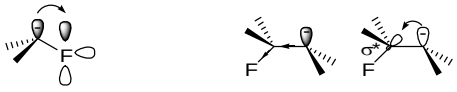
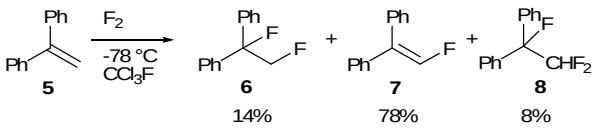


Figure 1-4: Fluorine effects on α and β carbanions.

2.2 Electrophilic fluorination reactions

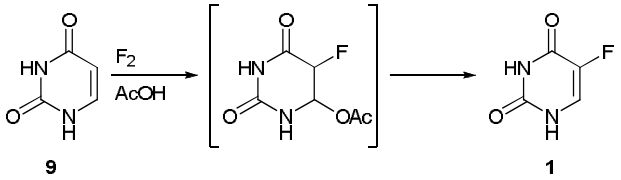
There are two main approaches to introducing a fluorine atom directly into a molecule to generate a C-F bond. One is by nucleophilic fluorination, involving a negatively charged fluoride ion. This method will be discussed in Section 2.3. The second is by electrophilic fluorination, which utilises an "F^+" reagent. The reagent is attacked by an electron rich centre. However, "F^+" cannot exist on its own and it is more correct to talk about reagents that are able to transfer "F^+" to an electron rich site.

Elemental fluorine is essentially an electrophilic fluorinating reagent. However, there are challenges associated with elemental fluorine, particularly due to its high reactivity and lack of selectivity, as well as its high toxicity. One example is the fluorination of 1,1-diphenylethene **5** which gives a mixture of mono- and poly- fluorinated products **6**, **7** and **8** (Scheme 1-1).[35]



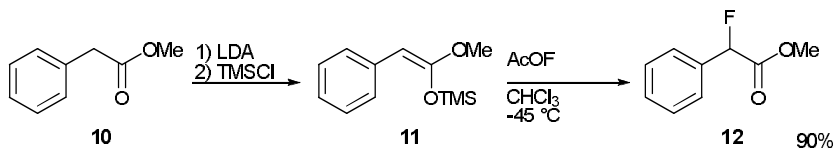
Scheme 1-1: Fluorination of 1,1-diphenylethylene with F_2.

However, under controlled conditions, synthesis using diluted F_2 in an inert gas such as nitrogen or argon has proven to be very successful.[36] An early example of such a success is the synthesis of 5-fluorouracil **1** and its related analogues (Scheme 1-2).[37, 38] The synthesis of 5-fluorouracil in this way is one of the few syntheses using elemental fluorine, which is still carried out in industry, [39] other than in uranium enrichment.



Scheme 1-2: Synthesis of 5-fluorouracil using F_2 by Cech.[37]

Due to a general reticence to using F_2, a large range of electrophilic fluorination reagents have been developed. In order to create such reagents, several strategies have emerged. One good candidate involves the use of RO-F type compounds, organofluoroxy reagents. An early example was the fluoroxytrifluoromethane, which has been extensively developed and used successfully for the fluorination of pharmaceutical products.[40, 41] Another example of a popular organofluoroxy reagent is acetyl hypofluorite. In 1981 this reagent was shown to fluorinate aromatic rings.[42] Acetyl hypofluorite[43] has been intensively studied in this regard,[42, 44] as well as for addition to double bonds,[45, 46] fluorination of lithium enolates[47] and synthesis of α-fluorocarboxylic acid derivatives from the corresponding carboxylic acids (Scheme 1-3).[48]

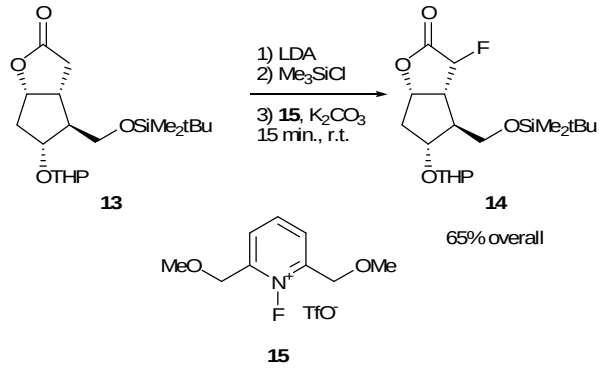


Scheme 1-3: Fluorination of methyl phenylacetate **10** with acetyl hypofluorite.[48]

Other XO-F electrophilic fluorinating agents have been developed such as perchloryl fluoride $FClO_3$, xenon difluoride, XeF_2 or caesium fluoroxysulfate, $CsSO_4F$. But many have shown a strong oxidising property or selectivity issues which compromises their utility.[36, 38]

Major progress in the field of electrophilic fluorinating reagents came with the development of the *N*-F reagents. The main advantage of this class of reagents comes from the lower electronegativity of the nitrogen compared to oxygen, and the corresponding higher strength of the *N*-F bond compared to the O-F bond. This decreases the electrophilicity of the *N*-F reagents, giving them improved stability and thus making them easier to handle. We can distinguish three types of *N*-F electrophilic fluorinating agents: the *N*-fluoropyrimidium triflates and derivatives, the sulfonyl derivatives $RSO_2N(F)R'$ and Selectfluor® and its derivatives.

The *N*-fluoropyrimidium triflates and derivatives, mostly developed by Umemoto,[49-51] have been used to fluorinate aromatic rings, carbanions, enol ethers and their derivatives. The choice of the counter ion is important and needs to be non-nucleophilic for their stability. Several counter ions have been explored (X^-= TfO^-, BF_4^-, ClO_4^- and SbF_6^-) but it was found that triflate has the highest reactivity.[49] The choice of ring substituents is also important as the fluorinating power increases with the decrease of the electron density of the N^+-F bond, giving access to a wide range of reactivity and selectivity.[49-51] A good example of the application of *N*-fluoropyrimidinium triflate is the preparation of the fluorinated Corey lactone **14** using 2,6-dimethoxymethyl-*N*-fluoropyrimidium triflate **15** (Scheme 1-4).[50] Umemoto reported only one stereoisomer, but unfortunately he was unable to determine the absolute configuration at the stereogenic centre carrying the fluorine atom.



Scheme 1-4: Preparation of a fluorinated Corey lactone.[50]

Since its preparation and study 15 years ago by Banks and co-workers[52, 53], Selectfluor **16** has become a fantastic tool in the area of electrophilic fluorination (Figure 1-5). Selectfluor is air stable and easy to manipulate. Its reactivity can be tuned by modifying the substituent on the second nitrogen. In order to increase its reactivity, a stronger electron-withdrawing group is required and the reagents can be classified from the less reactive to strongly reactive: CH_3, C_2H_5, C_8H_7 < CH_2Cl < CF_3CH_2.[53] They have found a wide range of applications, including fluorination of aryl groups, nucleosides,[54-56] steroids[57] and other building blocks and organic substrates.[39]

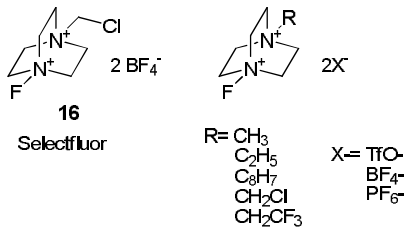


Figure 1-5: Selectfluor and related derivatives.

In 1984, a study on *N*-alkyl-*N*-fluorosulfonamides by Barnette *et al*[58] demonstrated an interesting reactivity in the presence of a base with a broad variety of compounds including

ketones, acids, malonates, organomagnesiums, and arenes, with fluorine transfer occurring in moderate to good yields. Unlike the pyridinium triflates and Selectflluor, the *N*-fluorosulfonimides are neutral and are also easy to handle (Figure 1-6). Taken together these properties have made this reagent and its derivatives very popular.

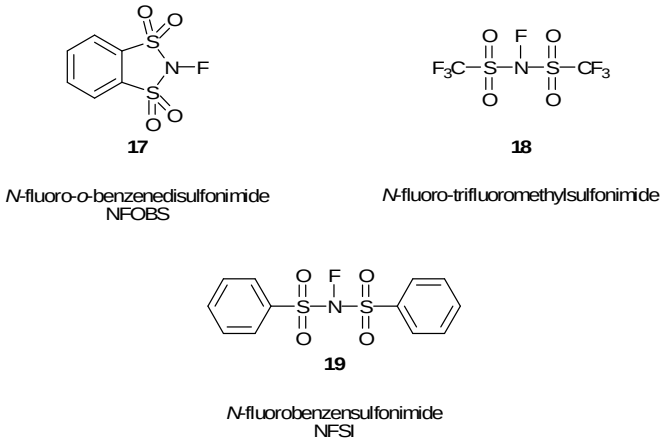


Figure 1-6: Examples of *N*-fluorosulfonimides, electrophilic fluorinating reagents.[59-61]

With electrophilic fluorination reagents now widely available, the way to prepare α-fluorinated carbonyls from enolates emerged, and with it came the challenge of asymmetric fluorination. A wide range of asymmetric fluorinating reagents have been created. Differing *et al.* described the first enantioselective fluorination reaction in 1988,[62] followed by Davis[63, 64] and Takeuchi[65, 66] using chiral *N*-fluorosultams (Figure 1-7) to undergo fluorination reactions on enolates with up to 88% ee (Scheme 1-5).

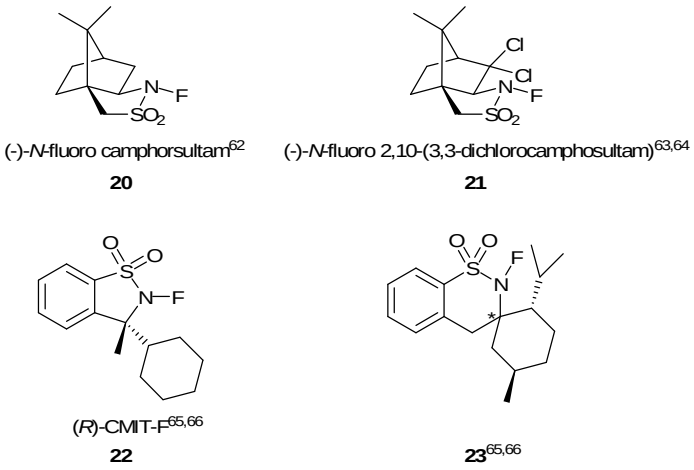
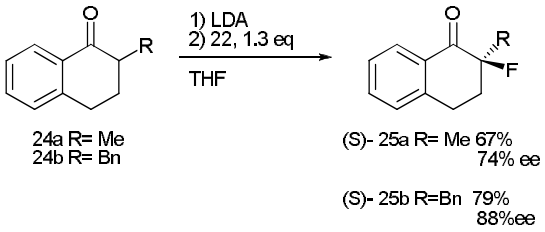


Figure 1-7: Selection of chiral *N*-fluorosultams developed by Differing (**20**),[62] Davies (**21**)[63, 64] or Takeuchi (**22** and **23**).[65, 66]



Scheme 1-5: Enantioselective fluorination using chiral *N*-fluorosultam **22**.[66]

Takeuchi *et al*[66] rationalised the reaction using the transition state hypothesis shown in Figure 1-8 to explain the (*S*) selectivity in the case of the fluorination of **24a**. The hypothesis is based on a X-ray crystallographic structure of (*R*)-CMIT-F **22**.[67] According to the X-ray structure, the nitrogen is highly pyramidalised and the fluorine is *anti* periplanar to the cyclohexyl group. The five membered ring is in an envelope conformation, resulting in a N-F bond which is almost perpendicular to the plane formed by the atoms S-$C_{aromatic}$-$C_{aromatic}$-C. The experimental evidence also suggests the importance of the coordination of the lithium enolate, as the addition of HMPA results in a drop in the enantioselectivity from 74% to 14% ee.

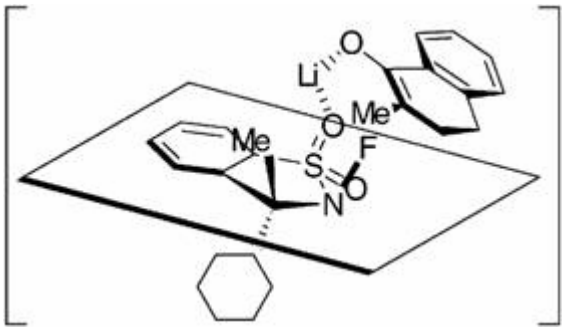
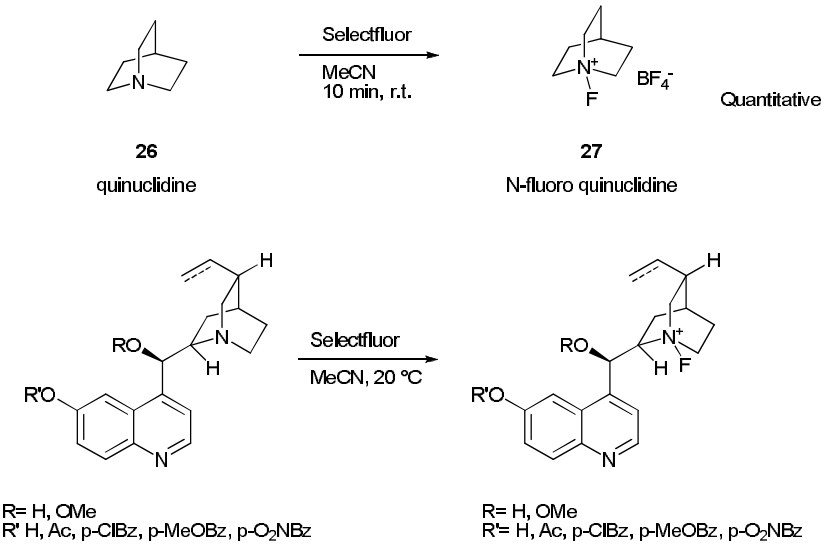


Figure 1-8: Transition-state model for the fluorination of the lithium enolate of **24** with (*R*)-**22**.[66]

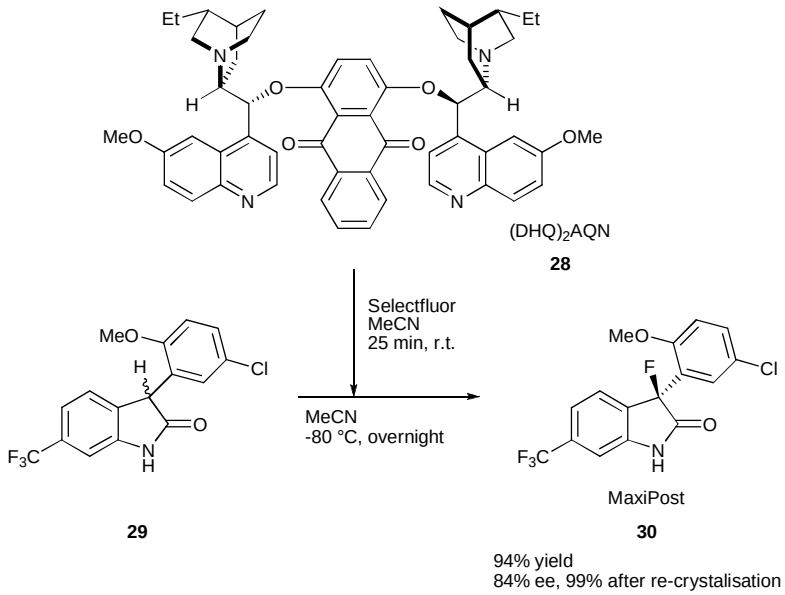
One limitation of these reagents is that none are commercially available and also the reactions require a stoichiometric quantity of the fluorination reagent. Furthermore, their preparation often requires several steps including fluorination with elemental fluorine or the explosive perchloryl fluoride.

Other approaches to achieving asymmetric electrophilic fluorination have been explored. Following the work of Banks *et al*[68] where they quantitatively and rapidly transferred the fluorine atom from Selectfluor to quinuclidine **26** giving *N*-fluoro quinuclidine **27**, Shibata *et al*[69-71] and Cahard *et al*[72, 73] and later Gouverneur *et al*[74] have used Selectfluor and cinchona alkaloids to successfully perform stereoselective fluorination reactions (Scheme 1-6).



Scheme 1-6: Fluorine exchange between Selectfluor and alkaloids.

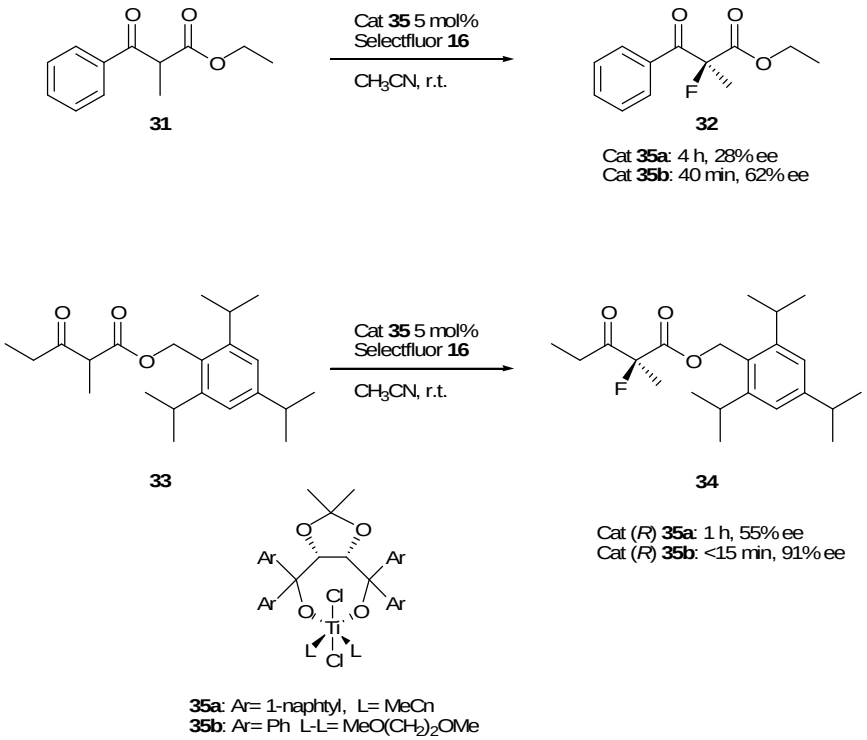
This method consists of exchanging fluorine from *N*-fluoroammonium salts such as Selectfluor to cinchona alkaloids, generating an asymmetric fluorinating reagent.[70, 73, 75] In contrast to the *N*-fluorosultams, the preparation of these fluorinating agents involves commercial starting materials and does not require F_2. This methodology has afforded the preparation of selectively fluorinated compounds from cyclic silyl enol ethers, β-ketoesters, oxindoles, β-cyanoesters and allyl silanes with good yields and moderate to good enantioselectivities (up to 91%, 80%, 84%, 87% and 96% ee respectively). Shibata *et al.*[71] have described the first asymmetric synthesis of MaxiPost **30**, a drug currently in phase III clinical trials to treat acute ischemic stroke. The preparation used hydroquinine anthraquinone-1,4-diyl diether or $(DHQ)_2AQN$ **28** as the cinchona derivative (Scheme 1-7).



Scheme 1-7: Enantioselective synthesis of Maxipost.[71]

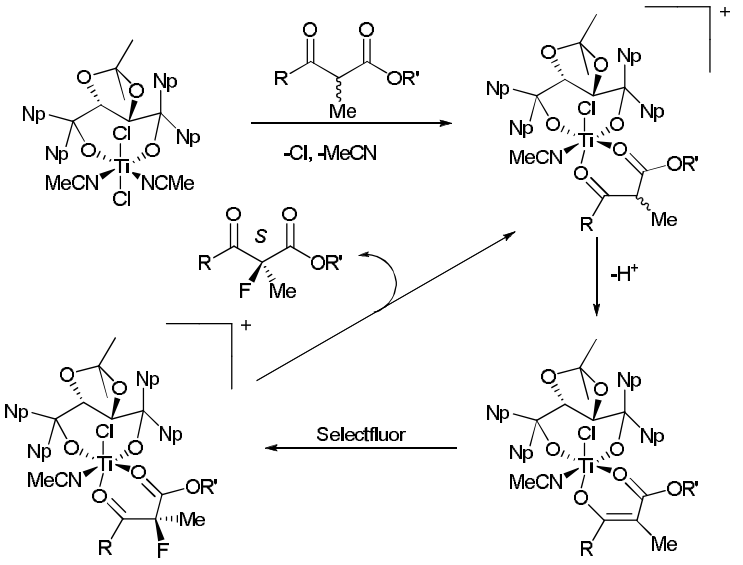
Attempts at using a catalytic amount of alkaloid failed due to the faster reaction of Selectfluor with carbanions compared to the rate of transfer of fluorine to the alkaloid. This approach is impressive but requires a screening of different cinchona alkaloids for each reaction as the choice of the alkaloid is important for the optimisation of the rate of transfer and thus the enantioselectivity for each substrate.

Several studies have shown that the presence of a Lewis acid during the fluorination of 1,3-dicarbonyls with *N*-F reagents will facilitate enolisation.[76] The first catalytic enantioselective electrophilic fluorination of a β-ketoester was reported by Togni and Hintermann in 2000 when they screened a series of transition metal complexes as Lewis acid candidates.[77] The best results were obtained using a titanium TADDOL complex with Selectfluor, giving high yields and high ee's ranging from 62 to 91% ee on branched β-ketoesters (Scheme 1-8).



Scheme 1-8: Catalytic enantioselective electrophile fluorination by Togni and Hintermann.[77]

Togni and Hintermann[78] also demonstrated that the presence of a bulky group on the catalytic species increases the enantiomeric excess, allowing an improvement from 28% to 62% and from 55% to 91% by going from catalyst **35a** to **35b**. The choice of the ester is important, and again, the larger the alcohol used to prepare the ester, the better the resultant enantiomeric excess. A mechanism has been proposed and validated by theoretical studies. The metal complex coordinates the bidentate β-ketoester which leads to a fast enolisation with elimination of chloride. Then the naphthyl group blocks the *Re* face of the enolate, directing attack to the *Si* face and giving the *S* enantiomer as observed (Scheme 1-9).



Scheme 1-9: Rationale mechanism of enantiomeric fluorination catalysed by Ti(taddol).[78]

This approach is limited to branched β-ketoesters, since the Ti catalyst can induce racemisation and difluorination by enolisation of the tertiary fluorinated α-carbon. Other studies have explored metal catalysed enantiomeric electrophilic fluorination using Pd,[79, 80] Zn,[81, 82] Ni and Cu[81] chiral complexes and applied this methodology not only to β-ketoesters, but also to β-ketophosphonates[83-85] and cyanoacetates.[86] Metal-mediated fluorinations emerge as a powerful tool to generate C-F bonds in high ee. Although a wide range of compounds can be fluorinated, the method is more often limited to substrates with two binding points, and the product must not be easily enolisable. In order to overcome these limitations, other approaches to enantioselective electrophilic fluorination have also been investigated.

Asymmetric organocatalytic methods have been applied to fluorination. Prolines are known to catalyse enantioselective intramolecular aldol condensations[87] and a wide range can be prepared to modulate their reactivity. In 2005, three research groups simultaneously and independently, reported on the direct α-fluorination of aldehydes using various cyclic secondary amines as catalysts with electrophilic fluorination reagents on hindered or

functionalised aldehydes. Collectively this method achieves excellent enantioselectivities and yields.[88-90] The biggest challenge was to find a catalyst that enabled enantiocontrolled C-F bond formation and at the same time suppressed product racemisation or difluorination. Jørgensen[89] and Barbas[90] described the fluorination of aldehydes using proline derivatives. Barbas *et al.*[90] demonstrated that NFSI gives the highest ee with excellent conversion using L-proline **36** (25% ee). They also screened several proline derivatives and imidazolidinones with various resulting chiral induction. Jørgensen demonstrated that pyrrolidine **37** (Figure 1-9) is an excellent catalyst as a chiral promoter, providing the alcohols after reduction of the aldehydes, with excellent ee's in a range from 91 to 97% and in very good yields.[90]

L-proline **36** | Ar= Ph-3,5-$(CF_3)_2$ **37**

Figure 1-7: Example of proline-based catalysts.[89, 90]

Jørgensen has suggested that the *E*-configured enamine is formed with iso-valeraldehyde where the bulky substituents of the pyrrolidine block the *Re* face. The consequence of this shielding is that the approach of the fluorinating agent will be from the *Si* face, providing excellent enantioselectivity (Figure 1-10).[89]

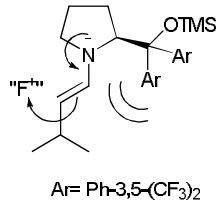
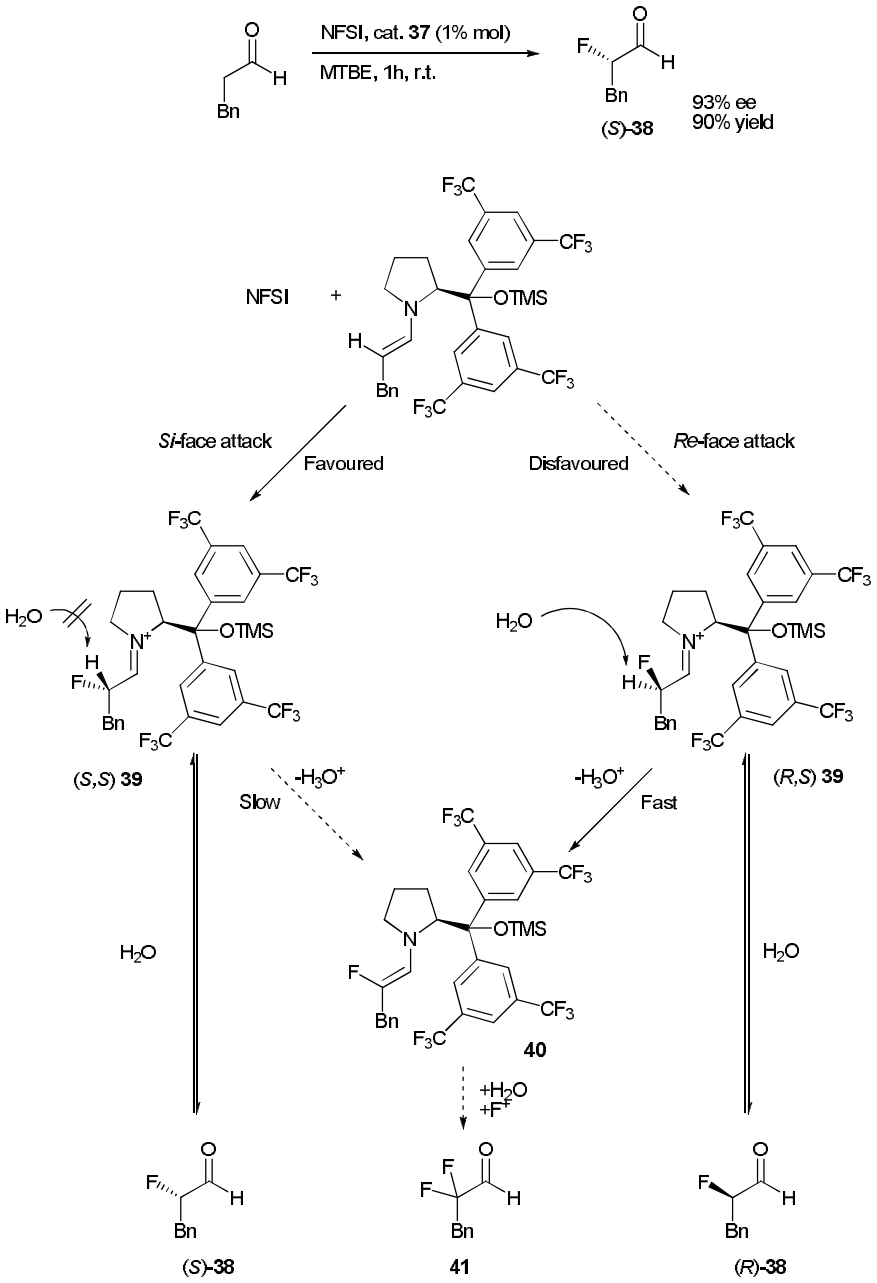


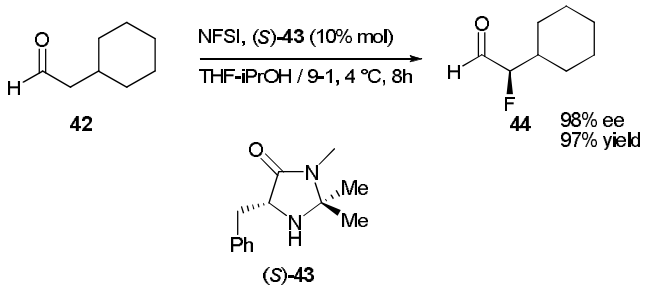
Figure 1-10: Jørgensen's rationale for *Re* face attack.[89]

Jørgensen also proposed an explanation for the configurational stability towards racemisation using pyrrolidine **37** as a catalyst (Scheme 1-10). The aryl substituent of the pyrrolidine points towards the enamine, forming preferentially the (*S, S*) imminium intermediate. The remaining hydrogen atom of intermediate (*S, S*)-**39** is then protected by the bulky aryl substituent, preventing deprotonation by nucleophilic attack of water, and thus preventing the formation of the fluorinated enamine. On the other hand, the hydrogen atom of the disfavoured (*R, S*)-**39** imminium intermediate is situated on the *Si*-face and can be easily attacked to give to the fluorinated enamine **40**, which then leads to racemisation or difluorination resulting in (*S*)-**38** or **41** as the products.



Scheme 1-10: Rationale for the configurational stability during the fluorination of aldehydes using the catalyst **37**.[89]

MacMillan *et al.*[88] and Barbas *et al.*[90] reported the use of commercially available imidazolidinones (*S*)-**43** and (*R*)-**43** respectively, to catalyse the fluorination of aldehydes by NFSI (Scheme 1-11). The aldehydes were rapidly converted to the corresponding α-fluoroalcohols by reduction.



Scheme 1-11: α-Fluorination of aldehydes catalysed by the imidazolidinone **43**.

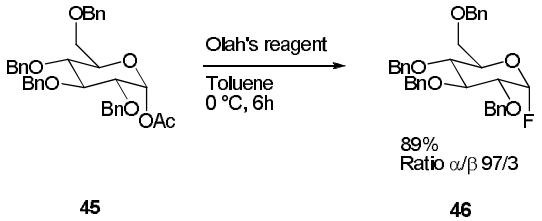
Both imidazolidinones show better enantiomeric excesses than the proline derivative catalysts with good yields (54 to 96%) and high enantioselectivities (91 to 99% ee). This method could be applied using a wide range of solvents, including acetone, as long as there is 10% of isopropanol as a co-solvent. Similar to pyrrolidine **37**, the imidazolidinone **43** tolerates bulky substituents at the α-position of the aldehyde, and with a wide range of functional groups such as esters, amines, carbamates, double bonds and aromatic rings. The reaction conditions also tolerate highly enolisable products such as 2-fluorophenylacetaldehyde and generate products with very high enantioselectivity (99% ee). The mechanistic details are not elucidated, but MacMillan hypothesised that the NFSI could "presumably participate in the requisite closed transition state *via* sulfone-proton bonding and concomitant fluorine/enamine activation".[88] This approach not only tolerates a wide range of α-substituted groups, including very bulky groups, but also requires commercially available, easy to use reagents and does not require specialist equipment.

2.3 Nucleophilic fluorination

The other general strategy used to fluorinate substrates involves nucleophilic fluorination, using fluoride ion itself or reagents able to realise fluoride ion release.

A large variety of fluoride salts are commercially available, such as KF, but the properties of fluoride make it hard to use as it is strongly solvated in protic solvents and, by consequence, a poor nucleophile. Also it forms a tight ion pair in most aprotic solvents, so the ion pairing must be overcome to increase its nucleophilic properties. The availability of fluoride ion can be increased in aprotic solvents by using a bulky cation, which delocalises the positive charge and then reduces ion pairing. One good example of such a reagent is the popular tetrabutylammonium fluoride (TBAF).

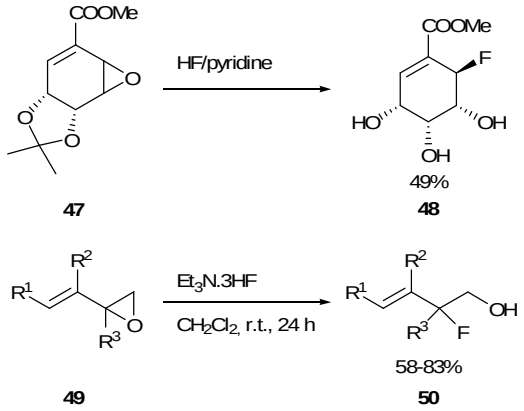
Another approach consists of the use of hydrogen fluoride (HF). Hydrogen fluoride is a low boiling (19.5 °C) liquid and it is highly corrosive, requiring specialist handling. In order to make it easier to manipulate it can be use in association with amines, such as triethylamine $Et_3N.3HF$ or pyridine (Olah's reagent; Pyridine.9HF).[91] But such reagents generally require an activated substrate as the amines reduce the nucleophilicity of the fluoride ion. Olah's reagent has been successfully employed in a wide variety of reactions including the fluorination of the anomeric position in carbohydrates (Scheme 1-12).[92]



45 46

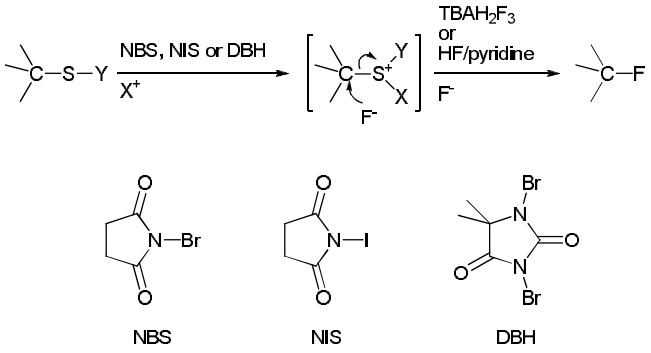
Scheme 1-12: Preparation of 1-fluoro-2,3,4,6-tetra-*O*-benzyl-1-deoxy-α-D-glucose using Pyr:HF (Olah's reagent).[92]

These reagents have been successfully applied to mediate epoxide ring opening, such as allylic epoxides **47** and **49** leading to the corresponding fluorinated analogue of shikimic acid **48** and to fluorhydrins **50**, generally in good yields (Scheme 1-13).[93, 94] In this case, the epoxide ring strain provides the activation required for the reaction to proceed.



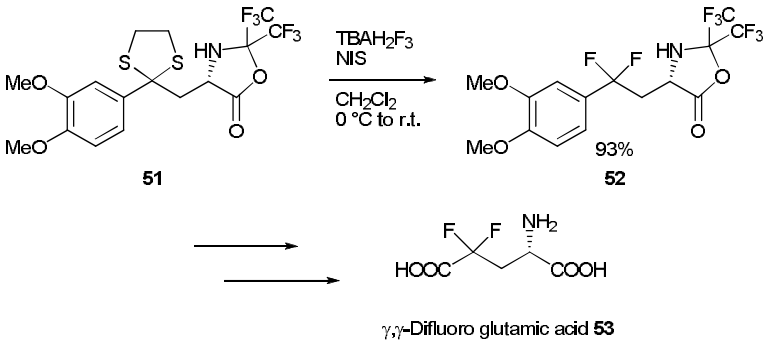
Scheme 1-13: Epoxide ring opening using HF derivatives.[93, 94]

Another fluorinating method for organosulfur compounds using these reagents consists of an oxidative desulfurisation-fluorination reaction, leading to polyfluorination in most cases. To activate the organosulfur substrate towards nucleophilic attack, the sulfur is oxidized by a positive halogen from NBS, NIS or DBH. Then the activated intermediate is attacked by fluoride ion, usually from HF/pyridine, or tetrabutylammonium dihydrogen trifluoride $TBAH_2F_3$ (Scheme 1-14).



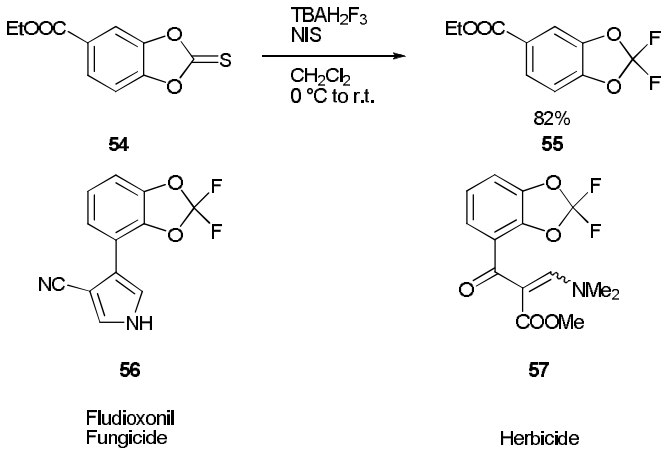
Scheme 1-14: Proposed mechanism for desulfurisation-fluorination.

The oxidative desulfurisation-fluorination has been used for the preparation of molecules of biological interest such as γ,γ-difluoroglutamic acid **53** from the dithioketal **51** (Scheme 1-15).[95]



Scheme 1-15: Synthesis of γ,γ-difluoroglutamic acid using oxidative desulfurisation-fluorination method.[95]

The preparation of the difluoromethylenedioxy moiety **55** from the thionecarbonate **54**, through oxidative desulfurisation-fluorination is a useful method for the preparation of molecules such as fludioxonil **56** or the herbicide **57** (Scheme 1-16).[96]

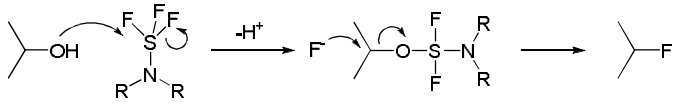


Scheme 1-16: Preparation of difluoromethylenedioxy compounds by oxidative desulfurisation-fluorination.[96]

This method can be applied to the preparation of a wide range of compounds, like difluorinated alkyl chains from a dithioketals, or trifluoromethyl amines, trifluoromethyl ethers, trifluoromethyl aryls and trifluoromethyl alkyl from dithioesters.

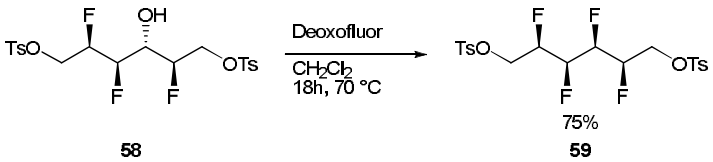
In 1975, Middleton *et al.*[97] reported the preparation of diethylaminosulfur trifluoride (DAST), a powerful fluorinating reagent which could replace hydroxyl groups and carbonyl oxygens by fluorine, to generate mono and gem-difluorinated products respectively. Lal *et al.*[98, 99] reported in 1999, the preparation and use of bis(2-methoxyethyl)aminosulfur trifluoride, known as Deoxofluor^{TM}, an evolution of DAST with better thermal stability (DAST is well known to undergo explosive degradation when used above 90 °C).

The mechanism for replacement of a hydroxyl group by a fluorine atom with DAST or Deoxofluor occurs in two steps. First, nucleophilic attack of the hydroxyl occurs to the sulphur and displaces a fluoride ion, forming a good leaving group and leading to the formation of HF *in-situ*. The released fluoride then attacks the carbon to form a C-F bond (Scheme 1-17).



Scheme 1-17: Mechanism of the dehydroxy-fluorination by DAST or its derivatives.

Fluoride attack is generally by a S_N2 process, allowing the creation of the C-F bond with stereocontrol (Scheme 1-18). A good example is the preparation of the all-*syn* four vicinal fluorine motif **59** from trifluoroalcohol **58**, and where the last fluorine atom is inserted with an inversion of configuration.[100]

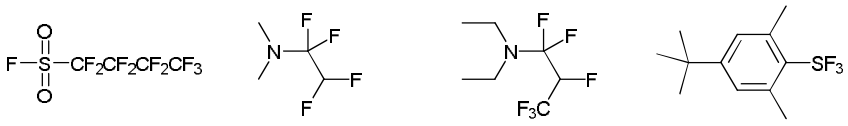


58 59

Scheme 1-18: Example of stereocontrol of dehydroxy-fluorination with Deoxofluor.[100]

The dialkylaminosulfur trifluorides can be used on a wide range of compounds such as alcohols to give the monofluorinated products, on ketones leading to gem-difluoro products, or on carboxylic acids as a method for the preparation of trifluoromethyl groups.[97, 99]

Several other reagents have been developed as alternatives to dialkylaminosulfur trifluorides to perform dehydroxy-fluorination following a similar reaction mechanism. Among these products we can find the perfluoro-1-butanesulfonyl chloride **60** (PBSF),[101] the commercially available tetrafluoroethyldimethylamine **61** (TFEDMA)[102] and Ishikawa fluorinating agent **62**,[103] or the Fluolead™ **63**, a novel fluorinating reagent introduced in 2009 also by Ishikawa (Figure 1-11).[104, 105]



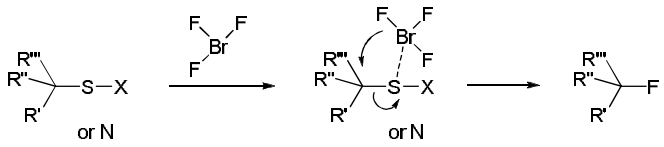
PBSF TFEDMA Ishikawa's reagent FLUOLEAD™

60 61 62 63

Figure 1-11: Alternatives to dialkylaminosulfur trifluorides.

The commercially available bromine trifluoride BrF_3 is an interesting fluorinating agent. It requires a heteroatom like N or S at the α position to the fluorinating site, but it

allows the preparation of α,α-difluoro ethers from thioesters, sulfonyl fluorides from sulfonyl chlorides, difluoroalkyls from ketones and α,α-difluoroesters from α-thioketal esters.[106] The mechanism is based on soft acid-soft base interactions between the bromine atom and the sulphur or nitrogen atom, positioning BrF_3 for an easy delivery of fluoride to the electrophilic carbon in the α position to the heteroatom (Scheme 1-19). In most cases the fluoride will substitute the sulphur or nitrogen atom to form a C-F bond.



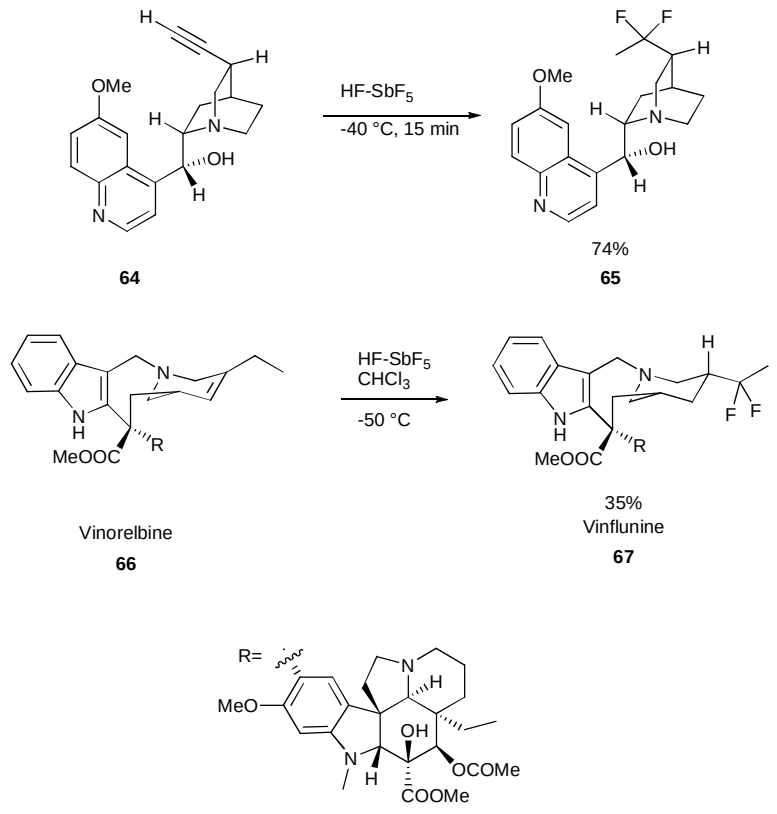
Scheme 1-19: Mechanism of fluorination by BrF_3.

One limitation of this reagent is its lack of reactivity towards ethers, as the oxygen plays the role of a hard base, and most of the time it leads to the slow deterioration of reagents.

Nucleophilic fluorinations with super acid (SbF_5/HF) have been intensively studied to perform mono- or di- fluorination in the β-position or γ-position of amines or sulfonamides. A super acid is, by the definition of Gillespie, 'any medium which is more acidic than 100% sulphuric acid.' In the case of SbF_5/HF (1/1), the reagent has been determined to be 10^{16} times more acidic than sulphuric acid. This super acid is characterised as a highly acidic, but weakly nucleophilic solvent.[107] Mono hydro-fluorination has been achieved from allylic amines or sulfonamides with moderate to excellent yields,[108] and difluorination has been performed with the corresponding alkyne in yields from 18 to 87%,[109] or from allylic amines in the presence of NBS to give the corresponding products in moderate yields.[110] Recently, Thibaudeau *et al.*[111] reported the preparation of 3- and 4- fluoropiperidines from *N*,*N*-diallylic amines and

amides with yields from 21 to 85%. *N*-Methylated amines as the protecting group provide the best results.

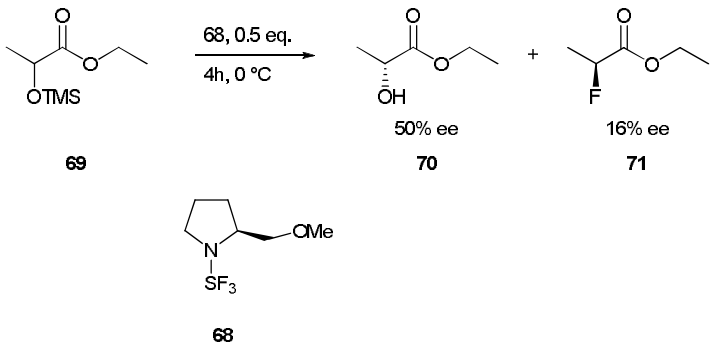
Two good examples of application of super acid HF-SbF_5 involve the preparation of difluoro cinchona alkaloid derivative **65** from the corresponding alkyne **64** with a yield of 74%, allowing the preparation of a new range of cinchona alkaloid derivatives (Scheme 1-20).[112] Another example is the preparation of vinflunine **67** from **66**, an anti-tumour agent currently in phase III clinical trials for treatment of bladder and lung cancers.[113, 114] This reaction start first with isomerisation to lead to the *exo*-double bond.



Scheme 1-20: Example of difluorination using HF-SbF_5.

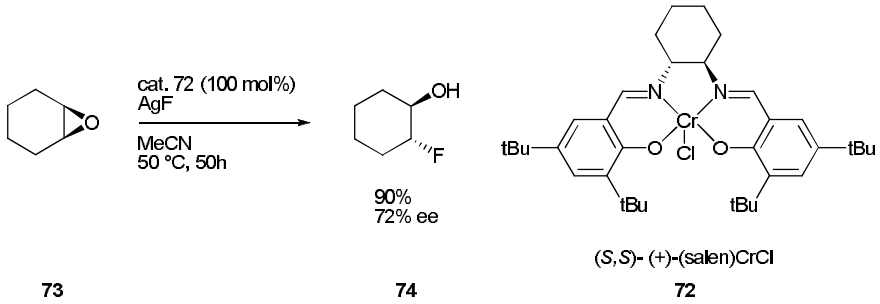
Unlike electrophilic fluorination, there are very few examples of enantioselective nucleophilic fluorination. In 1989, Sampson et *al.* prepared a homochiral aminosulfur trifluoride **68** derived from *(S)*-proline.[115] But the first results were not encouraging, as a

kinetic resolution using this reagent with ethyl 2-(trimethylsiloxy)propanoate **69** led to the (*S*)-fluorinated ester **71** with 16% ee and the alcohol derivative **70** with a 50% ee (Scheme 1-21).[115]



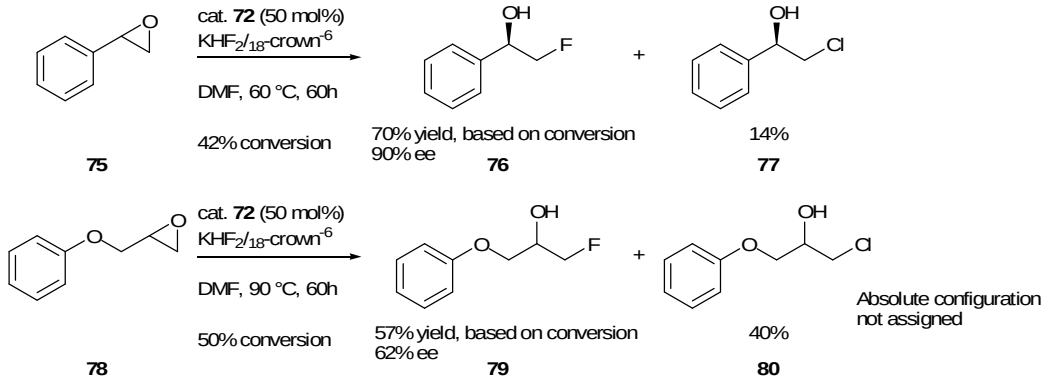
Scheme 1-21: Fluorination with homochiral aminosulfur trifluoride derived from *(S)*-proline.

The best results for an enantioselective nucleophilic fluorination have been reported by Haufe *et al.* in 2000 and 2001 on asymmetric ring opening of *meso* and racemic epoxides.[116, 117] Initial attempts using 5-10 mol% of europium complexes or zinc tartrate on *meso* epoxides gave the corresponding fluorohydrins in poor and good yields respectively, but with poor enantioselectivities (4-10% ee). However, when the reaction was carried out with cyclohexene oxide **73** and Jacobsen's (salen)-chromium chloride **72** in the presence of a variety of fluoride sources, 43 to 72% ee in favour of the (*R*,*R*)-(-)-2-fluorocyclohexanol **74** was achieved. The best result was obtained with a stoechiometric amount of Jacobsen's catalyst **72** and silver fluoride as a fluoride source (Scheme 1-22). Catalyst loadings were high and when the catalyst was reduced to 50 mol%, the ee, went from 72 to 66%.



Scheme 1-22: Enantioselective epoxide ring opening on *meso* cyclohexene oxide **73**.

Racemic epoxides, such as styrene oxide **75** and phenyl glycidyl ether **78**, under similar conditions gave the fluorhydrins **76** and **79** respectively and in 74 and 65% ee. In the case of the fluorhydrin **79**, the absolute configuration was not assigned. Along with these products, the chlorhydrins **77** and **80** were also obtained as side products (Scheme 1-23).



Scheme 1-23: Asymmetric epoxide opening using KHF_2.

According to the enantio- and diastereo- control of the epoxide ring-opening reactions developed by Haufe and co-worker, these reactions are more likely to occur through a S_N2 process. Indeed, no rearrangement product or diastereoisomers were detected by ^{19}F NMR of the reaction mixture, suggesting a S_N2 type reaction.

3 Conclusion

We have seen in this chapter the importance of the properties of the fluorine atom and its role in the development of biologically active molecules in medicinal chemistry. Fluorine can increase the *in vivo* half life of a molecule, or can be used to increase the lipophilicity, without dramatically altering the shape of a molecule. Different methods have been reviewed on how to generate the C-F bond in organic chemistry followed by an overview of the current status of enantioselective fluorination. There are a variety of methods for creating a C-F bond enantioselectively using electrophilic fluorinating agents, however there are few involving enantioselective nucleophilic fluorination.

Chapter 2 of this thesis is dedicated to the study of nucleophilic fluorination *via* the Prins reaction to form 4-fluorotetrahydropyrans and 4-fluoropiperidines.

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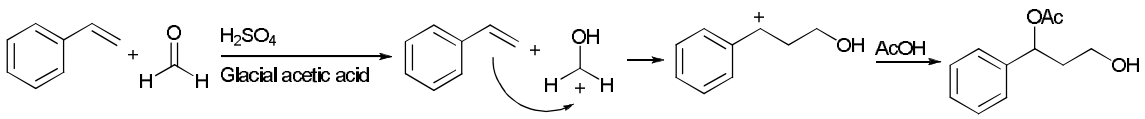
Chapter 2: Prins cyclisation with fluorination

1 Introduction

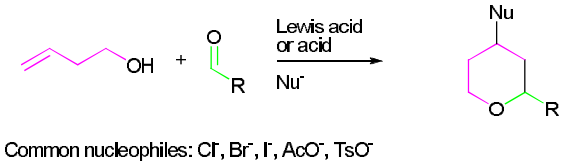
1.1 The Prins cyclisation

The Prins reaction is a reaction involving the condensation of an olefin with an aldehyde. The first report on the condensation of olefins with aldehydes was carried out by Kriewitz in 1899.[1, 2] He reported the formation of unsaturated alcohols when α-pinene or pentadiene was heated in a seal tube with paraformaldehyde. However it wasn't until 1919 that the first comprehensive study was carried out by H. J. Prins.[3, 4] Using water or glacial acetic acid as a solvent, he performed reactions with styrene, α-pinene and camphene with formaldehyde. With water as a solvent, 1,3-butanediols or unsaturated alcohols were obtained. However, with glacial acetic acid, esters from acetic acid were usually obtained (Scheme 2-1). Since the first condensations of olefins with aldehydes, this type of reaction has commonly been called the Prins reaction.



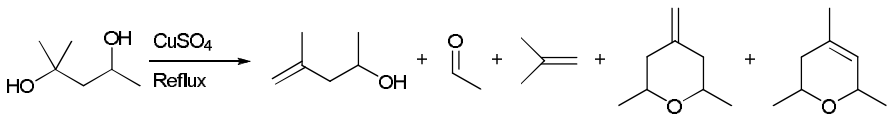
Scheme 2-1: Example of condensation of an olefin with an aldehyde carried out by H. J. Prins in 1919.[3]

The Prins cyclisation reaction is a reaction leading to tetrahydropyrans from a homoallylic alcohol and an aldehyde, in the presence of a Lewis acid and a nucleophile. Common nucleophiles used for this reaction are bromide,[5-8] chloride,[5, 6, 8-11] iodide,[5] acetate[7, 11-15] and tosylate[11] (Scheme 2-2).



Scheme 2-2: General case for the Prins cyclisation reaction.

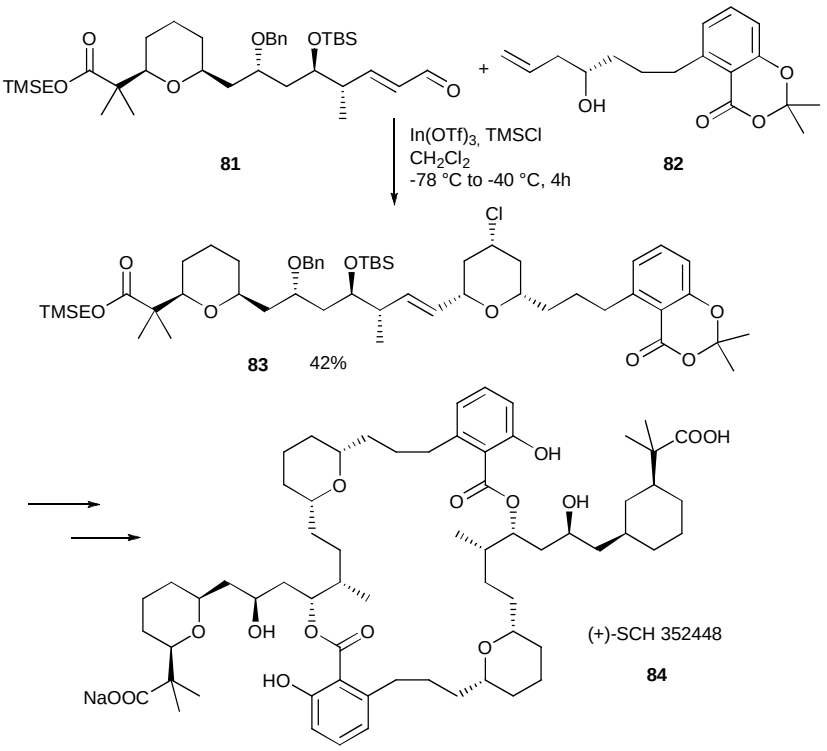
The first report on the identification of pyrans during a Prins reaction was by Ballard *et al.*[16, 17] while they were investigating the dehydration of 2-methyl-2,4-pentanediol. The dehydration led to a complex mixture including 4-methylpent-4-en-2-ol, acetaldehyde and a dihydropyran (Scheme 2-3).



Scheme 2-3: First report of formation of pyran by a Prins cyclisation reaction.

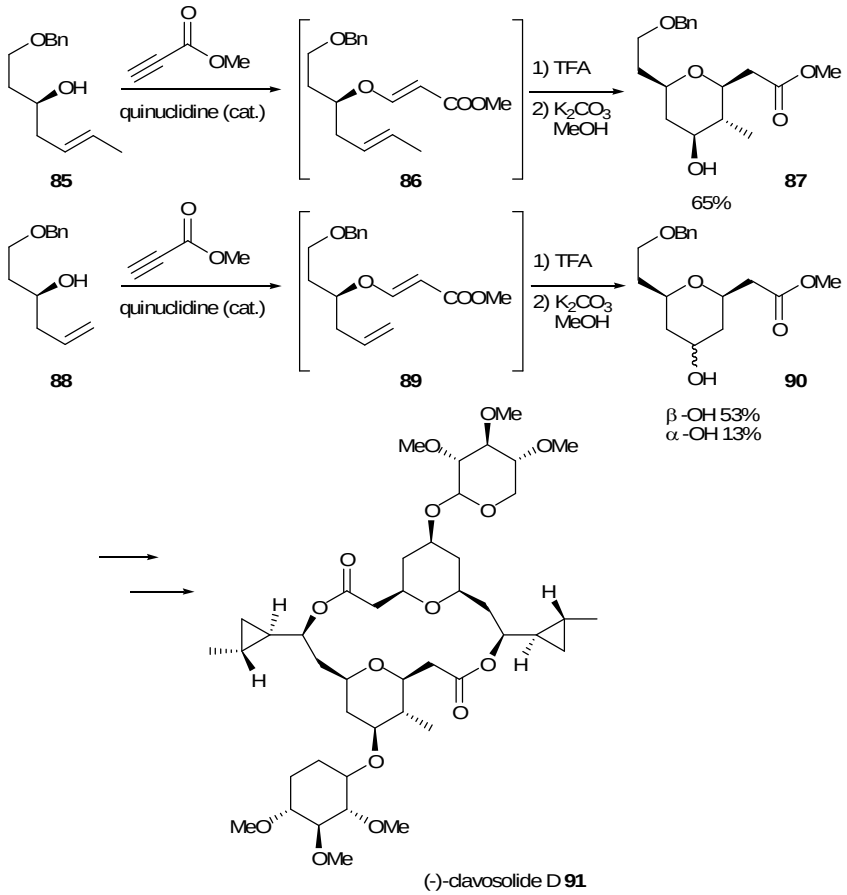
The tetrahydropyran motif is common in natural products, inciting the development of methodology to form tetrahydropyran rings efficiently from complex, advanced synthons. Loh *et al.*[18] used the Prins reaction as key step in the formal synthesis of the natural product (+)-SCH 351448 **84**, a novel activator of the low density lipoprotein receptor promoter. The α,β-unsaturated aldehyde **81** and the homoallylic alcohol **82** were substrates for the Prins cyclisation to access intermediate 4-chlorotetrahydropyran **83** (Scheme 2-4). After

optimisation using different Lewis acids, the tetrahydropyran **83** was prepared using $In(OTf)_3$ in the presence of TMSCl in a 42% yield.



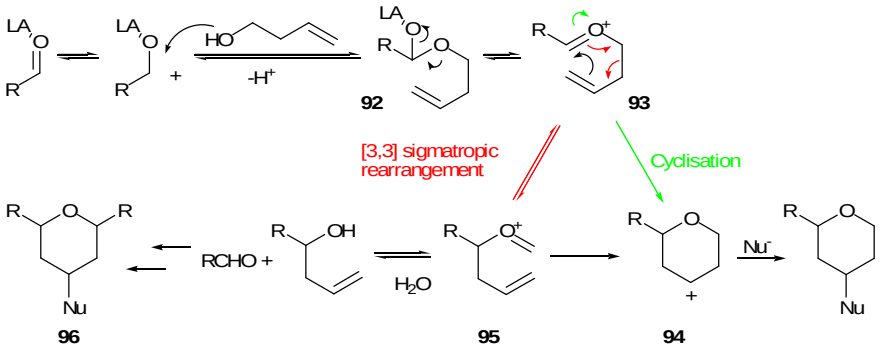
Scheme 2-4: Application of the Prins cyclisation to the synthesis of (+)-SCH 351448 **84**.[18]

Another example involved the synthesis of (-)-clavosolide D **91**, a natural product extracted from *Myastra clavosa*, a marine sponge found in the Philippines (Scheme 2-5).[19] This unsymmetrical molecule possesses two tetrahydropyrans, one is trisubstituted (**87**) while the other is tetrasubstituted (**90**). Both have been prepared using Prins methodology, using the enol ethers **86** and **89** prepared *in-situ* from alcohols **85** and **88** respectively. The tetrahydropyrans **87** and **90** were obtained after hydrolysis of the resultant trifluoroacetate esters. Tetrahydropyran **87** was obtained as a single stereoisomer in 65% yield over the two steps, while tetrahydropyran **90** was obtained as a 4/1 mixture in favour of the all-equatorial β-product.



Scheme 2-5: Prins methodology for the total synthesis of (-)-clavosolide **91**.[19]

The mechanism of the Prins cyclisation has been investigated by several research groups,[11, 14] and the consensus is as follows: first the alcohol attacks an activated aldehyde to form a hemiketal intermediate such as **92** (Scheme 2-6). This intermediate then undergoes dehydration after activation to generate oxonium intermediate **93**. From there, the reaction can follow one of two routes. The first is the cyclisation of the oxonium intermediate to form cyclic carbocation **94**, which is then attacked by a nucleophile to give the expected 4-subtituted tetrahydropyran. Alternatively a [3,3] sigmatropic rearrangement of **93** can occur leading to the oxonium isomer **95**.[13] This isomer can either cyclise to **94** or it can revert to an alcohol and an aldehyde, and undergo another Prins reaction to produce trisubstituted tetrahydropyran **96** as a side product.



Scheme 2-6: Mechanistic hypothesis relating to the Prins reaction.

According to theory calculations reported by Alder *et al.*, carbocation **94** prefers a *chair-like* conformation.[20] The R substituent is most likely to hold an equatorial orientation, and then the nucleophile can attack from either the top or bottom of the plane of the molecule. This leads to two separate diastereoisomers, termed the *syn* and *anti* products.

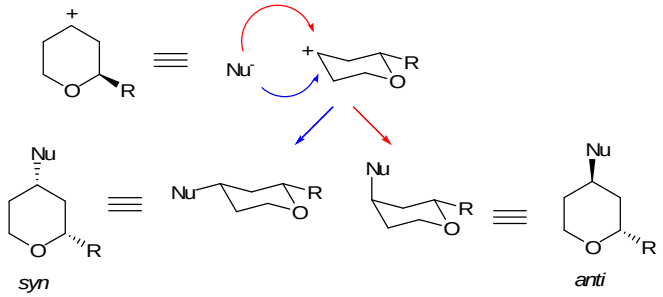
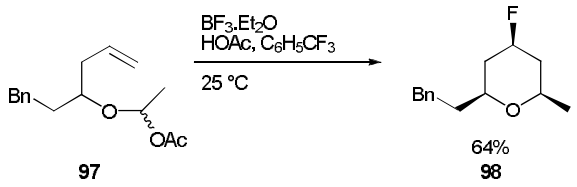


Figure 2-1: Origin of diastereoisomer selectivity in the Prins reaction.

1.2 The Prins cyclisation reaction in fluorine chemistry

Several publications have reported the formation of 4-fluorotetrahydropyrans as unexpected by-products of Prins cyclisations, when $BF_3.OEt_2$ was used as a Lewis acid, and

especially when the nucleophile is acetic acid (Scheme 2-7). This was first observed by Rychnovsky *et al.*[12] in 1996, and then by several other research groups.[7, 8, 11, 14, 21, 22] The fluorine atom became incorporated due to fluoride ion quenching the intermediate carbocation, depending on the ratio of $BF_3.OEt_2$/nucleophile or the presence of reagents such as TMSOAc to trap free fluoride ion.



Scheme 2-7: Prins reaction leading to the 4-fluorotetrahydropyran **98** by Jaber *et al.*[7]

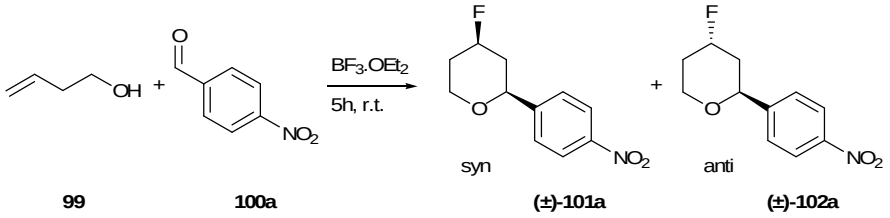
This represents a novel approach to C-F bond formation in organic chemistry. A focus of this research programme aimed to explore the Prins fluorination reaction and to try to define the limits of the methodology, as a contribution to organo-fluorine synthesis.

2 Oxa-Prins reaction

2.1 Solvent study

An investigation of the literature reveals very few examples of the Prins fluorination reaction, and in those cases they were unwanted by-products. Therefore the first step of our study aimed to identify the optimal solvent in which to carry out the reaction. The publications to date have described the Prins fluorination cyclisation with dichloromethane as the solvent, although it was not clear if this solvent was in any way optimal.

The reaction chosen for this study involved but-3-en-1-ol **99** (1 mmol) as the alcohol in a reaction with 4-nitrobenzaldehyde **100** (1 mmol) using $BF_3.OEt_2$ (1 mmol) in 10 mL of solvant. With this choice of reactants, only two major products are formed, the (±)-*syn* and the (±)-*anti* fluorotetrahydropyrans **101** and **102** respectively (Scheme 2-8).



Scheme 2-8: Prins fluorination of **99** and **100a** using $BF_3.OEt_2$ (1 eq).

Solvents were selected over a wide range of polarity. With hexane and toluene as the solvent, complete conversion (100%) was observed (by ^1H NMR) after 5h, while the conversion was 67% with dichloromethane as the solvent (Table 2-1). The reaction in dichloromethane gave a 2/1 diastereoisomer ratio in favour of the *syn* product. It is noteworthy that in the case of dichloromethane, increasing the reaction time beyond 5h did not improve the conversion.

When the solvent showed some Lewis base properties such as *N*,*N*-dimethylformamide (DMF), diethyl ether or tetrahydrofuran (THF), no reaction occurred. This could be due to the co-ordinating effect of the solvent out-competing the coordination of the reagents and reducing the activating effect of the reactivity of $BF_3.OEt_2$.

Solvent	Conversion (5h, r.t.)	Diastereoisomeric ratio **101a**/**102a**
Dichloromethane	67%	2/1
Hexane	100%	1/1
Toluene	100%	1.5/1
Diethyl ether	No reaction	/
THF	No reaction	/
DMF	No reaction	/

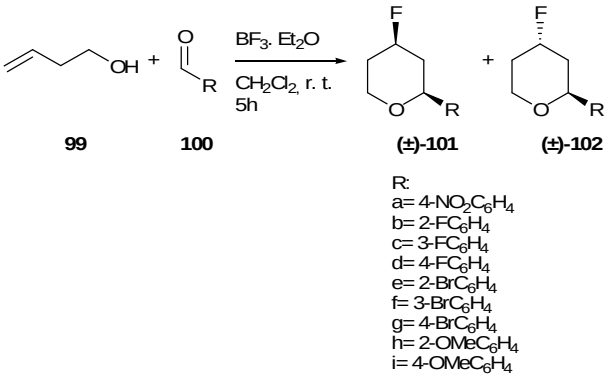
Table 2-1: The effect of solvent on the Prins fluorination reaction between alcohol **99** and aldehyde **100a** in the presence of $BF_3.OEt_2$ (1eq) at r.t.. Conversions were determined by ^1H NMR and diastereoselectivity was determined by ^{19}F NMR.

For subsequent studies on diastereoselectivity of the Prins fluorination reaction, dichloromethane was used as the solvent of choice, as this solvent gave the highest diastereoselectivity even though less polar solvents gave higher conversions under the conditions studied.

2.2 Influence of the aldehyde

It was of interest to determine whether the nature of the aldehyde has an effect on the reaction. This investigation was carried out with the but-3-en-1-ol **99** and $BF_3.OEt_2$ in dichloromethane at room temperature (Scheme 2-9).

In order to carry out this study, two groups of structurally different aldehydes were considered, benzaldehydes and aliphatic aldehydes.



Scheme 2-9: Prins reaction with but-3-en-1-ol **99** and various aldehydes in the presence of $BF_3.OEt_2$ (1 eq).

In the first instance, a range of benzaldehydes (Table 2-2) were explored. For those with an electron withdrawing group on the phenyl ring (entry a-g), the conversions are between 65 and 73% and the diastereoselectivity is between 5.4/1 and 1.9/1. In both series of fluoro- and bromo- benzaldehydes, a significantly lower diastereoselectivity resulted when the substituents were at the *meta*- position compared to the *ortho*- and *para*- positions.

In the case of electron donating groups (entries h-j), the conversions drop dramatically, and these reactions were inefficient, or in some cases no reaction occurred at all. This was particularly the case with the *ortho*-methoxybenzaldehyde substrates (entries i and j). These observations could perhaps be explained by chelation of the BF_3 group to a highly enolised aldehyde rendering the aldehyde, with the *ortho*-methoxy group, unreactive (Figure 2-2). In the case of pyridine-4-carboxaldehyde and indole-3-carboxaldehyde (entries k and l), again no reactions were observed.

Entry	Aldehyde	conversion	d.r (**101**/**102**)
a	4-nitrobenzaldehyde	67%	1.9/1
b	2-fluorobenzaldehyde	66%	4.5/1
c	3-fluorobenzaldehyde	66%	3.4/1
d	4-fluorobenzaldehyde	66%	4.5/1
e	2-bromobenzaldehyde	65%	5.4/1
f	3- bromobenzaldehyde	73%	3.8/1
g	4- bromobenzaldehyde	90%	4.8/1
h	2-methoxybenzaldehyde	< 5%	1.3/1
i	4- methoxybenzaldehyde	20%	2.4/1
j	2,3,6-trimethoxybenzaldehyde	No reaction	-
k	pyridine-4-carboxaldehyde	No reaction	-
l	Indole-3-carboxaldehyde	No reaction	-

Conversions determined by ^{1}H NMR, d.r. determined by ^{19}F NMR

Table 2-2: Prins reaction of homoallylic alcohol **99** with aromatic aldehydes **100a-j** and $BF_3.OEt_2$ (1eq) in CH_2Cl_2 at room temperature (5h) to give fluoropyrans **101a-j** and **102a-j**.

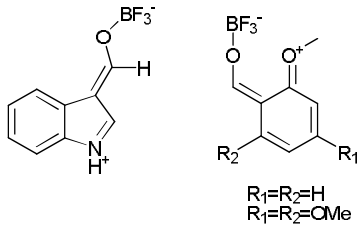
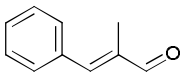
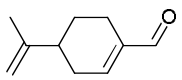
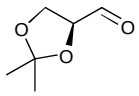
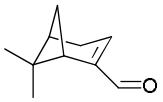


Figure 2-2: Possible chelation of $BF_3.OEt_2$ to 2-methoxybenzaldehyde **100h**, 2,4,6-trimethoxybenzaldehyde **100j** and indole-3-carboxaldehyde **100l**.

In the case of the non-aromatic aldehydes (Table 2-3), saturated aldehyde (entry m), gave good conversion under Prins fluorination conditions and pyran products were obtained with diastereoselectivities of 2/1. In the case of α,β-unsaturated aldehydes (entries n, o, q), the conversions dropped considerably again consistent with the ready enolisation of such aldehydes with $BF_3.OEt_2$. In the case of dimethyl-1,3-dioxolane-4-carboxaldehyde (entry p), the poor conversion might be due to degradation of the aldehyde or strong coordination with $BF_3.OEt_2$.

Entry	Aldehyde	Conversion	d.r (5/6)
m	Hexanal	76%	2/1
n	α-methylcinnamaldehyde 	<5%	1/1
o	perilla aldehyde 	<5%	-
p	dimethyl-1,3-dioxolane-4-carboxaldehyde 	<5%	-
q	Myrtenal 	<5%	1/1/1/1

Conversion determined by ^{1}H NMR, d.r. determined by ^{19}F NMR.

Table 2-3: Prins fluorination conversions and diastereoselectivities with but- 3-en-1-ol **99** and aldehydes **100m-q** with $BF_3.OEt_2$ (1eq) leading to fluoropyrans **101m-r** and **102m-r** at r.t..

It is clearly demonstrated that benzaldehydes substituted with electron withdrawing groups undergo efficient reactions to generate the corresponding 4-fluoropyrans, whereas methoxy- substituted benzaldehydes are poor substrates. Also α,β-unsaturated aldehydes and enolisable aldehydes are poor substrates for the Prins fluorination reaction.

2.3 Influence of the temperature on the Prins fluorination

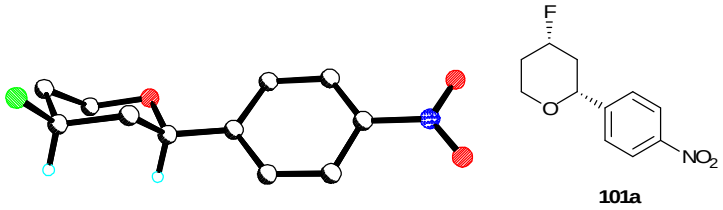
It appeared appropriate to determine the impact of temperature on the Prins fluorination reaction, and in particular to explore the effect of temperature on the diastereoselectivity. Three aldehydes were selected for reaction at different temperatures in reactions with but-3-en-1-ol **99** and $BF_3.OEt_2$ (1 eq) (Table 2-4). When the temperature was lowered to -20 °C the diastereoselectivity increased significantly from 2/1 to 10/1 and with good yields. However, temperatures below -20 °C did not improve the diastereoselectivity, and only increased the reaction time (entry a'). Lowering the temperature to -20 °C is clearly an attractive modification to the reaction conditions in order to improve dramatically the diastereoselectivity.

99 100 (±)-101 (±)-102

Entry	Aldehyde	Temperature	Time	d.r (101/102)	Yield (101)
a’	4-nitrobenzaldehyde	-20 °C	5h	10/1	61%
a”	4-nitrobenzaldehyde	-60 °C	7h	10/1	62%
r’	benzaldehyde	-20 °C	5h	10/1	59%
m’	hexanal	-20 °C	5h	10/1	66%

Table 2-4: Prins fluorination reaction of homoallylic alcohol **99** with aromatic aldehydes **100a**, **100m** and **100r** at -20 °C.

The major diastereoisomer formed in the reaction between the but-3-en-1-ol **99** and aldehydes **100a**, **100m** and **100r** is the *syn* isomer **101** in all cases. This configuration was confirmed by X-ray crystal structure analysis of the major 4-nitrobenzaldehyde adduct, **101a** (Figure 2-3).



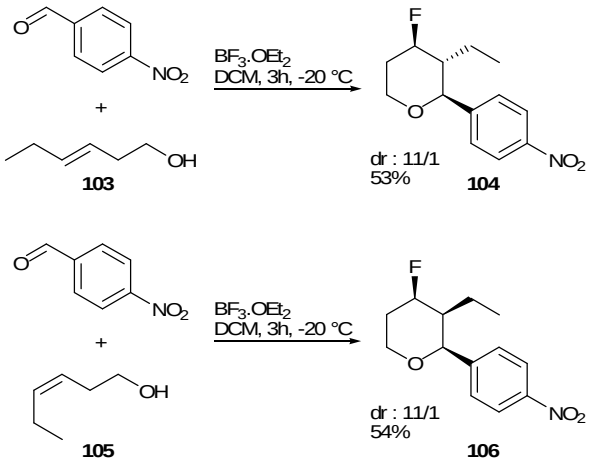
101a

Figure 2-3: X-ray structure of the *syn* stereoisomer **101a**.

2.4 Influence of the alcohol on the Prins fluorination reaction

2.4.1 Influence of substituents on the double bond.

The study then investigated the importance of the structural features of the alcohol on the reaction. Prins fluorination reactions were carried out with hex-3-en-1-ol **103** and **105**. It is interesting to note that when *E* and *Z* hex-3-en-1-ols **103** and **105** are used as substrates, then only the two diastereoisomers **(±)-104** and **(±)-106** were observed, each time with very good diastereoselectivities and in good yields (Scheme 2-10).



Scheme 2-10: Prins cyclisations reaction using (*E*)- and (*Z*)- hex-3-en-1-ols **103** and **105** with 4-nitrobenzaldehyde at -20 °C.

This can be explained by assuming that the Prins reaction proceeds through a mechanism involving a [3,3]-sigmatropic-like rearrangement from intermediate **93** to generate the cyclic carbocation **94**, driven by the electronegativity of the oxonium cation. This type of rearrangement involves a chair-like intermediate (Figure 2-4). When the double bond is substituted, only one chair-like intermediate can be obtained, depending of the configuration

of the double bond, leading to carbocation **108** from intermediate **107** and carbocation **110** from intermediate **109**.

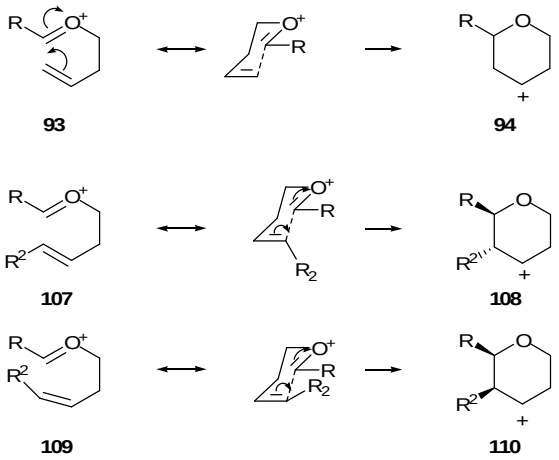


Figure 2-4: Chair-like intermediates in the Prins reaction.

To achieve the stereoselectivty shown during the reactions, the oxonium intermediates must be in *E* configuration to obtain the carbocations **108** and **110** from alcohols **103** and **105** respectively. Indeed, the *Z*-oxonium intermediate from alcohol **103** would have lead to carbocation **110** and alcohol **105** would have lead to carbocation **108** instead (Figure 2-5).

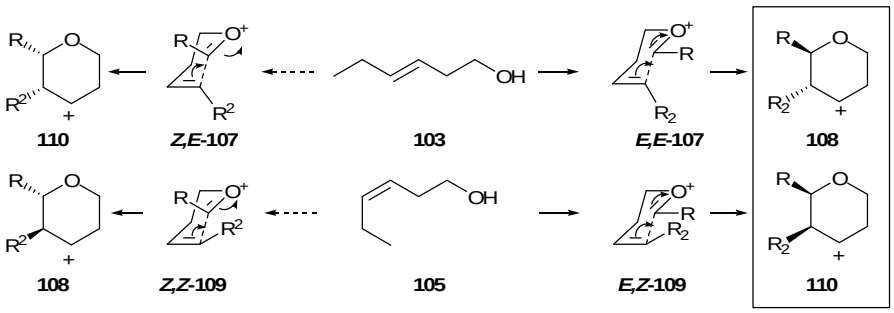
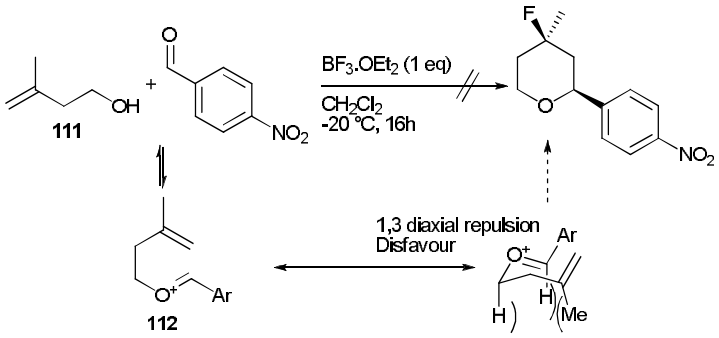


Figure 2-5: The oxonium intermediate adopt a E configuration in order to obtain tetrahydropyrans 104 and 106 from alcohol 103 and 105 respectively.

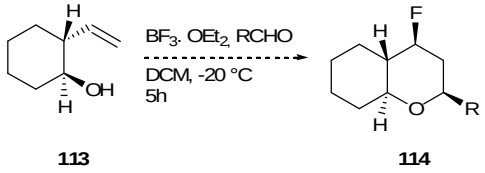
The Prins fluorination reaction was explored with alcohol **111**, possessing a methyl group on the double bond in the γ-position. Unfortunately at -20 °C and after 16h, no product could be detected. The absence of any reaction under these conditions could be explained by the difficulty in generating the oxonium intermediate **112**, to achieve a chair-like conformation due to 1,3 diaxial repulsion between the methyl and the axial hydrogens (Scheme 2-11).



Scheme 2-11: Unsuccessful Prins fluorination cyclisation with alcohol **111**.

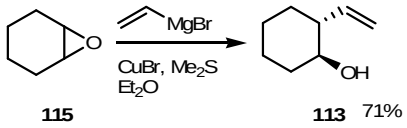
2.4.2 Influence of substituents at the α- and β- positions of the alcohol

The cyclic alcohol **113** was explored for generating bicyclic products such as **114** (Scheme 2-12).



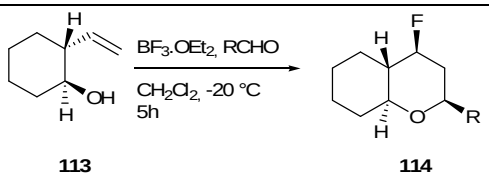
Scheme 2-12: Prins fluorination reaction of alcohol **113** to give bicyclic products **114**.

Alcohol **113** was prepared by reaction of vinyl magnesium bromide on cyclohexene oxide **115** in the presence of Cu(I)Br/dimethyl sulfide as previously described.[23] This was an efficient reaction which proceeded with a yield of 71% and gave only the *trans* product (Scheme 2-13).



Scheme 2-13: Synthesis of vinyl alcohol **111.**[23]

The reactions were conducted at -20 °C, and the *syn* products **114a** and **114b** were obtained from benzaldehyde **101s** and 4-nitrobenzaldehyde **101a** respectively with a good diastereoselectivity of 10/1 and in good yields (Table 2-5).

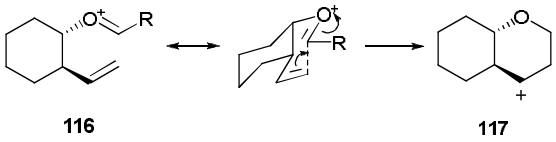


Entry	Aldehyde	d.r	Yield (*Syn* product **114**)
a	benzaldehyde	10/1	59%
b	4-nitrobenzaldehyde	10/1	57%

Table 2-5: Prins fluorination reaction with alcohol **113** at -20 °C.

In this case, a chair-like intermediate derived from **116** is most probably favoured because of the rigidity of the cyclohexyl ring. Indeed, only one chair conformer is reasonable,

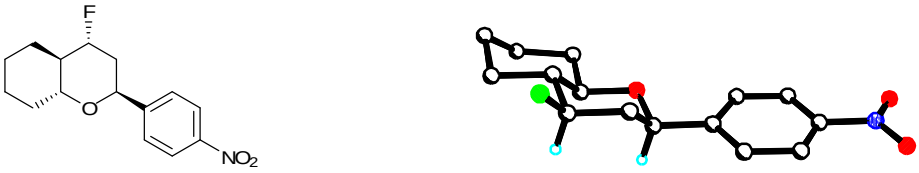
where both the hydroxyl and allyl substituents lie in an equatorial position off the cyclohexyl ring (Figure 2-6).



116 117

Figure 2-6: Chair-like intermediate derived from **115**.

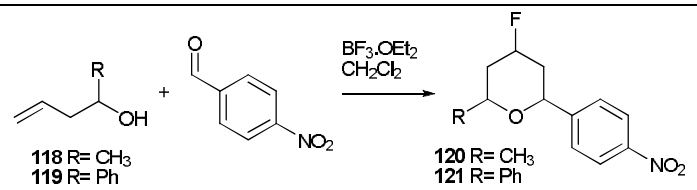
After isolation an X-ray derived structure of the bicyclic product **114b** was solved after recrystallisation. The resultant structure confirmed that the major stereoisomer is the *syn* product (Figure 2-7).



114b

Figure 2-7: Crystal structure of the *syn*-bicyclic tetrahydropyran **114b**.

The influence of the substituent at the α-position of the alcohol was investigated using pent-4-en-2-ol **118** and 1-phenylbut-3-en-1-ol **119** in reactions with 4-nitrobenzaldehyde (Table 2-6). In both cases, the reactions displayed a lack of diastereoselectivity. Indeed, up to six different fluorinated compounds were formed during the reaction. The situation did not improve even when the reaction temperature was lowered as far as -80 °C. Individual components of the mixture could not easily be separated by chromatography.

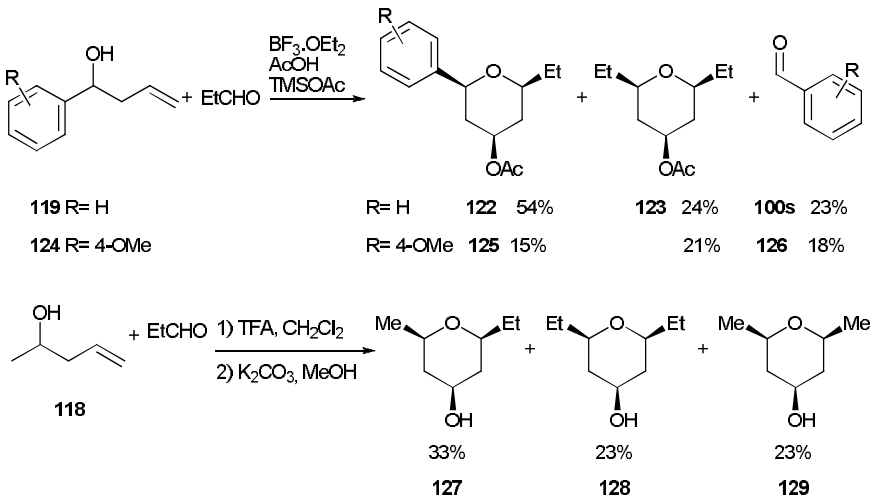


Alcohol	Temperature	t	Conversion	Ratio of diastereoisomers formed (determined by ^{19}F NMR)
1-Me **118**	-20 °C	5h	75%	5.0/2.0/1.7/1.3/1.0
1-Me **118**	-60 °C	8h	70%	15.7/6.0/1.3/1.0/2.7
1-Me **118**	-80 °C	8h	45%	8.2/3.2/1.2/1.0/2.2
1-Ph **119**	-20 °C	5h	78%	17.2/7.4/4.2/3.6/2.3/1.0
1-Ph **119**	-60 °C	8h	60%	14.5/9.7/5.5/2.0/21.5/1.0
1-Ph **119**	-80 °C	8h	60%	8.8/2.1/1.5/1.9/11.3/1.0

Table 2-6: Prins fluorination reactions between alcohols **118** and **119** and 4-nitrobenzaldehyde with $BF_3.OEt_2$ (1eq) generated many stereoisomers.

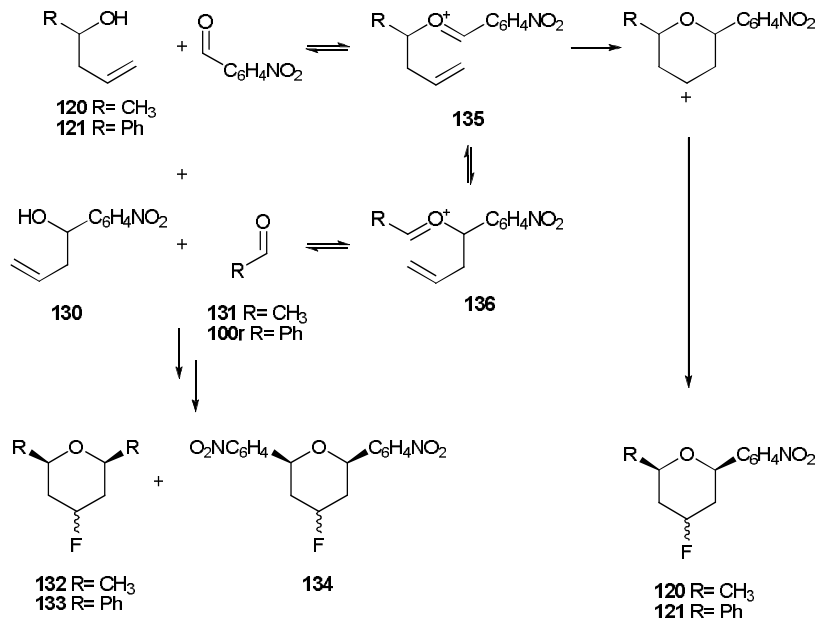
Most Prins publications report clean reactions with one major product when using α-substituted alcohols,[7, 10, 12, 15] however similar results were reported by Willis *et al.*.[13, 14] They reacted alcohol **119** with propanal, in the presence of acetic acid, $BF_3.OEt_2$ and TMSOAc (Scheme 2-14). When the alcohol is substituted at the α-position by a phenyl ring, the expected tetrahydropyran **122** and 2,6-diethyl tetrahydropyran **123** are obtained as well as benzaldehyde, in 54%, 24% and 23% yields respectively. The presence of a methoxy group on the aromatic ring at the α-position on the alcohol **124**, influenced greatly the ratio between the different pyrans **123**, **125** and **126**, favouring the tetrahydropyran **123**. Tetrahydropyran **123** is most probably obtained after a [3,3] sigmatropic rearrangement followed by hydrolysis of the oxonium intermediate, as described in Scheme 2-6.

In the case of the Prins reaction with pent-4-en-2-ol **118**, Willis *et al.* obtained three compounds.[13, 14] The major tetrahydropyran **127** arose directly without a [3,3]-sigmatropic rearrangement of the oxonium intermediate. The two minor tetrahydropyrans **128** and **129** are the products of the reaction coming from either propanal and pent-4-en-2-ol **118** or ethanal and hex-5-en-3-ol, followed by hydrolysis of the oxonium intermediate. Both of these minor tetrahydropyrans are most probably formed as result of a [3,3]-sigmatropic rearrangement.



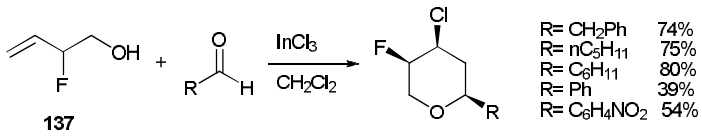
Scheme 2-14: Prins reactions between α-substituted alcohols and propanal.[13, 14]

According to those results, it is reasonable to propose that in our case the products obtained are tetrahydropyrans **120** and **121** coming from direct cyclisation of the oxonium intermediate. It follows that the minor products are formed from aldehydes **131** or **100r** and alcohol **130** formed *in situ* after [3,3] sigmatropic rearrangement of the oxonium intermediate **135**. This would therefore generate tetrahydropyrans **132** and **134**, or **133** and **134** (Scheme 2-15). Individual components of the mixture could not easily be separated by chromatography.



Scheme 2-15: Proposed fluorinated product profile from the Prins fluorination reaction of alcohols **120** and **121**.

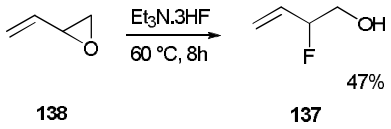
Dobbs *et al.*[6] described a Prins cyclisation involving 2-fluorobut-3-en-1-ol **137** in the presence of $InCl_3$ with various aldehydes. This generated 4-chloro-5-fluoropyrans in high diastereoisomeric selectivity (Scheme 2-16) where chloride ion is the nucleophile. It is noteworthy that the resultant pyrans always have the fluorine in an axial position.



Scheme 2-16: Prins reaction involving the 2-fluorobut-3-en-1-ol **137**.[6]

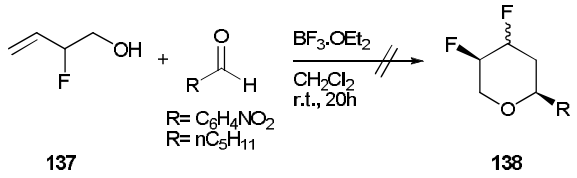
It was therefore interesting to explore the Prins fluorination reaction with alcohol **137**, to try to obtain 4,5-difluoropyrans. However at the outset we were aware that the presence of a fluorine atom in the α-position of the intermediate carbocation could have a strong destabilising effect on the outcome of the reaction.

The alcohol **137** was prepared by treatment of butadiene monoxide **138** with 3HF.Et_3N (60 °C, 8h, 47%) (Scheme 2-17).[24]



Scheme 2-17: Preparation of the fluorohydrin **13**.[24]

The Prins fluorination reaction of fluoro alcohol **137** was explored with 4-nitrobenzaldehyde **100a** and hexanal **100m** at r.t. and with 1 equivalent of BF_3.OEt_2. After 20h, only starting materials were recovered without any evidence for the difluorinated product (Scheme 2-18).

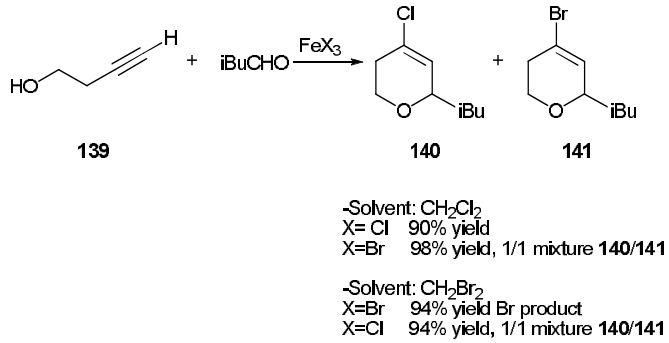


Scheme 2-18: Failed preparation of 4,5-difluoropyrans **138**.

2.4.3 Prins fluorination with a homo propargylic alcohol

The ability of homopropargylic alcohol **139** to react in a modified Prins fluorination reaction was explored. Martín *et al.*[25] reported a Prins cyclisation reaction involving homopropargylic alcohol **139** to generate 5,6-dihydro-2*H*-pyrans, using FeX_3 as a Lewis acid (X=Cl, Br). They found evidence of a halogen exchange reaction between this Lewis acid and the solvent. Indeed, when the halogens of the solvent do not match those of the Lewis acid,

the chloro- or bromo-products **140** and **141** are obtained in a ratio 1/1. When the halogens of the solvent and the Lewis acid match, then only one halogenated product was obtained (Scheme 2-19). Martín proposed two possibilities to explain these results. First, there is a possible halogen exchange between FeX_3 and the solvent. The other possibility is the reaction of the intermediate carbocation and the solvent.

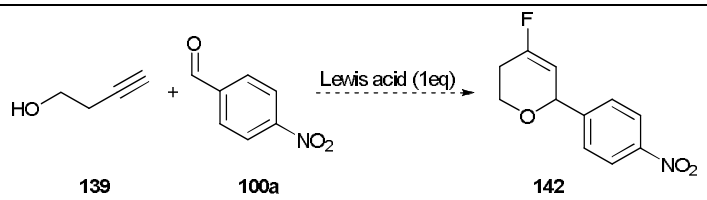


Scheme 2-19: Prins cyclisation reaction of a homopropargylic alcohol.[25]

Martín *et al*. also performed the reaction using InX_3, but the reaction time had to be increased from a few minutes to 24 h, and with lower yields, between 73 and 80%.[25] Another study demonstrated the Prins cyclisation reaction with homopropargylic alcohol **139** to give chloro products using $SnCl_4$, but again, the yields were moderate.[26]

In our study, homopropargylic alcohol **139** and 4-nitrobenzaldehyde **100a** were selected as a standard set of reagents (Table 2-7). The first attempts to carry out the Prins fluorination reaction were carried out with $BF_3.OEt_2$ in dichloromethane at -20 °C and then at room temperature, but none of these conditions lead to the anticipated fluorinated product **142** derived from homopropargylic alcohol **139**. Only starting materials or degradation products were recovered (Table 2-7, entry a and b). The use of iron trifluoride (FeF_3) in several

solvents such as CH_2Cl_2, toluene or CH_3CN did not result in the formation of product **142** and only starting materials or degradation products were again observed (entry c-e).



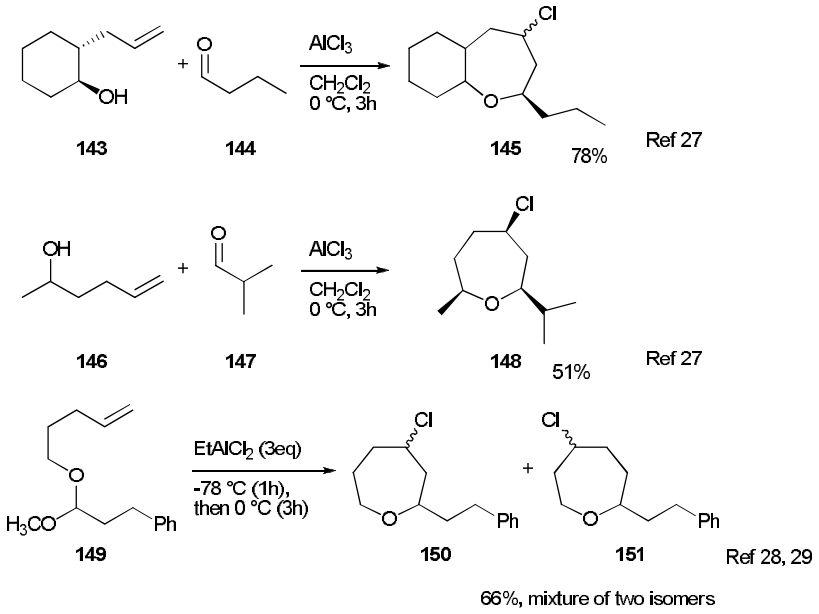
139 100a 142

Entry	Lewis acid	Solvent	Temperature	Results
a	$BF_3.OEt_2$	CH_2Cl_2	-20 °C	No reaction
b	$BF_3.OEt_2$	CH_2Cl_2	r.t.	Degradation
c	FeF_3	CH_2Cl_2	r.t.	No reaction
d	FeF_3	Toluene	r.t.	No reaction
e	FeF_3	CH_3CN	r.t.	No reaction

Table 2-7: Conditions used in Prins fluorination reactions with homoallylic alcohol **139**.

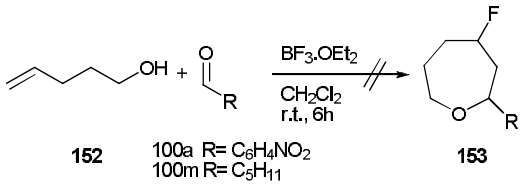
*2.2.4 Prins fluorination with pent-4-en-1-ol **152** to form oxepanes.*

Several publications have reported the formation of seven-membered rings *via* Prins cyclisation reactions using AlX_3 (X= Br or Cl),[27] $EtAlCl_2$[28] or $SnCl_4$[28, 29] as Lewis acids (Scheme 2-20).



Scheme 2-20: Formation of oxepanes *via* Prins cyclisation reactions.[27-29]

It was therefore interesting to investigate the behaviour of $BF_3.OEt_2$ towards the formation of larger rings, and more precisely if it would allow the formation of oxepanes **153** from pent-4-en-1-ol **152**. Unfortunately, despite considerable efforts (increasing the amount of $BF_3.OEt_2$ up to 3eq), the reaction between pent-4-en-1-ol **152** with 4-nitrobenzaldehyde **100a** or hexanal **100m** and $BF_3.OEt_2$ led only to the recovery of starting material (Scheme 2-21).

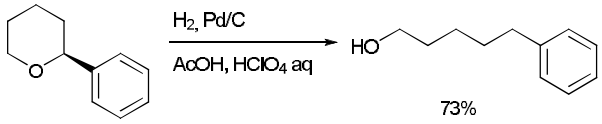


Scheme 2-21: Failed formation of oxepane **153** from pent-4-en-1-ol **152**.

2.5 Hydrogenation of Prins fluorination products

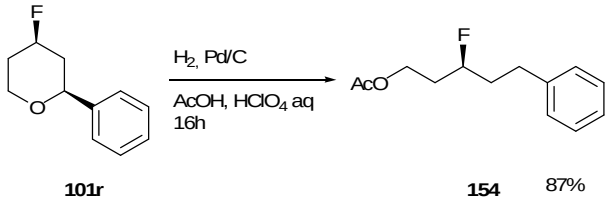
The products of the Prins fluorination reaction with aromatic aldehydes are α-arylpyrans. Such compounds should be amenable to hydrogenolysis to generate a saturated acyclic alcohol with fluorine at the γ- position. This appeared an attractive reaction, and would provide a novel method for the synthesis of γ-fluoroalcohols.

Baker *et al.*[30] reported a study on the hydrogenolysis of benzyl ethers with hydrogen. In that study, he described the hydrogenolysis of 2-phenyltetrahydropyran using Pd/C in acetic acid with a catalytic amount of perchloric acid, leading to the acyclic alcohol in 73% (Scheme 2-22).



Scheme 2-22: Hydrogenation of 2-phenyltetrahydrofuran by Baker.[30]

Accordingly an attempt was made to open the tetrahydropyran **101r** by hydrogenolysis following Baker's method (Scheme 2-23).[30] This proved successful and led to the corresponding opened chain ester **154** in good yield (70%). This is an attractive result as more complex pyrans could lead to functionalised chains and be used to prepare a diversity of fluorinated alcohols.



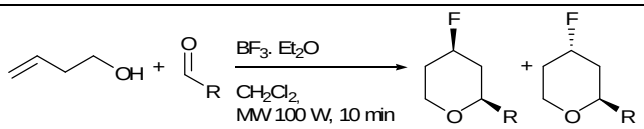
Scheme 2-23: Opening of the tetrahydropyran **101s'** by hydrogenation.

2.6 Prins fluorination reaction under microwave conditions

In order to improve the Prins fluorination method the reaction was now explored under microwaves conditions. No such approach has yet been reported. The reaction was carried out with but-3-en-1-ol **99** and a variety of aldehydes in the presence of $BF_3.OEt_2$ (Table 2-8). Dichloromethane was used as a solvent and irradiation was carried out for 10 min at 100W.

It is accepted that microwaves accelerate reactions not only because of a thermal effect, but also because of a superheating effect. Indeed, the comparison between a microwave enhanced reaction and a reaction heated 'classically' shows a difference of reaction rate.[31] This is due to a very fast heating, and the temperatures reached are very high. The heat transfer is also far more efficient.

The reaction is very efficient, with conversions generally higher than those under the more classical conditions (Table 2-8, entry 2-4, 6). However, the diastereoselectivity decreased compared to the previous reactions in every case, and interestingly with an inversion of diastereoselectivity in the case of the products from 4-methoxybenzaldehyde (entry 6).



99 100 101 102

Entry	Aldehyde **100**	d.r (**101**/**102**)	Conversion with microwave	d.r. (**101**/**102**) at r.t.	Conversion at r.t.
1	4-Nitrobenzaldehyde	1.5/1	53%	1.9/1	67%
2	Hexanal	1.8/1	91%	2/1	76%
3	2-Bromobenzaldehyde	3/1	92%	5.4/1	65%
4	3-Bromobenzaldehyde	1.8/1	93%	3.8/1	73%
5	4-Bromobenzaldehyde	2.3/1	83%	4.8/1	90%
6	4-methoxybenzaldehyde	1/1.2	41%	2.4/1	20%
7	Benzaldehyde	3.4/1	66%	/	/

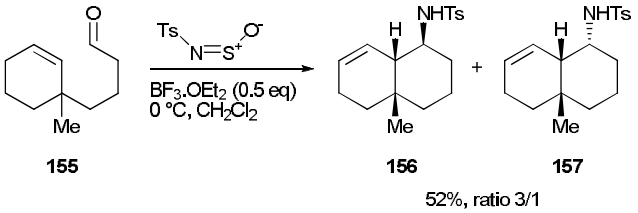
Table 2-8: Prins fluorination reactions with homoallylic alcohol **99** under microwave conditions (100W, 10 min.).

In this section, a study of the different parameters of the fluoro-Prins reaction was reported. It revealed that the temperature has a great influence on the diastereoselectivity. When the temperature is dropped from r.t. to -20 °C, the diastereoselectivity increases from 2/1 to 10/1. It was shown too that the aliphatic aldehydes are good substrates for the reaction, while only benzaldehydes with electron withdrawing groups give good yields. The substituents on the alcohol are very important as they can induce a very good stereoselectivity (substituted double bond, presence of a cyclohexyl group) or could give several products (α-substituted alcohol) as well as no reaction (fluoro alcohol, pent-4-en-1-ol). The reaction under microwaves reduces the reaction time without having a strong impact on the diastereoselectivities. Then the hydrogenation of 2-phenyl-4-fluorotetrahydrofuran was successful, increasing the interest of the Prins fluorination reaction.

3 Aza-*Prins fluorination reactions*

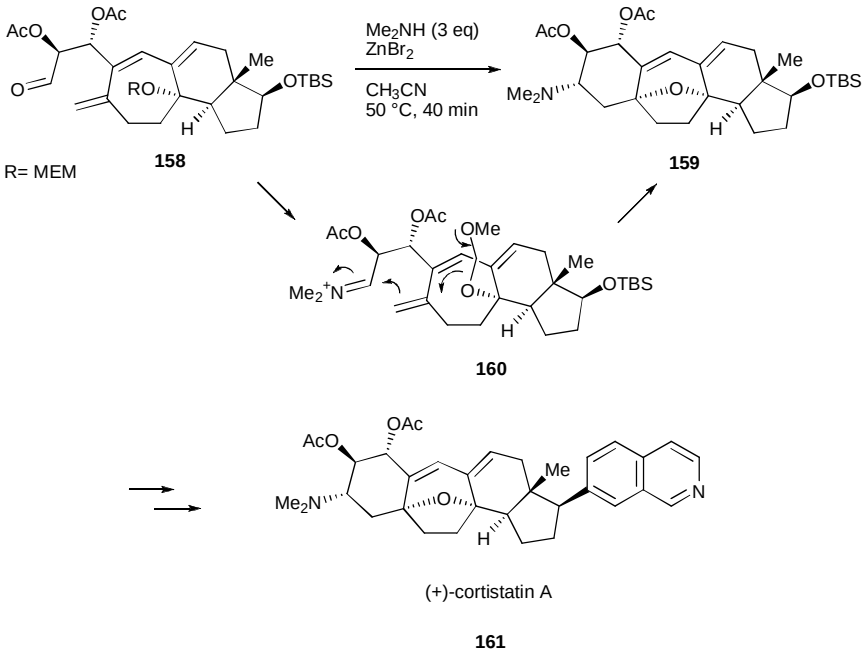
3.1 Introduction

The *aza*-Prins cyclisation, defined as a Prins reaction were the alcohol is replaced by an amine has been relatively widely explored. The first examples of *aza*-Prins reactions were carried out by Weinreb in 1988 and involved the reaction shown in Scheme 2-24, leading to the homoallylic amines **156** and **157** after formation of the iminium intermediate.[32]



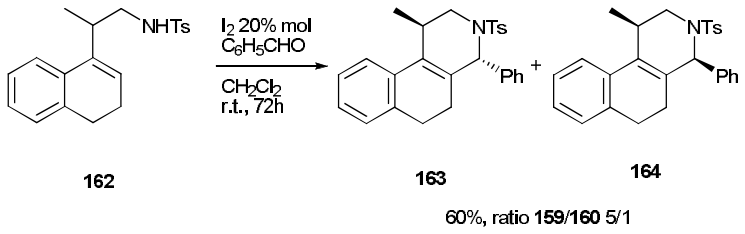
Scheme 2-24: Weinreb's example of *aza*-Prins reaction leading to cyclic homoallylic amine.[32]

This methodology has been employed by Lee *et al.*[33] to synthesise (+)-cortistatin A **161**, an anti-angiogenic steroidal alkaloid which was isolated from the marine sponge *Corticium simplex*.[34] This is an elaborate example on a complex molecular framework. Firstly, the iminium **160** is formed and then an *aza*-Prins cyclisation occurs, triggered by the attack of the hydroxyl formed by decomposition of the MEM group. The hydroxyl forms an epoxide, leading to the formation of two of the rings of product **159** (Scheme 2-25).



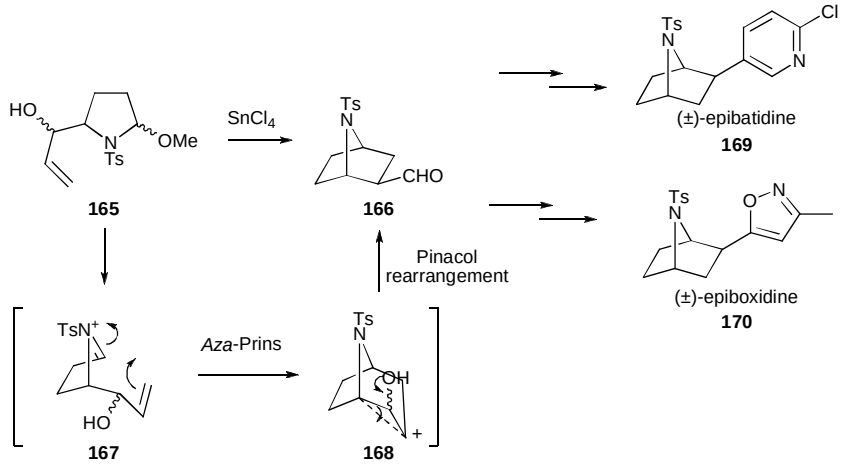
Scheme 2-25: Synthesis of (+)-cortistatin A through an *aza*-Prins reaction as reported by Lee *et al.*[33]

More recently, the *aza*- Prins cyclisation reaction has gained increased interest from the scientific community and several publications have reported the formation of piperidines from homoallylic amines and aldehydes in the presence of Lewis acids (Scheme 2-26). A wide range of Lewis or other acids[35-37] were used, such as FeX_3 (X=Br or Cl),[38, 39] PMA,[40] GaI_3/I_2,[41] $InCl_3$,[42] I_2[43] or $Et_4NF/5HF$[44] leading to the incorporation of various nucleophiles such as halogens Cl^-, Br^-, I^- and very recently F^- or HO^-.



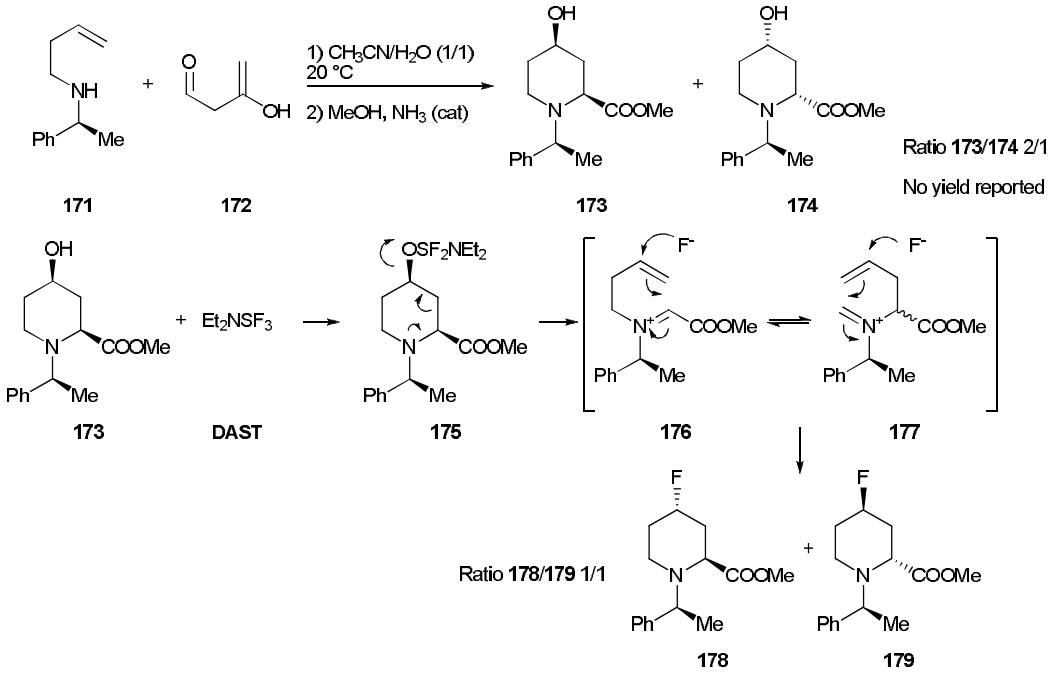
Scheme 2-26: An example of the *aza*-Prins cyclisation reaction leading to *N*-containing heterocycles.[43]

The syntheses of (±)-epibatidine **169**, the powerful analgesic isolated from the skin of the frog *Epipedobates tricolour*, and (±)-epiboxidine **170**, a synthetic derivative, have been reported by Armstrong *et al.*[45] using an *aza*-Prins-pinacol rearrangement approach (Scheme 2-27). The *aza*-Prins cyclisation of **165** lead to the bicyclic intermediate **168**, which immediately undergoes a pinacol rearrangement to give the 7-azabicyclo[2.2.1]heptane **166**. This emerged as a common precursor to (±)-epibatidine **169** and (±)-epiboxidine **170**.



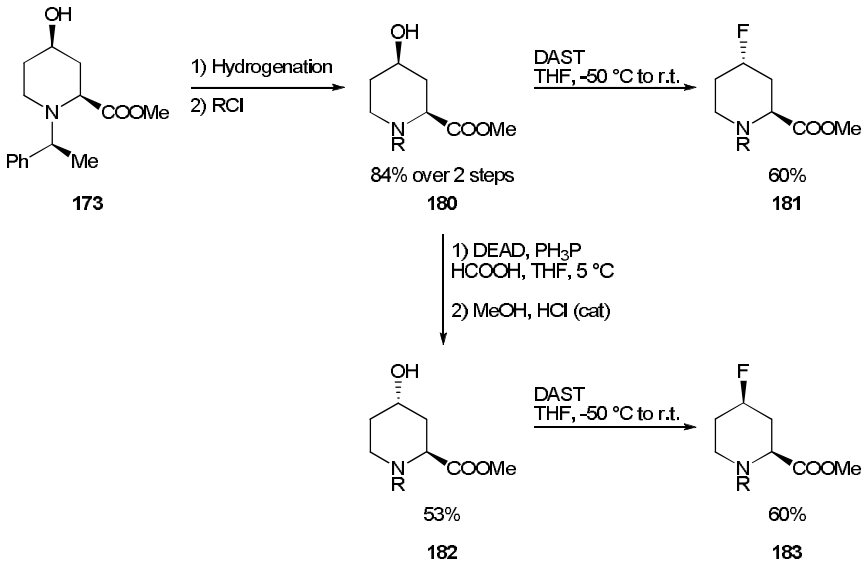
Scheme 2-27: Synthesis of (±)-epibatidine **169** and (±)-epiboxidine **170** through *aza*-Prins-pinacol rearrangements.[45]

Prior to this project there was only one example of the synthesis of 4-fluoropiperidines *via* an *aza*-Prins cyclisation. This was described by Golubev *et al.*, and is not straightforward.[46] It involved the conversion of 4-hydroxypiperidines to 4-fluoropiperidines. The method is not efficient, as the direct fluorination of **173** with DAST led to a loss of diastereoselectivity, due to a Grob-type fragmentation (Scheme 2-28).



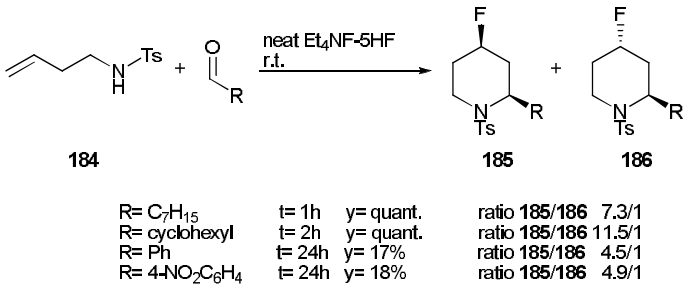
Scheme 2-28: Gobulev *et al.*'s preparation of 4-fluoropiperidines *via* the *aza*-Prins reaction.[46]

The replacement of the *N*-1,1-phenylethyl protecting group by that with stronger electron withdrawing properties managed to reduce the loss of diastereoselectivity during the fluorination step, to form fluoropiperidine **181** in a 60% yield (Scheme 2-29). Unfortunately, the paper did not report which protecting group was used to successfully carry out the fluorination. To obtain the other diastereoisomer **183**, a Mitsunobu reaction was realised on the 4-hydroxypiperidine **180** to give alcohol **182** after hydrolysis of the ester, and then this was transformed to 4-fluoropiperidine **183** by DAST and again in a 60% yield.



Scheme 2-29: Preparation of 4-fluoropiperidines by a final deoxyfluorination reaction.

It was only in 2008, towards the end of this project, that the preparation of 4-fluoropiperidines directly *via aza*-Prins fluorination reaction was reported by Kishi *et al.*[47] The reaction was performed unusually in ionic liquid media, using $Et_4NF/5HF$ as the acid to catalyse the reaction. The presence of the electron withdrawing tosyl group on the amine appears to be crucial to avoid protonation of the free amine which would block the reaction. The reaction is substrate sensitive. Aromatic aldehydes are less good substrates by comparison to aliphatic aldehydes (Scheme 2-30). Indeed, in the case of aliphatic aldehydes, the reaction time took 1-2 h. The reaction is quantitative and shows moderate to good diastereoselectivity (7.3/1 to 11.5/1), while aromatic aldehydes required extended reaction times and led to a mixture of diastereoisomers with a ratio of 4.5/1 to 4.9/1. In general the yields were much poorer (17-18%) with aromatic aldehydes.



Scheme 2-30: First example of *aza*-Prins fluorination reaction reported in 2008.[47]

The lack of reactivity of aromatic aldehydes could be explained by conjugation of the aromatic ring to the protonated form of the aldehyde leading to substantial enol character under these acidic conditions. This would stabilise the aldehyde toward nucleophilic attack compare to the aliphatic aldehydes (Figure 2-8).

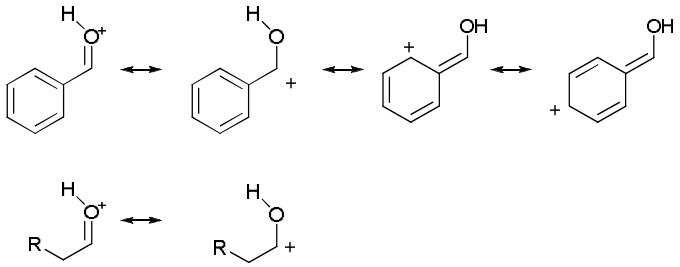


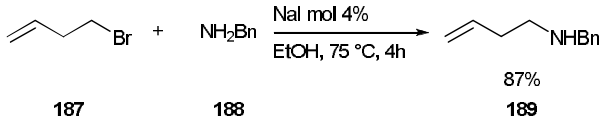
Figure 2-8: Enolisation of the aromatic aldehydes may reduce their activity relative to aliphatic aldehydes.

The exploration of the fluoro- *aza*-Prins cyclisation reaction using $BF_3.OEt_2$ had been ongoing in St Andrews prior to Kishi's report.

3.2 Protecting groups

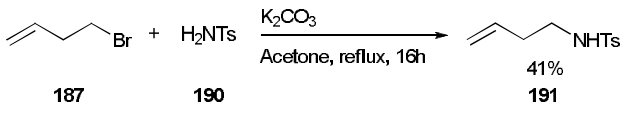
Our first investigations of the *aza*-Prins fluorination involved investigating the protecting group on the amine. Most examples of *aza*-Prins cyclisation reaction reported so far use either the *N*-benzyl or *N*-tosyl group on the amine, thus amines **189** and **191** were explored in fluorination reactions.

N-Benzylbut-3-enyl-1-amine **189** was prepared according the procedure of McCann[47] by reaction of 1-bromobut-3-ene **187** with benzylamine **188** in the presence of a catalytic amount of sodium iodide. The reaction was efficient and the product amine **189** could be recovered in 87% yield (Scheme 2-31).[48]



Scheme 2-31: Preparation of *N*-benzylbut-3-enyl-1-amine **189**.[48]

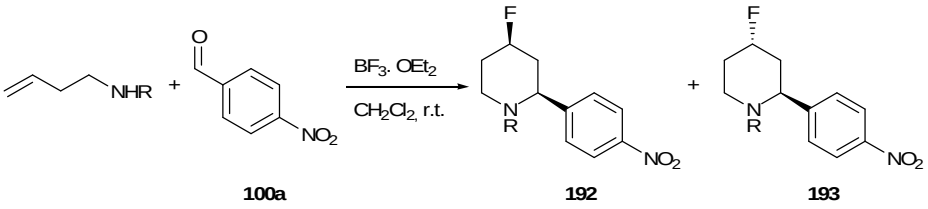
The *N*-tosylbut-3-enyl-1-amide **191** was also prepared in a relatively straight forward manner in a reaction of 1-bromo-but-3-ene **187** with *N*-tosylamine **190** (Scheme 2-32).[49] The reaction was catalysed by potassium carbonate and the *N*-tosyl amine product was furnished in a moderate yield (41%).



Scheme 2-32: Preparation of *N*-tosylbut-3-enyl-1-amine **191**.[49]

The protected homoallylic amines **189** and **191** were then explored in reactions with 4-nitrobezaldehyde **100a** and $BF_3.OEt_2$ in dichloromethane at room temperature (Scheme 2-34).

Dichloromethane was selected as solvent as it gave the best results in the oxa study, and was reported on almost all the publications on *aza*-Prins cyclisation reaction. After 48 hour reactions the desired fluorinated diastereoisomers **192** and **193** were generated from **191** in a ratio of 1/1 and with a conversion of 70% (Table 2-9). However, no conversion was observed in the case of the benzyl-protected amine **189** after 24 hours. In view of this, the rest of this study was carried out using the *N*-tosylbut-3-enyl-1-amine **191** as the protected γ-olefinic amine. In this case, the conversion and diastereoselectivity are comparable to the *oxa*-Prins fluorination reactions: e.g. 67% conversion and 1.9/1 diastereoisomeric ratio in the case of 4-nitrobenzaldehyde **100a**.



100a **192** **193**

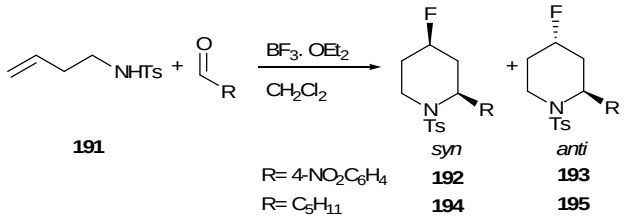
Amine	Time	Conversion	Diastereoselectivity
NHTs **191**	48h	70%	1/1
NHBn **189**	24h	/	/

Table 2-9: Reaction between the protected amines **189** or **191** and 4-nitrobenzaldehyde in the presence of $BF_3.OEt_2$ (1eq) at r.t.

3.3 Temperature study

It was demonstrated in section 2.3 that temperature had a significant influence on the diastereoselectivity of the *oxa*-Prins fluorination reaction. In order to established the influence of the temperature on the corresponding *aza*-Prins reactions, two aldehydes, hexanal and 4-

nitrobenzaldehyde, were explored with *N*-tosylbut-3-enyl-1-amine **191** and $BF_3.Oet_2$ (1 eq) in dichloromethane (Table 2-10). The temperature had no obvious effect on the diastereoisomeric ratio. When the temperature was lowered to -20 °C, the diastereoselectivity remained the same at 1/1 in the *aza*- series. Not unexpectedly the reaction time increased considerably from 48 hours to 72 hours to obtain the same level of conversion. This lack of improvement in the *aza*-Prins diastereoselectivity contrasts significantly with the *oxa*-Prins fluorination reactions.



Entry	Aldehyde	T	Time	d.r (*syn*/*anti*)	Yield
a	4-Nitrobenzaldehyde	r. t.	48h	1/1	65%
b	4-Nitrobenzaldehyde	-20 °C	72h	1/1	71%
c	Hexanal	r. t.	48h	2/1	75%
d	Hexanal	-20 °C	72h	2.1/1	74%

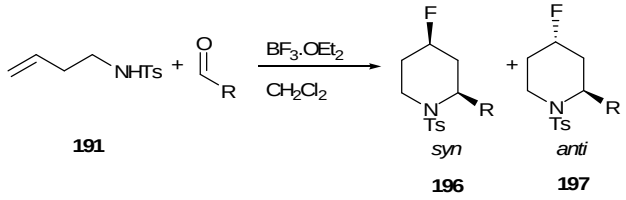
The diastereoselectivity was determined by isolation of the products.

Table 2-10: Diastereoselectivity ratios of the *Aza* prins reactions between *N*-tosylbut-3-enyl-1-amine **191** and an aldehyde with $BF_3.OEt_2$ in CH_2Cl_2 at ambient temperature and at -20 °C.

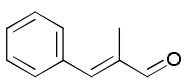
3.4 Influence of the aldehyde

The influence of the aldehyde was investigated for the *aza*-Prins fluorination reaction (Table 2-11). In the case of benzaldehydes, when the aromatic ring is substituted by an electron withdrawing group, the conversions are very good (entry a-f). However the

diastereoisomeric ratios remain lower than those found for the *oxa*- Prins reactions. However, when the aromatic aldehyde carries an electron donating methoxy group, the conversions drop to ~23% (entry g). For aliphatic aldehydes, the conversions are very high, but again, the diastereoselectivity remains poor (entry h-j). Similar to the *oxa*- Prins fluorinations, there was no reaction when an α,β-unsaturated aldehyde was used as a substrate (entry k). Overall, the purifications are difficult, and in some case, the diastereoisomers could not be separated.



191 *syn* **196** *anti* **197**

Entry	Aldehyde	d.r (196/197)	Yield
a	4-Nitrobenzaldehyde	1/1	61%
b	4-Bromobenzaldehyde	1/1	68%
c	3-Bromobenzaldehyde	2/1	59%
d	2-Bromobenzaldehyde	1/1.6	49%
e	4-Fluorobenzaldehyde	1.8/1	68%
f	3-Fluorobenzaldehyde	2/1	66%
g	4-Methoxybenzaldehyde	2.5/1	23%
h	Hexanal	2/1	73%
i	Acetaldehyde	1/1	73%
j	Isobutylaldehyde	2/1	82%
k	α-Methylcinnamaldehyde 	/	No reaction

Diastereomeric ratio determined after isolation of each product or by ^{19}F NMR of the mixture

Table 2-11: *Aza* prins reaction between amine **191** and various aldehydes in the presence of $BF_3.OEt_2$ (1 eq) at r.t.

A suitable crystal of piperidine **197b** was obtained for X-ray structure analysis and the resultant structure shows that the product has the C-F bond and the aromatic ring *anti* to each other (Figure 2-9). In this case the tosyl group is almost perpendicular to the plane of the piperidine. This could be due to a better aryl stacking in the crystal packing.

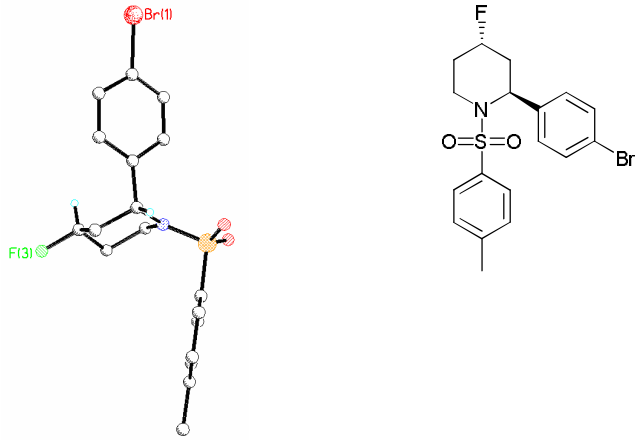
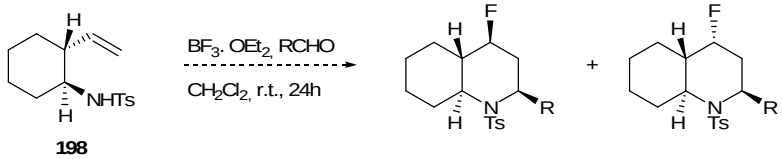


Figure 2-9: Crystal structure of piperidine **197b**.

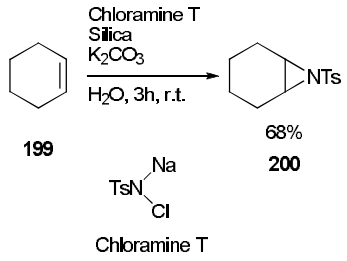
3.5 Influence of the amine

In order to study the influence of the structure of the homoallylic amine on the *aza*-Prins fluorination reaction, the formation of the bicyclic piperidines was explored using cyclic tosylamide **198** (Scheme 2-33).



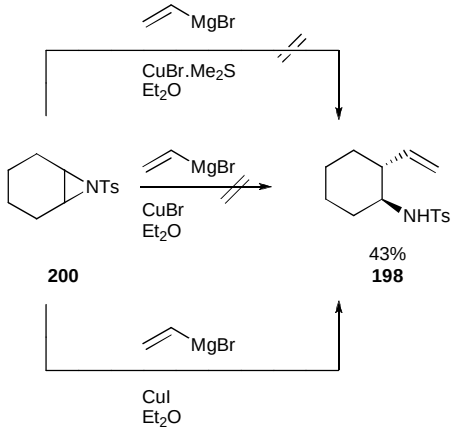
Scheme 2-33: Exploration of the *aza*-Prins fluorination reaction with the *N*-(2-vinylcyclohexyl)tosylamide **198**.

N-(2-Vinylcyclohexyl)tosylamide **198** was prepared in two steps. The first step required the synthesis of the aziridine **200** from cyclohexene **199**. This reaction was achieved with chloramine T in presence of potassium carbonate and silica in water, following the protocol of Minikata (Scheme 2-34).[50] The reaction proved straightforward and aziridine **200** was obtained in 68% yield.



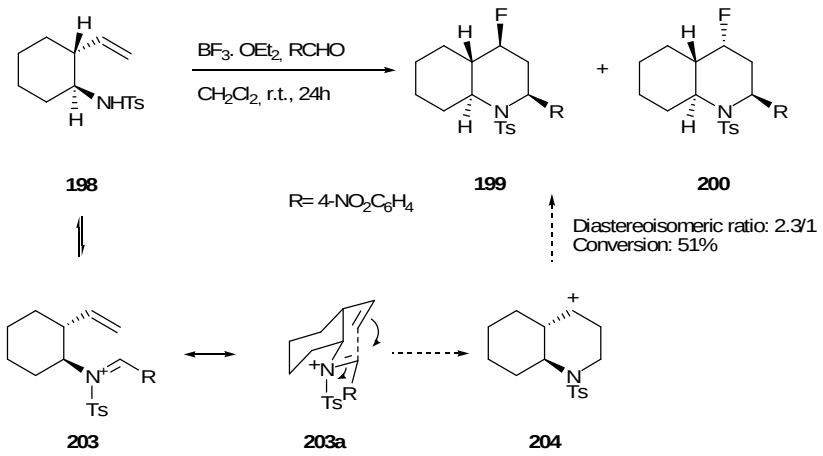
Scheme 2-34: Preparation of the aziridine **200** from cyclohexene.[50]

The next step involved aziridine ring-opening to generate the desired *N*-(2-vinylcyclohexyl)tosylamide **198**. When vinylmagnesium bromide was used with CuBr/Me_2S or CuBr in diethylether, only degradation products were observed (Scheme 2-35). However, the use of CuI instead of CuBr/Me_2S, under otherwise identical conditions, resulted in the successful opening of the aziridine ring in 43%.



Scheme 2-35: Aziridine opening, leading to the *N*-(2-vinylcyclohexyl)tosylamide **198**.

With *N*-(2-vinylcyclohexyl)tosylamide **198** in hand, *aza*-Prins fluorinations were explored with 4-nitrobenzaldehyde and $BF_3.OEt_2$ at r.t. The chair-like transition state **203a** can only reasonably lead to carbocation **204** because of the restrictions imposed by the cyclohexyl ring. Therefore, only product **199** and its diastereoisomer **200** should be obtained. After 48 hours, a mixture of the anticipated diastereoisomers **199** and **200** was generated in a moderate 51% conversion (Scheme 2-36). However, it proved impossible to separate the diastereoisomers by standard chromatographic methods.



Scheme 2-36: Preparation of bicyclic *aza*-Prins fluorination products (**199** and **200**) using *N*-tosylamide **198**.

Other modifications of the reaction were explored. In particular, the influence of an ethyl substituent at the terminus of the double bond was investigated. Both geometric (*Z*) and (*E*) isomers **205** and **206** were explored. Thus the *N*-(hex-3-enyl)-1-tosylamides **205** and **206** were prepared from the corresponding precursor alcohols **103** and **105** (Figure 2-10).

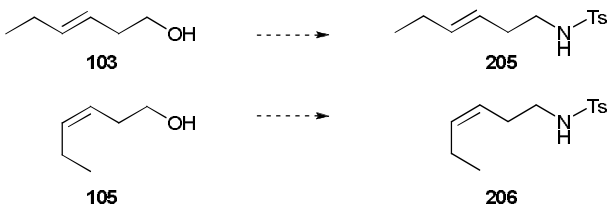
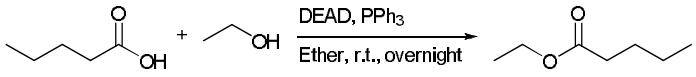


Figure 2-10: The tosylamides **205** and **206** with *E* and *Z* double bond were prepared from the corresponding alcohols **103** and **105**.

Two routes were investigated to these tosylamides. The first involved the formation of the tosylamides in one step through a Mitsunobu reaction. The Mitsunobu reaction was first reported by Oyo Mitsunobu in 1967.[51] In this publication, Mitsunobu described the conversion of an alcohol to an ester, using the corresponding acid and diethyl azodicarboxylate (DEAD) and triphenylphosphine (Scheme 2-37).



Scheme 2-37: Example of an early Mitsunobu esterification from 1967.[51]

The hydroxyl group can be substituted under Mitsunobu conditions into other functional groups such as esters,[51-53] sulphonamides[52, 54-56] or imides.[52] During the reaction, the alcohol is activated through a phosphonium salt while the nucleophile is activated by deprotonation, leading to a S_N2 reaction (Figure 2-11).

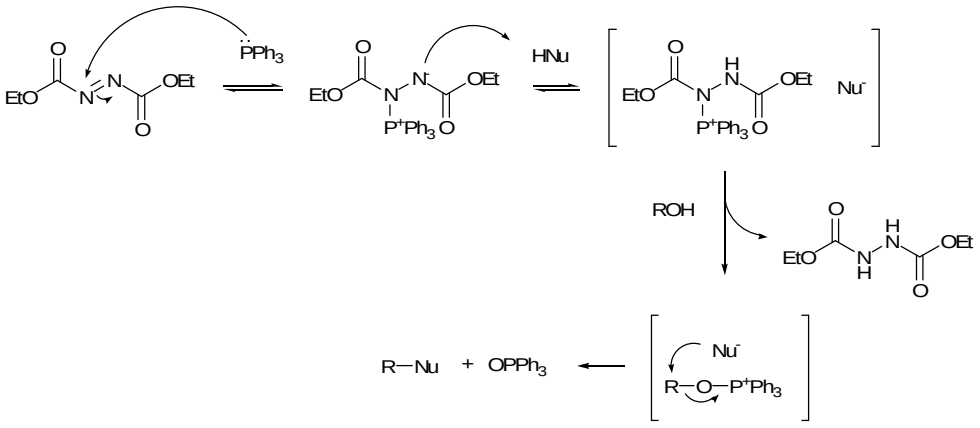
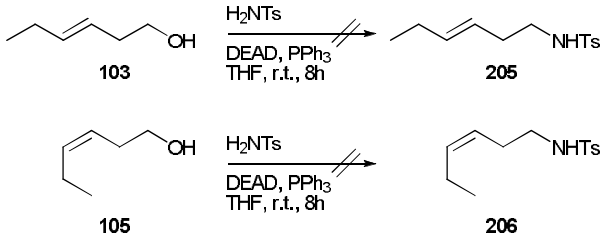


Figure 2-11: Mechanism for the Mitsunobu reaction using DEAD and triphenylphosphine.

Several publications have reported the formation of sulfonamides from 2-nitrobenzenesulphonamide using the Mitsunobu reaction but none describe the use of tosylamide as a substrate. In this study Mitsunobu conditions were explored to transform a primary alcohol to a tosylamide in one step, by activation with triphenylphosphine and diethyl azodicarboxylate (DEAD), and then using tosylamide as the nucleophile. However, despite considerable effort, the reactions failed and the tosylamides were not obtained (Scheme 2-38).



Scheme 2-38: Failed preparation of the tosylamides **205** and **206** under Mitsunobu conditions.

A second pathway explored the preparation of tosylamides **205** and **206** by a two step process. First it was envisaged that alcohols **103** and **105** could be converted to their

corresponding bromides **207** and **208**, and then the bromides could be converted to the desired tosylamides **205** and **206** after nucleophilic displacement (Figure 2-12).

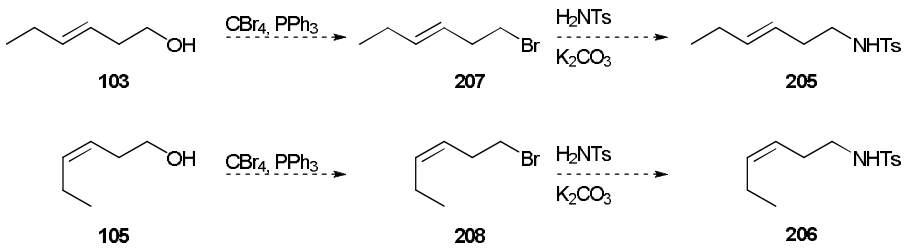
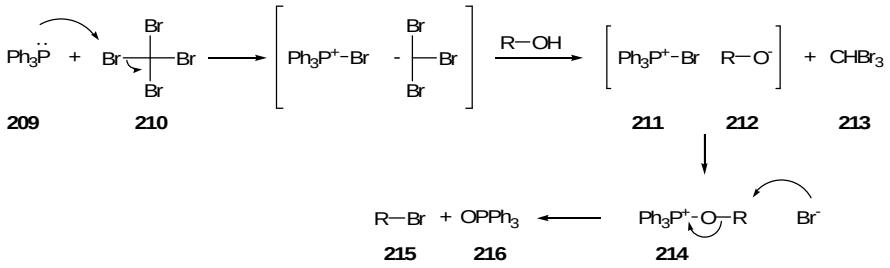


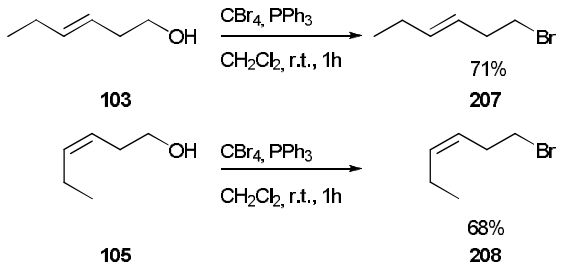
Figure 2-12: Alternative strategy for the preparation of tosylamides **205** and **206** by a two step route from alcohol **103** and **104**.

The mechanism of the bromination reaction is summarised in Scheme 2-39.[57, 58]



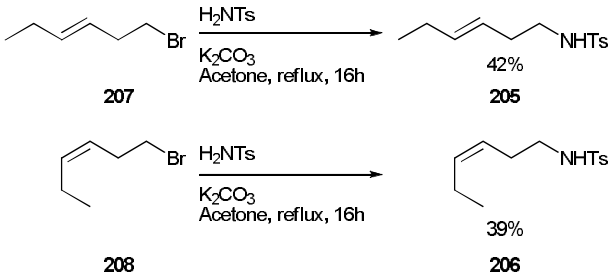
Scheme 2-39: Mechanism of the bromination reaction from an alcohol with CBr_4 and PPh_3.

(*E*)- And (*Z*)-1-bromohex-3-enes **207** and **208** were readily prepared from (*E*)- and (*Z*)-hex-3-en-1-ols **103** and **105** using carbon tetrabromide and triphenylphosphine in 68 and 71% yields respectively (Scheme 2-40).[59]



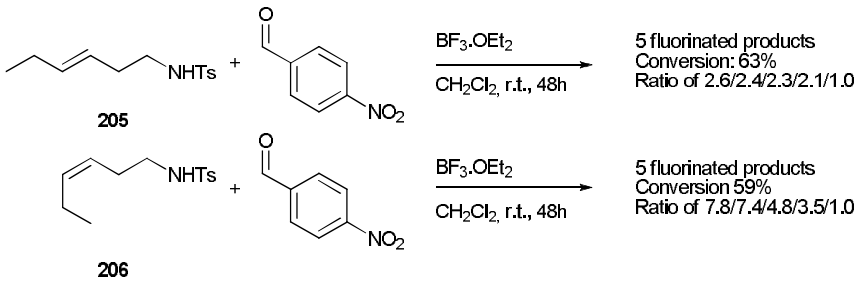
Scheme 2-40: Conversion of (*E*)- and (*Z*)-hex-3-en-1-ols **103** and **105** to (*E*)- and (*Z*)-1-bromohex-3-enes **207** and **208**.

(*E*)- And (*Z*)-1-bromohex-3-enes **207** and **208** were then converted to the corresponding (*E*)- and (*Z*)-*N*-(hex-3-enyl)-1-tosylamides **205** and **206** in 39% and 42% yields respectively using tosylamides and K_2CO_3 (Scheme 2-41).



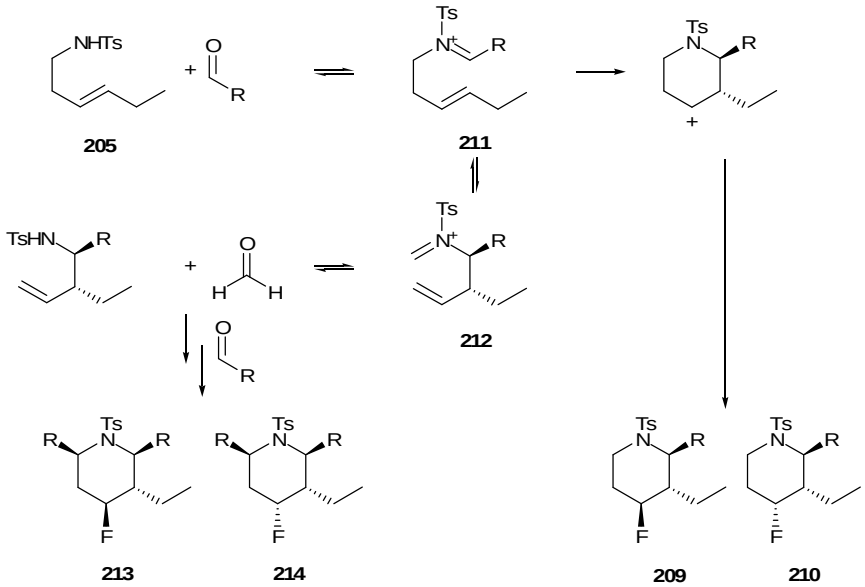
Scheme 2-41: Synthesis of to the (*Z*)- and (*E*)-*N*-(hex-3-enyl)-1-tosylamide **206** and **205**.

With these two tosylamides in hand, *aza*-Prins fluorinations were explored. The reactions were carried out with 4-nitrobenzaldehyde **100a** and $BF_3.OEt_2$ (1 eq). In both cases, a complex mixture of fluorinated products was generated, as determined by ^{19}F-NMR (Scheme 2-42). Individual components of the mixture could not easily be separated by chromatography.



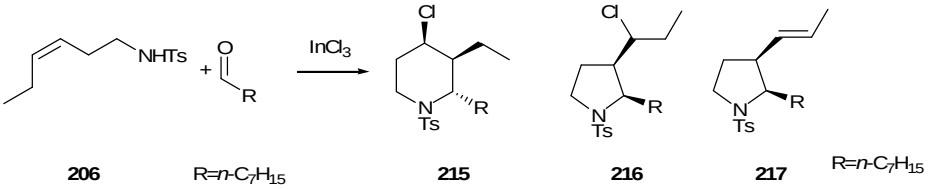
Scheme 2-42: *Aza*-Prins fluorination reactions between (*E*) and (*Z*) hex-3-enyl-1-tosylamides **205** and **206** and 4-nitrobenzaldehyde with $BF_3.OEt_2$.

Clearly two of the fluorinated products are likely to be the expected *aza*-Prins adducts **209** and **210** with the fluorine atom either in an axial or an equatorial position. The other products may result from [3,3] sigmatropic rearrangements of putative intermediate **211** during the reaction. This would lead to tetrasubstituted piperidines **213** and **214** by reaction of intermediate **212** with 4-nitrobenzaldehyde (Scheme 2-43). However this hypothesis remains speculative.



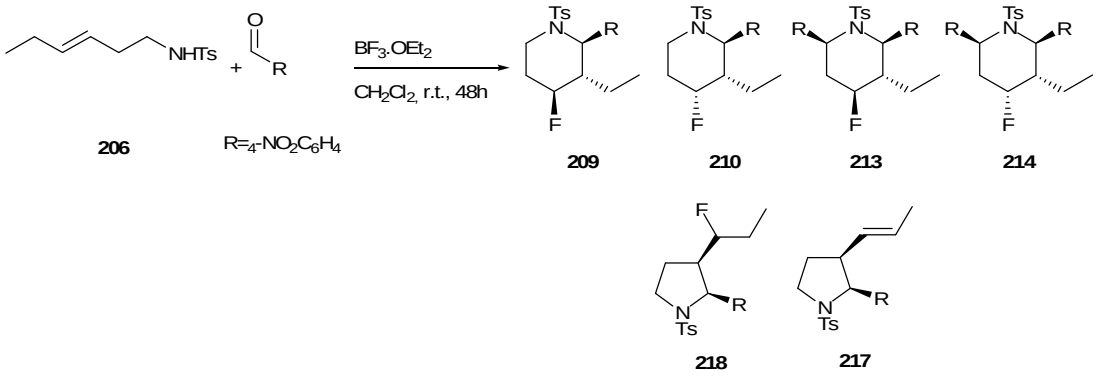
Scheme 2-43: Rationale for the formation of several fluorinated products during the *aza*-Prins reaction of tosylamide **205** and 4-nitrobenzaldehyde.

Moreover, very recently Dobbs *et al*[60] reported the formation of pyrrolidines as well as the piperidines *via* aza-Prins reaction between the amines **205** and **206** and several aldehydes when he used $InCl_3$ (Scheme 2-44).



Scheme 2-44: Formation of pyrrolidines and piperidine by *aza*-Prins reaction.[60]

Similarly the formation of several fluorinated products can be rationalised in the reaction of 4-nitrobenzaldehyde and tosylamides **206**. A complex mixture arose most likely due to the formation of the two expected *aza*-Prins products as well as the formation of other products *via* [3,3] sigmatropic rearrangements and pyrrolidines (Scheme 2-45).

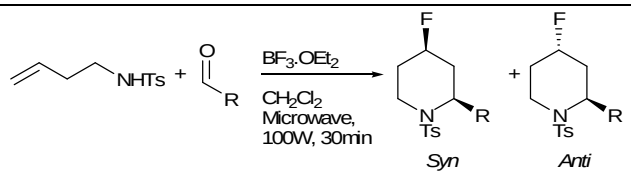


Scheme 2-45: Possible product profile formed during the *aza*-Prins fluorination reaction between tosylamide **205** and 4-nitrobenzaldehyde.

3.6 Aza-Prins reaction under microwave conditions

In overview the *aza*-Prins fluorination reaction has allowed the formation of 4-fluoropiperidines by reaction of a tosylamide with an aldehyde in the presence of $BF_3.OEt_2$. However, the reaction times are long (~ 48 h). The use of microwave conditions to carry out these reactions appears attractive, particularly to shorten the long reaction times.

The use of microwaves to carry out an *aza*-Prins cyclisations reaction has never been reported in the literature. Therefore, the experiments were carried out using the same conditions as the *oxa*-Prins fluorination. It emerged that the reaction needs 30 min. to convert the tosylamide **191** to 4-fluoropiperidines **196** and **197**. Under the microwave conditions the reaction is much more efficient, showing similar conversions to the more classical *oxa*-Prins reactions (Table 2-12). Overall, the diastereoselectivity decreased a little under the microwave conditions (entry c, d and f), it but showed a noticeable improvement in the cases which used 4-bromobenzaldehyde (entry b).



191 **196** **197**

Entry	Aldehyde	d.r **196**/**197**	Yield	d.r. at r.t	Yield at r.t.
a	4-Nitrobenzaldehyde	1.3/1	57%	1/1	61%
b	4-Bromobenzaldehyde	1.9/1	67%	1/1	68%
c	4-Fluorobenzaldehyde	1.5/1	63%	1.8/1	68%
d	Isobutyraldehyde	1.9/1	83%	2/1	82%
e	Acetaldehyde	1.2/1	77%	1/1	73%
f	Hexanal	1.9/1	79%	2/1	73%

Diastereoisomeric ratio determined by isolation of the products or by 19 NMR of the mixture

Table 2-12: Aza-Prins reaction carried out under microwave (100 W) with $BF_3.OEt_2$ (1 eq) during 30 minutes.

With the reaction time reduced from 48 h to 30 min, the microwave conditions appear to be an attractive alternative, especially as the diastereoselectivity remains approximatively the same.

4 Conclusion

Selective methods for fluorination are finding increasing utility in pharmaceutical, agrochemicals and fine chemicals research. The $BF_3.OEt_2$-mediated Prins cyclisation reaction offers another methodology by which to create 4-fluoropiperidines and 4-fluorotetrahydropyrans. This research has demonstrated the importance of temperature on the diastereoselectivity of the *oxa*-Prins reaction. It has also shown that the choice of aldehyde is important, as electron rich benzaldehydes were poor substrates as were α,β-unsaturated aldehydes. However, the presence of electron withdrawing groups on aromatic aldehydes increased the efficiency of the reaction. The presence of substituents on the alcohol also emerged as an important parameter. A substituent at the δ- position to the OH- group lead to only two diastereoisomers, while a substituent α- to the aldehyde gave up to six different fluorinated products. Also a γ-methyl group blocked the reaction. New Prins fluorination reactions were explored under microwave conditions, reducing the reaction time to 10 min with an improved conversion. However this was accompanied by a reduction in diastereoselectivity.

The *aza*-Prins fluorination reaction is a newly developed methodology with very few examples in the literature. This reaction required much longer reaction times compared with the *oxa*-Prins fluorination. Only the tosylamine **191** was a suitable substrate, which is a clear limitation. It was less sensitive to temperature, and did not show any diastereoselectivity improvement on cooling. The specificity of the aldehyde is similar to the *oxa*-Prins reaction. Electron rich benzaldehydes and α,β-unsaturated aldehydes were poor substrates whereas 4-nitrobenzaldehyde was a good substrate. Finally it was shown that the *aza*-Prins fluorination could be significantly accelerated under microwave conditions, reducing the reaction time

from 48 hours to 30 minutes without impacting to much the conversion or the diastereoselectivity.

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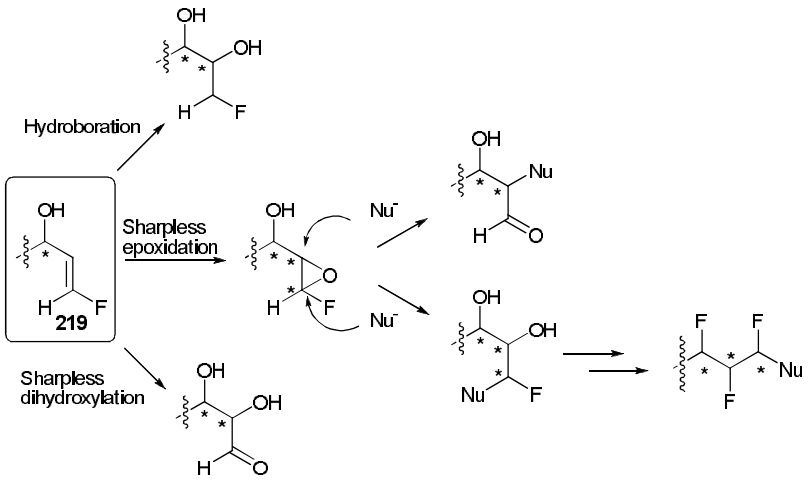
Chapter 3: α-Fluoro-alkene synthesis

1 Synthetic approach to γ-hydroxy-α-vinylfluoride

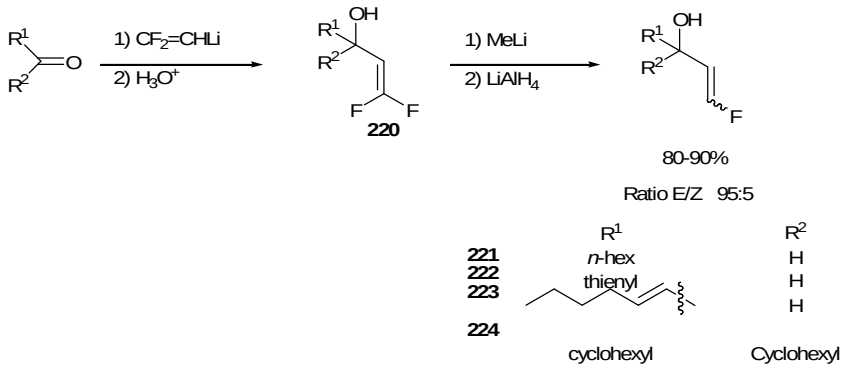
1.1 The γ–hydroxy-α-vinylfluoride moiety

Despite the growing interest in fluorine in organic chemistry, few investigations have been carried out on the synthesis of α-fluoroallylic alcohols **219**. This moiety is interesting as a potential building block for the preparation of a wide range of fluorinated products. Indeed, several transformations such as hydroborations, Sharpless dihydroxylations and Sharpless epoxidations, with the potential to undergo subsequent epoxide-ring opening reactions (Scheme 3-1), could clearly deliver a variety of novel products.



Scheme 3-1: The potential of α-fluoroallylic alcohols **219**.

α–Fluoroallylic alcohols have been synthesised by F. Tellier and R. Sauvêtre[1, 2] (Scheme 3-2). The condensation of an aldehyde or a ketone with lithium 1,1-difluoroethene gave intermediate **220**, which by the action of methyllithium and lithium aluminium hydride led to the γ-hydroxy-α-vinylfluorides **221-224** in good yields (80-90%),[1] and good stereoselectivities (ratio *E/Z* 95/5 in all the examples).



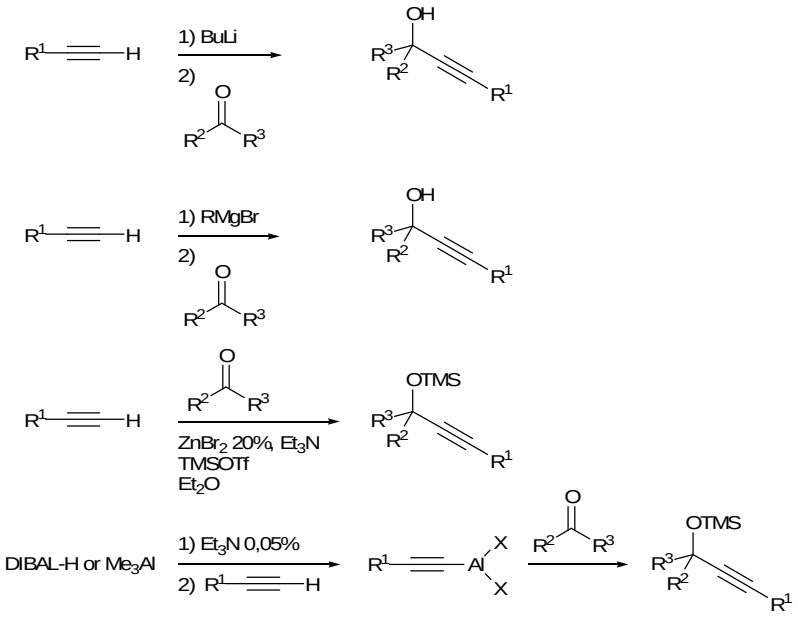
Scheme 3-2: First synthesis of γ-hydroxy-α-vinylfluoride, by Sauvêtre *et al.*[1]

However, the difluoroallylic alcohol intermediates **220** are very unstable.[2-5] Moreover, the necessary 1,1-difluoroethene used to prepare 1,1-difluoroethene lithium is very flammable. With these considerations, it appeared attractive to find an alternative route to this rare class of compounds.

1.2 Preparation of a fluorinated olefin from propargylic alcohol

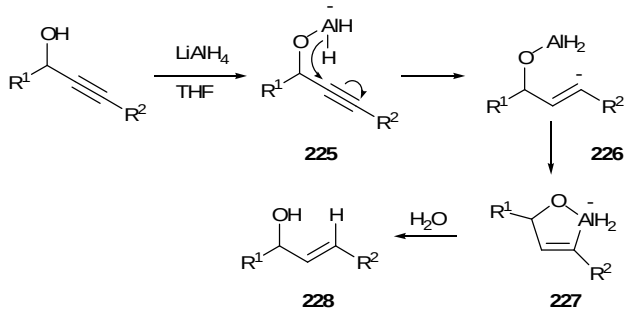
The first approach that was considered involved the reduction of propargylic alcohols with *in situ* electrophilic fluorination. Propargylic alcohols are common intermediates in

synthesis and are relatively easy to prepare. Several methods have been reported for their synthesis. The most common involves deprotonation of an alkyne with a base such as BuLi[6-9] or a Grignard[10, 11] reagent, followed by nucleophilic attack of the resultant alkynyl anion to a ketone or aldehyde (Scheme 3-3). There are also examples of coupling reactions using organoaluminium[12] or organozinc[13-15] intermediates.



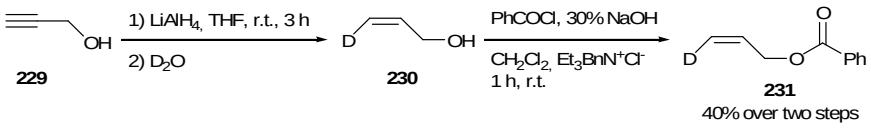
Scheme 3-3: Examples for the preparation of propargylic alcohols.

Moreover, an early study by Djerassi *et al.*[16] showed that treatment of propargylic alcohol with lithium aluminium hydride in THF gives exclusively a *cis* reduction leading to *E*-allylic alcohols **228**. Djerassi explained this result with a mechanism involving complexation of the aluminium with the propargylate oxygen to generate intermediate **225** (Scheme 3-4). Then intramolecular hydride transfer occurs, followed by the formation of the pentacyclic aluminium intermediate **227**. Hydrolysis releases the *(E)*-allylic alcohol **228**.



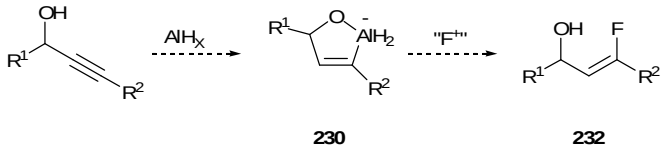
Scheme 3-4: Mechanistic rationale of the reduction of propargylic alcohol by $LiAlH_4$.[16]

Numerous publications report the reduction of propargylic alcohols to allylic alcohols using aluminium hydrides such as diisobutylaluminium hydride (DIBAL-H),[17] sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al®)[18-21] or $LiAlH_4$.[22-25] Moreover, O'Hagan *et al.*[26] described the stereospecific reduction of propargylic alcohol **229** to generate [3-^{2}H]-allylic alcohol **230** using $LiAlH_4$ and by adding D_2O at the end of the reaction. Esterification of the allylic alcohol lead to the *Z*-[3-^{2}H]-prop-2-en-1-yl benzoate **231** (Scheme 3-5).[26] This inserted a deuterium atom at the α-position, in 40% yield over the two steps. It is noteworthy that only the *Z* product was obtained.



Scheme 3-5: Preparation of *Z*-[3-^{2}H]-allylic ester **227** using $LiAlH_4$.[26]

Modification of this reaction appeared attractive to explore a possible preparation of α-vinylfluoride compounds directly, by reduction of the triple bond followed by *in situ* treatment of the pentacyclic aluminium intermediate **228** with an electrophilic fluorination reagent to trap the anion. The strategy is illustrated in Scheme 3-6.



Scheme 3-6: Synthetic pathway to α-fluorinated allylic alcohols.

For this study, propargylic alcohols **233**, **234** and **235** were selected (Figure 3-1). Alcohol **233** possesses a terminal alkyne while alcohol **234** has a pendant hexyl chain. Propargylic alcohol **235** is a primary alcohol. These propargylic alcohols were selected to explore the effect of substituents on a potential reduction-fluorination sequence.

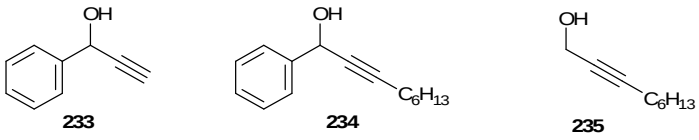
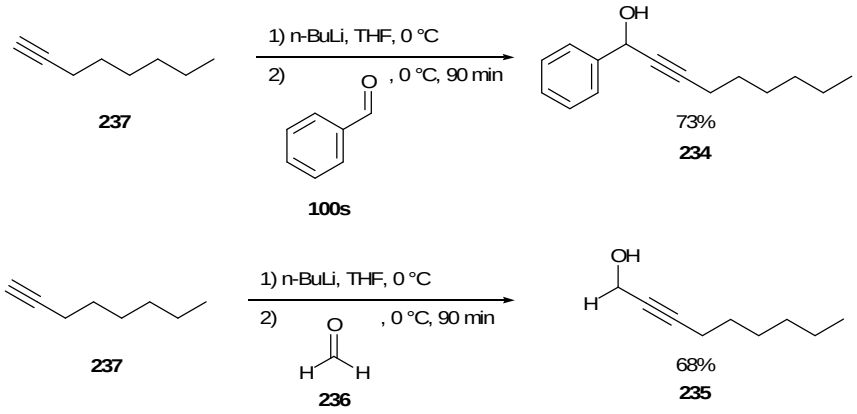


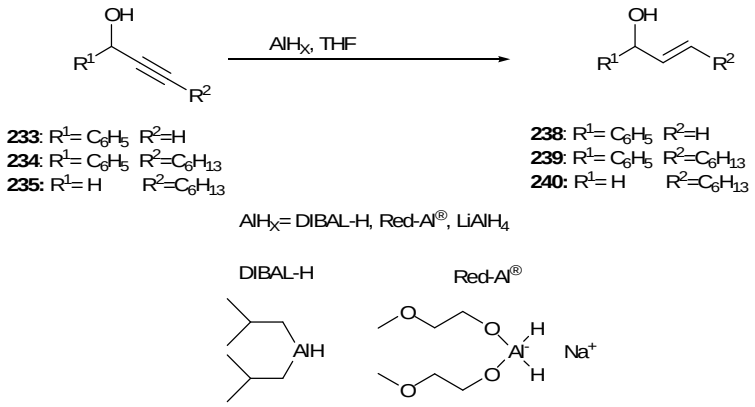
Figure 3-1: Selected propargylic alcohols **233**, **234** and **235**.

Propargylic alcohol **233** is a commercially available compound. On the other hand, **234** and **235** had to be prepared. These substrates were obtained by reaction of benzaldehyde **100s** or formaldehyde **236** and 1-octyne **237** in the presence of *n*-butyllithium. The reactions were relatively straightforward giving yields of 73% and 68% respectively (Scheme 3-7).



Scheme 3-7: Preparation of propargylic alcohols **234** and **235**.

Before the fluorination reaction was attempted, it was important to explore optimal propargylic alcohol reducing conditions for this reaction using aluminium hydride DIBAL-H, Red-Al and $LiAlH_4$ reagents (Scheme 3-8).

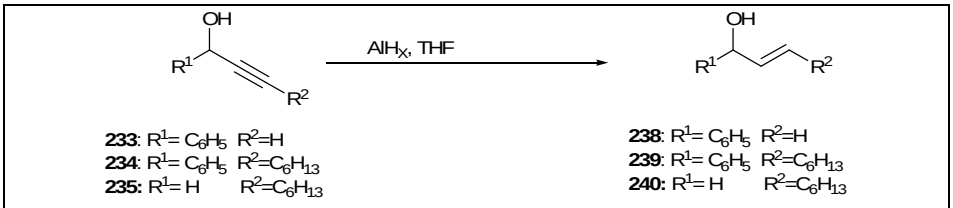


Scheme 3-8: Reduction of propargylic alcohols to allylic alcohols using aluminium hydride reagents.

The first reductive reagent explored was diisobutylaluminium hydride (DIBAL-H, in solution in THF). With only one hydride, it was anticipated that it may display better control on the reaction. However DIBAL-H gave no reaction, even under reflux in THF (Table 3-1) and only starting material was recovered at the end of the reaction.

As an alternative strategy, sodium *bis*(2-methoxyethoxy)aluminium hydride (Red-Al) was explored. Red-Al can reduce propargylic diols[18]at room temperature in THF to give the (*E*) allylic diol. Unfortunately, again no reaction occurred at room temperature. However, when the reaction was carried out in THF at reflux, alcohol **235** did give the expected *E* allylic alcohol **240**, and in 77% yield, without a trace of the *Z* isomer detected by ^{1}H NMR. In the case of the alcohols **233** and **234**, only degradation was observed.

Lithium aluminium hydride emerged as the best reagent for this study, as it was able to reduce all three propargylic alcohols **233**, **234** and **235** in a stereospecific manner to give specifically the (*E*)-allylic alcohols **238**, **239**, **240** in 89%, 91% and 87% yields respectively.



233: $R^1 = C_6H_5$ $R^2 = H$
234: $R^1 = C_6H_5$ $R^2 = C_6H_{13}$
235: $R^1 = H$ $R^2 = C_6H_{13}$

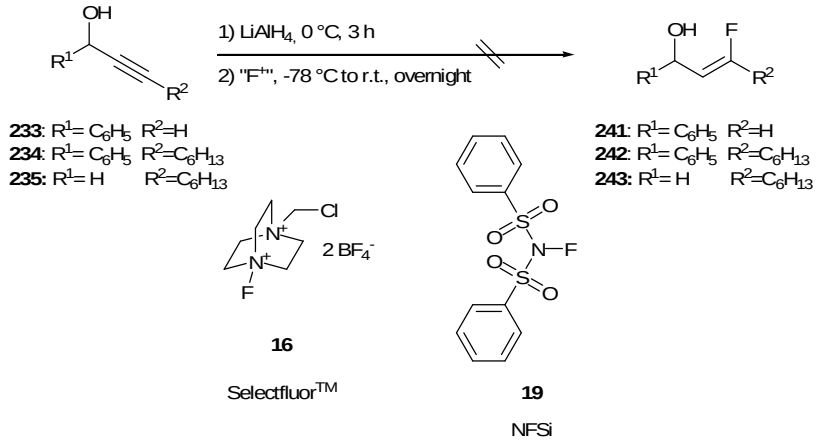
238: $R^1 = C_6H_5$ $R^2 = H$
239: $R^1 = C_6H_5$ $R^2 = C_6H_{13}$
240: $R^1 = H$ $R^2 = C_6H_{13}$

Starting material	AlH_x	Temperature	Time	Isolated product
233	DIBAL-H	-78 °C to r.t.	3h	Starting material.
233	DIBAL-H	Reflux	3h	Starting material
234	DIBAL-H	-78°C to r.t.	3h	Starting material
234	DIBAL-H	Reflux	3h	Starting material
235	DIBAL-H	Reflux	3h	Starting material
233	Red-Al	Reflux	3h	Degradation
234	Red-Al	r.t.	3h	Starting material
234	Red-Al	Reflux	3h	Degradation
235	Red-Al	Reflux	3h	**240**, 77%, *E/Z*: 100/0
233	$LiAlH_4$	r.t.	3h	**238**, 89%,
234	$LiAlH_4$	r.t.	3h	**239**, 91%, *E/Z* 100/0
235	$LiAlH_4$	r.t.	3h	**240**, 87%, *E/Z* 100/0

Table 3-1: Reductions of propargylic alcohols **233**, **234** and **235** to allylic alcohols.

In order to explore a coupled fluorination reaction of the intermediate organometallic species, Selectfluor™ **16** and *N*-fluorobenzenesulfonimide **19** (NFSI) were chosen as potential electrophilic fluorinating reagents (Scheme 3-9).[27] After reaction of the propargylic alcohols with $LiAlH_4$ for 3h, the reaction was cooled to -78°C and then Selectfluor™ was introduced. Unfortunately, no fluorinated alcohols **241**, **242** or **243** were obtained. Crude reaction products were scanned by ^{19}F NMR where very low concentrations of organofluorine

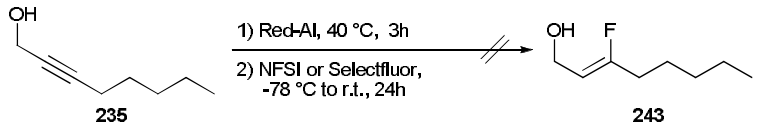
compounds could be detected. There was no improvement even after two days at r.t.. These poor results may be due to the poor solubility of Selectfluor^{TM} in THF or the lack of reactivity of the organometallic complex. Following similar protocols, Selectfluor^{TM} was replaced by NFSI **19**,[27-29] but the reactions were again unsuccessful. The results were no better when the reactions were heated under reflux or with the addition of triethylamine as a base (Table 3-2).



Alcohol	"F+" donor reagent	Temperature	Results
233	Selectfluor^{TM}	r.t.	No fluorinated product
234	Selectfluor^{TM}	r.t.	No fluorinated product
235	Selectfluor^{TM}	r.t.	No fluorinated product
233	NFSI	r.t.	No fluorinated product
234	NFSI	r.t.	No fluorinated product
233	NFSI	Reflux	Degradation
233	NFSI, Et_3N	-78 °C to reflux	Degradation

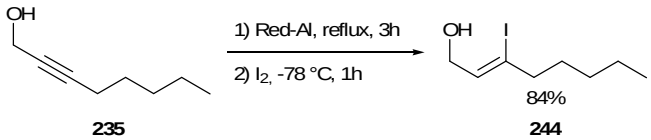
Table 3-2: Exploration of the reductive-fluorination reactions of alcohols **233**, **234** and **235** using $LiAlH_4$.

Due to the lack of success of these reduction-fluorination reactions, $LiAlH_4$ was replaced by Red-Al. Indeed, RedAl was able to reduce propargylic alcohol **235** to the corresponding allylic alcohol **240** and this combination emerged as a candidate for the reductive fluorination reaction. However, when the reaction was performed with alcohol **235**, no organic-fluorine product was observed by ^{19}F NMR. Only the allylic alcohol **240** and non fluorinated degradation products were identified (Scheme 3-9).



Scheme 3-9: Exploring the hydroalumination-fluorination reaction using Red-Al with alcohol **235**.

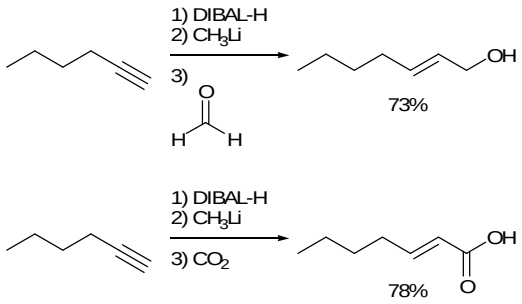
Due to the lack of success, a test reaction using iodine instead of an electrophilic fluorinating reagent was carried out. The test reduction was explored using Red-Al and alcohol **235**, and by quenching the reaction with iodine (I_2) at -78 °C. This gave the expected γ-iodo allylic alcohol **244** in 84% yield after 1h (Scheme 3-10). This was an efficient reaction with iodine, but was completely unsuccessful with the electrophilic fluorinating reagents Selectfluor and NFSI.



Scheme 3-10: Reductive iodination of propargylic alcohol **235**.

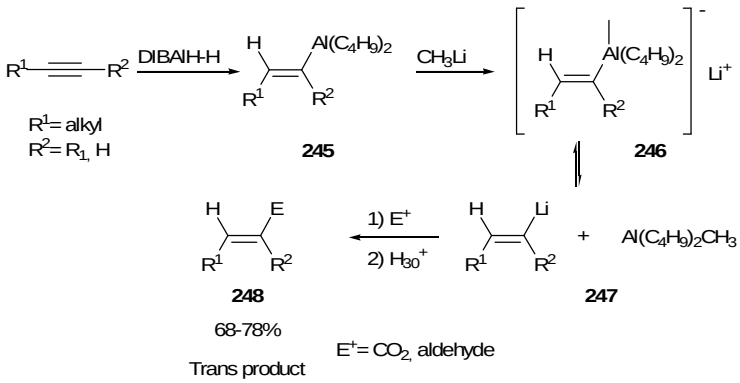
Clearly Selectfluor and NFSI are not reactive enough even though they are considered to be among the most useful electrophilic fluorination reagents. Another approach using a

DIBAL-H/CH_3Li couple as the reducing agent was investigated. Indeed, several publications report the reduction of terminal or disubstituted alkynes by DIBAL-H and CH_3Li followed by attack of an electrophile (Scheme 3-11).[30-32]



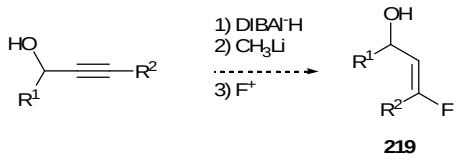
Scheme 3-11: Example of hydroalumination followed by attack of an electrophile, Zweifel *et al.*[30]

A terminal or a symmetrically disubstituted alkyne is treated with a solution of DIBAL-H, and then with methyllithium. The resultant product is an equilibrium between the ionic organoaluminium **246** and the alkene-lithium form **247**. This alkene-lithium then reacts with an electrophile, such as an aldehyde or carbon dioxide to lead to the elaborated alkene (Scheme 3-11). Generally addition to the triple bond gives exclusively the *cis* isomer.



Scheme 3-11: Reduction of alkyne to alkene with DIBAL-H/CH_3Li.[30]

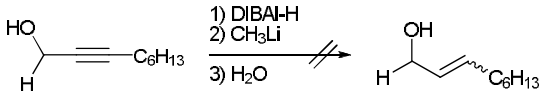
It appeared attractive to explore this method in an attempt to prepare the γ-hydroxy-α-vinylfluorides by treatment of the organolithium intermediate with an electrophilic fluorinating reagent (Scheme 3-12).



219

Scheme 3-12: Exploration of the reduction-fluorination reaction of propargylic alcohols using DIBAL-H/CH_3Li.

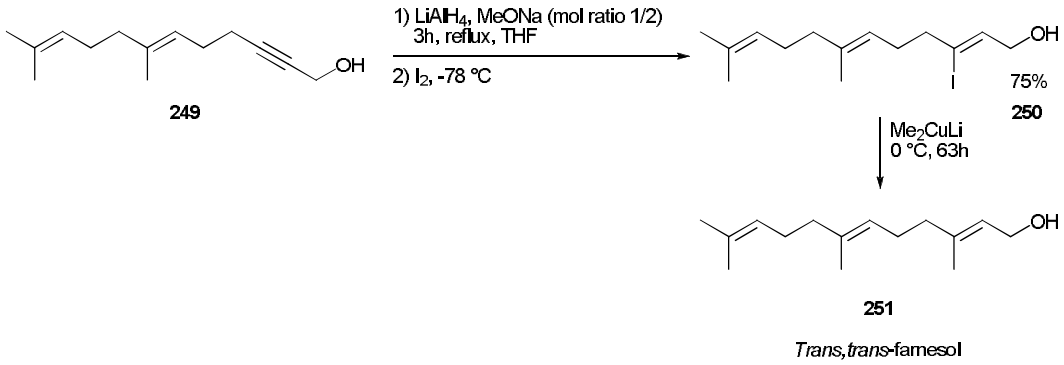
To investigate this reaction, propargylic alcohol **235** was selected as a model substrate, as it demonstrated good reactivity toward the reduction step (Scheme 3-13). However, reduction followed by hydrolysis of the organoaluminium intermediate did not give the expected allylic alcohol **240** but only starting material and degradation products.



235 **240**

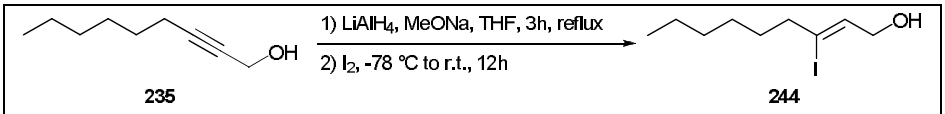
Scheme 3-13: Attempt preparation of allylic alcohol **243** by reduction of propargylic alcohol **235** by DIBAL-H/CH_3Li.

Corey *et al.*[33] reported the synthesis of *trans,trans*-farnesol **251**, with a selective reductive iodination of propargylic alcohol to γ-iodo allylic alcohol **250** as the key step. To achieve this reduction, Corey carried out a hydroalumination reaction using a $LiAlH_4$/MeONa couple, followed by treatment with I_2 to generate alcohol **250** in 75% (Scheme 3-14).



Scheme 3-14: Preparation of α-iodo allylic alcohol **250** by Corey *et al.* using a $LiAlH_4$/MeONa couple.[33]

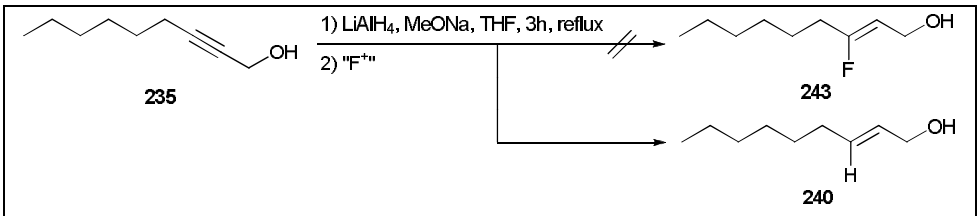
Following Corey's method, the iodo alcohol **244** was prepared from propargylic alcohol **235** (Table 3-3). The key publication did not give details of the reaction, just the ratio of the reagents ($LiAlH_4$/MeONa 1/2) so this had to be optimised. After an investigation of a number of conditions, it appears that the optimum conditions required 1.5 eq of $LiAlH_4$ and 3 eq of MeONa.



Alcohol	$LiAlH_4$ (mol eq)	MeONa (mol eq)	Yields
235	0.75	1.5	53%
235	1	2	65%
235	1.5	3	73%
235	2	4	71%

Table 3-3: Optimisation of the hydroalumination-iodination of alcohol **235.**

The next stage was now to carry out the hydroalumination-fluorination of alcohol **235** using the conditions previously established. Unfortunately, when I_2 was replaced by NFSI or Selectfluor, fluorinated products were not observed by ^{19}F NMR of the product mixture. The reduced alcohol **240** was an obvious product in all of these trial reactions (Table 3-4).



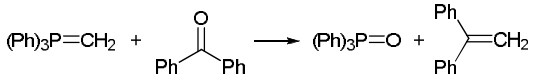
Alcohol	"F^+" donor	Temperature	Time	Results
235	Selectfluor	-78 °C to r.t.	12h	Alcohol **240**
235	NFSI	-78 °C to r.t.	12h	Alcohol **240**
235	Selectfluor	Reflux	6h	Alcohol **240**
235	NFSI	Reflux	6h	Alcohol **240**

Table 3-4: Attempted preparation of γ-fluoro allylic alcohol by hydroalumination-fluorination.

Clearly this reaction does not work when moving from iodine to fluorine. We then decided to consider a new strategy for the synthesise of γ-fluoro allylic alcohols. This involved a Wittig-Horner approach.

1.3 Preparation of a fluorinated double bond *via* a Wittig-type reaction

The Wittig reaction is a well known and useful tool in organic synthesis. It involves the creation of olefins by reaction of a phosphonium ylide with an aldehyde or a ketone. Wittig *et al.* reported in 1954 the reaction between the phosphonium ylide **252** and benzophenone **253** leading to the olefin **255** and triphenylphosphine oxide **254** (Scheme 3-15).[34]

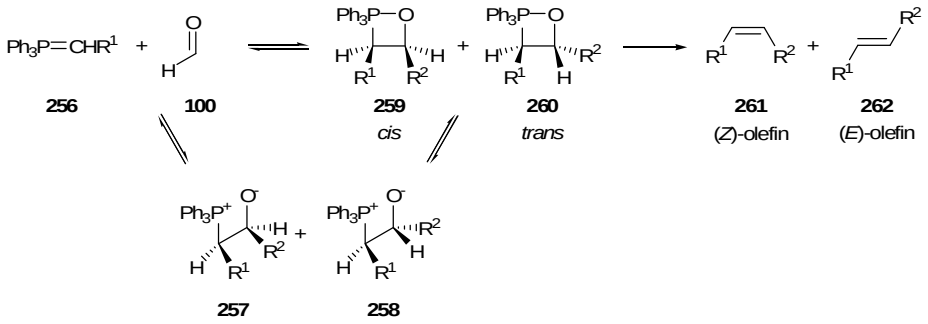


252 **253** **254** **255**

Scheme 3-15: First report of olefin formation between a phosphorus ylide and diphenylketone **253** by Wittig.[34]

The mechanism of the Wittig reaction has been intensively investigated but is still not fully elucidated.[35-37] The first step involves the formation of four membered ring oxaphosphetane intermediates **259** and **260** (Scheme 3-16). It is the formation of this intermediate which is not completely clear. The mechanism goes first by the formation of betaines **257** and **258** by attack of the carbanion to the carbonyl, and then the betaines form the oxaphosphetanes **259** and **260** respectively. Both steps are reversible. The formation of the betaines and its place in the mechanism are not yet fully established even if there is some evidence for their existence. Oxaphosphetanes have been observed by ^{31}P MNR, suggesting a reversible [2+2] cycloaddition between the ylide and the carbonyl.[36, 38, 39] The oxaphosphetanes **259** and **260** decompose irreversibly to give olefins **261** and **262** respectively, as well as triarylphosphine oxide. The driving force for the reaction is the formation of the stable phosphine oxide. The geometry of the product olefin depends on the ylide **256**. If the ylide is not stabilised by the substituent R_1, the equilibrium is displaced in

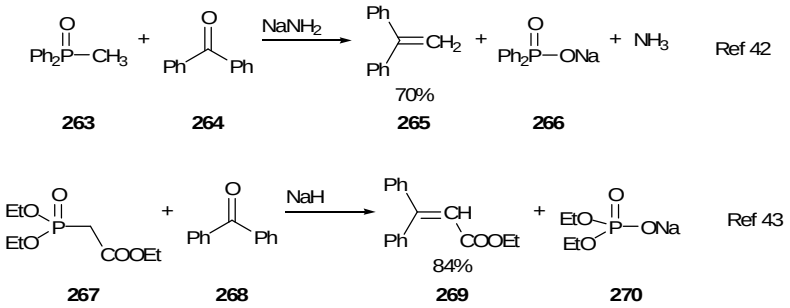
favour of the *cis*-oxaphosphetane, leading to the (*Z*)-olefin **261**. However, if the phosphonium ylide is stabilised, the less reactive *trans*-oxaphosphetane **260** will be favoured, generating the (*E*)-olefin.



Scheme 3-16: Mechanism of the Wittig reaction.[35, 36]

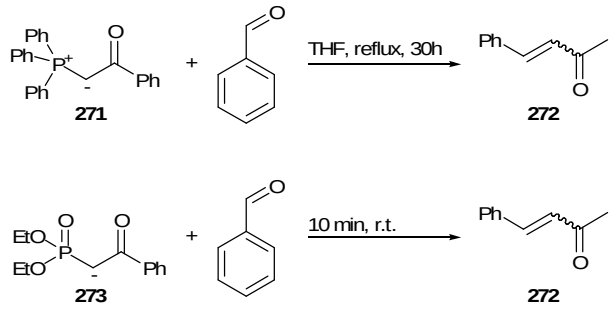
Different factors also favour the formation of one olefin over the other, such as the substituents on the phosphine[40] or the presence of lithium salts.[36-38]

In 1958, Horner *et al.*[41] reported a modified Wittig reaction using alkylated phosphine oxides instead of a triarylphosphonium ylide. In that publication, Horner described the formation of olefin **266** using methyl diphenylphosphine oxide **263** and benzophenone **264** in 70% yield (Scheme 3-17).[41] Three years later, Wadsworth and Emmons reported the reaction between phosphonate carbanions and ketones to form olefins as shown in Scheme 3-17.[42]



Scheme 3-17: Examples of modified Wittig reactions by Horner[41] and Emmons.[42]

This group of modified Wittig reactions are named Wittig-Horner or Horner-Emmons reactions. The change from a trialkylphosphine to a dialkylphosphine oxide or a phosphonate brings several advantages. The first advantage is the increased nucleophilicity of the phosphonate carbanion compared to the phosphonium ylide, due to a weaker stabilisation of the negative charge by the valence shell of the phosphorous atom in the case of the phosphonate. Thus, a wider range of aldehydes and ketones react with phosphonate carbanions, and often under milder reaction conditions, generating the corresponding olefins.[42] For example, phosphonium ylide **271** reacts with benzaldehyde under reflux in THF to obtain olefin **272**, while phosphonate **273** reacts smoothly with benzaldehyde at room temperature (Scheme 3-18).[42, 43]

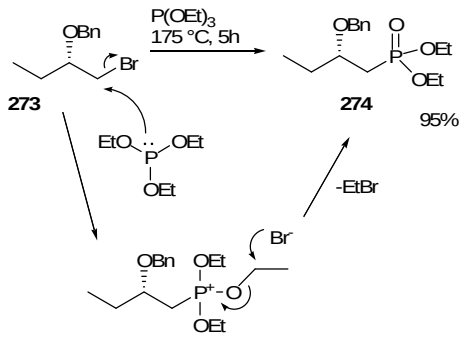


Scheme 3-18: Difference in reactivity between phosphonium ylide **271** and phosphonate carbanion **273**.[42, 43]

Moreover, alkylation on the α-carbon is possible due to the increased reactivity of the phosphonate carbanion, whereas it is very difficult to mediate such an alkylation with phosphonium ylides.[42, 44]

Also phosphonates can be easily prepared by different methods. The most common involves trialkyl phosphite and an alkyl halide, in an Arbuzov reaction. One example is the preparation of (*S*)-(+)-diethyl 2-benzyloxybutylphosphonate **274** from (*S*)-(+)-1-

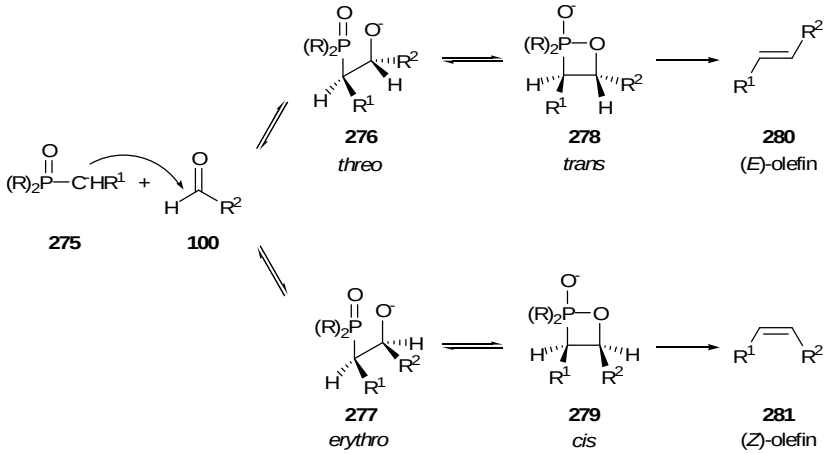
bromomethyl-propyl benzyl ether **273** and triethyl phosphite (Scheme 3-19).[45] The reaction is initiated by nucleophilic attack of the phosphorus to the alkyl bromide **273**. This is followed by dealkylation of the triethoxyphosphonium salt by attack of the bromide ion to the ethyl group, leading to phosphonate **274** in 95% yield. To avoid competition between the starting alkyl bromide and the ethyl bromide by-product, the ethyl bromide is removed as it is formed, as its boiling point is 37-40 °C at atmospheric pressure.



Scheme 3-19: Preparation of a phosphonate by the Arbuzov reaction.[45]

Phosphonates are also water-soluble and can easily be removed at the end of the reaction.

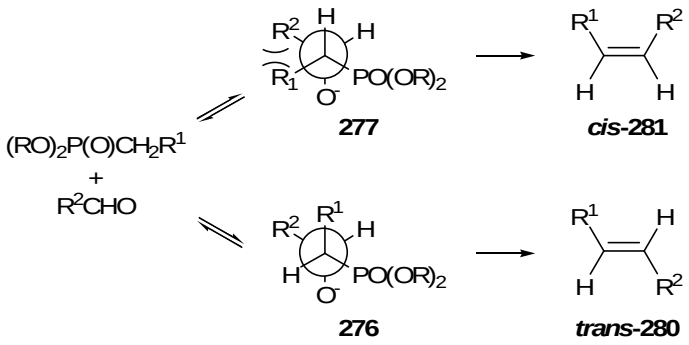
The mechanism of the Wittig-Horner or Horner-Emmons reaction, using diarylphosphine oxide or phosphonate, is similar to the Wittig reaction. After deprotonation of the α-carbon, anion **275** attacks the carbonyl to generate oxanions **276** and **277**. Subsequent decomposition *via* the four membered intermediates **278** and **279** leads to olefins **280** and **281** respectively (Scheme 3-20).



Scheme 3-20: Mechanism of Horner-Emmons reaction.

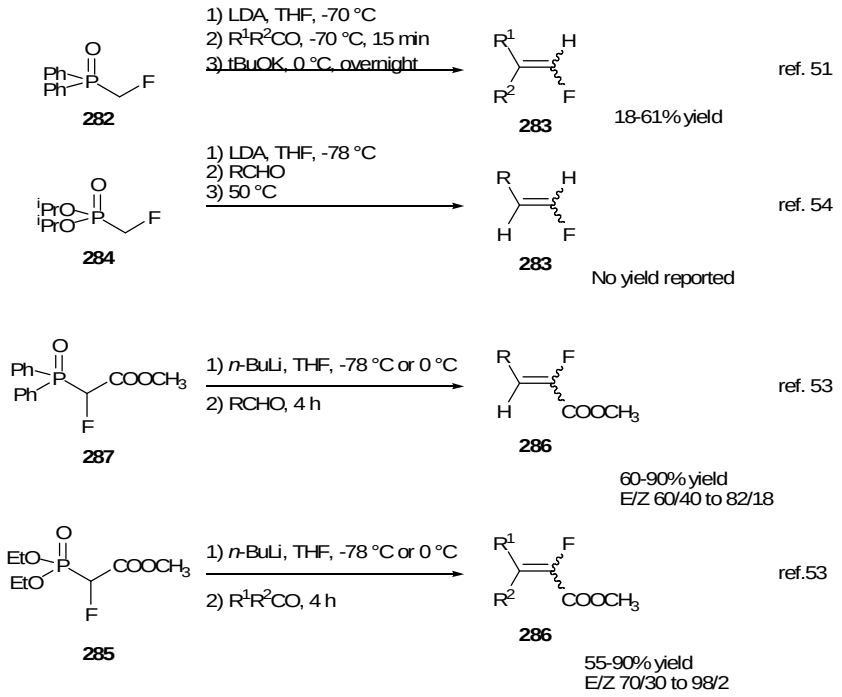
The reversibility of the formation of the aldolates is well established. However, in the case of the phosphonate, few reports of direct observation of the reaction intermediates have been published.[46] On the other hand, in the case of phosphine oxides, numerous examples of the isolation of the intermediate β-hydroxyphosphine oxides can be found.[47] Moreover, an X-ray structure determination of the *erythro*-2-diphenylphosphinoyl-1-phenylpropan-1-ol isomer has been reported.[48]

The reaction favours the formation of the *trans* olefin. Indeed, due to steric effects in the eclipsed conformation, the formation rate of *erythro* betaine **277** is lower than the *threo* betaine **276** (Scheme 3-21).[49] In a similar manner, decomposition of *threo* betaine **276** to a *trans* olefin is faster than the decomposition of the *erythro* betaine **277** to a *cis* olefin.



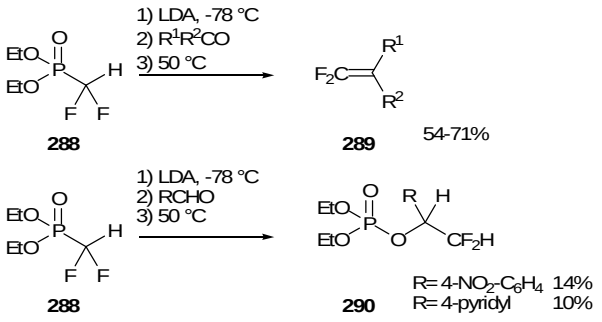
Scheme 3-21: Steric effects are the origin of the stereoselectivity of the Horner-Emmons reaction.[49]

Several publications have reported Wittig-Horner reactions with fluoromethylphosphonates **284** and **285** or fluoromethyl phosphine oxides **282** and **287** leading to fluorinated double bonds (Scheme 3-22).[50-53] In the case of (diisopropyl) fluoromethylphosphonate **284**, the reaction was heated in order to obtain the fluoro-olefins **283**.[51] And in the case of phosphine oxide **282** the yields and the stereoselectivity was poor to moderate.[50] The reaction of diethyl (α-fluoro-β-methyl acetate)methylphosphonate **285** with an aldehyde leads principally to the *E*-product **286**, whereas with diphenyl (α-fluoro-β-methyl acetate)phosphine oxide **287** this selectivity decreases.[50, 52]



Scheme 3-22: Examples of fluorinated olefin synthesis using Wittig-Horner reactions.

Moreover, Obayashi *et al.*[54] reported the formation of *gem*-difluoro-olefins using diethyl difluoromethylphosphonate **288** and an aldehyde or a ketone. The reactions were efficient and proceeded in good yields. It is noteworthy that the reaction does not give the expected olefin when R_1 is a nitrobenzyl or a 4-pyridinyl group, but the corresponding phosphate in low yields.

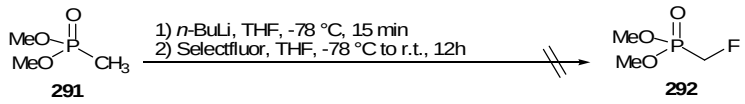


Scheme 3-23: Preparation of *gem*-difluoro-olefins by Obayashi.[54]

Thus, dialkyl fluoromethylphosphonate appeared to be a good candidate to investigate the preparation of γ-hydroxy-α-vinylfluorides.

1.3.1Preparation of the fluoromethylphosphonate

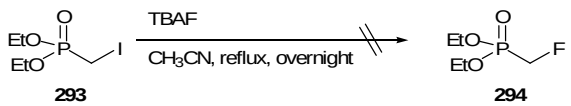
Several approaches were taken to address the preparation of the fluoromethylphosphonate. The first involved deprotonation of dimethyl methylphosphonate **291** with *n*-butyllithium followed by treatment with Selectfluor™ (Scheme 3-24).[55-57] Unfortunately, this was unsuccessful with only the recovery of starting material and degradation products.



291 **292**

Scheme 3-24: Attempt to prepare dimethyl fluoromethylphosphonate **292** by reaction with BuLi and Selectfluor.

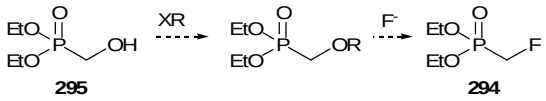
A second approach explored the preparation of diethyl fluoromethylphosphonate **294** from diethyl iodomethylphosphonate **293** by reaction with tetrabutylammonium fluoride (TBAF) (Scheme 3-25). Unfortunately, once again this was unsuccessful with only starting material and degradation products recovered.



293 **294**

Scheme 3-25: Attempt to prepare (diethyl) fluoromethylphosphonate **294** by reaction of TBAF on (diethyl) iodomethylphosphonate **293**

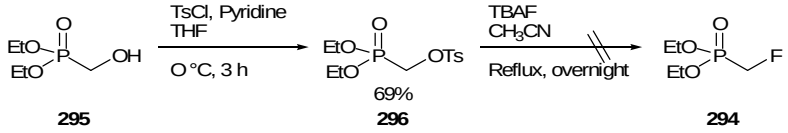
Due to the lack of success with a one step preparation, a two step strategy was explored. Several publications have reported the preparation of α-fluorophosphonates from hydroxymethylphosphonates.[50, 58] These papers describe activation of hydroxymethylphosphonate by tosylation[50, 59] or triflation[56, 60] followed by fluoride ion displacement (Scheme 3-26).



295 **294**

Scheme 3-26: General strategy of the two-steps preparation of fluoromethylphosphonate **294**.

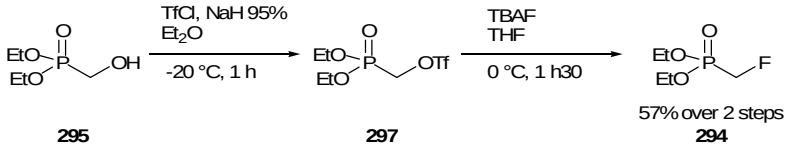
First the hydroxyl function of diethyl hydroxymethylphosphonate **295** was activated by tosylation using *para*-toluenesulfonyl chloride. This gave the tosylated intermediate **296** in 69% yield (Scheme 3-27).[50, 59] Unfortunately subsequent fluorination with TBAF was unsuccessful under classical conditions.



295 **296** **294**

Scheme 3-27: Two step attempt to prepare the fluoromethylphosphonate **294**.

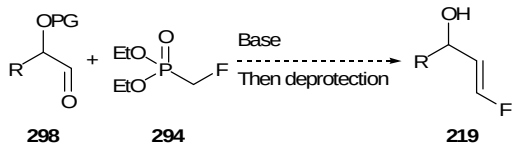
However, activation of the hydroxyl group as a triflate led to intermediate **297** and then treatment of this triflate with TBAF did result in the fluoromethylphosphonate **294** in 57% over the two steps.[58, 60]



Scheme 3-27: Preparation of the fluoromethylphosphonate **294** from hydroxymethylphosphonate **295** in two steps.

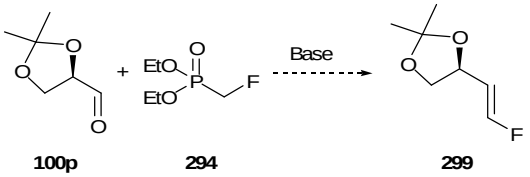
1.3.2 The Horner-Emmons reaction

With phosphonate **294** in hand, the next step was to explore the Horner-Emmons reaction. The ideal substrate for the preparation of γ-hydroxy-α-vinylfluoride would be a protected α-hydroxyaldehyde **298** which would lead to γ-hydroxy-α-vinylfluoride, after deprotection of the allylic alcohol (Scheme 3-28).



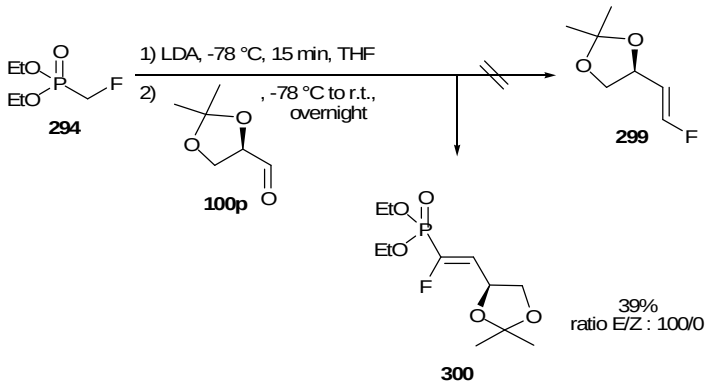
Scheme 3-28: Strategy to prepare γ-hydroxy-α-vinylfluoride *via* a Horner-Emmons reaction.

For this study, (*R*)-(+)-2,2-dimethyl-1,3-dioxolane-4-carboxaldehyde **100p**, was selected as it is a commercially available material and offers an interesting building block for subsequent elaboration (Scheme 3-29).



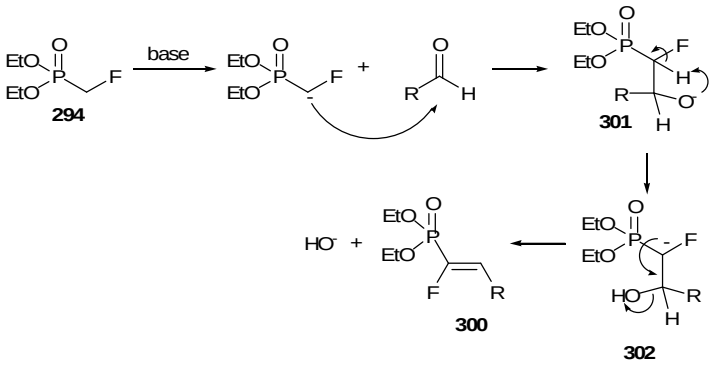
Scheme 3-29: Proposed route to 4-((*E*)-2-fluorovinyl)-2,2-dimethyl-1,3-dioxolane **299**.

However, the reaction between the phosphonate **294** and aldehyde **100p** in the presence of LDA did not lead to the γ-hydroxy-α-vinylfluoride **299** as expected, but gave (*E*)-diethyl-1-fluoro-2-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)vinylphosphonate **300** in 39% yield (Scheme 3-30). Interestingly, this gave only the *E*-isomer of the product with no trace of the *Z*-isomer, as determined by ^{31}P and ^{19}F NMR.



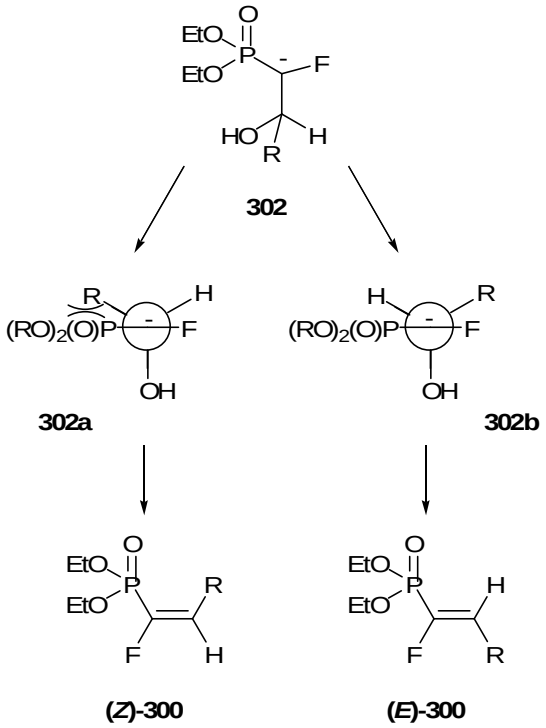
Scheme 3-30: Unexpected formation of fluorovinylphosphonate **300**.

The reaction clearly starts like a Horner-Emmons reaction, but after attack of the anion to the carbonyl group, the alkoxide **301** generated attacks the acidic proton *alpha* to the fluorine, giving **302**. This is followed by elimination of the alcohol, leading to the fluorovinylphosphonate **300** (Scheme 3-31).



Scheme 3-31: Rationale for the formation of fluorovinylphosphonate **300**.

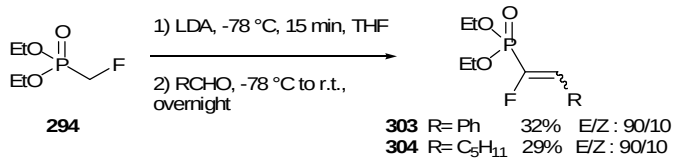
The stereoselectivity of the double bond can be explained by steric effects. The hydroxyl group needs to be perpendicular to the plane of the developing double bond, resulting in two different configurations of intermediate **302** (Scheme 3-32). Intermediate **302a** possesses a bulky phosphonate group and the R group has the *cis* configuration, inducing a strong steric influence. On the other hand intermediate **302b** has its two groups *anti* to each other reducing the steric effect. Intermediate **302b** should be favoured over **302a**, and lead to generate *E* fluorovinylphosphonate **300**.



Scheme 3-32: Rationale of the stereoselectivity of the reaction leading to (*E*)-fluorovinylphosphonate **300**.

In order to probe if this result was specific to aldehyde **100p**, two other aldehydes were investigated under the reaction conditions. These were benzaldehyde **100r** and hexanal **100m** (Scheme 3-33). In both cases only the α-fluorovinylphosphonates **303** and **304** were

obtained with an *E*/*Z* ratio of 10/1 (determined by ^{19}F NMR) and in 32% and 29% yields respectively. There were no traces of fluoro-olefins in either case as judged by ^{19}F-NMR. Thus, under these conditions, diethyl fluoromethylphosphonate condensation with aldehydes, either aromatic or aliphatic, leads to the α-fluorovinylphosphonates, without the generation of the anticipated fluoro-olefins.

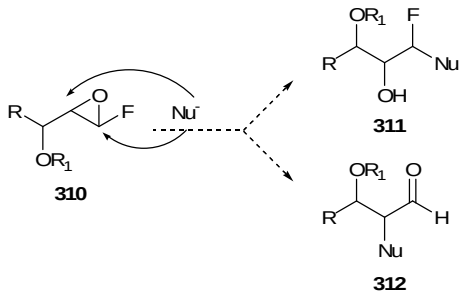


Scheme 3-33: Fluorovinylphosphonate synthesis with benzaldehyde **100r** and hexanal **100m**.

Due to the lack of success in generating fluoro-olefins no further investigations were pursued *via* Horner-Emmons reaction using a fluoromethylphosphonate. Instead another strategy was studied, towards a different target.

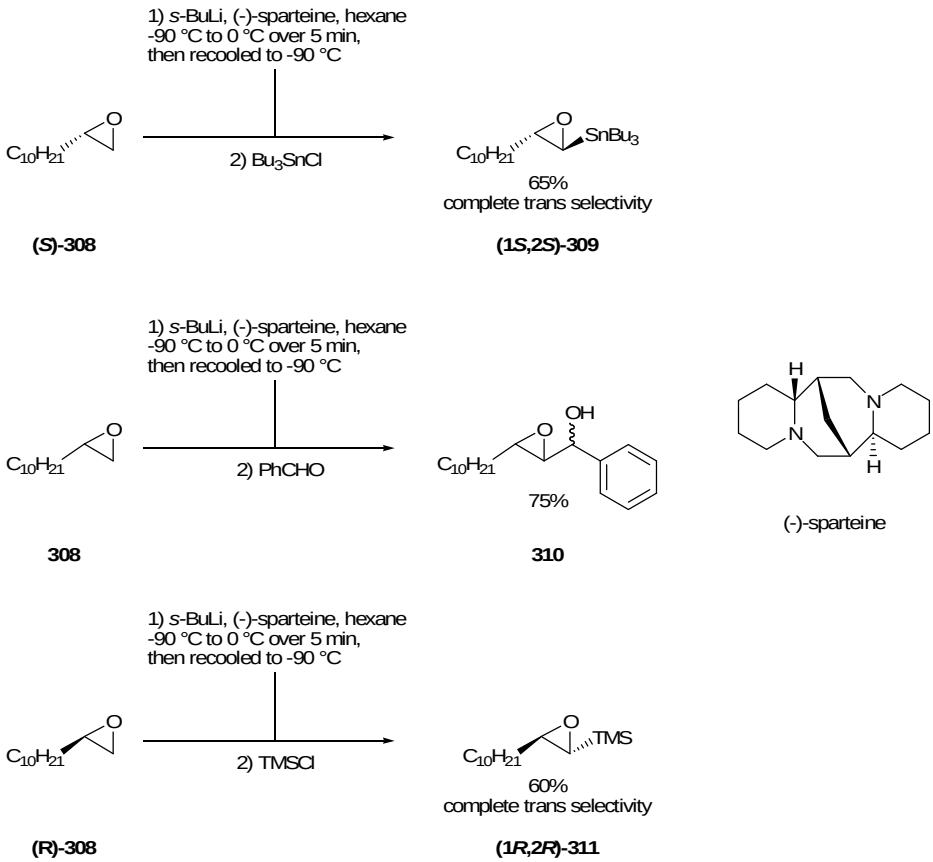
2 Exploration of fluoroepoxides

Due to the difficulty in preparing γ-hydroxy-α-vinylfluorides, the target of this aspect of the research was changed and the preparation of α-fluoroepoxides was now investigated. Fluoroepoxides are less versatile building blocks than fluoroolefins, but these molecules are good substrates to investigate ring opening reactions (Scheme3-34). In order to test the epoxide-ring opening reaction, a pathway leading directly to fluoroepoxide **305** was investigated.



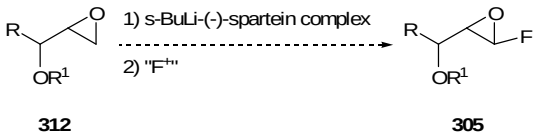
Scheme 3-34: Fluoroepoxides as building blocks.

The strategy chosen to prepare the fluoroepoxides was based on a method developed by Hodgson *et al.*[61] After deprotonation of the epoxide with a chiral base, the resultant anion was trapped with either Bu_3SnCl, an aldehyde or TMSCl leading to the substituted epoxides **309**, **310** or **311** respectively.[61] Moreover, if the epoxide is chiral, only one enantiomer is obtained (Scheme 3-35).



Scheme 3-35: Preparation of substituted epoxides by Hodgson *et al.*[61]

It was anticipated that by using an electrophilic fluorinating reagent to trap the anion at the end of the reaction, then this may offer a method to α-fluoroepoxides (Scheme 3-36).

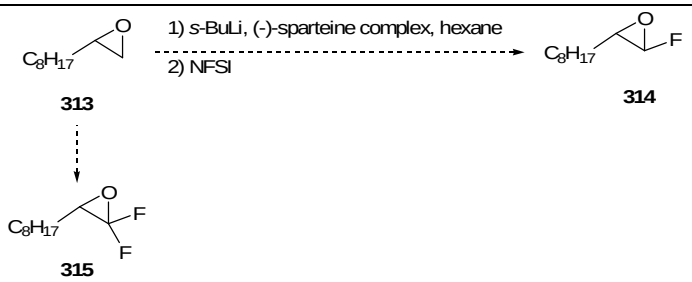


312 **305**

Scheme 3-36: Putative route to fluoroepoxides **310**.

In order to establish the feasibility of the fluorination reaction, a model study was carried out with 1-decaepoxide **313** to examine fluorination at the terminal position of the epoxide.

Accordingly, epoxide **313** was treated with 1.2 eq. of the *s*-BuLi-(-)sparteine complex and NFSI (Table 3-5). After 10 min, the presence of a new signal in ^{19}F NMR spectrum of the reaction mixture was detected (Figure 3-2). Increasing the reaction time to 15 min improved the intensity of the signal. However all attempts to purify/characterise this new product failed. The fluorinated compound appeared to be too unstable. It is reasonable that compound **314** formed, and noteworthy that with 2.3 equivalents of the *s*-BuLi-sparteine complex and NFSI as the electrophilic fluorination reagent, a new difluorinated product was detected by ^{19}F NMR. Unfortunately, in this case too, the new product could not be purified or characterised due to its instability.



s-BuLi-sparteine (eq)	Temperature	Time	Results (^{19}F NMR)
1.2	-90 °C, quench at -50 °C	10 min	Fluorinated compound
1.2	-90 °C, quench at -50 °C	15 min	Fluorinated compound
2.3	-90 °C, quench at 0 °C	30 min	Difluorinated product

Table 3-5: Attempted fluoroepoxide **314** formation.

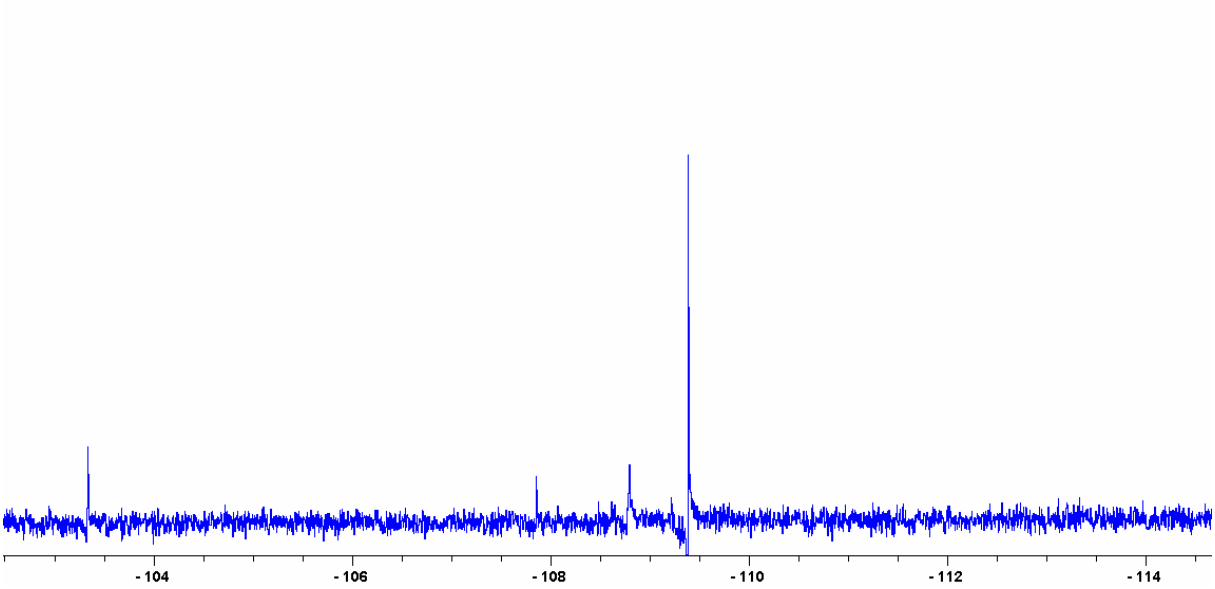


Figure 3-2: New signal in the ^{19}F NMR spectrum of the reaction mixture. This is possibly fluoroepoxide **314**.

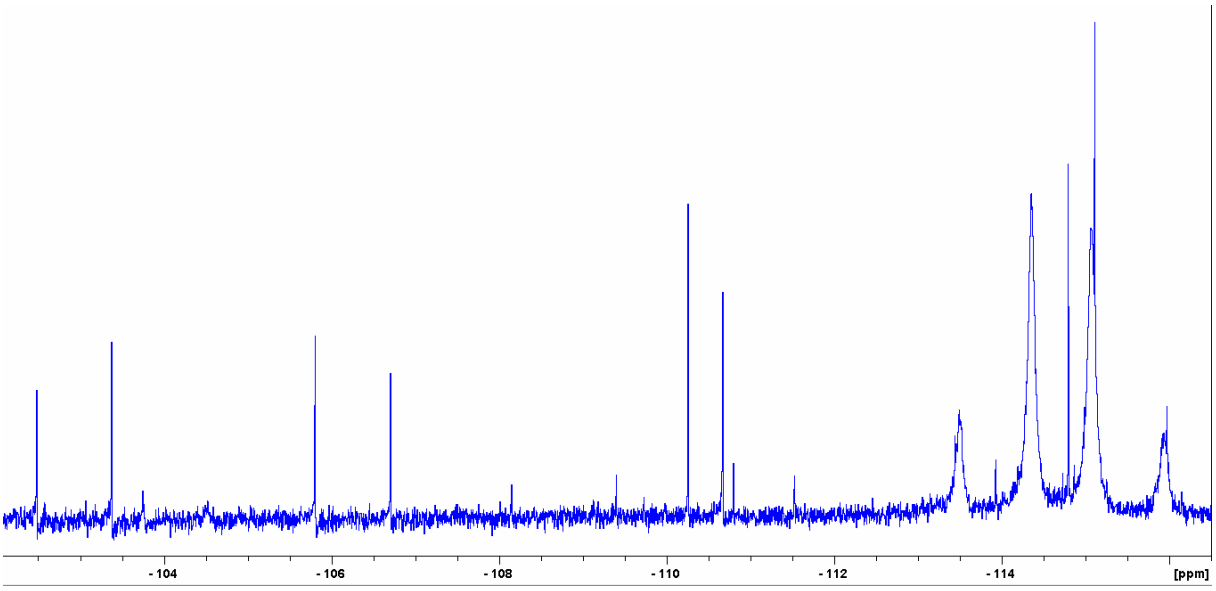
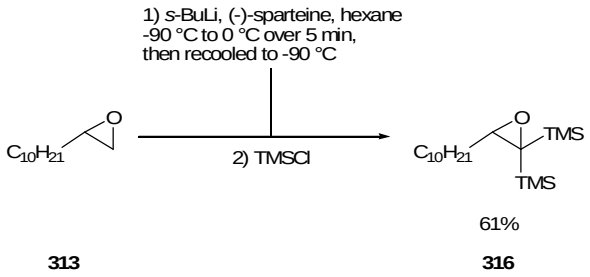


Figure 3-3: ^{19}F-NMR spectrum of the reaction mixture when using 2.3 eq of base. The presence of an AB pattern is apparent when 2.3 eq of *s*-BuLi/(-)-sparteine was used, suggesting the formation of difluoroepoxide **315**.

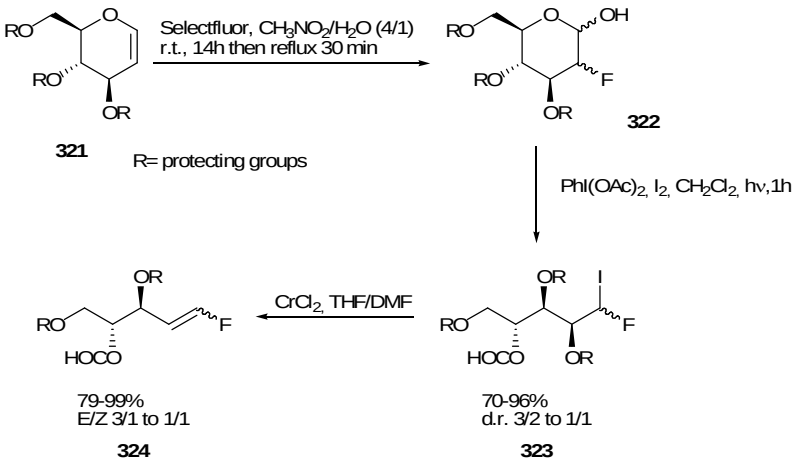
Indeed, Hodgson *et al.*[61] reported the synthesis of the disilylated product **316** using 3.3 eq. of the *s*-BuLi-(-)-sparteine complex (Scheme 3-37).



Scheme 3-37: Example of preparation of disilylated epoxide from1-dodecaepoxide.

Due to these unsuccessful preliminary results, this project was abandoned. The products could not be isolated and characterised and this was clearly limiting.

Subsequent to this study, León *et al.* have published a new method for the preparation of γ-halo allylic alcohols from protected 2-deoxy-hex-1-enitols, in three steps and with high yields (Scheme 3-40).[62] The first step involved the formation of fluorohydrin **322** by reaction of Selectfluor on an enol ether. Then an alkoxy radical fragmentation (ARF) was performed to produce the *gem*-fluoro-iodo alcohol **323**.[63-65] Finally a chromium chloride promoted elimination was undertaken to give γ-hydroxy-α-vinylfluoride **324** in very good yields but poor stereoselectivities.[62]



Scheme 3-40: Recent preparation of γ-hydroxy-α-vinylfluorides reported by León *et al.*[62-65]

3 Conclusion

γ-Hydroxy-α-vinylfluorides are an interesting class of building blocks which have the potential to generate a wide range of different fluorinated molecules. However, at the outset, only one synthesis of γ-hydroxy-α-vinylfluoride had been reported.

The first method explored in this study was the reductive-fluorination of propargylic alcohols using aluminium hydrides. However, although the reduction step was successful, the electrophilic fluorination failed and did not lead to the desired γ-hydroxy-α-vinylfluorides. The addition of methyllithium or sodium methoxide did not promote the fluorination step. These outcomes may be due to the lack of reactivity of the electrophilic fluorination reagents towards the organoaluminium intermediate. Another route to γ-hydroxy-α-vinylfluoride was then explored.

The second strategy involved a Horner-Emmons reaction between a fluoromethylphosphonate and an α-hydroxyaldehyde. However, the outcome of the reaction unexpectedly gave fluorovinylphosphonates, with good stereoselectivity, rather than the desired γ-hydroxy-α-vinylfluoride.

Finally, the preparation of terminal fluoroepoxides was investigated, using s-BuLi/(-)-sparteine couple to deprotonate the epoxide and then trap the resulting anion with an electrophilic fluorinating reagent. Initial results were encouraging, however, product stability proved a problem and prevented the isolation and characterisation of the intermediate organofluorine products.

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Chapter 4: Experimental

General information:

All reagents of synthetic grade were used as supplied. If further purification or drying was required, the procedures used are detailed in Armarego and Perrin, "Purification of laboratory chemicals" 4th Ed.[1]

Room temperature (r.t.) refers to 20-25 ^{o}C. Air and moisture sensitive reactions were carried out under an inert atmosphere using oven-dried glassware (>140 ^{o}C). Reaction progress was monitored by thin layer chromatography (TLC) performed using Merck, Kieselgel 60 plates. Compounds were detected by either UV or by the use of an appropriate staining agent.

Column chromatography was performed using Merck Kieselgel 60 silica gel (230 - 400 mesh). $MgSO_4$ was used as a drying agent.

Nuclear magnetic resonance (NMR) spectra were measured using a Bruker Avance 300 operating at 300 MHz for ^{1}H, 75 MHz for ^{13}C, 282 MHz for ^{19}F, and 121 MHz for ^{31}P or a Bruker Avance II 400 operating at 400 MHz for ^{1}H, 100 MHz for ^{13}C, 376 MHz for ^{19}F. All chemical shifts (δ) are reported in parts per million (ppm) and are quoted relative to the residual proton peak of $CDCl_3$ or D_2O. Coupling constants (*J*) are given in Hertz (Hz). Spectral coupling patterns are designated as follows; d: doublet; t: triplet; q: quartet; m: multiplet and br: broad signal.

GC-MS analyses were obtained using an Agilent 5890 gas chromatograph equipped with an Agilent 5973N mass-selective detector. High-resolution mass spectrometry was performed on a Waters LCT or GCT time-of-flight mass spectrometer.

Melting points were measured using a GallenKamp Griffin MPA350.BM2.5 melting point apparatus and are uncorrected.

X-ray crystallographic data (Appendices) were measured on a Rigaku MM007 generator with Saturn detector with confocal optics Mo-Kα radiation (λ = 0.7107) using a 0.3° width steps accumulating area detector frames spanning a hemisphere of reciprocal space; the reflections were corrected for Lorentz and polarisation effect. Absorption effects were corrected on the basis of multiple equivalent reflections. The structure was solved by direct methods and refined by full matrix least squares on F^2 using the program SHELXTL. All hydrogen atoms were included in calculated positions using a riding model. All non-hydrogen atoms were refined as anisotropic.

All infra red (IR) spectra were recorded in the range 4000-440 cm^{-1} on a Nicolet Avatar 360 FT-IR.

General method for the *Oxa*-Prins reaction

Boron trifluoride diethyl etherate (0.5 mmol, 1.0 eq) was added to a solution of the aldehyde (0.5 mmol, 1 eq) in dichloromethane (5 mL). After 5 min, the alcohol (0.5 mmol, 1 eq) was added, and the mixture was stirred for 5 h. Water and dichloromethane were then added and the layers were separated. The aqueous layer was extracted into dichloromethane, and then the organic layers were dried, filtered and concentrated. The residue was then purified over silica.

General method for the *Aza*-Prins reaction

Boron trifluoride diethyl etherate (0.5 mmol, 1.0 eq) was added to a solution of the aldehyde (0.5 mmol, 1 eq) in dichloromethane (5 mL). After 5 min, the *N*-(tosyl)-1-aminobut-3-ene (0.5 mmol, 1 eq) was added, and the mixture was stirred 36 h. Water and dichloromethane were then added and the layers were separated. The aqueous layer was extracted into dichloromethane, and then the organic layers were dried, filtered and concentrated. The residue was then purified over silica.

General method for the *Oxa*-Prins reaction under microwave conditions

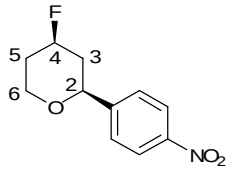
Boron trifluoride diethyl etherate (0.5 mmol, 1.0 eq) was added to a solution of the aldehyde (0.5 mmol, 1 eq) in dichloromethane (5 mL). After 5 min, the alcohol (0.5 mmol, 1 eq) was added, and the mixture irradiated during 10 min with microwaves (100 W). Water and dichloromethane were then added and the layers were separated. The aqueous layer was extracted into dichloromethane, and then the organic layers were dried, filtered and concentrated. The residue was then purified over silica.

General method for the *Aza*-Prins reaction under microwave conditions

Boron trifluoride diethyl etherate (0.5 mmol, 1.0 eq) was added to a solution of the aldehyde (0.5 mmol, 1 eq) in dichloromethane (5 mL). After 5 min, the *N*-(tosyl)-1-aminobut-3-ene (0.5 mmol, 1 eq) was added, and the mixture irradiatede during 30 min by microwaves (100 W). Water and dichloromethane were then added and the layers were separated. The aqueous layer was extracted into dichloromethane, and then the organic layers were dried, filtered and concentrated. The residue was then purified over silica.

(±)-4-Fluoro-2-(4-nitrophenyl)tetrahydropyrans 101a and 102a.[2]

Products **(±)-101a** and **(±)-102a** were prepared according to the general procedure outlined for the Oxa-Prins reaction from 4-nitrobenzaldehyde **100a** (76 mg, 0.5 mmol), but-3-en-1-ol **99** (45 µL, 0.5 mmol) and boron trifluoride (65 µL, 0.5 mmol) in dichloromethane (5 mL).

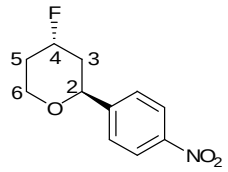


(±)-101a

Product **(±)-101a** was isolated after purification over silica gel (hexane/diethyl ether, 8/2; R_f= 0.34) as a white solid (general procedure: 47 mg, 41 %, procedure with microwaves: 33 mg, 29 %, general procedure at -20 °C: 70mg, 61 %).

NMR: δ_H (300 MHz, $CDCl_3$): 8.21 (2H, d, *J*= 8.60 Hz, Ar), 7.52 (2H, d, *J*= 8.60 Hz, Ar), 4.84 (1H, dtt, *J*= 49.0 Hz, 10.9 Hz, 4.9 Hz, H_4), 4.43 (1H, dt, *J*= 11.5 Hz, 1.8 Hz, H_2), 4.25 (1H, dtd, *J*= 11.9 Hz, 5.7 Hz, 1.8 Hz, H_6), 3.58 (1H, tt, *J*= 12.3 Hz, 1.8 Hz, H_6), 2.39 (1H, dtt, *J*= 12.3 Hz, 4.9 Hz, 2.1 Hz, H_3), 2.20-2.09 (1H, m, H_5), 1.86 (1H, tddd, *J*= 12.3 Hz, 11.1 Hz, 9.9 Hz, 5.3 Hz, H_5) and 1.67 (1H, dtd, *J*= 12.3 Hz, 11.5 Hz, 9.5 Hz, H_3); δ_C (75 MHz, $CDCl_3$): 148.6 (Cq, Ar), 147.4 (Cq, Ar), 126.4 (CH, Ar), 123.6 (CH, Ar), 88.7 (CH, d, *J*= 177.7 Hz, C_4), 76.4 (CH, d, *J*= 11.5 Hz, C_2), 65.3 (CH_2, d, *J*= 11.6 Hz, C_6), 40.4 (CH_2, d, *J*= 17.7 Hz, C_3) and 32.6 (CH_2, d, *J*= 17.7 Hz, C_5); δ_F (282 MHz, $CDCl_3$): -170.7 (dm, *J*= 49.0 Hz); HRMS *m/z*: $[MH]^+$: 226.0879, calculated 226.0878; Mp: 80-82 °C; IR: υ_{max} (neat)/cm^{-1}: 2976, 2942, 2853, 1521, 1348, 1320, 1181, 1133, 1078 and 849.

Data in agreement with literature.



(±)-102a

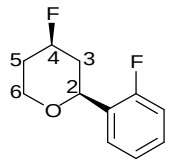
Product **(±)-102a** was isolated after purification over silica gel (hexane/diethyl ether, 8/2, R_f= 0.22) as a white solid (general procedure: 23 mg, 20 %, procedure with microwaves: 20 mg, 18 %).

NMR: δ_H (300 MHz, $CDCl_3$): 8.21 (2H, d, *J*= 8.88 Hz, Ar), 7.53 (2H, d, *J*= 8.88 Hz, Ar), 5.11 (1H, dtt, *J*= 47.7 Hz, 2.9 Hz, 2.6 Hz, H_4), 4.87 (1H, dd, *J*= 11.8 Hz, 2.2 Hz, H_2), 4.10-3.97 (2H, m, 2xH_6), 2.21 (1H, dddt, *J*= 14.4 Hz, 10.7 Hz, 3.3 Hz, 2.2 Hz, H_3), 2.06-1.87 (2H, m, 2xH_5) and 1.74 (1H, dddd, *J*= 43.0Hz, 14.1Hz, 5.9Hz, 2.2Hz, H_3); δ_C (75 MHz, $CDCl_3$): 149.6 (Cq, Ar), 147.3 (Cq, Ar), 126.3 (CH, Ar), 123.6 (CH, Ar), 86.3 (CH, d, *J*= 169.6 Hz, C_4), 73.1 (CH, C_2), 63.0 (CH_2, d, *J*= 11.6 Hz, C_6), 38.7 (CH_2, d, *J*= 20.3 Hz, C_3) and 30.4 (CH_2, d, *J*= 21.1 Hz, C_5); δ_F (282 MHz, $CDCl_3$): -186 (dm, *J*= 47.7 Hz); HRMS *m/z*: $[MH]^+$: 226.0874, calculated 226.0879; Mp : 100-102 °C; IR: υ_{max} (neat)/cm^{-1}: 3080, 2974, 2852, 1514, 1345, 1207, 1150, 1069, 872 and 857.

Data in agreement with literature.

(±)-2-(2-Fluorophenyl)-4-fluorotetrahydropyrans 101b and 102b.

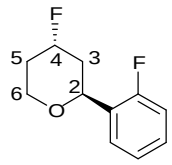
Products **(±)-101b** and **(±)-102b** were prepared according to the general procedure outlined for the Oxa-Prins reaction from 2-fluorobenzaldehyde **100b** (53 µL, 0.5 mmol), but-3-en-1-ol **99** (45 µL, 0.5 mmol) and boron trifluoride (65 µL, 0.5 mmol) in dichloromethane (5 mL).



(±)-101b

Product **(±)-101b** was isolated after purification over silica gel (hexane/diethyl ether, 8/2 R_f= 0.36) as a colorless oil (50 mg, 50 %).

NMR: δ_H (300 MHz, $CDCl_3$): 7.50 (1H, td, *J*= 7.5 Hz, 5.6 Hz, Ar), 7.32-7.23 (1H, m, Ar), 7.17 (1H, td, *J*= 7.5 Hz, 1.2 Hz, Ar), 7.03 (1H, ddd, *J*= 10.6 Hz, 8.2 Hz, 1.2 Hz, Ar), 4.84 (1H, dtt, *J*= 49.2 Hz, 11.0 Hz, 5.0 Hz, H_4), 4.66 (1H, dt, *J*= 11.4 Hz, 1.7 Hz, H_2), 4.23 (1H, dtd, *J*= 12.0 Hz, 5.7 Hz, 1.7 Hz, H_6), 3.60 (1H, tt, *J*= 12.3 Hz, 1.9 Hz, H_6), 2.38 (1H, dtt, *J*= 12.3 Hz, 5.0 Hz, 1.8 Hz, H_3), 2.20-2.09 (1H, m, H_5), 1.87 (1H, tddd, *J*= 12.5 Hz, 11.0 Hz, 10.1 Hz, 5.2 Hz, H_5) and 1.72 (1H, dtd, *J*= 12.1 Hz, 11.0 Hz, 9.5 Hz, H_3); δ_C (75 MHz, $CDCl_3$): 159.2 (Cq, d, *J* = 246.0 Hz, *C*Ar-F), 129.1 (CH, d, *J*= 8.0 Hz, Ar), 128.4 (Cq, Ar), 127.1 (CH, d, *J*= 4.2 Hz, Ar), 124.4 (CH, d, *J*= 3.5 Hz, Ar), 115.2 (CH, d, *J*= 21.7 Hz, Ar), 89.0 (CH, d, *J*= 176.9 Hz, C_4), 71.4 (CH, dd, *J*= 12.6 Hz, 3.6 Hz, C_2), 65.5 (CH_2, d, *J*= 11.7 Hz, C_6), 39.5 (CH_2, d, *J*= 18.1 Hz, C_3) and 32.9 (CH_2, d, *J*= 18.1 Hz, C_5); δ_F (282 MHz, $CDCl_3$): -120.3 to -120.4 (m) and -170.5 (dm, *J*= 49.2 Hz); HRMS *m/z:* $[MH, -HF]^+$: 179.0871, calculated 179.0872; IR: υ_{max} (neat)/cm^{-1}: 2961, 2932 and 2855, 1589, 1494, 1455, 1230, 1183, 1159, 1084, 1044 and 982.



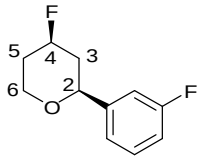
(±)-102b

Product **(±)-102b** was isolated after purification over silica gel (hexane/diethyl ether, 8/2 R_f= 0.28) as a colorless oil (10 mg, 10 %).

NMR: δ_H (300 MHz, $CDCl_3$): 7.48 (1H, td, *J*= 7.5 Hz, 1.9 Hz, Ar), 7.30-7.21 (1H, m, Ar), 7.15 (1H, td, *J*= 7.5 Hz, 1.4 Hz, Ar), 7.03 (1H, ddd, *J*= 10.5 Hz, 8.1 Hz, 1.4 Hz, Ar), 5.09 (1H, dquint, *J*= 48.1 Hz, 2.9 Hz, H_4), 5.08 (1H, dd, *J*= 11.7 Hz, 2.0 Hz, H_2), 4.07-4.00 (2H, m, 2xH_6), 2.28-2.16 (1H, m, H_3) and 2.07-1.69 (3H, m, 2xH_5, H_3); δ_C (75 MHz, $CDCl_3$): 159.2 (Cq, d, *J* = 246.0 Hz, *C*Ar-F), 129.2 (CH, d, *J*= 8.1 Hz, Ar), 126.9 (CH, d, *J*= 4.0 Hz, Ar), 126.4 (Cq, Ar), 124.4 (CH, d, *J*= 3.5 Hz, Ar), 115.3 (CH, d, *J*= 21.3 Hz, Ar), 86.8 (CH, d, *J*= 169.1 Hz, C_4), 68.9 (CH, C_2), 63.3 (CH_2, C_6), 37.7 (CH_2, d, *J*= 22.3 Hz, C_3) and 30.3 (CH_2, d, *J*= 22.4 Hz, C_5); δ_F (282 MHz, $CDCl_3$): 119.5 to -119.6 (m) and -186.4 to -187.0 (m); HRMS *m/z:* $[MH, -HF]^+$: 179.0874, calculated 179.0872; IR: υ_{max} (neat)/cm^{-1}: 3017, 2918, 2852, 1589, 1491, 1460, 1270, 1183, 1135, 1089 and 962.

(±)-2-(3-Fluorophenyl)-4-fluorotetrahydropyrans 101c and 102c.

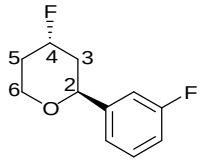
Products **(±)-101c** and **(±)-102c** were prepared according to the general procedure outlined for the Oxa-Prins reaction from 3-fluorobenzaldehyde **100c** (55 μL, 0.5 mmol), but-3-en-1-ol **99** (45 μL, 0.5 mmol) and boron trifluoride (65 μL, 0.5 mmol) in dichloromethane (5 mL).



(±)-101c

Product **(±)-101c** was isolated after purification over silica gel (hexane/diethyl ether, 8/2 R_f= 0.32) as a colorless oil (55 mg, 55 %).

NMR: δ_H (300 MHz, $CDCl_3$): 7.31-7.19 (1H, m, Ar), 7.09-7.00 (2H, m, Ar), 6.93 (1H, tdd, *J*= 8.4 Hz, 2.6 Hz, 1.1 Hz, Ar), 4.76 (1H, dtt, *J*= 49.1 Hz, 11.0 Hz, 5.0 Hz, H_4), 4.27 (1H, dt, *J*= 11.5 Hz, 1.8 Hz, H_2), 4.16 (1H, dtd, *J*= 12.0 Hz, 5.7 Hz, 1.8 Hz, H_6), 3.50 (1H, tt, *J*= 12.3 Hz, 1.8 Hz, H_6), 2.29 (1H, dtt, *J*= 12.3 Hz, 4.9 Hz, 2.1 Hz, H_3), 2.13-2.01 (1H, m, H_5), 1.79 (1H, tddd, *J*= 12.5 Hz, 11.0 Hz, 9.9 Hz, 5.0 Hz, H_5) and 1.65 (1H, dtd, *J*= 12.2 Hz, 11.3 Hz, 9.6 Hz, H_3); δ_C (75 MHz, $CDCl_3$): 162.8 (Cq, d, *J* = 247.0 Hz, *C*Ar-F), 143.9 (Cq, dd, *J*= 8.6 Hz, 1.2 Hz, Ar), 129.9 (CH, d, *J*= 8.2 Hz, Ar), 121.3 (CH, d, *J*= 2.8 Hz, Ar), 114.6 (CH, d, *J*= 21.9 Hz, Ar), 112.8 (CH, d, *J*= 21.9 Hz, Ar), 89.2 (CH, d, *J*= 176.2 Hz, C_4), 77.0 (CH, d, *J*= 12.7 Hz, C_2), 65.4 (CH_2, d, *J*= 11.5 Hz, C_6), 40.5 (CH_2, d, *J*= 17.3 Hz, C_3) and 32.9 (CH_2, d, *J*= 17.3 Hz, C_5); δ_F (282 MHz, $CDCl_3$): -113.3 to -113.4 (m) and -170.5 (dm, *J*= 49.1 Hz); HRMS *m/z:* [MH, -HF]$^+$: 179.0870, calculated 179.0872; IR: υ_{max} (neat)/cm^{-1}: 3017, 2919, 2854, 1590, 1491, 1448, 1272, 1186, 1138, 1073 and 962.



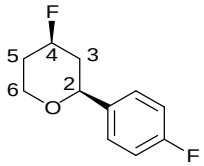
(±)-102c

Product **(±)-102c** was isolated after purification over silica gel (hexane/diethyl ether, 8/2 R_f= 0.24) as a colorless oil (7 mg, 7 %).

NMR: δ_H (300 MHz, $CDCl_3$): 7.35-7.28 (1H, m, Ar), 7.16-7.07 (2H, m, Ar), 7.0-6.93 (1H, m, Ar), 5.10 (1H, dquint, *J*= 47.8 Hz, 2.8 Hz, H_4), 4.76 (1H, dd, *J*= 12.2 Hz, 2.5 Hz, H_2), 4.05-3.99 (2H, m, 2xH_6), 2.23-2.13 (1H, m, H_3), 2.06-1.88 (2H, m, 2xH_5) and 1.79 (1H, dddd, *J*= 43.5 Hz, 14.5 Hz, 11.5 Hz, 2.1 Hz, H_3); δ_C (75 MHz, $CDCl_3$): 162.9 (Cq, *J*= 249.3 Hz, *C*Ar-F), 147.1 (Cq, Ar), 129.9 (CH, d, *J*= 9.7 Hz, Ar), 121.2 (CH, d, *J*= 2.8 Hz, Ar), 114.4 (CH, d, *J*= 22.5 Hz, Ar), 112.7 (CH, d, *J*= 22.5 Hz, Ar), 86.7 (CH, d, *J*= 169.1 Hz, C_4), 73.4 (CH, C_2), 63.1 (CH_2, C_6), 38.6 (CH_2, d, *J*= 21.9 Hz, C_3) and 30.5 (CH_2, d, *J*= 21.9 Hz, C_5) ; δ_F (282 MHz, $CDCl_3$): -113.4 to -113.5 (m) and -186.1 to -186.5 (m) ; HRMS *m/z*: $[MH, -HF]^+$: 179.0882, calculated 179.0872; IR: υ_{max} (neat)/cm^{-1}: 3075, 2962, 2856, 1592, 1488, 1447, 1257, 1174, 1139, 1082 and 984.

(±)-2-(4-Fluorophenyl)-4-fluorotetrahydropyrans 101d and 102d.

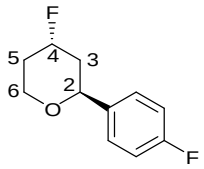
Products **(±)-101d** and **(±)-102d** were prepared according to the general procedure outlined for the Oxa-Prins reaction from 4-fluorobenzaldehyde **100d** (53 µL, 0.5 mmol), but-3-en-1-ol **99** (45 µL, 0.5 mmol) and boron trifluoride (65 µL, 0.5 mmol) in dichloromethane (5 mL).



(±)-101d

Product **(±)-101d** was isolated after purification over silica gel (hexane/diethyl ether, 8/2 R_f= 0.32) as a colorless oil (49 mg, 49 %).

NMR: δ_H (400 MHz, $CDCl_3$): 7.33 (2H, dd, *J*= 8.7 Hz, 5.6 Hz, Ar), 7.05 (2H, t, *J*= 8.7 Hz, Ar), 4.82 (1H, dtt, *J*= 49.1 Hz, 11.0 Hz, 5.9 Hz, H_4), 4.31 (1H, dt, *J*= 11.6 Hz, 1.8 Hz, H_2), 4.21 (1H, dtd, *J*= 11.9 Hz, 5.7 Hz, 1.7 Hz, H_6), 3.57 (1H, tt, *J*= 12.3 Hz, 1.8 Hz, H_6), 2.32 (1H, dtt, *J*= 12.3 Hz, 4.8 Hz, 2.1 Hz, H_3), 2.17-2.09 (1H, m, H_5), 1.85 (1H, tddd, *J*= 12.5 Hz, 11.0 Hz, 9.9 Hz, 5.1 Hz, H_5) and 1.74 (1H, dtd, *J*= 12.2 Hz, 11.3 Hz, 9.6 Hz, H_3); δ_C (75 MHz, $CDCl_3$): 162.3 (CH, d, *J*= 249.0 Hz, Ar), 137.9 (Cq, Ar), 127.6 (CH, d, *J*= 8.5 Hz, Ar), 115.3 (CH, d, *J*= 21.2 Hz, Ar), 89.2 (CH, d, *J*= 177.2 Hz, C_4), 77.2 (CH, d, *J*= 11.3 Hz, C_2), 65.4 (CH_2, d, *J*= 11.8 Hz, C_6), 40.5 (CH_2, d, *J*= 17.6 Hz, C_3) and 32.9 (CH_2, d, *J*= 17.7 Hz, C_5); δ_F (376 MHz, $CDCl_3$): -115.0 to -115.1 (m) and -170.4 (dm, *J*= 49.1 Hz); HRMS *m/z*: $[MH, -HF]^+$: 179.0870, calculated 179.0872; IR: υ_{max} (neat)/cm^{-1}: 2972, 2929, 1498, 1447, 1290, 1186, 1137, 1080 and 834.



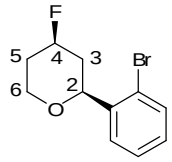
(±)-102d

Product **(±)-102d** was isolated after purification over silica gel (hexane/diethyl ether, 8/2 R_f= 0.21) as a colorless oil (10 mg, 10 %).

NMR: δ_H (400 MHz, $CDCl_3$): 7.33 (2H, dd, *J*= 8.8 Hz, 5.7 Hz, Ar), 7.04 (2H, t, *J*= 8.8 Hz, Ar), 5.10 (1H, dquint, *J*= 48.0 Hz, 2.6 Hz, H_4), 4.74 (1H, dd, *J*= 12.0 Hz, 2.3 Hz, H_2), 4.04-3.98 (2H, m, 2xH_6), 2.20-2.10 (1H, m, H_3), 2.06-1.8 (2H, m, 2xH_5) and 1.81 (1H, dddd, *J*= 43.7 Hz, 14.4 Hz, 11.8 Hz, 2.2 Hz, H_3); δ_C (75 MHz, $CDCl_3$): 162.1 (Cq, d, *J*= 245.0 Hz), 137.9 (Cq, Ar), 127.4 (CH, d, *J*= 8.1 Hz, Ar), 115.2 (CH, d, *J*= 20.5 Hz, Ar), 86.7 (CH, d, *J*= 168.1 Hz, C_4), 73.4 (CH, C_2), 63.1 (CH_2, C_6), 38.6 (CH_2, d, *J*= 20.7 Hz, C_3) and 30.5 (CH_2, d, *J*= 20.5 Hz, CH_5); δ_F (376 MHz, $CDCl_3$): -115.4 to -115.5 (m) and -186.1 to -186.5 (m); HRMS *m/z*: $[MH, -HF]^+$: 179.0874, calculated 179.0872; IR: υ_{max} (neat)/cm^{-1}: 2977, 2926, 1447, 1276, 1181, 1123, 1086 and 977.

(±)-2-(2-Bromophenyl)-4-fluorotetrahydropyrans 101e and 102e.

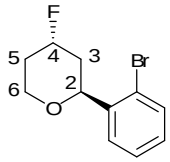
Products **(±)-101e** and **(±)-102e** were prepared according to the general procedure outlined for the Oxa-Prins reaction from 2-bromobenzaldehyde **100e** (58 µL, 0.5 mmol), but-3-en-1-ol **99** (45 µL, 0.5 mmol) and boron trifluoride (65 µL, 0.5 mmol) in dichloromethane (5 mL).



(±)-101e

Product **(±)-101e** was isolated after purification over silica gel (hexane/diethyl ether, 8/2 R_f= 0.35) as a colorless oil (general procedre: 68 mg, 52 %, procedure with microwaves: 87 mg, 67 %).

NMR: δ_H (300 MHz, $CDCl_3$): 7.59-7.50 (2H, m, Ar), 7.40-7.32 (1H, td, *J*= 7.5 Hz, 1.1 Hz, Ar), 7.20-7.12 (1H, td, *J*= 7.8 Hz, 1.7 Hz, Ar), 4.83 (1H, dtt, *J*= 49.0 Hz, 10.1 Hz, 5.0 Hz, H_4), 4.65 (1H, dt, *J*= 11.3 Hz, 1.9 Hz, H_2), 4.23 (1H, dtd, *J*= 11.7 Hz, 5.7 Hz, 1.6 Hz, H_6), 3.61 (1H, tt, *J*= 12.3 Hz, 1.8 Hz, H_6), 2.52 (1H, dtt, *J*= 12.3 Hz, 4.8 Hz, 2.1 Hz, H_3), 2.20-2.09 (1H, m, H_5), 1.87 (1H, tddd, *J*= 12.5 Hz, 10.8 Hz, 10.0 Hz, 5.1 Hz, H_5) and 1.54 (1H, dtd, *J*= 12.3 Hz, 11.3 Hz, 9.3 Hz, H_3); δ_C (75 MHz, $CDCl_3$): 140.5 (Cq, Ar), 132.5 (CH, Ar), 129.0 (CH, Ar), 127.8 (CH, Ar), 127.4 (CH, Ar), 121.3 (Cq, Ar), 88.9 (CH, d, *J*= 177.2 Hz, C_4), 76.7 (CH, d, *J*= 12.2 Hz, C_2), 65.4 (CH_2, d, *J*= 11.9 Hz, C_6), 39.2 (CH_2, d, *J*= 17.4 Hz, C_3) and 32.9 (CH_2, d, *J*= 17.7 Hz, C_5); δ_F (376 MHz, $CDCl_3$): -170.3 (dm, *J*= 49.0 Hz); HRMS *m/z*: $[MH, -HF]^+$: 239.0072; 241.0061, calculated 239.0072, 241.0051; IR: υ_{max} (neat)/cm^{-1}: 3067, 2962, 2854, 1568, 1473, 1440, 1371, 1249, 1158, 1082, 1082, 982, 754 and 679.



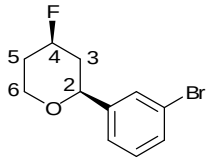
(±)-102e

Product **(±)-102e** was isolated after purification over silica gel (hexane/diethyl ether, 8/2 R_f= 0.22) as a colorless oil (general procedure: 10 mg, 8 %, general with microwaves: 26 mg, 20 %).

NMR: δ_H (300 MHz, $CDCl_3$): 7.57-7.50 (2H, m, Ar), 7.38-7.30 (1H, m, Ar), 7.17-7.10 (1H, m, Ar), 5.10 (1H, dd, *J*= 11.6 Hz, 2.1 Hz, H_2), 5.09 (1H, dquint, *J*= 47.8 Hz, 2.8 Hz, H_4), 4.08-4.03 (2H, m, 2xH_6), 2.45-2.33 (1H, m, H_3), 2.12-1.81 (2H, m, 2xH_5) and 1.60 (1H, dddd, *J*= 43.8 Hz, 14.4 Hz, 11.55 Hz, 2.1 Hz, H_3); δ_C (75 MHz, $CDCl_3$): 141.5 (Cq, Ar), 132.6 (CH, Ar), 128.8 (CH, Ar), 127.7 (CH, Ar), 127.2 (CH, Ar), 121.5 (Cq, Ar), 86.5 (CH, d, *J*= 168.9 Hz, C_4), 73.3 (CH, C_2), 63.2 (CH_2, C_6), 37.2 (CH_2, d, *J*= 20.6 Hz, C_3) and 30.6 (CH_2, d, *J*= 19.9 Hz, C_5); δ_F (376 MHz, $CDCl_3$): -186.8 to -187.4 (m); HRMS *m/z*: $[MH, -HF]^+$: 239.0076; 241.0051, calculated 239.0072, 241.0051; IR: υ_{max} (neat)/cm^{-1}: 3064, 2953, 2864, 1567, 1470, 1428, 1369, 1254, 1147, 1072, 1021, 982, 751 and 705.

(±)-2-(3-Bromophenyl)-4-fluorotetrahydropyrans 101f and 102f.

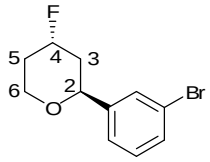
Products **(±)-101f** and **(±)-102f** were prepared according to the general procedure outlined for the Oxa-Prins reaction from 3-bromobenzaldehyde **100f** (58 µL, 0.5 mmol), but-3-en-1-ol **99** (45 µL, 0.5 mmol) and boron trifluoride (65 µL, 0.5 mmol) in dichloromethane (5 mL).



(±)-101f

Product **(±)-101f** was isolated after purification over silica gel (hexane/diethyl ether, 8/2 R_f= 0.35) as a colorless oil (general procedure: 71 mg, 55 %, procedure with microwaves: 72 mg, 55 %).

NMR: δ_H (300 MHz, $CDCl_3$): 7.56-7.53 (1H, m, Ar), 7.44 (1H, dt, *J*= 7.3 Hz, 1.9 Hz), 7.30-7.20 (2H, m, Ar), 4.82 (1H, dtt, *J*= 48.9 Hz, 11.0 Hz, 5.0 Hz, H_4), 4.30 (1H, dt, *J*= 11.7 Hz, 2.0 Hz, H_2), 4.22 (1H, dtd, *J*= 12.2 Hz, 5.6 Hz, 1.8 Hz, H_6), 3.56 (1H, tt, *J*= 12.2 Hz, 1.8 Hz, H_6), 2.34 (1H, dtt, *J*= 12.3 Hz, 5.0 Hz, 2.0 Hz, H_3), 2.19-2.08 (1H, m, H_5), 1.86 (1H, tddd, *J*= 12.3Hz, 11.0 Hz, 9.8 Hz, 5.0 Hz, H_5) and 1.71 (1H, dtd, *J*= 11.9 Hz, 11.5 Hz, 9.6 Hz, H_3); δ_C (75 MHz, $CDCl_3$): 143.5 (Cq, Ar), 130.8 (CH, Ar), 130.0 (CH, Ar), 128.9 (CH, Ar), 124.3 (CH, Ar), 122.5 (Cq, Ar), 89.0 (CH, d, *J*= 177.0 Hz, C_4), 76.9 (CH, d, *J*= 12.4 Hz, C_2), 65.4 (CH_2, d, *J*= 12.4 Hz, C_6), 40.5 (CH_2, d, *J*= 17.8 Hz, C_3) and 32.8 (CH_2, d, *J*= 17.8 Hz, CH_5); δ_F (282 MHz, $CDCl_3$): -170.5 (dm, *J*= 48.9 Hz); HRMS *m/z*: $[MH, -HF]^+$: 239.0102; 241.0059, calculated 239.0072, 241.0051; IR: υ_{max} (neat)/cm^{-1}: 3066, 2960, 2853, 1568, 1474, 1428, 1369, 1249, 1158, 1082, 1041, 783, 695 and 681.



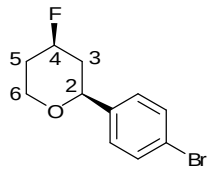
(±)-102f

Product **(±)-102f** was isolated after purification over silica gel (hexane/diethyl ether, 8/2 R_f= 0.26) as a colorless oil (general procedure: 15 mg, 11 %, procedure with microwaves: 34 mg, 26 %).

NMR: δ_H (300 MHz, $CDCl_3$): 7.56-7.51 (1H, m, Ar), 7.41 (1H, dt, *J*= 7.4 Hz, 1.8 Hz, Ar), 7.29-7.18 (2H, m, Ar), 5.09 (1H, dquint, *J*= 47.9 Hz, 2.8Hz, H_4), 4.73 (1H, dd, *J*= 11.7 Hz, 2.2 Hz, H_2), 4.05-3.97 (2H, m, 2xH_6), 2.24-2.10 (1H, m, H_3), 2.09-1.82 (2H, m, 2xH_5) and 1.78 (1H, dddd, *J*= 43.4 Hz, 14.5 Hz, 11.7 Hz, 2.1 Hz H_3); δ_C (75 MHz, $CDCl_3$): 144.5 (Cq, Ar), 130.6 (CH, Ar), 130.0 (CH, Ar), 128.9 (CH, Ar), 124.3 (CH, Ar), 122.6 (Cq, Ar), 86.6 (CH, d, *J*= 169.0 Hz, C_4), 73.3 (CH, C_2), 63.0 (CH_2, C_6), 38.6 (CH_2, d, *J*= 21.1 Hz, C_3) and 30.5 (CH_2, d, *J*= 20.0 Hz, C_5); δ_F (282 MHz, $CDCl_3$): -186.0 to -186.7 (m); HRMS *m/z*: $[MH, -HF]^+$: 239.0076; 241.0051, calculated 239.0072, 241.0051; IR: υ_{max} (neat)/cm^{-1}: 3065, 2954, 2865, 1568, 1475, 1428, 1361, 1255, 1115, 1072, 1043, 867, 780 and 689.

(±)-2-(4-Bromophenyl)-4-fluorotetrahydropyrans 101g and 102g.

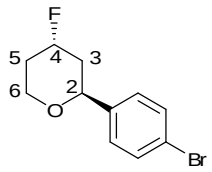
Products **(±)-101g** and **(±)-102g** were prepared according to the general procedure outlined for the Oxa-Prins reaction from 4-bromobenzaldehyde **100g** (92 mg, 0.5 mmol), but-3-en-1-ol **99** (45 µL, 0.5 mmol) and boron trifluoride (65 µL, 0.5 mmol) in dichloromethane (5 mL).



(±)-101g

Product **(±)-101g** was isolated after purification over silica gel (hexane/diethyl ether, 8/2 R_f= 0.35) as a white solid (general procedure: 92 mg, 71 %, procedure with microwaves: 71 mg, 55 %).

NMR: δ_H (300 MHz, $CDCl_3$): 7.49 (2H, d, *J*= 8.33 Hz, Ar), 7.23 (2H, d, *J*= 8.33 Hz, Ar), 4.81 (1H, dtt, *J*= 48.9 Hz, 11.0 Hz, 5.1 Hz, H_4), 4.29 (1H, dt, *J*= 11.6 Hz, 1.9 Hz, H_2), 4.21 (1H, dtd, *J*= 12.0 Hz, 5.8 Hz, 1.8 Hz, H_6), 3.56 (1H, tt, *J*= 12.3 Hz, 1.9 Hz, H_6), 2.32 (1H, dtt, *J*= 12.3 Hz, 4.8 Hz, 2.1 Hz, H_3), 2.18-2.08 (1H, m, H_5), 1.85 (1H, tddd, *J*= 12.5 Hz, 11.0 Hz, 9.9 Hz, 5.1 Hz, H_5) and 1.79-1.62 (1H, m, H_3); δ_C (75 MHz, $CDCl_3$): 140.3 (Cq, Ar), 131.5 (Cq, Ar), 127.5 (CH, Ar), 121.6 (CH, Ar), 89.1 (CH, d, *J*= 177.6 Hz, C_4), 77.0 (CH, d, *J*= 11.5 Hz, C_2), 65.4 (CH_2, d, *J*= 12.0 Hz, C_6), 40.4 (CH_2, d, *J*= 17.0 Hz, C_3) and 32.8 (CH_2, d, *J*= 18.3 Hz, C_5); δ_F (282 MHz, $CDCl_3$): -169.9 (dm, *J*= 48.9 Hz); HRMS *m/z*: $[MH, -HF]^+$: 239.0072, 241.0057, calculated 239.0072, 241.0051; Mp: 36-38 °C; IR: υ_{max} (neat)/cm^{-1}: 3082, 2959, 2856, 1588, 1489, 1453, 1362, 1247, 1158, 1089, 978, 822 and 589.



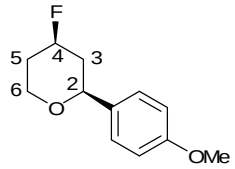
(±)-102g

Product **(±)-102g** was isolated after purification over silica gel (hexane/diethyl ether, 8/2 R_f= 0.26) as a colorless oil (general procedure: 18 mg, 14 %, procedure with microwaves: 26 mg, 20 %).

NMR: δ_H (300 MHz, $CDCl_3$): 7.48 (2H, d, *J*= 8.44 Hz, Ar), 7.23 (2H, d, *J*= 8.44 Hz, Ar), 5.08 (1H, dquint, *J*= 48.1 Hz, 2.8 Hz, H_4), 4.72 (1H, dd, *J*= 11.8 Hz, 2.3 Hz, H_2), 4.04-3.98 (2H, m, 2xH_6), 2.15 (1H, dddt, *J*= 14.6 Hz, 11.1 Hz, 3.3 Hz, 2.2 Hz,m H_3) and 2.06-1.63 (3H, m, 2xH_5, H_3); δ_C (75 MHz, $CDCl_3$): 145.9 (Cq, Ar), 136.0 (Cq, Ar),131.5 (CH, Ar), 127.4 (CH, Ar), 86.5 (CH, d, *J*= 169.1 Hz, C_4), 73.4 (CH, C_2), 63.0 (CH_2, C_6), 38.7 (CH_2, d, *J*= 20.8 Hz, C_3) and 30.5 (CH_2, d, *J*= 21.5 Hz, C_5); δ_F (282 MHz, $CDCl_3$): -185.8 to -186.6 (m); HRMS *m/z*: $[MH, -HF]^+$: 239.0077; 241.0052, calculated 239.0072, 241.0051; Mp: 39-41 °C; IR: υ_{max} (neat)/cm^{-1}: 3079, 2918, 2850, 1580, 1475, 1360, 1255, 1202, 1146, 1069, 1007 and 814.

(±)-4-Fluoro-2-(4-methoxyphenyl)tetrahydropyrans 101h and 102h.

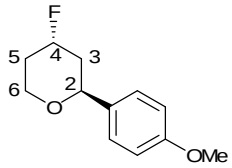
Products **(±)-101h** and **(±)-102h** were prepared according to the general procedure outlined for the Oxa-Prins reaction from 4-methoxybenzaldehyde **100h** (60 μL, 0.5 mmol), but-3-en-1-ol **99** (45 μL, 0.5 mmol) and boron trifluoride (65 μL, 0.5 mmol) in dichloromethane (5 mL). The product was isolated as a white solid as a mixture of diastereoisomers after purification over silica gel (hexane/diethyl ether, 8/2 R_f= 0.27) (general procedure: 17 mg, 16 %, mixture ratio *syn*/*anti* 2.5/1, procedure with microwaves: 39 mg, 37 %, mixture ratio *syn*/*anti* 1/1.9. The ratio has been determined by ^{1}H NMR).



(±)-101h

Product **(±)-101h**, identified from mixture of diastereoisomers:

NMR: δ_H (300 MHz, $CDCl_3$): 7.33-7.25 (2H, m, Ar), 6.93-6.85 (2H, m, Ar), 4.81 (1H, dtt, *J*= 49.2 Hz, 11.0 Hz, 5.0 Hz, H_4), 4.28 (1H, dt, *J*= 11.5 Hz, 2.0 Hz, H_2), 4.20 (1H, dtd, *J*= 12.0 Hz, 5.4 Hz, 1.7 Hz, H_6), 3.81 (3H, s, OCH_3), 3.57 (1H, tt, *J*= 12.2 Hz, 2.0 Hz, H_6), 2.31 (1H, dtt, *J*= 12.4 Hz, 5.0 Hz, 2.1 Hz, H_3), 2.21-2.07 (1H, m, H_5) and 2.07-1.71 (2H, m, H_5, H_3); δ_C (75 MHz, $CDCl_3$): 158.0 (Cq, Ar), 134.3 (Cq, Ar), 127.2 (CH, Ar), 113.8 (CH, Ar), 89.4 (CH, d, *J*= 176.6 Hz, C_4), 77.6 (CH, C_2), 65.4 (CH_2, d, *J*= 12.4 Hz, C_6), 55.2 (CH_3, OCH_3), 40.3 (CH_2, d, *J*= 17.1 Hz, C_3) and 32.9 (CH_2, d, *J*= 16.2 Hz, C_5); δ_F (282 MHz, $CDCl_3$): -170.1 (dm, *J*= 49.2 Hz); HRMS *m/z*: $[MH]^+$: 211.1133, calculated 211.1134; IR of the mixture: υ_{max} (neat)/cm^{-1}: 3079, 2932, 2858, 1518, 1450, 1347, 1295, 1169, 1081, 951, 854 and 586.



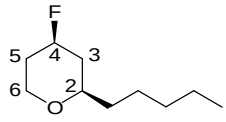
(±)-102h

Product **(±)-102h**, identified from mixture of diastereoisomers:

NMR: δ_H (300 MHz, $CDCl_3$): 7.33-7.25 (2H, m, Ar), 6.93-6.85 (2H, m, Ar), 5.92 (1H, dquint, *J*= 48.0 Hz, 2.8 Hz, H_4), 4.71 (1H, dd, *J*= 11.6 Hz, 2.2 Hz, H_2), 4.04-3.97 (2H, m, 2xH_6), 3.81 (3H, s, OCH_3), 2.21-2.07 (1H, m, H_3) and 2.07-1.71 (3H, m, 2xH_2, H_3); δ_C (75 MHz, $CDCl_3$): 159.0 (Cq, Ar), 134.3 (Cq, Ar), 127.1 (CH, Ar), 113.8 (CH, Ar), 86.9 (CH, d, *J*= 168.6 Hz, C_4), 73.7 (CH, C_2), 63.1 (CH_2, C_6), 55.2 (CH_3, OCH_3), 38.4 (CH_2, d, *J*= 20.7 Hz, CH_3) and 30.6 (CH_2, d, *J*= 20.7 Hz, C_5); δ_F (282 MHz, $CDCl_3$): -185.8 to -186.4 (m); HRMS *m/z*: $[MH]^+$: 211.1133, calculated 211.1134; IR of the mixture: υ_{max} (neat)/cm^{-1}: 3079, 2932, 2858, 1518, 1450, 1347, 1295, 1169, 1081, 951, 854 and 586.

(±)-4-Fluoro-2-pentyltetrahydropyrans 101m and 102m.

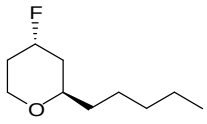
Products **(±)-101m** and **(±)-102m** were prepared according to the general procedure outlined for the Oxa-Prins reaction from hexanal **100m** (61 μL, 0.5 mmol), but-3-en-1-ol **99** (45 μL, 0.5 mmol) and boron trifluoride (65 μL, 0.5 mmol) in dichloromethane (5 mL).



(±)-101m

Product **(±)-101m** was isolated after purification over silica gel (hexane/diethyl ether, 8/2 R_f= 0.37) as a pale yellow oil (general procedure: 42 mg, 48 %, procedure with microwave: 51 mg, 58 %, general procedure at -20 °C: 57 mg, 66 %).

NMR: δ_H (400 MHz, $CDCl_3$): 4.63 (1H, dtt, *J*= 49.2 Hz, 11.0 Hz, 5.1 Hz, H_4), 4.02 (1H, dtd, *J*= 11.7 Hz, 5.7 Hz, 1.8 Hz, H_6), 3.35 (1H, tt, *J*= 12.3 Hz, 1.6 Hz, H_6), 3.23 (1H, dddt, *J*= 11.3 Hz, 7.1 Hz, 4.7 Hz, 1.8 Hz, H_2), 2.07 (1H, dtt, *J*= 12.1 Hz, 5.1 Hz, 1.8 Hz, H_3), 2.03-1.96 (1H, m, H_5), 1.76-1.62 (1H, tddd, *J*= 12.3 Hz, 11.0 Hz, 9.9 Hz, 5.1 Hz, H_5), 1.61-1.20 (9H, m, H_3, 4xCH_2 pentyl) and 0.88 (3H, t, *J*= 6.7 Hz, CH_3 pentyl); δ_C (100 MHz, $CDCl_3$): 89.3 (CH, d, *J*= 176.2 Hz, C_4), 75.7 (CH, d, *J*= 10.9 Hz, C_2), 64.9 (CH_2, d, *J*= 11.4 Hz, C_6), 38.7 (CH_2, d, *J*= 17.1 Hz, C_3), 36.0 (CH_2, CH_2 pentyl), 33.1 (CH_2, d, *J*= 17.4 Hz, C_5), 31.7 (CH_2, CH_2 pentyl), 25.1 (CH_2, CH_2 pentyl), 22.5 (CH_2, CH_2 pentyl) and 14 (CH_3, CH_3 pentyl); δ_F (282 MHz, $CDCl_3$): -169.8 (dm, *J*= 49.2 Hz); HRMS *m/z*: $[MH, -HF]^+$: 155.1435, calculated 155.1436; IR: υ_{max} (neat)/cm^{-1}: 2955, 2931, 2858, 1456, 1367, 1163, 1085 and 1005.



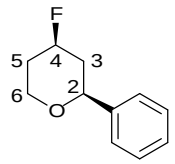
102m

Product **(±)-102m** was isolated after purification over silica gel (hexane/diethyl ether, 8/2 R_f= 0.29) as a colorless oil (general procedure: 20 mg, 23 %, procedure with microwaves: 26 mg, 30 %).

NMR: δ_H (400 MHz, $CDCl_3$): 4.99 (1H, dquint, *J*= 48.1 Hz, 2.7 Hz, H_4), 3.88-3.76 (2H, m, 2xH_6), 3.65 (1H, dddd, *J*= 11.6 Hz, 7.0 Hz, 4.4 Hz, 2.1 Hz, H_2), 1.90-1.70 (2H, m, H_3, H_5), 1.59-1.21 (10H, m, H_5, H_3, 4xCH_2 pentyl) and 0.89 (3H, t, *J* = 7.13 Hz, CH_3 pentyl); δ_C (100 MHz, $CDCl_3$): 86.9 (CH, d, *J*= 169.3 Hz, C_4), 71.9 (CH, C_2), 62.5 (CH_2, C_6), 36.8 (CH_2, d, *J*= 19.6 Hz, C_3), 36.1 (CH_2, CH_2 pentyl), 31.8 (CH_2, CH_2 pentyl), 31.0 (CH_2, d, *J*= 19.6 Hz, C_5), 25.0 (CH_2, CH_2 pentyl), 22.6 (CH_2, CH_2 pentyl) and 14.1 (CH_3, CH_3 pentyl); δ_F (282 MHz, $CDCl_3$): -185.2 to -185.8 (m); HRMS *m/z*: $[MH, -HF]^+$: 155.1435, calculated 155.1436; IR: υ_{max} (neat)/cm^{-1}: 2934, 2927, 2858, 1462, 1365, 1200, 1146, 1073 and 1005.

(±)-4-Fluoro-2-phenyltetrahydropyrans 101r and 102r.[2]

Products **(±)-101r** and **(±)-102r** were prepared according to the general procedure outlined for the Oxa-Prins reaction from freshly distilated benzaldehyde **100r** (50 µL, 0.5 mmol), but-3-en-1-ol **99** (45 µL, 0.5 mmol) and boron trifluoride (65 µL, 0.5 mmol) in dichloromethane (5 mL).

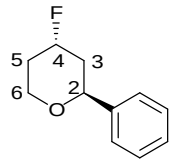


(±)-101r

Product **(±)-101r** was isolated after purification over silica gel as a single diastereoisomer (hexane/diethyl ether, 8/2 Rf= 0.22) as a colorless oil (general procedure: 19 mg, 21 %, procedure with microwaves: 8 mg, 9 %, general procedure at -20 °C: 54 mg, 59 %).

NMR: δ_H (400 MHz, $CDCl_3$): 7.30-7.16 (5H, m, Ar), 4.74 (1H, dtt, *J*= 49.1 Hz, 10.9 Hz, 5.0 Hz, H_4), 4.23 (1H, dt, *J*= 11.6 Hz, 1.8 Hz, H_2), 4.13 (1H, dtd, *J*= 11.9 Hz, 5.7 Hz, 1.8 Hz, H_6), 3.48 (1H, tt, *J*= 12.2 Hz, 1.8 Hz, H_6), 2.26 (1H, dtt, *J*= 12.3 Hz, 4.9 Hz, 2.1 Hz, H_3), 2.04 (1H, dddt, *J*= 12.3 Hz, 6.9 Hz, 4.3 Hz, 2.0 Hz, H_5) and 1.86-1.60 (2H, m, H_3, H_5); δ_C (100 MHz, $CDCl_3$): 141.2 (Cq, Ar), 128.4 (CH, Ar), 127.8 (CH, Ar), 125.8 (CH, Ar), 89.3 (CH, d, *J*= 176.9 Hz, C_4), 77.8 (CH, d, *J*= 11.3 Hz, C_2), 65.4 (CH_2, d, *J*= 11.9 Hz, C_6), 40.5 (CH_2, d, *J*= 17.0 Hz, C_5) and 32.9 (CH_2, d, *J*= 17.6 Hz, C_3); δ_F (282 MHz, $CDCl_3$): -170.2 (dm, *J*= 49.1 Hz); HRMS *m/z*: $[MNa]^+$: 203.0843, calculated 203.0848; IR: υ_{max} (neat)/cm^{-1}: 3064, 3032, 2960, 2853, 1494, 1453, 1374, 1249, 1158, 1081, 980, 757 and 699.

Data in agreement with literature.



(±)-**102r**

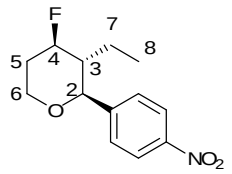
Product **(±)-102r** was isolated as a mixture of diastereoisomer with **101r** after purification over silica gel (hexane/diethyl ether, 8/2 Rf= 0.20) as a colorless oil (general procedure: 32 mg, 35 %, mixture ratio *syn*/*anti* 2.4/1, procedure with microwaves: 47 mg, 52 %, mixture ratio *syn*/*anti* 2.7/1).

From mixture of diastereoisomers :

NMR: δ_H (400 MHz, $CDCl_3$): 7.29-7.17 (5H, m, Ar), 5.01 (1H, dquint, *J*= 48.1 Hz, 3.2 Hz, H_4), 4.67 (1H, dd, *J*= 11.9 Hz, 2.6 Hz, H_2), 3.95-3.91 (2H, m, 2xH_6), 2.14-2.00 (1H, m, H_3) and 1.98-1.62 (3H, m, 2xH_5, H_3); δ_C (75 MHz, $CDCl_3$): 142.2 (Cq, Ar), 128.5 (CH, Ar), 127.6 (CH, Ar), 125.8 (CH, Ar), 86.9 (CH, d, *J*= 168.7 Hz, C_4), 74.1 (CH, C_2), 63.1 (CH_2, C_6), 38.6 (CH_2, d, *J*= 21.0 Hz, C_3) and 30.6 (CH_2, d, *J*= 22.4 Hz, C_5); δ_F (282 MHz, $CDCl_3$): -185.9 to -186.4 (m); HRMS *m/z*: $[MNa]^+$: 203.0846, calculated 203.0848; IR of the mixture of diastereoisomers: υ_{max} (neat)/cm^{-1}: 3064, 3032, 2960, 2853, 1494, 1453, 1374, 1249, 1158, 1081, 980, 757 and 699.

Data in agreement with literature.

(±)-3-Ethyl-4-fluoro-2-(4'-nitrophenyl)tetrahydropyran 104.

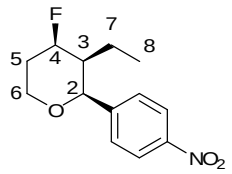


(±)-104

Tetrahydropyran **(±)-104** was prepared according to the general procedure outlined for the Oxa-Prins reaction from 4-nitrobenzaldehyde **100a** (151 mg, 1 mmol), *(E)*-hex-3-en-1-ol **103** (118 μL, 1 mmol) and boron trifluoride (127 μL, 1 mmol) in dichloromethane (10 mL) to give the title compound after purification over silica gel (hexane/diethyl ether, 8/2 R_f= 0.31) as a white solid (67 mg, 53 %).

NMR: δ_H (300 MHz, $CDCl_3$): 8.22 (2H, d, *J*= 9.0 Hz, Ar), 7.53 (2H, d, *J*= 9.0 Hz, Ar), 4.64 (1H, dtd, *J*= 49.2 Hz, 10.6 Hz, 4.9 Hz, H_4), 4.19-4.08 (2H, m , H_2, OH_6), 3.57 (1H, tdd, *J*= 12.5 Hz, 2.1 Hz, 1.5 Hz, H_6), 2.19 (1H, dddd, *J*= 12.2 Hz, 6.8 Hz, 4.9 Hz, 2.0 Hz, H_5), 2.02 (1H, m, H_5), 1.79 (1H, qt, *J*= 9.7 Hz, 4.9 Hz, H_3), 1.46-1.31 (1H, m, H_7), 1.28-1.17 (1H, m, H_7) and 0.74 (3H, td, *J*= 7.6 Hz, 0.9 Hz, 3xH_8); δ_C (75 MHz, $CDCl_3$): 147.7 (Cq, Ar), 146.9 (Cq, Ar), 128.3 (CH, Ar), 123.6 (CH, Ar), 91.8 (CH, d, *J*= 178.8 Hz, C_4), 81.5 (CH, d, *J*= 9.9 Hz, C_2), 65.4 (CH_2, d, *J*= 12.9 Hz, C_6), 49.0 (CH, d, *J*= 17.4 Hz, C_3), 32.9 (CH_2, d, *J*= 18.5 Hz, C_5) and 20.0 (CH_2, C_7), 10.5 (CH_3, C_8); δ_F (282 MHz, $CDCl_3$): -176.6 (dm, *J*= 49.2 Hz); HRMS *m/z*: $[MNa]^+$: 276.1015, calculated 276.1012; Mp: 81-83 °C; IR: υ_{max} (neat)/cm^{-1}: 3110, 3080, 2966, 2858, 1605, 1522, 1347, 1198, 1155, 1088, 1025, 852 and 814.

(±)-3-Ethyl-4-fluoro-2-(4'-nitrophenyl)tetrahydropyran 106.



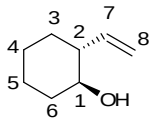
(±)-106

Tetrahydropyran **(±)-106** was prepared according to the general procedure outlined for the Oxa-Prins reaction from 4-nitrobenzaldehyde **100a** (151 mg, 1 mmol), *(Z)*-hex-3-en-1-ol **105** (118 μL, 1 mmol) and boron trifluoride (127 μL, 1 mmol) in dichloromethane (10 mL) to give the title compound after purification over silica gel (hexane/diethyl ether, 8/2 R_f= 0.23), as a white solid (68 mg, 54 %).

NMR: δ_H (300 MHz, $CDCl_3$): 8.21 (2H, d, *J*= 8.9 Hz, Ar), 7.50 (2H, d, *J*= 8.9 Hz, Ar), 4.96 (1H, ddt, *J*= 48.6 Hz, 11.6 Hz, 5.1 Hz, H_4), 4.51 (1H, t, *J*= 2.3 Hz, H_2), 4.21 (1H, dtd, *J*= 11.6 Hz, 6.1 Hz, 1.5 Hz, H_6), 3.56 (1H, dddd, *J*= 12.3 Hz, 12.0 Hz, 2.9 Hz, 1.5 Hz, H_6), 2.23 (1H, m, H_3), 2.02 (1H, dddd, *J*= 24.5 Hz, 12.6 Hz, 8.2 Hz, 5.5 Hz, H_5), 1.95-1.85 (1H, m, H_5), 1.50 (1H, dqd, *J*= 14.6 Hz, 7.6 Hz, 4.9 Hz, H_7), 1.21 (1H, dqd, *J*= 14.6 Hz, 7.6 Hz, 5.8 Hz, H_7) and 0.47 (3H, dt, *J*= 7.6 Hz, 0.8 Hz, 3xH_8); δ_C (75 MHz, $CDCl_3$): 147.9 (Cq, Ar), 146.0 (Cq, Ar), 126.3 (CH, Ar), 123.4 (CH, Ar), 92.4 (CH, d, *J*= 183.0 Hz, C_4), 79.0 (CH, d, *J*= 9.4 Hz, C_2), 65.2 (CH_2, d, *J*= 11.9 Hz, C_6), 47.0 (CH, d, *J*= 16.2 Hz, C_3), 27.2 (CH_2, d, *J*= 18.7 Hz, C_5), 14.7 (CH_2, d, *J*= 1.7 Hz, C_7) and 14.4 (CH_3, d, *J*= 1.8 Hz, C_8); δ_F (282 MHz, $CDCl_3$): -177.2 (dm, *J*= 48.6 Hz); HRMS *m/z*: $[MNa]^+$: 276.1019, calculated 276.1012; Mp: 81-83 °C; IR: υ_{max} (neat)/cm^{-1}: 3112, 3080, 2966, 2876, 1601, 1519, 1346, 1171, 1104, 1072, 1026 and 856.

(±)-*trans*-2-Vinylcyclohexanol 113.[3]

To a solution of cyclohexene oxide **115** (500 μL, 5 mmol) in diethyl ether (2 mL) at -20 °C was added CuBr.Me_2S (102 mg, 0.5 mmol) and vinylmagnesium bromide (6 mL, 6 mmol). After 10h, the the mixture was hydrolysed with a solution of saturated ammonium chloride and the layers were separated. The aqueous layer was extracted into diethyl ether then the organic layers were dried, concentrated and purified over silica gel. Alcohol **(±)-113** was obtained as a colorless oil (447 mg, 71%).



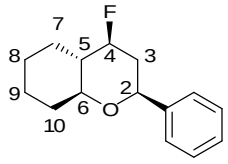
(±)-113

NMR: δ_H (400 MHz, $CDCl_3$): 5.68 (1H, ddd, *J*= 17.2 Hz, 10.2 Hz, 8.7 Hz, H_7), 5.16 (1H, ddd, *J*= 17.2 Hz, 1.9 Hz, 0.7 Hz, H_8), 5.12 (1H, dd, *J*= 10.2 Hz, 1.9 Hz, H_8), 3.24 (1H, td, *J*= 10.0 Hz, 4.4 Hz, H_1), 2.06-1.98 (1H, m, H_6), 1.96-1.84 (1H, m, H_2), 1.79-1.70 (2H, m, H_5 or H_4, H_3), 1.69-1.64 (1H, m, H_5 or H_4) and 1.31-1.15 (4H, H_3, H_5, H_4, H_6); δ_C (75 MHz, $CDCl_3$): 140.8 (CH, C_7), 116.7 (CH_2, C_8), 72.7 (CH, C_1), 51.2 (CH, C_2), 33.8 (CH_2, C_6), 31.1 (CH_2, C_3), 25.1 (CH_2, C_5 or C_4) and 24.7 (CH_2, C_5 or C_4); LRMS *m/z*: $[MNa]^+$: 149.1, calculated 149.1; IR: υ_{max} (neat)/cm^{-1}: 3384, 2918, 2851, 1697, 1446, 1303, 1200 and 1057.

Data in agreement with literature.

(±)-4-Fluoro-2-phenyloctahydrochromene 114a.

Product **(±)-114a** was prepared according to the general procedure outlined for the Oxa-Prins reaction from benzaldehyde **100r** (102 μL, 1.0 mmol), 2-vinyl-cyclohexanol **113** (126 mg, 1.0 mmol) and boron trifluoride (126 μL, 0.1 mmol) in dichloromethane (10 mL). The product was isolated after purification over silica gel (hexane/diethyl ether, 8/2 R_f= 0.27) as a pale yellow oil (69 mg, 59 %).

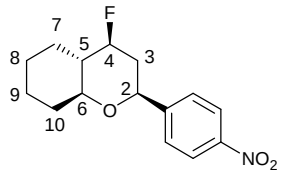


(±)-114a

NMR: δ_H (400 MHz, $CDCl_3$): 7.39-7.33 (4H, m, Ar), 7.31-7.27 (1H, m, Ar), 4.46 (1H, dtd, *J*= 49.9 Hz, 10.4 Hz, 5.0 Hz, H_4), 4.44 (1H, dt, *J*= 11.82 Hz, 2.0 Hz, H_2), 3.16 (1H, tdd, *J*= 10.4 Hz, 4.2 Hz, 1.5 Hz, H_6), 2.35 (1H, dtd, *J*= 12.4 Hz, 4.7 Hz, 2.0 Hz, H_3), 2.21 (1H, ddt, *J*= 13.3 Hz, 5.6 Hz, 3.0 Hz, H_7), 2.05 (1H, m, H_{10}), 1.91-1.81 (2H, m, H_3 and H_8), 1.80-1.72 (H, m, H_8), 1.60-1.42 (2H, m, H_{10}, H_5), 1.40-1.24 (2H, m, 2xH_9) and 1.10-1.00 (1H, m, H_7); δ_C (75 MHz, $CDCl_3$): 136.3 (Cq, Ar), 128.5 (CH, Ar), 127.7 (CH, Ar), 126.0 (CH, Ar), 93.6 (CH, d, *J*= 177.7 Hz, C_4), 78.7 (CH, d, *J*= 8.8 Hz, C_6), 77.1 (CH, d, *J*= 12.5 Hz, C_2), 47.9 (CH, d, *J*= 16.9 Hz, C_5), 40.4 (CH_2, d, *J*= 17.4 Hz, C_3), 32.0 (CH_2, C_{10}), 26.9 (CH_2, C_7), 24.9 (CH_2, C_8 or C_9) and 24.7 (CH_2, C_8 or C_9); δ_F (282 MHz, $CDCl_3$): -179.9 (dm, *J*= 49.9 Hz); HRMS *m/z*: $[MNa]^+$: 257.1318, calculated 257.1319; IR: υ_{max} (neat)/cm^{-1}: 3027, 2920, 2851, 1449, 1372, 1278, 1183, 1123, 1072, 1034, 997, 756 and 698.

(±)-4-Fluoro-2-(4-nitrophenyl)octahydrochromene 114b.

Product **(±)-114b** was prepared according to the general procedure outlined for the Oxa-Prins reaction from 4-nitrobenzaldehyde **100a** (121 mg, 0.87 mmol), 2-vinyl-cyclohexanol **113** (110 mg, 0.87 mmol) and boron trifluoride (110 μL, 0.87 mmol) in dichloromethane (10 mL) to give the title compound. The product was isolated after purification over silica gel (hexane/diethyl ether, 8/2 R_f= 0.20) as a white solid (80 mg, 57 %).

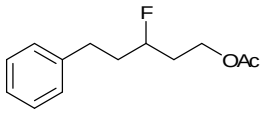


(±)-114b

NMR: δ_H (300 MHz, $CDCl_3$): 8.21 (2H, d, *J*= 8.9 Hz, Ar), 7.54 (2H, d, *J*= 8.9 Hz, Ar), 4.55 (1H, m, H_2), 4.47 (1H, dtd, *J*= 49.6 Hz, 10.4 Hz, 4.9 Hz, H_4), 3.18 (1H, tdd, *J*= 10.3 Hz, 4.1 Hz, 1.4 Hz, H_6), 2.38 (1H, dtd, *J*= 12.3 Hz, 4.5 Hz, 2.3 Hz, H_3), 2.21 (1H, ddt, *J*= 13.2 Hz, 5.3 Hz, 3.0 Hz, H_7), 2.10-2.00 (1H, m, H_{10}), 1.91-1.81 (1H, m, H_9 or H_8), 1.81-1.68 (2H, m, H_3, H_9 or H_8), 1.60-1.39 (2H, m, H_5, H_{10}), 1.39-1.18 (2H, m, H_9, H_8) and 1.13-0.96 (1H, m, H_7); δ_C (75 MHz, $CDCl_3$): 148.7 (Cq, Ar), 147.3 (Cq, Ar), 126.5 (CH, Ar), 123.6 (CH, Ar), 92.8 (CH, d, *J*= 178.8 Hz, C_4), 78.7 (CH, d, *J*= 9.3 Hz, C_6), 75.7 (CH, d, *J*= 12.0 Hz, C_2), 47.7 (CH, d, *J*= 17.4 Hz, C_5), 40.4 (CH_2, d, *J*= 18.5 Hz, C_3), 31.9 (CH_2, C_7), 26.7 (CH_2, C_{10}), 24.8 (CH_2, C_8 or C_9) and 24.5 (CH_2, C_8 or C_9); δ_F (282 MHz, $CDCl_3$): -181.7 (dm, *J*= 49.6 Hz); HRMS *m/z*: $[MNa]^+$: 302.1170, calculated 302.1168; Mp: 77-79 °C; IR: υ_{max} (neat)/cm^{-1}: 3080, 2932, 2858, 1604, 1519, 1348, 1169, 1081, 1049 and 854.

(±)-3-Fluoro-5-phenylpentan-1-yl acetate 154.

Pd on charcoal (4 mg) was added to a solution of 4-fluoro-2-phenyltetrahydropyran **101r** (47 mg, 0.26 mmol) in acetic acid (4 mL) and perchloric acid (40 μL, 60% in water), and then the mixture was placed under a balloon of hydrogen and stirred for 16 h. Then the mixture was filtered through celite and the product was extracted into ethyl acetate. The organic layer was dried, filtered and concentrated and the title compound was obtained after purification over silica (hexane/diethyl ether 7/3 R_f= 0.25) as a colorless oil (41 mg, 70%).

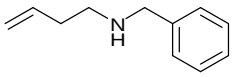


154

NMR: δ_H (400 MHz, $CDCl_3$): 7.37-7.28 (2H, m, Ar), 7.26-7.17 (3H, m, Ar), 4.63 (1H, dtt, *J*= 49.5 Hz, 8.6 Hz, 3.6 Hz, C*H*F), 4.30-4.13 (2H, m, CH_2CH_2O), 2.84 (1H, ddd, *J*= 13.8 Hz, 9.9 Hz, 5.5 Hz, $ArCHHCH_2$), 2.72 (1H, ddd, *J*= 13.8 Hz, 9.4 Hz, 7.1 Hz, $ArCHHCH_2$), 2.12-1.75 (4H, m, $ArCH_2CH_2$, OCH_2CH_2) and 1.97 (3H, s, $C=OCH_3$); δ_C (100 MHz, $CDCl_3$): 171.0 (Cq, $C=OCH_3$), 141.2 (Cq, Ar), 128.5 (CH, Ar), 128.4 (CH, Ar), 126.0 (CH, Ar), 90.2 (CH, d, *J*= 168.6 Hz, *C*HF), 60.6 (CH, d, *J*= 4.7 Hz, CH_2CH_2OH), 36.9 (CH_2, d, *J*= 21.0 Hz, $HOCH_2CH_2$), 34.2 (CH_2, d, *J*= 21.0 Hz, $ArCH_2CH_2$), 31.2 (CH_2, d, *J*= 4.7 Hz, $ArCH_2CH_2$) and 20.9 (CH_3, $C=OCH_3$); δ_F (282 MHz, $CDCl_3$): -185.1 to -185.7 (m); HRMS *m/z*: $[MNa]^+$: 247.1109, calculated 247.1110; IR: υ_{max} (neat)/cm^{-1}: 3027, 2932, 1739, 1385, 1365, 1248, 1046, 746 and 700.

***N*-Benzyl-4-butenylamine 189.**[4]

Benzylamine **188** (1.92 mL, 17.6 mmol) was added to a solution of 1-bromobut-3-ene **187** (360 µL, 3.55 mmol) and sodium iodide (27 mg, 0.18 mmol) in ethanol (10 mL). After 4h at 75 °C, the mixture was concentrated under vacuum, and then water and diethyl ether were added. The layers were separated and the aqueous layer was extracted into diethyl ether. The organic extract was dried, filtered and concentrated. The title compound was obtained after purification over silica (hexane/diethyl ether 6/4 R_f= 0.30) as a pale yellow oil (497 mg, 87%).



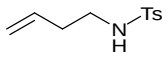
189

NMR: δ_H (300 MHz, $CDCl_3$): 7.32-7.16 (5H, m, Ar), 5.75 (1H, ddt, *J*= 17.1 Hz, 10.2 Hz, 6.8 Hz, CH_2=C*H*), 5.05 (1H, ddd, *J*= 17.1 Hz, 3.5 Hz, 1.5 Hz, C*H*H=CH), 5.00 (1H, dddd, *J*= 10.2 Hz, 2.1 Hz, 1.3 Hz, 1.1 Hz, C*H*H=CH), 3.70 (2H, s, NCH_2Ph), 2.66 (2H, t, *J*= 6.8 Hz, CH_2CH_2NH) and 2.24 (2H, qt, *J*= 6.8 Hz, 1.3 Hz, CHCH_2CH_2NH); δ_C (100 MHz, $CDCl_3$): 143.1 (Cq, Ar), 136.5 (CH, CH_2=*C*H), 128.5 (CH, Ar), 127.1 (CH, Ar), 126.6 (CH, Ar), 116.2 (CH_2, *C*H_2=CH), 53.2 (CH_2, N*C*H_2Ph), 48.1 (CH_2, CH_2*C*H_2N), 34.2 (CH_2, CH_2=CH*C*H_2) and 21.5 (CH_3, ArCH_3); LRMS *m/z*: $[MH]^+$: 161, calculated 161; IR: υ_{max} (neat)/cm^{-1}: 3308, 2922, 2852, 1666, 1604, 1452, 1208, 1152, 1075, 737 and 698.

Data in agreement with literature.

***N*-Tosyl-4-butenylamine 191.**[5]

1-Bromobut-3-ene **187** (1.01 ml, 10 mmol) was added to a solution of tosylamine **190** (1.71g, 10 mmol), and potassium carbonate (1.65 g, 12 mmol) in acetone (100 mL). After 4h at reflux, the mixture was concentrated under vacuum, and then was water and diethyl ether were added. Then the layers were separated and the aqueous layer was extracted into diethyl ether. The organic layers were dried, filtered and concentrated. The title compound was obtained after purification over silica (hexane/diethyl ether 6/4 R_f= 0.24) as a pale yellow oil (922 mg, 41%).



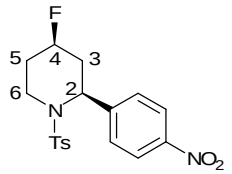
191

NMR: δ_H (300 MHz, $CDCl_3$): 7.78 (2H, d, *J*= 8.1 Hz, Ar), 7.29 (2H, *J*= 8.1 Hz, Ar), 5.62 (1H, ddt, *J*= 16.9 Hz, 10.3 Hz, 6.8 Hz, CH_2=C*H*), 5.08-4.97 (2H, m, CH_2=CH), 4.76 (1H, t broad, *J*= 5.8 Hz, N*H*), 3.00 (2H, td, *J*= 6.8 Hz, 5.8 Hz, CH_2CH_2NH), 2.42 (3H, m, ArCH_3) and 2.19 (2H, qt, *J*= 6.8 Hz, 1.4 Hz, CHCH_2CH_2NH); δ_C (100 MHz, $CDCl_3$): 143.2 (Cq, Ar), 138.1 (Cq, Ar), 130.0 (CH, Ar), 127.1 (CH, Ar), 136.2 (CH, CH_2=*C*H), 116.4 (CH_2, *C*H_2=CH), 48.1 (CH_2, *C*H_2NHTs), 34.3 (CH_2, CH_2=CH*C*H_2) and 21.5 (CH_3, ArCH_3); LRMS *m/z*: $[MH]^+$: 225.1, calculated 225.1; IR: υ_{max} (neat)/cm^{-1}: 3283, 3075, 2974, 2924, 2868, 1641, 1597, 1493, 1323, 1158, 1090, 1085, 990, 920 and 813.

Data in agreement with literature.

(±)-4-Fluoro-2-(4-nitrophenyl)-*N*-(tosyl)piperidines 192 and 193.[2]

Piperidines **192** and **193** were prepared according to the general procedure outlined for the *Aza*-Prins reaction from 4-nitrobenzaldehyde **100a** (76 mg, 0.5 mmol), *N*-tosyl-4-butenylamine **191** (112mg, 0.5 mmol) and boron trifluoride (65 μL, 0.5 mmol) in dichloromethane (5 mL).

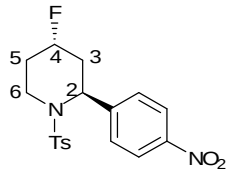


(±)-192

Product **(±)-192** was isolated after purification over silica gel (hexane/diethyl ether, 7/3 R_f= 0.33) as a colorless oil (general procedure: 59 mg, 31 %, procedure with microwaves: 62 mg, 33 %).

NMR: δ_H (400 MHz, $CDCl_3$): 8.21 (2H, d, *J*= 8.8 Hz, Ar), 7.76 (2H, d, *J*= 8.3, Ar), 7.55 (2H, d, *J*= 8.8 Hz, Ar), 7.36 (2H, d, *J*= 8.3 Hz, Ar), 5.42 (1H, s broad, H_2), 4.54 (1H, dtt, *J*= 48.3 Hz, 10.4 Hz, 4.5 Hz, H_4), 4.03-3.94 (1H, m, H_6), 3.10-2.99 (1H, m, H_6), 2.68-2.58 (1H, m, H_3), 2.47 (3H, s, ArCH_3), 1.98-1.86 (1H, m, H_5), 1.79 (1H, dddd, *J*= 13.8 Hz, 10.8 Hz, 8.6 Hz, 5.7 Hz, H_3) and 1.49 (1H, ttd, *J*= 12.5 Hz, 10.2 Hz, 4.8 Hz, H_5); δ_C (100 MHz, $CDCl_3$): 147.3 (Cq, Ar), 145.8 (Cq, Ar), 144.1 (Cq, Ar), 137.2 (Cq, Ar), 130.1 (CH, Ar), 127.6 (CH, Ar), 127.0 (CH, Ar), 124.0 (CH, Ar), 86.0 (CH, d, *J*= 174.5 Hz, C_4), 55.4 (CH, d, *J*= 12.5 Hz, C_2), 40.2 (CH_2, d, *J*= 11.7 Hz, C_6), 34.0 (CH_2, d, *J*= 20.3 Hz, C_3), 30.8 (CH_2, d, *J*= 19.5 Hz, C_5) and 21.6 (CH_3, ArCH_3); δ_F (376 MHz, $CDCl_3$): -176.2 (dm, *J*= 48.3 Hz); HRMS *m/z*: $[MNa]^+$: 401.0947, calculated 401.0947; Mp: 127-129 °C; IR: υ_{max} (neat)/cm^{-1}: 3043, 2941, 2873, 1598, 1519, 1493, 1346, 1159, 1094, 1015 and 856.

Data in agreement with literature.



(±)-193

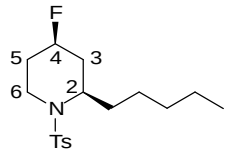
Product **(±)-193** was isolated after purification over silica gel (hexane/diethyl ether, 7/3 R_f= 0.22) as a colorless oil (general procedure: 56 mg, 30 %, procedure with microwaves: 46 mg, 24 %).

NMR: δ_H (300 MHz, $CDCl_3$): 8.15 (2H, d, *J*= 9.1 Hz, Ar), 7.75 (2H, d, *J*= 8.40 Hz, Ar), 7.50 (2H, d, *J*= 9.1 Hz, Ar), 7.32 (2H, d, *J*= 8.40 Hz, Ar), 5.35 (1H, d broad, *J*= 6.6 Hz, H_2), 4.90 (1H, dtt, *J*= 47.3 Hz, 3.8 Hz, 2.2 Hz, H_4), 3.85 (1H, dd, *J*= 14.6 Hz, 4.6 Hz, H_6), 3.35 (1H, ddd, *J*= 14.6 Hz, 12.9 Hz, 3.1 Hz, H_6), 2.75-2.66 (1H, m H_3), 2.45 (3H, s, ArCH_3), 2.01 (1H, dddd, *J*= 43.8 Hz, 15.4 Hz, 6.9 Hz, 2.4 Hz, H_3) and 1.82-1.60 (2H, m, 2xH_5); δ_C (100 MHz, $CDCl_3$): 147.3 (Cq, Ar), 146.8 (Cq, Ar), 143.9 (Cq, Ar), 137.6 (Cq, Ar), 130.0 (CH, Ar), 127.4 (CH, Ar), 126.9 (CH, Ar), 123.5 (CH, Ar), 85.9 (CH, d, *J*= 172.6 Hz, C_4), 52.9 (CH, s, C_2), 36.6 (CH_2, s, C_6), 32.1 (CH_2, d, *J*= 19.7 Hz, C_3), 28.8 (CH_2, d, *J*= 21.2 Hz, C_5) and 21.6 (CH_3, ArCH_3); δ_F (376 MHz, $CDCl_3$): -182.2 to -182.8 (m); HRMS *m/z*: $[MNa]^+$: 401.0956, calculated 401.0947; Mp: 148-150 °C; IR: υ_{max} (neat)/cm^{-1}: 3081, 2940, 2851, 1598, 1519, 1494, 1345, 1158, 1091 and 888.

Data in agreement with literature.

(±)-4-Fluoro-2-pentyl-*N*-(tosyl)piperidines 194 and 195.

Piperidines **(±)-194** and **(±)-195** were prepared according to the general procedure outlined under *Aza*-Prins reaction from hexanal **100m** (61 µL, 0.5 mmol), *N*-tosyl-4-butenylamine **191** (112mg, 0.5 mmol) and boron trifluoride (65 µL, 0.5 mmol) in dichloromethane (5 mL) to give the title compounds. The products were isolated as a mixture of diastereoisomer after purification over silica gel (hexane/diethyl ether, 7/3 R_f= 0.26) as colorless oils (general procedure: 119 mg, 73 %, mixture ratio *syn*/*anti* 2/1, procedure with microwaves: 129 mg, 79 %, mixture ratio *syn*/*anti* 1.9/1).

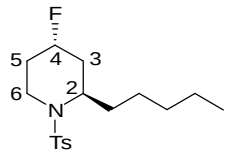


(±)-194

Analysis as a mixture of diastereoisomers **(±)-194** and **(±)-195**:

NMR: δ_H (300 MHz, $CDCl_3$): 7.77-7.68 (2H, m, Ar), 7.33-7.25 (2H, m, Ar), 4.72 (1H, dtt, *J*= 48.7 Hz, 11.3 Hz, 4.9 Hz, H_4), 4.24-4.12 (1H, m, H_2), 4.05-3.88 (1H, m, H_6), 3.03 (1H, dddd, *J*= 14.9 Hz, 13.1 Hz, 2.4 Hz, 1.2 Hz, H_6), 2.42 (3H, s, ArC*H*$_3$), 2.02-1.83 (2H, m, H_3, H_5), 173-1.12 (10H, m, H_5, H_3, 4xC*H*$_2$ pentyl) and 0.87 (3H, t, *J*= 6.7 Hz, C*H*$_3$ pentyl); δ_C (75 MHz, $CDCl_3$): 143.7 (Cq, Ar), 138.2 (Cq, Ar), 129.8 (CH, Ar), 126.9 (CH, Ar), 87.0 (CH, d, *J*= 173.0 Hz, C_4), 53.6 (CH, d, *J*= 13.0 Hz, OC_2), 38.7 (CH_2, d, *J*= 12.3 Hz, C_6), 34.2 (CH_2, d, *J*= 18.2 Hz, C_3), 32.2 (CH_2, pentyl), 31.4 (CH_2, pentyl), 31.2 (CH_2, d, *J*= 21.7 Hz, C_5), 26.0 (CH_2, pentyl), 22.4 (CH_2, pentyl), 21.5 (CH_3, Ar*C*H$_3$) and 13.9 (CH_3, pentyl); δ_F (282 MHz, $CDCl_3$): -176.0 (dm, *J*= 48.7 Hz); HRMS *m/z*: $[MNa]^+$: 350.1559, calculated 350.1566; IR

from the mixture of diastereoisomers: υ_{max} (neat)/cm^{-1}: 2952, 2918, 2851, 1457, 1331, 1300, 1200, 1144 and 811.



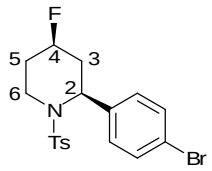
(±)-195

Analysis as a mixture of diastereoisomers **(±)-194** and **(±)-195**:

NMR: δ_H (300 MHz, $CDCl_3$): 7.77-7.68 (2H, m, Ar), 7.33-7.25 (2H, m, Ar), 4.83 (1H, dtt, *J*= 47.5 Hz, 3.0 Hz, 2.9 Hz, H_4), 4.05-3.88 (1H, m, H_2), 3.72 (1H, dd, *J*= 14.3 Hz, 4.9 Hz, H_6), 3.31 (1H, ddd, *J*= 14.3 Hz, 13.3 Hz, 2.8 Hz, H_6), 2.41 (3H, s, ArCH_3), 2.02-1.83 (1H, m, H_3), 1.83-1.73 (1H, m, H_5), 1.73-1.12 (10H, m, H_5, H_3, 4xCH_2 pentyl) and 0.85 (3H, t, *J*= 6.6 Hz, CH_3 pentyl); δ_C (75 MHz, $CDCl_3$): 143.0 (Cq, Ar), 138.5 (Cq, Ar), 129.6 (CH, Ar), 126.9 (CH, Ar), 87.0 (CH, d, *J*= 170.0 Hz, C_4), 51.4 (CH, C_2), 35.0 (CH_2, C_6), 32.2 (CH_2, pentyl), 31.9 (CH_2, d, *J*= 19.2 Hz, C_3), 31.1 (CH_2, pentyl), 29.2 (CH_2, d, *J*= 21.4 Hz, C_5), 26.4 (CH_2, pentyl), 22.4 (CH_2, pentyl), 21.4 (CH_3, Ar*C*H_3) and 13.9 (CH_3, pentyl); δ_F (282 MHz, $CDCl_3$): -179.9 to -180.7 (m); HRMS *m/z*: $[MNa]^+$: 350.1559, calculated 350.1566; IR as a mixture of diastereoisomers: υ_{max} (neat)/cm^{-1}: 2952, 2918, 2851, 1457, 1331, 1300, 1200, 1144 and 811.

(±)-2-(4-Bromophenyl)-4-fluoro-*N*-(tosyl)piperidines 196b and 197b.

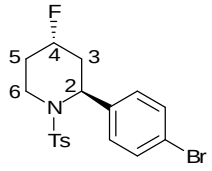
Piperidines **(±)-196b** and **(±)-197b** were prepared according to the general procedure outlined for the *Aza*-Prins reaction from 4-bromobenzaldehyde **100d** (92 mg, 0.5 mmol), *N*-tosyl-4-butenylamine **191** (112mg, 0.5 mmol) and boron trifluoride (65 μL, 0.5 mmol) in dichloromethane (5 mL).



(±)-196b

Product **(±)-196b** was isolated after purification over silica gel (hexane/diethyl ether, 7/3 R_f= 0.35) as a white solid (general procedure: 72 mg, 35 %, procedure with microwave: 90 mg, 44 %).

NMR: δ_H (400 MHz, $CDCl_3$): 7.76 (2H, d, *J*= 8.1 Hz, Ar), 7.47 (2H, d, *J*= 8.4 Hz, Ar), 7.34 (2H, d, *J*= 8.4 Hz, Ar), 7.23 (2H, d, *J*= 8.1 Hz, Ar), 5.35 (1H, s broad, H_2), 4.57 (1H, dtt, *J*= 48.5 Hz, 10.8 Hz, 4.5 Hz, H_4), 4.02-3.92 (1H, m, H_6), 3.06-2.97 (1H, m, H_6), 2.64-2.55 (1H, m H_3), 2.46 (3H, s, ArCH_3), 1.92-1.83 (1H, m, H_5), 1.76-1.65 (1H, m, H_3) and 1.44 (1H, ttd, *J*= 12.6 Hz, 10.3 Hz, 4.8 Hz, H_5); δ_C (100 MHz, $CDCl_3$): 143.8 (Cq, Ar), 137.6 (Cq, Ar), 136.9 (Cq, Ar), 131.9 (CH, Ar), 130.0 (CH, Ar), 128.3 (CH, Ar), 126.9 (CH, Ar), 121.5 (Cq, Ar), 86.4 (CH, d, *J*= 174.6 Hz, C_4), 55.2 (CH, d, *J*= 12.4 Hz, C_2), 39.9 (CH_2, d, *J*= 12.4 Hz, C_6), 33.5 (CH_2, d, *J*= 20.2 Hz, C_3), 30.9 (CH_2, d, *J*= 18.9 Hz, C_5) and 21.6 (CH_3, ArCH_3); δ_F (376 MHz, $CDCl_3$): -175.8 (dm, *J*= 47.6 Hz); HRMS *m/z*: $[MNa]^+$: 434.0199, 436.0182, calculated 434.0202, 436.0181; Mp: 131-133 °C; IR: υ_{max} (neat)/cm^{-1}: 3058, 2935, 2862, 1594, 1485, 1342, 1155, 1093, 1009, 816 and 668.



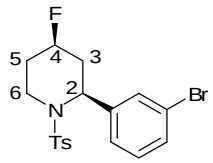
(±)-197b

Product **(±)-197b** was isolated after purification over silica gel (hexane/diethyl ether, 7/3 R_f= 0. 22) as a white solid (general procedure: 68 mg, 33 %, procedure with microwaves: 47 mg, 23 %).

NMR: δ_H (300 MHz, $CDCl_3$): 7.76 (2H, d, *J*= 8.2 Hz, Ar), 7.48 (2H, d, *J*= 8.4 Hz, Ar), 7.34 (2H, d, *J*= 8.2 Hz, Ar), 7.23 (2H, d, *J*= 8.4 Hz, Ar), 5.19 (1H, d broad, *J*= 6.4 Hz, H_2), 4.87 (1H, dtt, *J*= 47.6 Hz, 3.2 Hz, 3.0 Hz, H_4), 3.84-3.72 (1H, m, H_6), 3.36 (1H, ddd, *J*= 14.5 Hz, 12.5 Hz, 3.4 Hz, H_6), 2.67-2.53 (1H, m H_3), 2.44 (3H, s, ArC*H*$_3$), 2.03 (1H, dddd, *J*= 43.0 Hz, 15.2 Hz, 6.7 Hz, 2.6 Hz, H_3), 1.82-1.71 (1H, m, H_5) and 1.70-1.53 (1H, m, H_5); δ_C (75 MHz, $CDCl_3$): 143.5 (Cq, Ar), 138.5 (Cq, Ar), 137.8 (Cq, Ar), 131.3 (CH, Ar), 129.8 (CH, Ar), 128.4 (CH, Ar), 126.9 (CH, Ar), 120.9 (Cq, Ar), 86.0 (CH, d, *J*= 171.9 Hz, C_4), 52.9 (CH, s, C_2), 36.6 (CH_2, d, *J*= 1.5 Hz, C_6), 31.9 (CH_2, d, *J*= 19.0 Hz, C_3), 29.1 (CH_2, d, *J*= 21.0 Hz, C_5) and 21.5 (CH_3, Ar*C*H_3); δ_F (282 MHz, $CDCl_3$): -181.2 to -181.7 (m); HRMS *m/z*: [MH, -HF]$^+$: 392.0311, 394.0311, calculated 392.0320, 394.0299; Mp: 121-123 °C; IR: υ_{max} (neat)/cm^{-1}: 3058, 2952, 2873, 1594, 1488, 1339, 1158, 1094, 1009, 814 and 671.

(±)-2-(3-Bromophenyl)-4-fluoro-*N*-(tosyl)piperidines 196c and 197c.

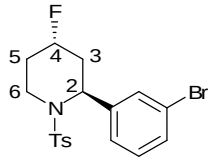
Piperidines **(±)-196c** and **(±)-197c** were prepared according to the general procedure outlined for the *Aza*-Prins reaction from 3-bromobenzaldehyde **100f** (58 μL, 0.5 mmol), *N*-tosyl-4-butenylamine **191** (112mg, 0.5 mmol) and boron trifluoride (65 μL, 0.5 mmol) in dichloromethane (5 mL).



(±)-196c

Product **(±)-196c** was isolated after purification over silica gel (hexane/diethyl ether, 7/3 R_f= 0.29) as a white solid (82 mg, 40 %).

NMR: δ_H (300 MHz, $CDCl_3$): 7.75 (2H, d, *J*= 8.7 Hz, Ar), 7.40-7.28 (4H, m, Ar), 7.26-7.18 (2H, m, Ar), 5.38 (1H, s broad, H_2), 4.58 (1H, dtt, *J*= 48.5 Hz, 10.8 Hz, 4.4 Hz, H_4), 4.06-3.94 (1H, m, H_6), 3.10-2.97 (1H, m H_6), 2.65-2.52 (1H, m H_3), 2.46 (3H, s, ArC*H*$_3$), 1.95-1.82 (1H, m, H_5), 1.73 (1H, dddd, *J*= 13.4 Hz, 11.1 Hz, 8.7 Hz, 5.6 Hz, H_3) and 1.44 (1H, ttd, *J*= 12.5 Hz, 10.3 Hz, 4.8 Hz, H_5); δ_C (75 MHz, $CDCl_3$): 143.8 (Cq, Ar), 140.3 (Cq, Ar), 137.6 (Cq, Ar), 130.6 (CH, Ar), 130.4 (CH, Ar), 130.0 (CH, Ar), 129.5 (CH, Ar), 126.9 (CH, Ar), 125.2 (CH, Ar), 123.1 (Cq, Ar), 86.3 (CH, d, *J*= 174.4 Hz, C_4), 55.1 (CH, d, *J*= 12.3 Hz, C_2), 40.0 (CH_2, d, *J*= 12.2 Hz, C_6), 33.6 (CH_2, d, *J*= 19.6 Hz, C_3), 31.0 (CH_2, d, *J*= 19.3 Hz, C_5) and 21.6 (CH_3, Ar*C*H_3); δ_F (282 MHz, $CDCl_3$): -175.8 (dm, *J*= 48.5 Hz); HRMS *m/z*: $[MNa]^+$: 434.0189, 436.0184, calculated 434.0202, 436.0181; Mp: 93-95 °C; IR: υ_{max} (neat)/cm^{-1}: 3058, 3036, 2918, 2868, 1594, 1566, 1476, 1339, 1155, 1093, 1018, 811, 741 and 660.



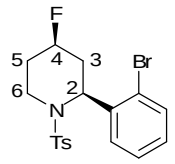
(±)-197c

Product **197c** was isolated after purification over silica gel (hexane/diethyl ether, 7/3 R_f= 0.19) as a white solid (40 mg, 19 %).

NMR: δ_H (400 MHz, $CDCl_3$): 7.70 (2H, d, *J*= 8.3 Hz, Ar), 7.35-7.29 (3H, m, Ar), 7.29-7.24 (2H, m, Ar), 7.18-7.13 (1H, m, Ar), 5.22 (1H, d broad, *J*= 6.4 Hz, H_2), 4.88 (1H, dtt, *J*= 47.5 Hz, 3.5 Hz, 2.8 Hz, H_4), 3.85-3.76 (1H, m, H_6), 3.38 (1H, ddd, *J*= 14.4 Hz, 12.6 Hz, 3.2 Hz, H_6), 2.64-2.54 (1H, m H_3), 2.44 (3H, s, ArCH_3), 1.98 (1H, dddd, *J*= 43.1 Hz, 15.1 Hz, 6.8 Hz, 2.6 Hz, H_3), 1.86-1.76 (1H, m, H_5) and 1.75-1.61 (1H, m, H_5); δ_C (100 MHz, $CDCl_3$): 143.7 (Cq, Ar), 142.0 (Cq, Ar), 137.8 (Cq, Ar), 130.0 (CH, Ar), 129.9 (CH, Ar), 129.8 (CH, Ar), 129.7 (CH, Ar), 126.9 (CH, Ar), 125.3(CH, Ar), 122.5 (Cq, Ar), 86.0 (CH, d, *J*= 172.2 Hz, C_4), 52.9 (CH, s, C_2), 36.8 (CH_2, s, C_6), 32.3 (CH_2, d, *J*= 19.3 Hz, C_3), 29.2 (CH_2, d, *J*= 21.2 Hz, C_5) and 21.6 (CH_3, Ar*C*H_3); δ_F (376 MHz, $CDCl_3$): -181.4 to -181.9 (m); HRMS *m/z*: $[MNa]^+$: 434.0201, 436.0183, calculated 434.0202, 436.0181; Mp: 105-107 °C; IR: υ_{max} (neat)/cm^{-1}: 3057, 2974, 2865, 1594, 1563, 1474, 1325, 1281, 1130, 1068, 886, 746, 710 and 648.

(±)-2-(2-Bromophenyl)-4-fluoro-*N*-(tosyl)piperidines 196d and 197d.

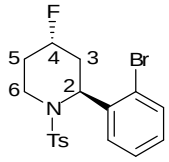
Piperidines **(±)-196d** and **(±)-197d** were prepared according to the general procedure outlined for the *Aza*-Prins reaction from 2-bromobenzaldehyde **100e** (58 μL, 0.5 mmol), *N*-tosyl-4-butenylamine **191** (112mg, 0.5 mmol) and boron trifluoride (65 μL, 0.5 mmol) in dichloromethane (5 mL).



(±)-196d

Product **(±)-196d** was isolated after purification over silica gel (hexane/diethyl ether, 7/3 R_f= 0.27) as a colorless oil (51 mg, 25 %).

NMR: δ_H (300 MHz, $CDCl_3$): 7.66 (2H, d, *J*= 8.3 Hz, Ar), 7.44 (1H, dd, *J*= 8.0 Hz, 1.5 Hz, Ar), 7.36 (1H, dd, *J*= 8.0 Hz, 2.0 Hz, Ar), 7.21-7.16 (3H, m, Ar), 7.07-7.01 (1H, m, Ar), 5.14 (1H, t, *J*= 6.0 Hz, H_2), 4.78 (1H, dtt, *J*= 48.5 Hz, 6.2 Hz, 3.8 Hz, H_4), 3.97-3.87 (1H, m, H_6), 3.71 (1H, dt, *J*= 13.9 Hz, 5.1 Hz, H_6), 2.41-2.29 (1H, m, H_3), 2.40 (3H, s, ArCH_3), 2.18-2.05 (1H, m, H_3) and 2.01-1.82 (2H, 2xH_5); δ_C (100 MHz, $CDCl_3$): 143.2 (Cq, Ar), 140.3 (Cq, Ar), 136.4 (Cq, Ar), 133.1 (CH, Ar), 129.5 (CH, Ar), 129.4 (CH, Ar), 127.3 (CH, Ar), 127.3 (CH, Ar), 127.2 (CH, Ar), 122.0 (Cq, Ar), 86.6 (CH, d, *J*= 173.8 Hz, C_4), 54.8 (CH, d, *J*= 6.3 Hz, C_2), 40.4 (CH_2, d, *J*= 6.3 Hz, C_6), 35.2 (CH_2, d, *J*= 20.2 Hz, C_3), 30.0 (CH_2, d, *J*= 20.8 Hz, C_5) and 21.4 (CH_3, ArCH_3); δ_F (282 MHz, $CDCl_3$): -179.3 to -179.7 (m); HRMS *m/z*: $[MNa, -HF]^+$: 414.0145, 416.0103, calculated 414.0139, 416.0119; IR: υ_{max} (neat)/cm^{-1}: 3058, 3025, 2918, 2840, 1594, 1563, 1460, 1328, 1158, 1090, 1020, 811, 749, 704 and 648.



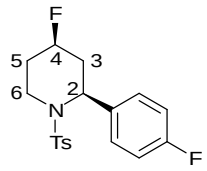
(±)-197d

Product **(±)-197d** was isolated after purification over silica gel (hexane/diethyl ether, 7/3 R_f= 0.18) as a colorless oil (49 mg, 24 %).

NMR: δ_H (400 MHz, $CDCl_3$): 7.50 (2H, d, *J*= 8.3 Hz, Ar), 7.42 (1H, dd, *J*= 8.0 Hz, 1.2 Hz, Ar), 7.37 (1H, dd, *J*= 7.8 Hz, 1.6 Hz, Ar), 7.24-7.16 (3H, m, Ar), 7.07 (1H, td, *J*= 7.6 Hz, 1.6 Hz, Ar), 5.21 (1H, dd, *J*= 7.7 Hz, 5.1 Hz, H_2), 4.81 (1H, dtt, *J*= 48.5 Hz, 6.4 Hz, 3.7 Hz, H_4), 3.81-3.70 (2H, m, 2xH_6), 2.44-2.29 (1H, m H_3), 2.40 (3H, s, ArC*H*$_3$), 2.19-1.99 (2H, m, H_3, H_5) and 1.92-1.77 (1H, m, H_5); δ_C (100 MHz, $CDCl_3$): 143.2 (Cq, Ar), 139.4 (Cq, Ar), 135.9 (Cq, Ar), 133.1 (CH, Ar), 129.3 (CH, Ar), 128.8 (CH, Ar), 128.8 (CH, Ar), 127.3 (CH, Ar), 127.2 (CH, Ar), 122.9 (Cq, Ar), 86.3 (CH, d, *J*= 172.4 Hz, C_4), 55.8 (CH, d, *J*= 6.7 Hz, C_2), 42.5 (CH_2, d, *J*= 6.3 Hz, C_6), 35.8 (CH_2, d, *J*= 20.7 Hz, C_3), 30.6 (CH_2, d, *J*= 20.7 Hz, C_5) and 21.5 (CH_3, Ar*C*H_3); δ_F (376 MHz, $CDCl_3$): -180.9 to -181.4 (m) ; HRMS *m/z*: $[MNa]^+$: 434.0195, 436.0186, calculated 434.0202, 436.0181; IR: υ_{max} (neat)/cm^{-1}: 3022, 2985, 2845, 1558, 1281, 1180, 1124, 1057, 892, 760 and 671.

(±)-2-(4-Fluorophenyl)-4-fluoro-*N*-(tosyl)piperidines 196e and 197e.

Piperidines **196e** and **197e** were prepared according to the general procedure outlined for the *Aza*-Prins reaction from 4-fluorobenzaldehyde **100d** (53 µL, 0.5 mmol), *N*-tosyl-4-butenylamine **191** (112mg, 0.5 mmol) and boron trifluoride (65 µL, 0.5 mmol) in dichloromethane (5 mL).

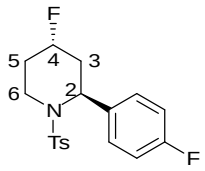


(±)-196e

Product **(±)-196e** was isolated after purification over silica gel (hexane/diethyl ether, 7/3 R_f= 0.21) as a white solid (general procedure: 78 mg, 44 %, procedure with microwaves: 66 mg, 38%).

NMR: δ_H (400 MHz, $CDCl_3$): 7.76 (2H, d, *J*= 8.3 Hz, Ar), 7.37-7.30 (4H, m, Ar), 7.07-7.01 (2H, m, Ar), 5.38 (1H, s broad, H_2), 4.60 (1H, dtt, *J*= 48.5 Hz, 10.9 Hz, 4.5 Hz, H_4), 4.03-3.93 (1H, m, H_6), 3.03 (1H, dddd, *J*= 14.7 Hz, 12.7 Hz, 2.6 Hz, 1.3 Hz, H_6), 2.66-2.56 (1H, m H_3), 2.46 (3H, s, ArC*H*$_3$), 1.92-1.83 (1H, m, H_5), 1.70 (1H, dddd, *J*= 13.4 Hz, 11.0 Hz, 8.7 Hz, 5.5 Hz, H_3) and 1.44 (1H, ttd, *J*= 12.6 Hz, 10.3 Hz, 4.8 Hz, H_5); δ_C (100 MHz, $CDCl_3$): 162.0 (Cq, d, *J*= 249.8 Hz, Ar), 143.7 (Cq, Ar), 137.8 (Cq, Ar), 134.5 (Cq, Ar), 130.0 (CH, Ar), 128.3 (CH, d, *J*= 8.0 Hz, Ar), 126.9 (CH, Ar), 115.7 (CH, d, *J*= 21.2 Hz, Ar), 86.5 (CH, d, *J*= 173.1 Hz, C_4), 55.1 (CH, d, *J*= 13.1 Hz, C_2), 39.9 (CH_2, d, *J*= 13.5 Hz, C_6), 33.6 (CH_2, d, *J*= 19.6 Hz, C_3), 31.0 (CH_2, d, *J*= 19.6 Hz, C_5) and 21.6 (CH_3, Ar*C*H$_3$); δ_F (376 MHz, $CDCl_3$): -115.6 to -115.7 (m) and -175.8 (dm, *J*= 48.5 Hz); HRMS *m/z*: $[MNa]^+$: 374.1001, calculated

374.1002; Mp: 111-113 °C; IR: υ_{max} (neat)/cm^{-1}: 3043, 2941, 2873, 1597, 1507, 1339, 1151, 1093 and 838.



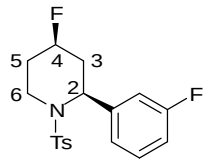
(±)-197e

The product **(±)-197e** was isolated after purification over silica gel (hexane/diethyl ether, 7/3 R_f= 0.12) as a colorless oil (general procedure: 42 mg, 24 %, procedure with microwave: 44 mg, 25%).

NMR: δ_H (400 MHz, $CDCl_3$): 7.71 (2H, d, *J*= 8.4 Hz, Ar), 7.35-7.25 (4H, m, Ar), 7.02-6.91 (2H, t, *J*= 8.4 Hz, Ar), 5.22 (1H, d broad, *J*= 6.3 Hz, H_2), 4.87 (1H, dtt, *J*= 47.6 Hz, 3.4 Hz, 3.0 Hz, H_4), 3.83-3.72 (1H, m, H_6), 3.37 (1H, ddd, *J*= 14.4 Hz, 12.6 Hz, 3.0 Hz, H_6), 2.66-2.55 (1H, m H_3), 2.44 (3H, s, ArCH_3), 1.96 (1H, dddd, *J*= 43.2 Hz, 15.3 Hz, 6.8 Hz, 2.7 Hz, H_3), 1.81-1.70 (1H, m, H_5) and 1.70-1.55 (1H, m, H_5); δ_C (100 MHz, $CDCl_3$): 161.7 (Cq, d, *J*= 245.6 Hz), 143.4 (Cq, Ar), 137.9 (Cq, Ar), 135.1 (Cq, d, *J*= 2.9 Hz, Ar), 129.8 (CH, Ar), 128.3 (CH, dd, *J*= 8.0 Hz, 2.5 Hz, Ar), 126.9 (CH, Ar), 115.0 (CH, d, *J*= 21.3 Hz, Ar), 86.1 (CH, d, *J*= 172.4 Hz, C_4), 52.9 (CH, s, C_2), 36.6 (CH_2, C_6), 32.0 (CH_2, d, *J*= 19.3 Hz, C_3), 29.1 (CH_2, d, *J*= 21.1 Hz, C_5) and 21.5 (CH_3, ArCH_3); δ_F (376 MHz, $CDCl_3$): -116.7 to 116.8 (m) and -180.8 to -181.3 (m); HRMS *m/z*: $[MNa]^+$: 374.1001, calculated 374.1002; Mp: 127-129 °C; IR: υ_{max} (neat)/cm^{-1}: 3043, 2920, 2873, 1597, 1508,1328, 1152, 1071, 1032 and 882.

(±)-2-(3-Fluorophenyl)-4-fluoro-*N*-(tosyl)piperidines 196f and 197f.

Piperidines **(±)-196f** and **(±)-197f** were prepared according to the general procedure outlined for ther *Aza*-Prins reaction from 3-fluorobenzaldehyde **100c** (55 µL, 0.5 mmol), *N*-tosyl-4-butenylamine **191** (112mg, 0.5 mmol) and boron trifluoride (65 µL, 0.5 mmol) in dichloromethane (5 mL).

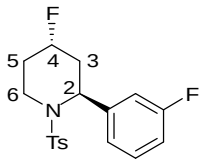


(±)-196f

Product **(±)-196f** was isolated after purification over silica gel (hexane/diethyl ether, 7/3 R_f= 0.22) as a white solid (78 mg, 44 %).

NMR: δ_H (300 MHz, $CDCl_3$): 7.77 (2H, d, *J*= 8.3 Hz, Ar), 7.35 (2H, *J*= 8.3 Hz, Ar), 7.30-7.22 (1H, m, Ar), 7.18-7.11 (1H, m, Ar), 7.09-7.01 (1H, m, Ar), 7.01-6.92 (1H, m, Ar), 5.41 (1H, s broad, H_2), 4.57 (1H, dtt, *J*= 48.5 Hz, 10.9 Hz, 4.5 Hz, H_4), 4.07-3.94 (1H, m, H_6), 3.03 (1H, dddd, *J*= 14.9 Hz, 12.8 Hz, 2.9 Hz, 1.2 Hz, H_6), 2.67-2.55 (1H, m, H_3), 2.46 (3H, s, ArC*H*$_3$), 1.94-1.82 (1H, m, H_5), 1.72 (1H, dddd, *J*= 13.4 Hz, 11.2 Hz, 8.6 Hz, 5.7 Hz, H_3) and 1.45 (1H, ttd, *J*= 12.7 Hz, 10.3 Hz, 4.9 Hz, H_5); δ_C (75 MHz, $CDCl_3$): 163.2 (Cq, d, *J*= 247.7 Hz, *C*HF), 143.7 (Cq, Ar), 140.7 (Cq, d, *J*= 7.7 Hz, Ar), 137.6 (Cq, Ar), 130.4 (CH, d, *J*= 8.7 Hz, Ar), 130.0 (CH, Ar), 129.5 (CH, d, *J*= 8.7 Hz, Ar), 126.9 (CH, Ar), 114.4 (CH, t, *J*= 21.3 Hz, Ar), 113.6 (CH, d, *J*= 22.7 Hz, Ar), 86.4 (CH, d, *J*= 174.9 Hz, C_4), 55.2 (CH, d, *J*= 12.5 Hz, C_2), 40.0 (CH_2, d, *J*= 11.7 Hz, C_6), 33.6 (CH_2, d, *J*= 20.5 Hz, C_3), 30.9 (CH_2, d, *J*= 19.0 Hz, C_5) and 21.5 (CH_3, Ar*C*H$_3$); δ_F (376 MHz, $CDCl_3$): -112.0 to -112.1 (m) and -175.2 (dm, *J*=

48.5 Hz); HRMS *m/z*: $[MNa]^+$: 374.1002, calculated 374.1002; Mp: 101-103 °C; IR: υ_{max} (neat)/cm^{-1}: 3065, 2944, 2877, 1614, 1590, 1488, 1341, 1160, 1096, 1019, 889, 736 and 674.



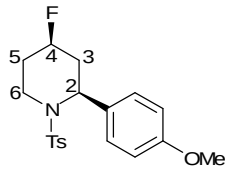
(±)-197f

Product **(±)-197f** was isolated after purification over silica gel (hexane/diethyl ether, 7/3 R_f= 0.14) as a white solid (39 mg, 22 %).

NMR: δ_H (300 MHz, $CDCl_3$): 7.73 (2H, d, *J*= 8.3 Hz, Ar), 7.30 (2H, d, *J*= 8.3 Hz, Ar), 7.24 (1H, dd, *J*= 8.0 Hz, 6.0 Hz, Ar), 7.14-7.08 (1H, m, Ar), 7.04-6.96 (1H, m, Ar), 6.95-6.85 (1H, m, Ar), 5.26 (1H, d broad, *J*= 6.6 Hz, H_2), 4.88 (1H, dtt, *J*= 47.3 Hz, 3.2 Hz, 2.8 Hz, C_4), 3.86-3.75 (1H, m, H_6), 3.38 (1H, ddd, *J*= 14.4 Hz, 12.6 Hz, 3.3 Hz, H_6), 2.68-2.55 (1H, m, H_3), 2.44 (3H, s, ArCH_3), 1.98 (1H, dddd, *J*= 43.6 Hz, 15.2 Hz, 6.9 Hz, 2.6 Hz, H_3), 1.82-1.72 (1H, m, H_5) and 1.71-1.53 (1H, m, H_5); δ_C (75 MHz, $CDCl_3$): 162.8 (Cq, d, *J*= 246.2 Hz, *C*HF), 143.5 (Cq, Ar), 142.3 (Cq, d, *J*= 6.7 Hz, Ar), 137.8 (Cq, Ar), 129.8 (CH, Ar), 129.6 (CH, d, *J*= 8.3 Hz, Ar), 126.9 (CH, Ar), 122.1 (CH, t, *J*= 2.3 Hz, Ar), 113.7 (CH, d, *J*= 21.0 Hz, Ar), 113.6 (CH, dd, *J*= 2.9 Hz, 2.4 Hz, Ar), 85.9 (CH, d, *J*= 172.2 Hz, C_4), 52.8 (CH, d, *J*= 6.7 Hz, C_2), 36.6 (CH_2, C_6), 32.0 (CH_2, d, *J*= 20.4 Hz, C_3), 29.0 (CH_2, d, *J*= 21.0 Hz, C_5) and 21.5 (CH_3, Ar*C*H_3); δ_F (376 MHz, $CDCl_3$): -113.4 to 113.5 (m) and -186.0 to -186.5 (m) ; HRMS *m/z*: $[MNa]^+$: 374.1013, calculated 374.1002; Mp: 111-113 °C; IR: υ_{max} (neat)/cm^{-1}: 2974, 2913, 2845, 1611, 1588, 1348, 1269, 1186, 1127, 1068, 903, 732 and 654.

(±)-4-Fluoro-2-(4-methoxyphenyl)-*N*-(tosyl)piperidines 196g and 197g.

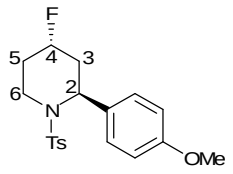
Piperidines **(±)-196g** and **(±)-197g** were prepared according to the general procedure outlined for the *Aza*-Prins reaction from 4-methoxybenzaldehyde **100i** (60 μL, 0.5 mmol), *N*-tosyl-4-butenylamine **191** (112mg, 0.5 mmol) and boron trifluoride (65 μL, 0.5 mmol) in dichloromethane (5 mL).



(±)-196g

Product **(±)-196g** was isolated after purification over silica gel (hexane/diethyl ether, 7/3 R_f= 0.19) as a pale yellow visquous oil (26 mg, 14 %).

NMR: δ_H (400 MHz, $CDCl_3$): 7.77 (2H, d, *J*= 8.3 Hz, Ar), 7.33 (2H, d, *J*= 8.3 Hz, Ar), 7.28 (2H, d, *J*= 8.3 Hz, Ar), 6.87 (2H, d, *J*= 8.3 Hz, Ar), 5.38 (1H, s broad, H_2), 4.64 (1H, dtt, *J*= 48.7 Hz, 10.9 Hz, 4.4 Hz, H_4), 4.02-3.91 (1H, m, H_6), 3.81 (3H, s, OCH_3), 3.02 (1H, dddd, *J*= 14.9 Hz, 12.7 Hz, 2.6 Hz, 1.0 Hz, H_6), 2.67-2.58 (1H, m H_3), 2.46 (3H, s, ArCH_3), 1.91-1.81 (1H, m, H_5), 1.68 (1H, dddd, *J*= 13.2 Hz, 11.2 Hz, 9.0 Hz, 5.7 Hz, H_3) and 1.43 (1H, ttd, *J*= 12.5 Hz, 10.5 Hz, 4.9 Hz, H_5); δ_C (100 MHz, $CDCl_3$): 158.8 (Cq, Ar), 143.5 (Cq, Ar), 138.0 (Cq, Ar), 129.9 (CH, Ar), 129.5 (Cq, Ar), 127.7 (CH, Ar), 126.9 (CH, Ar), 114.2 (CH, Ar), 86.8 (CH, d, *J*= 176.8 Hz, C_4), 55.3 (CH_3, OCH_3), 55.1 (CH, d, *J*= 12.9 Hz, C_2), 39.8 (CH_2, d, *J*= 12.5 Hz, C_6), 33.5 (CH_2, d, *J*= 19.6 Hz, C_3), 31.1 (CH_2, d, *J*= 18.3 Hz, C_5) and 21.5 (CH_3, ArCH_3); δ_F (376 MHz, $CDCl_3$): -175.6 (dm, *J*= 48.7 Hz); HRMS *m/z*: $[MNa]^+$: 386.1201, calculated 386.1202; IR of the mixture of diastereoisomers: υ_{max} (neat)/cm^{-1}: 2974, 2918, 2845, 1510, 1348, 1303, 1180, 1144, 1012, and 881.



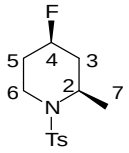
(±)-197g

Product **(±)-197g** was isolated as a mixture of diastereoisomers (*syn*/*anti*, 1/2.2) after purification over silica gel (hexane/diethyl ether, 7/3) as a pale yellow visquous oil (13 mg, 7 %).

NMR: δ_H (400 MHz, $CDCl_3$): 7.74-7.67 (2H, m, Ar), 7.30-7.21 (4H, m, Ar), 6.84-6.77 (2H, m, Ar), 5.19 (1H, d broad, *J*= 6.2 Hz, H_2), 4.87 (1H, dtt, *J*= 47.8 Hz, 3.6 Hz, 2.7 Hz, H_4), 3.79 (3H, s, OC*H*$_3$), 3.77-3.70 (1H, m, H_6), 3.40 (1H, ddd, *J*= 14.5 Hz, 12.2 Hz, 3.4 Hz, H_6), 2.66-2.55 (1H, m H_3), 2.43 (3H, s, ArC*H*$_3$), 1.97 (1H, dddd, *J*= 42.6 Hz, 15.2 Hz, 6.8 Hz, 2.8 Hz, H_3), 1.82-1.74 (1H, m, H_5) and 1.70-1.64 (1H, m, H_5); δ_C (100 MHz, $CDCl_3$): 148.6 (Cq, Ar), 143.3 (Cq, Ar), 138.0 (Cq, Ar), 131.3 (Cq, Ar), 129.7 (CH, Ar), 127.9 (CH, Ar), 127.0 (CH, Ar), 113.5 (CH, Ar), 86.3 (CH, d, *J*= 173.7 Hz, C_4), 55.2 (CH_3, O*C*H$_3$), 53.2 (CH, C_2), 36.7 (CH_2, C_6), 32.1 (CH_2, d, *J*= 19.9 Hz, C_3), 29.1 (CH_2, d, *J*= 19.6 Hz, C_5) and 21.5 (CH_3, Ar*C*H$_3$); δ_F (376 MHz, $CDCl_3$): -180.1 to -180.6 (m); HRMS *m/z*: $[MNa]^+$: 386.1208, calculated 386.1202; IR of the mixture of diastereoisomers: υ_{max} (neat)/cm^{-1}: 2952, 2918, 2845, 1608, 1591, 1337, 1303, 1146, 1090 and 833.

(±)-4-Fluoro-2-methyl-*N*-(tosyl)piperidines 196i and 197i.

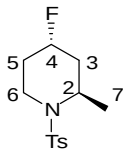
Piperidines **(±)-196i** and **(±)-197i** were prepared according to the general procedure outlined under *Aza*-Prins reaction from acetaldehyde **100r** (28 μL, 0.5 mmol), *N*-tosyl-4-butenylamine **191** (112mg, 0.5 mmol) and boron trifluoride (65 μL, 0.5 mmol) in dichloromethane (5 mL) to give the title compounds (general procedure: 99 mg, 73 %, mixture ratio *syn*/*anti* 1.2/1, procedure with microwaves: 104 mg, 77 %, mixture ratio *syn*/*anti* 1.2/1).



(±)-196i

Analysis from a mixture of diastereoisomers **(±)-196i** and **(±)-197i**:

NMR: δ_H (300 MHz, $CDCl_3$): 7.75-7.66 (2H, m, Ar), 7.34-7.24 (2H, m, Ar), 4.77 (1H, dtt, *J*= 48.5 Hz, 10.9 Hz, 4.7 Hz, C_4), 4.42-4.29 (1H, m, H_2), 3.94-3.79 (1H, m, H_6), 3.10 (1H, dddd, *J*= 13.9 Hz, 12.7 Hz, 2.7 Hz, 1.2 Hz, H_6), 2.42 (3H, s, ArC*H*$_3$), 2.08-1.96 (1H, m H_5), 1.95-1.45 (3H, m, H_5, 2xH_3) and 1.12, (3H, d, J= 7.1 Hz, 3xH_7); δ_C (75 MHz, $CDCl_3$): 143.3 (Cq, Ar), 137.6 (Cq, Ar), 129.7 (CH, Ar), 126.8 (CH, Ar), 86.7 (CH, d, *J*= 173.0 Hz, C_4), 49.0 (CH, d, *J*= 12.8 Hz, C_2), 38.6 (CH_2, d, *J*= 12.5 Hz, C_6), 36.7 (CH_2, d, *J*= 18.6 Hz, C_3), 31.7 (CH_2, d, *J*= 19.1 Hz, C_5), 21.4 (CH_3, Ar*C*H_3) and 17.0 (CH_3, C_7); δ_F (282 MHz, $CDCl_3$): -178.3 (dm, *J*= 48.5 Hz); HRMS *m/z*: $[MNa]^+$: 294.0942, calculated 294.0940; IR from the mixture of diastereoisomers: υ_{max} (neat)/cm^{-1}: 3058, 3030, 2941, 2873, 1594, 1348, 1331, 1160, 1001 and 813.



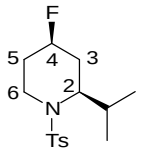
(±)-197i

Analysis from a mixture of diastereoisomers **(±)-196i** and **(±)-197i**:

NMR: δ_H (300 MHz, $CDCl_3$): 7.75-7.66 (2H, m, Ar), 7.34-7.24 (2H, m, Ar), 4.88 (1H, dtt, *J*= 47.3 Hz, 3.1 Hz, 2.9 Hz, H_4), 4.29-4.16 (1H, m, H_2), 3.70 (1H, dd broad, *J*= 13.7 Hz; 5.3 Hz, H_6), 3.31 (1H, td, *J*= 13.1 Hz, 2.7 Hz, H_6), 2.41 (3H, s, ArCH_3), 1.95-1.45 (4H, m, 2xH_3, 2xH_5) and 1.17 (3H, dd, *J*= 7.2 Hz, 1.8 Hz, 3xH_7); δ_C (75 MHz, $CDCl_3$): 143.1 (Cq, Ar), 138.0 (Cq, Ar), 129.6 (CH, Ar), 126.8 (CH, Ar), 86.8 (CH, d, *J*= 170.3 Hz, C_4), 46.9 (CH, C_2), 34.7 (CH_2, C_6), 34.6 (CH_2, d, *J*= 18.9 Hz, C_3), 29.8 (CH_2, d, *J*= 21.4 Hz, C_5), 21.4 (CH_3, ArCH_3) and 17.9 (CH_3 C_7); δ_F (282 MHz, $CDCl_3$): -179.8 to -180.4 (m); HRMS *m/z*: $[MNa]^+$: 294.0942, calculated 294.0940; IR from a mixture of diastereoisomers: υ_{max} (neat)/cm^{-1}: 3058, 3030, 2941, 2873, 1594, 1348, 1331, 1160, 1001 and 813.

(±)-4-Fluoro-2-isobutyl-*N*-(tosyl)-piperidines 196j and 197j.

Piperidines **(±)-196j** and **(±)-197j** were prepared according to the general procedure outlined for the *Aza*-Prins reaction from isobutyraldehyde **100s** (45 µL, 0.5 mmol), *N*-tosyl-4-butenylamine **191** (112mg, 0.5 mmol) and boron trifluoride (65 µL, 0.5 mmol) in dichloromethane (5 mL). The product was isolated as a mixture of diastereoisomers after purification over silica gel (hexane/diethyl ether, 7/3 R_f= 0.19) as a pale yellow oil (general procedure: 111 mg, 82 %, mixture ratio *syn*/*anti* 1/1, procedure with microwaves: 112 mg, 83 %, mixture ratio *syn*/*anti* 1.2/1).

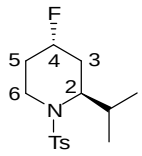


(±)-196j

Analysis from a mixture of diastereoisomers **(±)-196j** and **(±)-197j**:

NMR: δ_H (300 MHz, $CDCl_3$): 7.74 (2H, d, *J*= 8.3 Hz, Ar), 7.31 (2H, *J*= 8.3 Hz, Ar), 4.67 (1H, dtt, *J*= 48.8 Hz, 11.3 Hz, 4.6 Hz, H_4), 4.04-3.92 (1H, m, H_6), 3.80-3.71(1H, m, H_2), 2.99 (1H, dddd, *J*= 15.3 Hz, 13.6 Hz, 2.7 Hz, 1.3 Hz, H_6), 2.44 (3H, s, ArCH_3), 2.21-2.10 (1H, m H_3), 1.93-1.75 (2H, m, H_3, CH(CH_3)$_2$), 1.37-1.22 (2H, m, H_5, H_3), 0.95 (3H, d, *J*= 6.8 Hz, CHCH_3) and 0.81 (3H, d, *J*= 6.77 Hz, CHCH_3); δ_C (75 MHz, $CDCl_3$): 143.3 (Cq, Ar), 138.4 (Cq, Ar), 129.8 (CH, Ar), 126.9 (CH, Ar), 86.9 (CH, d, *J*= 172.2 Hz, C_4), 60.1 (CH, d, *J*= 12.3 Hz, C_2), 39.1 (CH_2, d, *J*= 12.5 Hz, C_6), 31.6 (CH_2, d, *J*= 17.7 Hz, C_3), 30.8 (CH_2, d, *J*= 19.2 Hz, C_5), 27.7 (CH, *C*H(CH_3)$_2$), 21.5 (CH_3, CH*C*H$_3$), 20.2 (CH_3, CH*C*H$_3$) and 19.9 (CH_3, Ar*C*H$_3$); δ_F (282 MHz, $CDCl_3$): -174.6 (dm, *J*= 48.8 Hz); HRMS *m/z*: $[MNa]^+$: 322.1256, calculated

322.1253; IR from the mixture of diastereoisomers: υ_{max} (neat)/cm^{-1}: 2969, 2918, 2868, 1454, 1337, 1303, 1208, 1149, 1090 and 818.



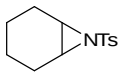
(±)-197j

Analysis from a mixture of diastereoisomers **(±)-196j** and **(±)-197j**:

NMR: δ_H (300 MHz, $CDCl_3$): 7.77-7.70 (2H, m, Ar), 7.35-7.28 (2H, m, Ar), 4.79 (1H, dtt, *J*= 48.3 Hz, 2.9 Hz, 2.6 Hz, H_4), 3.80-3.67 (1H, H_6), 3.54 (1H, dd, *J*= 10.9 Hz, 6.2 Hz, H_2), 3.29 (1H, ddd, *J*= 15.0 Hz, 13.4 Hz, 3.0 Hz, H_6), 2.41 (3H, s, ArCH_3), 2.29-2.08 (2H, m, H_3, $CH(CH_3)_2$), 1.74-1.34 (3H, m, 2xH_5, H_3), 0.94 (3H, d, J= 6.5 Hz, $CHCH_3$) and 0.85 (3H, d, *J*= 6.6 Hz, $CHCH_3$); δ_C (75 MHz, $CDCl_3$): 143.0 (Cq, Ar), 138.6 (Cq, Ar), 129.6 (CH, Ar), 126.9 (CH, Ar), 87.2 (CH, d, *J*= 170.0 Hz, C_4), 57.9 (CH, C_2), 35.5 (CH_2, C_6), 29.1 (CH_2, d, *J*= 19.8 Hz, C_3), 28.9 (CH, $CH(CH_3)_2$), 28.7 (CH_2, d, *J*= 20.7 Hz, C_5), 21.5 (CH_3, ArCH_3), 20.7 (CH_3 $CHCH_3$) and 20.1 (CH_3 $CHCH_3$); δ_F (282 MHz, $CDCl_3$): -181.8 (qt, *J*= 48.3 Hz, 11.8 Hz); HRMS *m/z*: $[MNa]^+$: 322.1256, calculated 322.1253; IR: υ_{max} (neat)/cm^{-1}: 2969, 2918, 2868, 1454, 1337, 1303, 1208, 1149, 1090 and 818.

***N*-(*p*-Tolylsulfonyl)-7-azabicyclo[4.1.0] heptane 200.**[6]

Silica (1.5 g) and chloramine T (2.73 g, 12 mmol) were added to a solution of cyclohexene **198** (304 μL, 3 mmol), I_2 (77 mg, 0.3 mmol) and potassium carbonate (829 mg, 6 mmol) in water (4.5 mL). After 3h at r.t., diethyl ether (10 mL) was added and the mixture was filtered. The layers were separated and the aqueous layer was extracted into diethyl ether. The organic layers were dried, filtered and concentrated. The title compound was obtained after purification over silica (hexane/diethyl ether, 6/4 R_f= 0.29) as a white solid (512 mg, 68%).



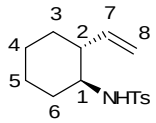
200

NMR: δ_H (400 MHz, $CDCl_3$): 7.73 (2H, *J*= 8.4 Hz, Ar), 7.24 (2H, *J*= 8.4 Hz, Ar), 2.95-2.88 (2H, m, CH_2CHN), 2.38 (3H, s, $ArCH_3$), 1.78-1.68 (4H, m, $2xCH_2CH_2CH$) and 1.42-1.09 (4H, m, $2xCH_2CH_2CH$); δ_C (75 MHz, $CDCl_3$): 143.8 (Cq, Ar), 135.5 (Cq, Ar), 129.3 (CH,, Ar), 127.3 (CH, Ar), 39.5 (CH, CH_2CHN), 22.5 (CH_2, CH_2CH_2CH), 21.3 (CH_3, $ArCH_3$) and 19.1 (CH_2, CH_2CH_2CH); HRMS *m/z*: $[MNa]^+$: 274.0878, calculated 274.0878; Mp: 55-56 °C (54-56 °C)[5]; IR: υ_{max} (neat)/cm^{-1}: 2935, 2857, 1594, 1437, 1317, 1155, 1090 and 844.

Data in agreement with literature.

***trans*-*N*-Tosyl-2-vinylcyclohexanamine 198.**

CuI (52 mg, 0.3 mmol) and vinylmagnesium bromide (1.66 mL, 4.1 mmol) were added to a solution of aziridine **200** (345 mg, 1.4 mmol) in diethyl ether (3 mL) at -20 °C. After 10h, the the mixture was hydrolysed with a solution of sat. ammonium chloride and the layers were separated. The aqueous layer was extracted into diethyl ether then the organic layers were dried, concentrated and purified over silica gel. The title compound **198** was obtained after purification over silica (hexane/diethyl ether 6/4 R_f= 0.16) as a colorless oil (165 mg, 43%).

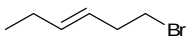


198

NMR: δ_H (400 MHz, $CDCl_3$): 7.72 (2H, d, *J*= 8.73 Hz, Ar), 7.29 (2H, *J*= 8.73 Hz, Ar), 5.20 (1H, ddd, *J*= 17.11 Hz, 9.9 Hz, 8.8 Hz, H_7), 5.00 (1H, ddd, *J*= 17.1 Hz, 2.0 Hz, 0.5 Hz, H_8), 4.93 (1H, dd, *J*= 10.0 Hz, 2.0 Hz, H_8), 4.37 (1H, d, *J*= 4.9 Hz, N*H*),2.75 (1H, ddd, *J*= 15.4 Hz, 9.9 Hz, 4.9 Hz, H_1), 2.44 (3H, s, ArCH_3), 2.16-2.07 (1H, m, H_6), 1.81 (1H, tdd, *J*= 9.9 Hz, 9.4 Hz, 3.8 Hz, H_2), 1.74-1.60 (3H, m, H_5, H_4, H_3) and 1.25-1.29 (4H, H_6, H_5, H_4, H_3); δ_C (100 MHz, $CDCl_3$): 143.2 (Cq, Ar), 140.3 (CH, C_7), 137..8 (Cq, Ar), 129.4 (CH, Ar), 127.2 (CH, Ar), 116.7 (CH_2, C_8), 56.4 (CH, C_1), 48.6 (CH, C_2), 33.8 (CH_2, C_6), 32.2, 24.8 and 24.8 (CH_2, C_3, C_4, C_5); HRMS *m/z*: $[MNa]^+$: 302.1192, calculated 302.1191; IR: υ_{max} (neat)/cm^{-1}: 3282, 2924, 2851, 1639, 1595, 1446, 1325, 1155, 1093 and 813.

***(E)*-1-Bromo-3-hexene 207.**[7]

Carbon tetrabromide (2.07 g, 6.2 mmol) was slowly added to a solution of alcohol **103** (585 μL, 5 mmol) and triphenylphosphine (1.99 g, 7.5 mmol) in CH_2Cl_2 (10 mL) at 0°C. After 1h at r.t., the resultant bromo-3-hexene **207** was directly distilled from the reaction (578 mg, 71%).



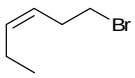
207

NMR: δ_H (400 MHz, $CDCl_3$): 5.53 (1H, dtt, *J*= 10.8 Hz, 7.3 Hz, 1.4 Hz, EtCH=C*H*), 5.33 (1H, dtt, *J*= 10.8 Hz, 7.2 Hz, 1.5 Hz, EtC*H*=CH), 3.35 (2H, t, *J*= 7.1 Hz, $CH_2C\mathit{H}_2Br$), 2.61 (2H, qt, *J*= 7.2 Hz, 1.5 Hz, $C\mathit{H}_2CH_2Br$), 2.07 (2H, quint d, *J*= 7.3 Hz, 1.4 Hz, $CH_3C\mathit{H}_2CH$) and 0.99 (3H, t, *J*= 7.5 Hz, $C\mathit{H}_3CH_2CH$); δ_C (75 MHz, $CDCl_3$): 134.6 (CH, Et*C*H=CH), 125.3 (CH, EtCH=*C*H), 32.5 (CH_2, $\mathit{C}H_2Br$), 30.5 (CH_2, $\mathit{C}H_2CH_2Br$), 20.7 (CH_2, $CH_3\mathit{C}H_2$) and 14.1 (CH_3, $\mathit{C}H_3CH_2$); LRMS *m/z*: $[M]^+$: 162.1, 164.1, calculated 162.0, 164.0; IR: υ_{max} (neat)/cm^{-1}: 3280, 2962, 2930, 2872, 1598, 1424, 1323, 1209, 1153, 1092, 967 and 813.

Data in agreement with literature.

***(Z)*-1-Bromo-3-hexene 208.**[7]

Carbon tetrabromide (2.07 g, 6.2 mmol) was slowly added to a solution of alcohol **105** (585 μL, 5 mmol) and triphenylphosphine (1.99 g, 7.5 mmol) in CH_2Cl_2 (10 mL) at 0°C. After 1h at r.t., the resultant bromo-3-hexene **208** was distilled directly from the reaction (553 mg, 68%).



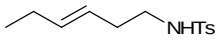
208

NMR: δ_H (400 MHz, $CDCl_3$): 5.60-5.46 (1H, m, EtCH=C*H*), 5.39-5.26 (1H, m, EtC*H*=CH), 3.36 (2H, td, *J*= 7.1 Hz, 1.5 Hz, CH_2CH_2Br), 2.61 (2H, q, *J*= 7.1 Hz, CH_2CH_2Br), 2.06 (2H, quint, *J*= 7.5 Hz, CH_3CH_2CH) and 0.98 (3H, t, *J*= 7.5 Hz, CH_3CH_2CH); δ_C (75 MHz, $CDCl_3$): 134.7 (CH, Et*C*H=CH), 125.2 (CH, EtCH=*C*H), 32.6 (CH_2, CH_2Br), 30.7 (CH_2, CH_2CH_2Br), 20.7 (CH_2, CH_3CH_2) and 14.1 (CH_3, CH_3CH_2) ; LRMS *m/z*: $[M]^+$: 162.1, 164.1, calculated 162.0, 164.0; IR: υ_{max} (neat)/cm^{-1}: 3012, 2963, 2932, 2873, 1652, 1457, 1208, 1150, 721 and 655.

Data in agreement with literature.

(*E*)-*N*-(tosyl)hex-3-en-1-amine 205.

(*E*)-1-Bromo-hex-3-ene **207** (325 mg, 2 mmol) was added to a solution of tosylamine **190** (684 mg, 2 mmol), and potassium carbonate (0.66 g, 4.8 mmol) in acetone (40 mL). After 4h at reflux, the mixture was concentrated under vacuum, and water and diethyl ether were added. Then the layers were separated and the aqueous layer was extracted into diethyl ether. The organic layers were dried, filtered and concentrated. The title compound was obtained after purification over silica (hexane/diethyl ether, 6/4 R_f= 0.28) as a pale yellow oil (212 mg, 42%).

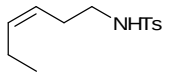


205

NMR: δ_H (400 MHz, $CDCl_3$): 7.75 (2H, d, *J*= 8.3 Hz, Ar), 7.30 (2H, d, *J*= 8.3 Hz, Ar), 5.45 (1H, dtt, *J*= 15.3 Hz, 6.3 Hz, 1.3 Hz, EtCH=C*H*), 5.17 (1H, dtt, *J*= 15.3 Hz, 6.9 Hz, 1.5 Hz, EtC*H*=CH), 4.77 (1H, t broad, *J*= 5.95 Hz, N*H*), 2.95 (2H, dd, *J*= 6.7 Hz, 6.3 Hz, CH_2CH_2N), 2.42 (3H, s, $ArCH_3$), 2.15-2.08 (2H, m, CH_2CH_2N), 1.99-1.90 (2H, m, CH_3CH_2CH) and 0.92 (3H, t, *J*= 7.5 Hz, CH_3CH_2CH); δ_C (75 MHz, $CDCl_3$): 143.4 (Cq, Ar), 137.0 (Cq, Ar), 136.1 (CH, Et*C*H=CH), 129.7 (CH, Ar), 127.1 (CH, Ar), 124.2 (CH, EtCH=*C*H), 42.5 (CH_2, CH_2N), 32.4 (CH_2, CH_2CH_2N), 25.2 (CH_2, CH_3CH_2), 21.5 (CH_3, $ArCH_3$) and 13.6 (CH_3, CH_3CH_2); HRMS *m/z*: $[MNa]^+$: 276.1038, calculated 276.1034; IR: υ_{max} (neat)/cm^{-1}: 3020, 2962, 2930, 1455, 1208, 1151, 966 and 638.

(*Z*)-*N*-(tosyl)hex-3-en-1-amine 206.

(*Z*)-1-Bromo-hex-3-ene **208** (325 mg, 2 mmol) was added to a solution of tosylamine **190** (684 mg, 2 mmol), and potassium carbonate (0.66 g, 4.8 mmol) in acetone (40 mL). After 4h at reflux, the mixture was concentrated under vacuum, and water and diethyl ether were added. The layers were separated and the aqueous layer was extracted into diethyl ether. The organic layers were dried, filtered and concentrated. The title compound was obtained after purification over silica (hexane/diethyl ether, 6/4 R_f= 0.27) as a pale yellow oil (197 mg, 39%).

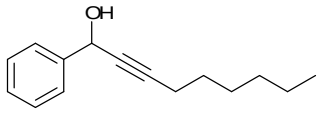


206

NMR: δ_H (400 MHz, $CDCl_3$): 7.75 (2H, d, *J*= 8.3 Hz, Ar), 7.30 (2H, d, *J*= 8.3 Hz, Ar), 5.53-5.41 (1H, m, EtCH=C*H*), 5.14 (1H, dtt, *J*= 10.8 Hz, 7.4 Hz, 1.4 Hz, EtC*H*=CH), 4.68 (1H, s broad, N*H*), 3.00-2.91 (2H, m, CH_2CH_2N), 2.42 (3H, s, $ArCH_3$), 2.24-2.15 (2H, m, CH_2CH_2N), 2.01-1.91 (2H, m, CH_3CH_2CH), 0.93, 0.92 and 0.91 (3H, t, *J*= 7.6 Hz, CH_3CH_2CH); δ_C (75 MHz, $CDCl_3$): 143.3 (Cq, Ar), 136.9 (Cq, Ar), 135.4 (CH, Et*C*H=CH), 129.6 (CH, Ar), 127.1 (CH, Ar), 123.9 (CH, EtCH=*C*H), 42.8 (CH_2, CH_2N), 27.3 (CH_2, CH_2CH_2N), 21.5 (CH_3, $ArCH_3$), 20.6 (CH_2, CH_3CH_2) and 14.1 (CH_3, CH_3CH_2); HRMS *m/z*: $[MNa]^+$: 276.1033, calculated 276.1034; IR: υ_{max} (neat)/cm^{-1}: 3277, 2963, 2929, 2868, 1597, 1490, 1323, 1158, 1093 and 813.

Phenyl-2-nonyn-1-ol 234.[8]

n-BuLi (2 mL, 5 mmol) was added to a solution of 1-octyne **237** (500 mg, 4.5 mmol) in THF (100 ml) at 0 ^{o}C and then benzaldehyde **100s** was added. After 90 min, a mixture of water and diethyl ether was slowly added at 0 ^{o}C, and then the layers were separated. The aqueous layer was extracted into diethyl ether, and then the organic layer was washed with brine, dried, filtered and concentrated. Purification over silica (cyclohexane/diethyl ether, 9/1 to 8/2 R_f= 0.30) gave **234** (718 mg, 73%) as a pale yellow oil.



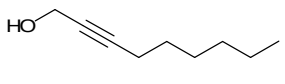
234

NMR: δ_H (300 MHz, $CDCl_3$): 7.44-7.13 (5H, m, H Ar), 5.31 (1H, s, C*H*OH), 2.15 (2H, td, *J*= 7.0 Hz, 2.0 Hz, C≡CCH_2), 1.48-1.13 (8H, m, $CH_3(CH_2)_4$) and 0.80 (3H, t, *J*= 6.4 Hz, CH_3CH_2); δ_C (75 MHz, $CDCl_3$): 141.2 (Cq, Ar), 128.5 (CH, Ar), 128.1 (CH, Ar), 126.6 (CH, Ar), 87.7 (Cq, *C*≡C), 79.8 (Cq, *C*≡C), 64.8 (CH, C≡C*C*HOH), 31.3 (CH_2, C≡CCH_2), 28.5, 28.5, 22.5, 18.8 (CH_2, $CH_3(CH_2)_4$) and 14.0 (CH_3); HRMS *m/z*: $[MNa]^+$: 239.1410, calculated 239.1412; IR: υ_{max} (neat)/cm^{-1}: 3357, 3063, 3031, 2931 and 2227.

Data in agreement with literature.

Non-2-yn-1-ol 235.[9]

n-BuLi (2 mL, 5 mmol) was added to a solution of 1-octyne **237** (500 mg, 4.5 mmol) in THF (100 ml) at 0 ^{o}C then *para*-formaldehyde (150 mg, 5 mmol) was added. After 90 min, a mixture of water and diethyl ether was slowly added at 0 ^{o}C. The layers were separated and the aqueous layer was extracted into diethyl ether. The organic layers were then washed with brine, dried, filtered and concentrated. Purification over silica (cyclohexane/ diethyl ether, 9/1 to 8/2 R_f= 0.24) gave **235** (431 mg, 68%) as a pale yellow oil.



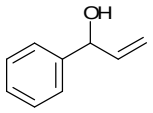
235

NMR: δ_H (300 MHz, $CDCl_3$): 4.23 (2H, t, *J*= 2.1, C*H*$_2$OH), 2.19 (2H, tt, *J*= 7.0 Hz, 2.1 Hz, C≡CC*H*$_2$), 2.10 (s broad, OH), 1.54-1.21 (8H, m, CH_3(C*H*$_2$)$_4$) and 0.87 (3H, t, *J*= 6.7 Hz, C*H*$_3$CH$_2$); δ_C (75 MHz, $CDCl_3$): 87.5 (Cq, *C*≡C), 80.0 (Cq, *C*≡C), 64.8 (CH_2, C≡C*C*H$_2$OH), 31.3 (CH_2, C≡C*C*H$_2$), 28.6, 28.5, 22.4, 18.7 (CH_2, CH_3(*C*H$_2$)$_4$) and 14.0 (CH_3); HRMS *m/z*: $[MNa]^+$: 141.1278, calculated 141.1279; IR: υ_{max} (neat)/cm^{-1}: 3338, 2952, 2924, 2857, 2285, 2224, 1457, 1429, 1135 and 1009.

Data in agreement with literature.

1-**Phenylprop-2-ene-1-ol 238.**[10]

$LiAlH_4$ (42 mg, 1.1 mmol) was added to a solution of 1-phenylprop-2-yn-1-ol **233** (150 mg, 1.1 mmol) in THF (4 ml) at room temperature. After 3 h, a mixture of water and diethyl ether was slowly added at 0 ^oC. After 30min the layers were separated, and the aqueous layer was extracted with diethyl ether. The organic layers were washed with brine, dried, filtered and concentrated. Purification over silica (cyclohexane/ diethyl ether 8/2 Rf= 0.20) gave **238** (136 mg, 89.3%).



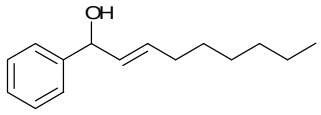
238

NMR: δ_H (300 MHz, $CDCl_3$): 7.58-7.26 (5H, m, Ar), 6.06 (1H, m, C*H*=CH_2), 5.36 (1H, dt, *J*= 17.3 Hz, 1.3 Hz, C*H*OH), 5.21 (2H, m, CH=CH_2) and 2.1 (1H, s broad, O*H*); ^{13}C, δ_C (75 MHz, $CDCl_3$): 142.5 (Cq, Ar), 140.1 (CH, *C*H=CH_2), 128.5 (CH, Ar), 127.7 (CH), 126.3 (CH), 115.1 (CH_2, CH=*C*H_2) and 75.3 (CH, *C*HOH); LRMS *m/z*: $[M]^+$: 134.07, calculated 134.07.

Data in agreement with literature.

Phenylnon-2-ene-1-ol 239.[11]

$LiAlH_4$ (17 mg, 0.5 mmol) was added to a solution of 1-phenylnon-2-yn-1-ol **234** (100 mg, 0.5 mmol) in THF (3 ml) at room temperature. After 3 h, a mixture of water and diethyl ether was slowly added at 0 ^oC. After 30 min the layers was separated. The aqueous layer was extracted into diethyl ether, and then the organic layers were washed with brine, dried, filtered and concentrated. Purification over silica (cyclohexane/diethyl ether 8/2 R_f= 0.24) gave **26** (92 mg, 91%).

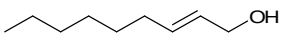


239

NMR: δ_H (300 MHz, $CDCl_3$): 7.50-7.15 (5H, m, Ar.), 5.73-5.53 (2H, m, C*H*=C*H*), 5.08 (1H, d, *J*= 6.5 Hz, C*H*OH), 1.97 (2H, dt, *J*= 7.2 Hz, 6.6 Hz, CH=CHCH_2), 1.89 (1H, s broad, OH), 1.42-1.18 (8H, m, $CH_3(CH_2)_4$) and 0.80 (3H, t, *J*= 6.9 Hz, CH_3CH_2); δ_C (75 MHz, $CDCl_3$): 143.3 (Cq), 132.9 (CH, CH=*C*HCHOH), 132.1 (CH, *C*H=CHCHOH), 128.4 (CH, Ar), 127.4 (CH, Ar), 126.1 (CH, Ar), 75.2 (CH,*C*HOH), 32.2 (CH_2, CH_2CH=CH), 31.6, 29.0, 28.8, 22.6 (CH_2, $CH_3(CH_2)_4$) and 14.1 (CH_3, $CH_3(CH_2)_4$); LRMS *m/z*: $[M]^+$: 218.2, calculated 218.2; IR: υ_{max} (neat)/cm^{-1}: 3355, 3025, 2952, 2918, 2851, 1664, 1600, 1490, 1451, 1004, 965, 746 and 696.

Non-2-en-1-ol 240.[12]

$LiAlH_4$ (24 mg, 0.7 mmol) was added to a solution of non-2-yn-1-ol **235** (100 mg, 0.7 mmol) in THF (3 ml) at room temperature. After 3 h, a mixture of water and diethyl ether was slowly added at 0 ^oC. After a further 30 min the layers was separated, and the aqueous layer was extracted into diethyl ether. The organic layers were washed with brine, dried, filtered and concentrated. Purification over silica (cyclohexane/diethyl ether 8/2 R_f= 0.22) gave alcohol **240** (88 mg, 87%).

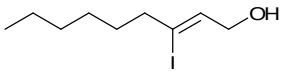


240

NMR: δ_H (300 MHz, $CDCl_3$): 5.73-5.54 (2H, m, C*H*=C*H*), 4.06 (2H, d, *J*= 5.1 Hz, CH_2OH), 1.96 (2H, dt, *J*= 7.2 Hz, 6.6 Hz, CH=CHCH_2), 1.86 (1H, s broad, OH), 1.36-1.14 (8H, m, $CH_3(CH_2)_4$) and 0.87 (3H, t, *J*= 7.0 Hz, CH_3CH_2); δ_C (75 MHz, $CDCl_3$): 133.3 (CH, CH=*C*HCH_2OH), 128.8 (CH, *C*H=CHCH_2OH), 63.6 (CH,*C*H_2OH), 32.2 (CH_2, *C*H_2CH=CH), 31.7, 29.1, 28.8, 22.5 (CH_2, $CH_3(CH_2)_4$) and 14.0 (CH_3, *C*$H_3(CH_2)_4$); LRMS *m/z*: $[MH]^+$: 143.2, calculated 143.1; IR: υ_{max} (neat)/cm^{-1}: 3456, 2924, 2857, 1723, 1653, 1462, 1264, 1166 and 973.

(*Z*)-3-Iodonon-2-en-1-ol 244.

$LiAlH_4$ (42 mg, 1.1 mmol) was added to a solution of alcohol **235** (100 mg, 0.7 mmol) and sodium methoxide (122 mg, 2.1 mmol) in THF (3 mL). After 3h at reflux, the reaction was cooled to -78 °C and I_2 (721 mg, 2.8 mmol) was added. The reaction was then allowed to warm up to r.t. over 12h. Water and diethyl ether were added and the layers were separated. The organic layer was washed with aq. Na_2SO_3 and the aqueous layer was extracted into diethyl ether. Then the organic layers were dried, fliltrated and concentrated. Purification over silica (hexane/diethyl ether 8/2 R_f= 0.21) gave **244** as an oil (137 mg, 73%).

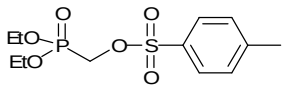


244

NMR: δ_H (300 MHz, $CDCl_3$): 5.80 (1H, tt, *J*= 5.8 Hz, 1.2 Hz, C*H*=CI), 4.17 (2H, d, *J*= 5.8 Hz, CH_2OH), 2.52-2.43 (2H, m, CH=CICH_2), 2.37 (1H, s broad, OH), 158-1.19 (8H, m, $CH_3(CH_2)_4$) and 0.87 (3H, t, *J*= 6.8 Hz, CH_3CH_2); δ_C (75 MHz, $CDCl_3$): 133.3 (CH, CI=*C*HCH_2OH), 110.6 (Cq, *C*I=CHCH_2OH), 67.2 (CH,*C*H_2OH), 45.1 (CH_2, *C*H_2CI=CH), 31.5, 29.1, 27.8, 22.5 (CH_2, $CH_3(CH_2)_4$) and 14.0 (CH_3, *C*$H_3(CH_2)_4$); HRMS *m/z*: $[MH]^+$: 269.0400, calculated 269.0402; IR: υ_{max} (neat)/cm^{-1}: 3266, 2918, 2851, 1639, 1454, 1423, 1200, 1146, 1001 and 500.

Diethyl toluenesulfonylmethylphosphonate 296.[13]

Triethylamine (430 μL, 3.1 mmol) was added dropwise to stirred solution of diethyl (hydroxymethyl)phosphonate **294** (440 μL, 3.0 mmol) in diethyl ether (3.6 ml). The mixture was then cooled to -10 ^{o}C, and a solution of tosyl chloride (594 mg, 3.1 mmol) in diethyl ether (3.6 ml) was added dropwise. After being stirred at 0 ^{o}C for 3 h, the mixture was allowed to warm to room temperature and was then stirred for another 3h. Diethyl ether was then added and the solid was filtered off. The solvent was removed under reduced pressure and the product was purified over silica (dichloromethane, 100%) to give **295** (636 mg, 69%) as a colorless oil.



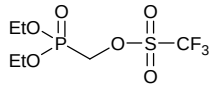
296

NMR: δ_H (300 MHz, $CDCl_3$): 7.71 (2H, d, *J*= 8.2 Hz, Ar), 7.30 (2H, d, *J*= 8.0 Hz, Ar), 4.11 (2H, d, *J*= 9.9 Hz, PCH_2OTs), 4.06 (4H, m, CH_3CH_2OP), 2.37 (3H, s, ArCH_3) and 1.23 (6H, td, *J*= 7.1 Hz, 0.4 Hz, $(CH_3CH_2O)_2P$); δ_C (75 MHz, $CDCl_3$): 145.6 (Cq, Ar), 131.7 (Cq, Ar), 130.4 (CH, Ar); 128.5 (CH, Ar), 63.1 (CH_3, d, *J*= 6.3 Hz, $(CH_3CH_2O)_2$), 61.7 (CH_2, d, *J*= 169.0 Hz, PCH_2OTs), 22.0 (CH_3, ArCH_3) and 16.0 (CH_3, d, *J*= 5.7 Hz, $(CH_3CH_2O)_2$); δ_P (121 MHz, $CDCl_3$): 16.4 (s); HRMS *m/z*: $[MNa]^+$: 345.0534, calculated 345.0538; IR: υ_{max} (neat)/cm^{-1}: 2980, 2924, 1597, 1493, 1365, 1258, 1188, 1096, 1018 and 816.

Data in agreement with literature.

Diethyl trifluoromethanesulfonylmethylphosphonate 297.[14]

Trifluoromethanesulfonyl chloride (360 mg, 2.1 mmol) was added to a suspension of sodium hydride 95% (58 mg, 2.3 mmol) in diethyl ether at -25°C (3 ml). This was followed immediately by the rapid dropwise addition of a solution of diethyl (hydroxymethyl)phosphonate **294** (300 mg, 1.8 mmol) in diethyl ether, maintaining an internal reaction temperature between -20 °C and -15 °C. After the resulting reaction mixture was stirred for 1 h at -20 °C, the mixture was rapidly filtered trough celite, diluted with dichloromethane and thoroughly washed with saturated aqueous sodium hydrogen carbonate. The solution was then was dried and concentrated to give **296**. This compound was not purified any further and was used directly for the fluorination step.



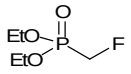
297

NMR: δ_H (300 MHz, $CDCl_3$): 4.60 (2H, d, *J*= 8.8 Hz, PC*H*$_2$OTf), 4.21 (4H, dq, *J*= 8.4 Hz, 7.1 Hz, $CH_3C\mathit{H}_2OP$) and 1.38 (6H, dt, *J*= 7.1Hz, 0.3Hz, C*H*$_3$$CH_2OP$); δ_C (75 MHz, $CDCl_3$): 117,0 (Cq, d, *J*= 318 Hz, CF_3), 66.3 (CH_2, d, *J*= 168.9 Hz, P*C*H_2OTf), 63.8 (CH_2, dd, *J*= 36.2 Hz, 6.3 Hz, ($CH_3C\mathit{H}_2O)_2$) and 16.3 (CH_3, d, *J*= 5.8 Hz, (*C*$H_3CH_2O)_2$); δ_P (121 MHz, $CDCl_3$): 13.4 (s); δ_F (282 MHz, $CDCl_3$): -74.4 (d, *J*= 1.8Hz, CF_3); HRMS *m/z*: $[MNa]^+$: 322.9937, calculated 322.9942; IR: υ_{max} (neat)/cm^{-1}: 1372, 1099, 1213, 1026 and 813.

Data in agreement with literature.

Diethyl fluoromethylphosphonate 294.[15]

A solution of TBAF (2 ml, 2 mmol) was added dropwise to a solution of the triflate **296** (500 mg, 1.6 mmol) in THF (3 ml) at 0 ^{o}C. The solution was stirred at 0 ^{o}C for 90 min. Solvents were then removed and dichloromethane was added. The organic layer was washed with water, dried and concentrated. Purification over silica (hexane/ethyl acetate 1/1) gave **293** (152 mg, 57% over two steps) as a pale yellow oil.



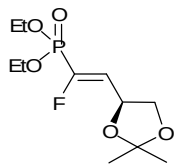
294

NMR: δ_H (300 MHz, $CDCl_3$): 4.76 (2H, dd, *J*= 46.8 Hz, 4.7 Hz, PC*H*$_2$F), 4.22 (4H, dq, *J*= 8.0 Hz, 7.1 Hz, $CH_3C\mathit{H}_2O$) and 1.37 (6H, t, *J*= 7.1Hz, C*H*$_3$$CH_2O$); δ_C (75 MHz, $CDCl_3$): 76.6 (CH_2, dd, *J*= 170.1 Hz, 180.0 Hz, P*C*H_2F), 63.0 (CH_2, d, *J*= 6.5 Hz, ($CH_3C\mathit{H}_2O)_2$) and 16.4 (CH_3, d, *J*= 5.5 Hz, (*C*$H_3CH_2O)_2$); δ_P (121 MHz, $CDCl_3$): 17.5 (d, *J*= 63.3Hz); δ_F (282 MHz, $CDCl_3$): -250.1 (td, *J*= 46.9Hz, 63.3Hz); LRMS *m/z*: $[MH]^+$: 171,0 calculated 171.0; IR: υ_{max} (neat)/cm^{-1}: 1256, 1029, 1394, 1371 and 1336.

Data in agreement with literature.

(*E*)-Diethyl 1-fluoro-2-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl) vinylphosphonate 300.[16]

LDA (280 µL, 0.6 mmol) was added to a solution of diethyl fluoromethylphosphonate **293** (100 mg, 0.59 mmol) in THF (6 ml) at -78 °C. After 15 min, a solution of (*R*)-(+)-2,2-dimethyl-1,3-dioxolane-4-carboxaldehyde **100p** (71 mg, 0.55 mmol) in THF (4 ml) was added at -78 °C, and the reaction was allowed to warm up to rt over 10h. A mixture of water and diethyl ether (1/1, 10 mL) was slowly added and the layers were separated. The aqueous layer was extracted into diethyl ether, and the organic layers were thus washed with brine, dried, filtered and concentrated. Purification over silica (cyclohexane/diethyl ether 1/1 R_f= 0.24) gave **299** (61 mg, 40%) as colourless oil.



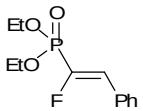
300

NMR: δ_H (300 MHz, $CDCl_3$): 6.00 (1H, td, *J*= 39.0 Hz, 7.8 Hz, C=C*H*), 5.01 (1H, m, C=CHC*H*), 4.15 (5H, m, $(CH_3CH_2O)_2$, C=CCHCHC*H*HO), 3.66 (1H, dd, *J*= 8.3 Hz, 7.0 Hz, C=CCHCHC*H*HO), 1.40 (6H, s, $(CH_3)_2C$) and 1.34 (6H, t, *J*= 7.1 Hz, CH_3CH_2O); δ_C (75 MHz, $CDCl_3$): 153.9 (Cq, dd, *J*= 281 Hz, 233 Hz, *C*FP), 123.9 (CH, dd, *J*= 27.3 Hz, 2.8 Hz, C=*C*H), 109.9 (Cq, $C(CH_3)_2$), 69.0 (CH, dd, *J*= 12.3 Hz, 7.0 Hz, C=C*C*H), 68.8 (CH_2, C=CHCH*C*H_2O), 63.4 (CH_2, d, *J*= 5.9 Hz, $(CH_3CH_2O)_2$), 26.5 (CH_3, $C(CH_3)_2$), 25.7 (CH_3, $C(CH_3)_2$) and 16.2 (CH_3, d, *J*= 6.4 Hz, $(CH_3CH_2O)_2$); δ_P (121 MHz, $CDCl_3$): 4.76 (dqd, *J*= 98.7Hz, 7.9 Hz, 1.3 Hz); δ_F (282 MHz, $CDCl_3$): -250.1 (dd, *J*= 39.0 Hz, 98.8 Hz); HRMS *m/z*: $[MNa]^+$: 305.0931, calculated 305.0930; IR: υ_{max} (neat)/cm^{-1}: 2957, 2924, 2845, 1725, 1454, 1376, 1258, 1155, 1096, 1023 and 800.

Data in agreement with literature.

(*E*)-Diethyl 1-fluoro-2-phenylvinylphosphonate 303.[17]

LDA (1.3 mL, 2.6 mmol) was added to a solution of diethyl fluoromethylphosphonate **293** (457 mg, 2.7 mmol) in THF (45 ml) at -78 °C. After 15 min, benzaldehyde **100r** (250µL, 2.5 mmol) was added at -78 °C. The reaction was allowed to warm up to r.t .overnight. Then a mixture of water and diethyl ether (1/1, 10 mL) was slowly added and the layers were separated and the aqueous layer was extracted into diethyl ether. The organic layers were washed with brine, dried, filtered and concentrated. Purification over silica (cyclohexane/diethyl ether 1/1 R_f= 0.30) gave **302** (212 mg, 32%) as colourless oil.



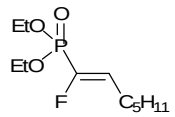
303

NMR: δ_H (300 MHz, $CDCl_3$): 7.66-7.56 (2H, m, Ar), 7.46-7.31 (3H, m, Ar), 6.74 (1H, dd, *J*= 42.3 Hz, 8.6 Hz, C=C*H*Ph), 4.21 (4H, m, CH_3CH_2O) and 1.39 (6H, t, *J*= 7.1 Hz, CH_3CH_2O); δ_C (75 MHz, $CDCl_3$): 150.0 (Cq, dd, *J*= 285 Hz, 236 Hz, C=*C*FP), 131.1 (Cq, dd, *J*= 14.3 Hz, 1.2 Hz, Ar), 129.9 (CH, d, *J*= 7.7 Hz, Ar), 129.4 (CH, d, *J*= 2.2 Hz, Ar), 128.6 (CH, Ar), 123.2 (CH, d, *J*= 30.0 Hz, C=*C*H), 63.1 (CH_2, d, *J*= 5.3 Hz, $(CH_3CH_2O)_2$) and 16.2 (CH_3, d, *J*= 5.5 Hz, $(CH_3CH_2O)_2$); δ_P (121 MHz, $CDCl_3$): 7.0 (d sextuplet, *J*= 97.8 Hz, 8.2 Hz); δ_F (282 MHz, $CDCl_3$): -127.2 (dd, *J*= 97.8 Hz, 42.3 Hz); HRMS *m/z*: $[MNa]^+$: 281.0714, calculated 281.0719; IR: υ_{max} (neat)/cm^{-1}: 2913, 2845, 1711, 1462, 1373, 1205, 1146, 1040, 718 and 696.

Data in agreement with literature.

(E)-Diethyl 1-fluorohept-1-enylvinylphosphonate 304.[12]

LDA (140 µl, 0.280 mmol) was added to a solution of diethyl fluoromethylphosphonate **293** (50 mg, 0.29 mmol) in THF (5 ml) at -78 °C. After 15 min, hexanal **100m** (30 µl, 0.27 mmol) was added at -78 °C, and the reaction was then allowed to warm up to r.t. overnight. A mixture of water and diethyl ether was slowly added and the layers were separated. The aqueous layer was then extracted into diethyl ether and the organic layers were washed with brine, then was dried, filtered and concentrated. Purification over silica (cyclohexane/diethyl ether 1/1 R_f= 0.29) gave **303** (21 mg, 29%) as colourless oil.



304

NMR: δ_H (300 MHz, $CDCl_3$): 5.96 (1H, qd, *J*= 7.7 Hz, 39.8 Hz, FPC=C*H*), 4.15 (4H, m, $(CH_3CH_2O)_2P$), 2.24 (2H, qd, *J*= 7.4 Hz, 2.2 Hz, C=CHCH_2), 1.4-1.25 (6H, m, $CH_3(CH_2)_3$), 1.36 (6H, td, *J*= 7.1 Hz, 0.6 Hz, $(CH_3CH_2O)_2P$) and 0.88 (3H, m, CH_3CH_2); δ_C (75 MHz, $CDCl_3$): 152.1 (Cq, dd, *J*= 283 Hz, 234 Hz, C=*C*FP), 126.83 (CH, dd, *J*= 5.8 Hz, 28.1 Hz, C=*C*H), 62.9 (CH_2, d, *J*= 5.3 Hz, $(CH_3CH_2O)_2P$), 29.7 (CH_2, $CH_3(CH_2)_3$), 27.9 (CH_2, $CH_3(CH_2)_4$), 24.0 (dd, *J*= 10.2 Hz, 4.7 Hz, C=CHCH_2), 22.3 (CH_2, $CH_3(CH_2)_3$), 16.2 (CH_3, d, *J*= 6.0 Hz, $(CH_3CH_2O)_2P$) and 13.9 (CH_3, CH_3CH_2); δ_P (121 MHz, $CDCl_3$): 6.76 (dqd, *J*= 103.2 Hz, 7.8 Hz, 1.4 Hz), δ_F (282 MHz, $CDCl_3$): -132.4 (dd, *J*= 102.7 Hz, 39.8 Hz); HRMS *m/z*: $[MNa]^+$: 275.1182, calculated 275.1188; IR: υ_{max} (neat)/cm^{-1}: 2963, 2935, 2873, 1474, 1381, 1264, 1222, 1146 and 1029.

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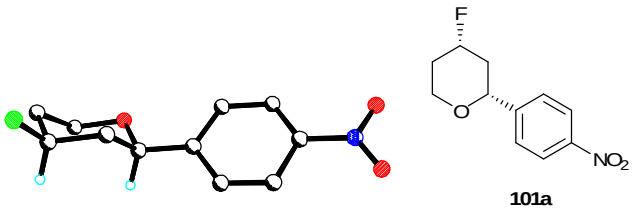
Appendix

X-ray structure of 4-fluoro-2-(4-nitrophenyl)pyran 101a



101a

Table 1. Crystal data and structure refinement for gldh2.

Identification code	gldh2	
Empirical formula	C11 H12 F N O3	
Formula weight	225.22	
Temperature	93(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 7.201(6) Å	α= 90°.
	b = 19.914(9) Å	β= 92.10(2)°.
	c = 21.937(9) Å	γ = 90°.
Volume	3144(3) $Å^3$	
Z	12	
Density (calculated)	1.428 Mg/m^3	
Absorption coefficient	0.116 mm^{-1}	
F(000)	1416	
Crystal size	0.2000 x 0.2000 x 0.0100 mm^3	
Theta range for data collection	2.05 to 25.35°.	
Index ranges	-8<=h<=8, -19<=k<=23, -26<=l<=26	
Reflections collected	14508	
Independent reflections	5019 [R(int) = 0.0980]	
Completeness to theta = 25.00°	87.9 %	
Absorption correction	Multiscan	

Max. and min. transmission	1.0000 and 0.9045
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5019 / 0 / 434
Goodness-of-fit on F^2	1.457
Final R indices [I>2sigma(I)]	R1 = 0.1692, wR2 = 0.4283
R indices (all data)	R1 = 0.2239, wR2 = 0.4656
Largest diff. peak and hole	0.795 and -0.513 e.$Å^{-3}$

Table 2. Bond lengths [Å] and angles [°] for gldh2.

O(1)-C(2)	1.427(11)
O(1)-C(6)	1.459(10)
C(2)-C(7)	1.540(11)
C(2)-C(3)	1.567(13)
C(3)-C(4)	1.524(11)
C(4)-F(4)	1.408(10)
C(4)-C(5)	1.520(13)
C(5)-C(6)	1.534(12)
C(7)-C(8)	1.382(12)
C(7)-C(12)	1.401(11)
C(8)-C(9)	1.379(13)
C(9)-C(10)	1.392(11)
C(10)-C(11)	1.337(13)
C(10)-N(10)	1.459(11)
N(10)-O(10)	1.246(11)
N(10)-O(11)	1.261(10)
C(11)-C(12)	1.414(13)
O(21)-C(22)	1.426(11)
O(21)-C(26)	1.434(10)
C(22)-C(27)	1.502(11)
C(22)-C(23)	1.571(12)
C(23)-C(24)	1.511(12)
C(24)-F(24)	1.434(9)
C(24)-C(25)	1.498(12)
C(25)-C(26)	1.550(12)
C(27)-C(28)	1.379(12)
C(27)-C(32)	1.423(11)

C(28)-C(29)	1.382(12)
C(29)-C(30)	1.423(11)
C(30)-C(31)	1.378(13)
C(30)-N(30)	1.469(10)
N(30)-O(30)	1.226(10)
N(30)-O(31)	1.239(9)
C(31)-C(32)	1.407(12)
O(41)-C(42)	1.409(11)
O(41)-C(46)	1.455(9)
C(42)-C(47)	1.514(10)
C(42)-C(43)	1.547(12)
C(43)-C(44)	1.526(10)
C(44)-F(44)	1.452(10)
C(44)-C(45)	1.487(13)
C(45)-C(46)	1.556(12)
C(47)-C(48)	1.397(13)
C(47)-C(52)	1.418(11)
C(48)-C(49)	1.386(12)
C(49)-C(50)	1.426(12)
C(50)-C(51)	1.412(13)
C(50)-N(50)	1.459(10)
N(50)-O(50)	1.213(10)
N(50)-O(51)	1.254(9)
C(51)-C(52)	1.363(11)

C(2)-O(1)-C(6)	108.7(6)
O(1)-C(2)-C(7)	110.6(7)
O(1)-C(2)-C(3)	109.2(7)
C(7)-C(2)-C(3)	107.5(7)
C(4)-C(3)-C(2)	108.5(7)
F(4)-C(4)-C(5)	108.6(7)
F(4)-C(4)-C(3)	109.4(7)
C(5)-C(4)-C(3)	110.7(7)
C(4)-C(5)-C(6)	108.9(8)
O(1)-C(6)-C(5)	110.8(7)
C(8)-C(7)-C(12)	120.0(8)
C(8)-C(7)-C(2)	118.3(7)
C(12)-C(7)-C(2)	121.5(8)

C(9)-C(8)-C(7)	121.6(7)
C(8)-C(9)-C(10)	117.6(9)
C(11)-C(10)-C(9)	122.1(8)
C(11)-C(10)-N(10)	121.0(7)
C(9)-C(10)-N(10)	116.9(8)
O(10)-N(10)-O(11)	120.4(7)
O(10)-N(10)-C(10)	121.8(7)
O(11)-N(10)-C(10)	117.8(8)
C(10)-C(11)-C(12)	121.1(8)
C(7)-C(12)-C(11)	117.4(9)
C(22)-O(21)-C(26)	110.5(6)
O(21)-C(22)-C(27)	111.4(7)
O(21)-C(22)-C(23)	108.1(7)
C(27)-C(22)-C(23)	110.9(7)
C(24)-C(23)-C(22)	109.3(7)
F(24)-C(24)-C(25)	109.5(7)
F(24)-C(24)-C(23)	108.2(7)
C(25)-C(24)-C(23)	110.2(7)
C(24)-C(25)-C(26)	108.2(7)
O(21)-C(26)-C(25)	110.5(7)
C(28)-C(27)-C(32)	119.3(7)
C(28)-C(27)-C(22)	119.0(7)
C(32)-C(27)-C(22)	121.7(8)
C(29)-C(28)-C(27)	124.0(7)
C(28)-C(29)-C(30)	116.3(8)
C(31)-C(30)-C(29)	121.3(7)
C(31)-C(30)-N(30)	120.4(7)
C(29)-C(30)-N(30)	118.3(8)
O(30)-N(30)-O(31)	125.0(7)
O(30)-N(30)-C(30)	119.1(7)
O(31)-N(30)-C(30)	115.9(8)
C(30)-C(31)-C(32)	121.4(8)
C(31)-C(32)-C(27)	117.7(9)
C(42)-O(41)-C(46)	110.8(6)
O(41)-C(42)-C(47)	110.5(7)
O(41)-C(42)-C(43)	111.8(7)
C(47)-C(42)-C(43)	109.7(7)
C(44)-C(43)-C(42)	106.7(7)

F(44)-C(44)-C(45)	107.6(7)
F(44)-C(44)-C(43)	106.8(6)
C(45)-C(44)-C(43)	111.7(7)
C(44)-C(45)-C(46)	109.7(7)
O(41)-C(46)-C(45)	110.0(7)
C(48)-C(47)-C(52)	118.5(7)
C(48)-C(47)-C(42)	118.7(7)
C(52)-C(47)-C(42)	122.8(9)
C(49)-C(48)-C(47)	122.5(8)
C(48)-C(49)-C(50)	116.9(9)
C(51)-C(50)-C(49)	121.8(7)
C(51)-C(50)-N(50)	120.7(7)
C(49)-C(50)-N(50)	117.3(9)
O(50)-N(50)-O(51)	122.4(7)
O(50)-N(50)-C(50)	120.4(7)
O(51)-N(50)-C(50)	117.1(8)
C(52)-C(51)-C(50)	118.7(8)
C(51)-C(52)-C(47)	121.5(9)

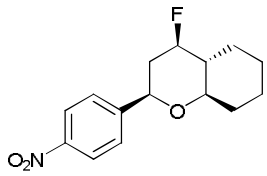
Table 3. Torsion angles [°] for gldh2.

C(6)-O(1)-C(2)-C(7)	176.4(7)
C(6)-O(1)-C(2)-C(3)	-65.5(8)
O(1)-C(2)-C(3)-C(4)	60.6(9)
C(7)-C(2)-C(3)-C(4)	-179.4(7)
C(2)-C(3)-C(4)-F(4)	-174.2(7)
C(2)-C(3)-C(4)-C(5)	-54.5(10)
F(4)-C(4)-C(5)-C(6)	173.9(6)
C(3)-C(4)-C(5)-C(6)	53.7(10)
C(2)-O(1)-C(6)-C(5)	65.4(9)
C(4)-C(5)-C(6)-O(1)	-58.5(9)
O(1)-C(2)-C(7)-C(8)	-159.7(8)
C(3)-C(2)-C(7)-C(8)	81.1(10)
O(1)-C(2)-C(7)-C(12)	14.6(12)
C(3)-C(2)-C(7)-C(12)	-104.6(9)
C(12)-C(7)-C(8)-C(9)	5.2(13)
C(2)-C(7)-C(8)-C(9)	179.7(8)

C(7)-C(8)-C(9)-C(10)	-4.7(13)
C(8)-C(9)-C(10)-C(11)	3.1(13)
C(8)-C(9)-C(10)-N(10)	-178.1(8)
C(11)-C(10)-N(10)-O(10)	-179.8(8)
C(9)-C(10)-N(10)-O(10)	1.4(12)
C(11)-C(10)-N(10)-O(11)	2.9(12)
C(9)-C(10)-N(10)-O(11)	-175.9(7)
C(9)-C(10)-C(11)-C(12)	-2.0(14)
N(10)-C(10)-C(11)-C(12)	179.3(8)
C(8)-C(7)-C(12)-C(11)	-3.8(13)
C(2)-C(7)-C(12)-C(11)	-178.1(8)
C(10)-C(11)-C(12)-C(7)	2.3(14)
C(26)-O(21)-C(22)-C(27)	174.3(7)
C(26)-O(21)-C(22)-C(23)	-63.6(8)
O(21)-C(22)-C(23)-C(24)	59.4(8)
C(27)-C(22)-C(23)-C(24)	-178.2(7)
C(22)-C(23)-C(24)-F(24)	-176.3(6)
C(22)-C(23)-C(24)-C(25)	-56.7(9)
F(24)-C(24)-C(25)-C(26)	174.6(6)
C(23)-C(24)-C(25)-C(26)	55.7(9)
C(22)-O(21)-C(26)-C(25)	64.8(9)
C(24)-C(25)-C(26)-O(21)	-59.2(9)
O(21)-C(22)-C(27)-C(28)	-165.8(8)
C(23)-C(22)-C(27)-C(28)	73.7(10)
O(21)-C(22)-C(27)-C(32)	14.2(11)
C(23)-C(22)-C(27)-C(32)	-106.2(9)
C(32)-C(27)-C(28)-C(29)	1.7(14)
C(22)-C(27)-C(28)-C(29)	-178.2(9)
C(27)-C(28)-C(29)-C(30)	-2.0(14)
C(28)-C(29)-C(30)-C(31)	1.4(13)
C(28)-C(29)-C(30)-N(30)	179.9(8)
C(31)-C(30)-N(30)-O(30)	176.8(8)
C(29)-C(30)-N(30)-O(30)	-1.6(12)
C(31)-C(30)-N(30)-O(31)	-3.3(12)
C(29)-C(30)-N(30)-O(31)	178.3(7)
C(29)-C(30)-C(31)-C(32)	-0.7(14)
N(30)-C(30)-C(31)-C(32)	-179.1(8)
C(30)-C(31)-C(32)-C(27)	0.4(13)

C(28)-C(27)-C(32)-C(31)	-0.9(12)
C(22)-C(27)-C(32)-C(31)	179.1(8)
C(46)-O(41)-C(42)-C(47)	173.8(6)
C(46)-O(41)-C(42)-C(43)	-63.7(8)
O(41)-C(42)-C(43)-C(44)	59.6(9)
C(47)-C(42)-C(43)-C(44)	-177.4(8)
C(42)-C(43)-C(44)-F(44)	-173.1(7)
C(42)-C(43)-C(44)-C(45)	-55.7(10)
F(44)-C(44)-C(45)-C(46)	172.2(6)
C(43)-C(44)-C(45)-C(46)	55.3(9)
C(42)-O(41)-C(46)-C(45)	60.3(9)
C(44)-C(45)-C(46)-O(41)	-55.8(9)
O(41)-C(42)-C(47)-C(48)	-164.4(7)
C(43)-C(42)-C(47)-C(48)	71.9(10)
O(41)-C(42)-C(47)-C(52)	16.5(11)
C(43)-C(42)-C(47)-C(52)	-107.2(9)
C(52)-C(47)-C(48)-C(49)	0.6(12)
C(42)-C(47)-C(48)-C(49)	-178.5(8)
C(47)-C(48)-C(49)-C(50)	-2.0(12)
C(48)-C(49)-C(50)-C(51)	3.5(12)
C(48)-C(49)-C(50)-N(50)	178.1(7)
C(51)-C(50)-N(50)-O(50)	174.9(8)
C(49)-C(50)-N(50)-O(50)	0.2(12)
C(51)-C(50)-N(50)-O(51)	-8.8(12)
C(49)-C(50)-N(50)-O(51)	176.6(7)
C(49)-C(50)-C(51)-C(52)	-3.5(13)
N(50)-C(50)-C(51)-C(52)	-177.9(7)
C(50)-C(51)-C(52)-C(47)	1.9(12)
C(48)-C(47)-C(52)-C(51)	-0.5(12)
C(42)-C(47)-C(52)-C(51)	178.6(8)

X-ray structure of 4-Fluoro-2-(4-nitrophenyl)octahydrochromene 114b.



114b

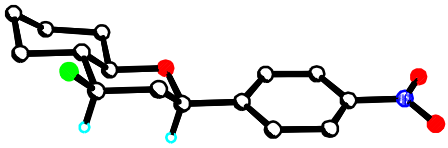


Table 1. Crystal data and structure refinement for gldh3.

Identification code	gldh3	
Empirical formula	C15 H18 F N O3	
Formula weight	279.30	
Temperature	173(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 18.055(3) Å	α= 90°.
	b = 8.2006(15) Å	β= 90.674(7)°.
	c = 18.324(3) Å	γ = 90°.
Volume	2712.9(8) $Å^3$	
Z	8	
Density (calculated)	1.368 Mg/m^3	
Absorption coefficient	0.868 mm^{-1}	
F(000)	1184	
Crystal size	0.200 x 0.030 x 0.010 mm^3	
Theta range for data collection	3.42 to 67.50°.	
Index ranges	-21<=h<=21, -9<=k<=9, -21<=l<=21	
Reflections collected	28815	
Independent reflections	4478 [R(int) = 0.2520]	
Completeness to theta = 67.00°	91.9 %	
Absorption correction	Multiscan	
Max. and min. transmission	1.0000 and 0.9537	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4478 / 0 / 362	
Goodness-of-fit on F^2	1.200	

Final R indices [I>2sigma(I)]	R1 = 0.2156, wR2 = 0.4531
R indices (all data)	R1 = 0.2593, wR2 = 0.4767
Largest diff. peak and hole	0.487 and -0.446 e.Å^{-3}

Table 2. Bond lengths [Å] and angles [°] for gldh3.

O(1)-C(2)	1.419(12)
O(1)-C(6)	1.453(13)
C(2)-C(3)	1.534(16)
C(2)-C(7)	1.555(15)
C(3)-C(4)	1.513(15)
C(4)-F(4)	1.409(13)
C(4)-C(5)	1.507(15)
C(5)-C(13)	1.500(16)
C(5)-C(6)	1.517(16)
C(6)-C(16)	1.522(15)
C(7)-C(12)	1.360(15)
C(7)-C(8)	1.408(16)
C(8)-C(9)	1.348(16)
C(9)-C(10)	1.364(16)
C(10)-C(11)	1.409(17)
C(10)-N(10)	1.472(14)
N(10)-O(11)	1.187(13)
N(10)-O(10)	1.220(14)
C(11)-C(12)	1.370(16)
C(13)-C(14)	1.531(16)
C(14)-C(15)	1.533(18)
C(15)-C(16)	1.510(18)
O(21)-C(22)	1.431(13)
O(21)-C(26)	1.464(13)
C(22)-C(27)	1.446(18)
C(22)-C(23)	1.566(18)
C(23)-C(24)	1.506(16)
C(24)-F(24)	1.409(13)
C(24)-C(25)	1.499(16)
C(25)-C(26)	1.495(16)
C(25)-C(33)	1.529(15)

C(26)-C(36)	1.528(16)
C(27)-C(28)	1.403(17)
C(27)-C(32)	1.411(17)
C(28)-C(29)	1.375(17)
C(29)-C(30)	1.392(18)
C(30)-C(31)	1.404(18)
C(30)-N(30)	1.444(16)
N(30)-O(30)	1.218(14)
N(30)-O(31)	1.220(14)
C(31)-C(32)	1.363(16)
C(33)-C(34)	1.516(17)
C(34)-C(35)	1.519(17)
C(35)-C(36)	1.559(17)

C(2)-O(1)-C(6)	110.2(8)
O(1)-C(2)-C(3)	110.1(10)
O(1)-C(2)-C(7)	105.6(9)
C(3)-C(2)-C(7)	111.2(9)
C(4)-C(3)-C(2)	107.6(9)
F(4)-C(4)-C(5)	107.6(9)
F(4)-C(4)-C(3)	107.8(8)
C(5)-C(4)-C(3)	110.3(9)
C(13)-C(5)-C(4)	114.5(10)
C(13)-C(5)-C(6)	108.9(10)
C(4)-C(5)-C(6)	107.4(10)
O(1)-C(6)-C(5)	111.6(9)
O(1)-C(6)-C(16)	106.0(9)
C(5)-C(6)-C(16)	111.4(9)
C(12)-C(7)-C(8)	117.5(11)
C(12)-C(7)-C(2)	122.0(10)
C(8)-C(7)-C(2)	120.4(10)
C(9)-C(8)-C(7)	121.5(12)
C(8)-C(9)-C(10)	118.9(11)
C(9)-C(10)-C(11)	122.5(10)
C(9)-C(10)-N(10)	120.2(10)
C(11)-C(10)-N(10)	117.3(11)
O(11)-N(10)-O(10)	121.1(11)
O(11)-N(10)-C(10)	120.7(10)

O(10)-N(10)-C(10)	118.2(11)
C(12)-C(11)-C(10)	115.9(12)
C(7)-C(12)-C(11)	123.6(11)
C(5)-C(13)-C(14)	110.9(10)
C(13)-C(14)-C(15)	109.4(9)
C(16)-C(15)-C(14)	112.5(10)
C(15)-C(16)-C(6)	111.6(10)
C(22)-O(21)-C(26)	113.5(9)
O(21)-C(22)-C(27)	109.5(10)
O(21)-C(22)-C(23)	109.2(10)
C(27)-C(22)-C(23)	112.0(10)
C(24)-C(23)-C(22)	109.8(10)
F(24)-C(24)-C(25)	111.3(10)
F(24)-C(24)-C(23)	109.1(10)
C(25)-C(24)-C(23)	113.1(10)
C(26)-C(25)-C(24)	109.5(10)
C(26)-C(25)-C(33)	110.2(10)
C(24)-C(25)-C(33)	114.3(10)
O(21)-C(26)-C(25)	110.5(9)
O(21)-C(26)-C(36)	106.8(9)
C(25)-C(26)-C(36)	113.1(10)
C(28)-C(27)-C(32)	117.2(11)
C(28)-C(27)-C(22)	121.7(11)
C(32)-C(27)-C(22)	120.9(11)
C(29)-C(28)-C(27)	122.5(12)
C(28)-C(29)-C(30)	118.8(11)
C(29)-C(30)-C(31)	119.9(11)
C(29)-C(30)-N(30)	119.8(11)
C(31)-C(30)-N(30)	120.2(12)
O(30)-N(30)-O(31)	123.8(12)
O(30)-N(30)-C(30)	117.1(13)
O(31)-N(30)-C(30)	119.0(11)
C(32)-C(31)-C(30)	120.5(12)
C(31)-C(32)-C(27)	121.0(11)
C(34)-C(33)-C(25)	111.1(10)
C(33)-C(34)-C(35)	111.7(10)
C(34)-C(35)-C(36)	110.2(10)
C(26)-C(36)-C(35)	108.4(10)

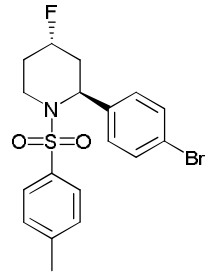
Table 3. Torsion angles [°] for gldh3.

C(6)-O(1)-C(2)-C(3)	62.1(12)
C(6)-O(1)-C(2)-C(7)	-177.8(9)
O(1)-C(2)-C(3)-C(4)	-60.5(12)
C(7)-C(2)-C(3)-C(4)	-177.2(9)
C(2)-C(3)-C(4)-F(4)	176.0(9)
C(2)-C(3)-C(4)-C(5)	58.8(13)
F(4)-C(4)-C(5)-C(13)	64.0(13)
C(3)-C(4)-C(5)-C(13)	-178.6(10)
F(4)-C(4)-C(5)-C(6)	-175.0(9)
C(3)-C(4)-C(5)-C(6)	-57.6(13)
C(2)-O(1)-C(6)-C(5)	-61.8(12)
C(2)-O(1)-C(6)-C(16)	176.8(9)
C(13)-C(5)-C(6)-O(1)	-177.2(9)
C(4)-C(5)-C(6)-O(1)	58.3(12)
C(13)-C(5)-C(6)-C(16)	-59.0(13)
C(4)-C(5)-C(6)-C(16)	176.5(10)
O(1)-C(2)-C(7)-C(12)	11.6(15)
C(3)-C(2)-C(7)-C(12)	131.0(11)
O(1)-C(2)-C(7)-C(8)	-172.0(10)
C(3)-C(2)-C(7)-C(8)	-52.6(15)
C(12)-C(7)-C(8)-C(9)	-1.9(18)
C(2)-C(7)-C(8)-C(9)	-178.4(11)
C(7)-C(8)-C(9)-C(10)	0.5(19)
C(8)-C(9)-C(10)-C(11)	1.5(18)
C(8)-C(9)-C(10)-N(10)	178.0(11)
C(9)-C(10)-N(10)-O(11)	-179.0(12)
C(11)-C(10)-N(10)-O(11)	-2.3(16)
C(9)-C(10)-N(10)-O(10)	2.0(17)
C(11)-C(10)-N(10)-O(10)	178.7(11)
C(9)-C(10)-C(11)-C(12)	-1.9(17)
N(10)-C(10)-C(11)-C(12)	-178.5(10)
C(8)-C(7)-C(12)-C(11)	1.4(17)
C(2)-C(7)-C(12)-C(11)	177.9(11)

C(10)-C(11)-C(12)-C(7)	0.4(17)
C(4)-C(5)-C(13)-C(14)	-178.3(10)
C(6)-C(5)-C(13)-C(14)	61.5(13)
C(5)-C(13)-C(14)-C(15)	-58.6(13)
C(13)-C(14)-C(15)-C(16)	53.4(14)
C(14)-C(15)-C(16)-C(6)	-51.9(14)
O(1)-C(6)-C(16)-C(15)	176.0(10)
C(5)-C(6)-C(16)-C(15)	54.5(14)
C(26)-O(21)-C(22)-C(27)	-178.1(10)
C(26)-O(21)-C(22)-C(23)	58.9(13)
O(21)-C(22)-C(23)-C(24)	-53.2(14)
C(27)-C(22)-C(23)-C(24)	-174.7(11)
C(22)-C(23)-C(24)-F(24)	176.9(10)
C(22)-C(23)-C(24)-C(25)	52.5(15)
F(24)-C(24)-C(25)-C(26)	-177.4(9)
C(23)-C(24)-C(25)-C(26)	-54.2(14)
F(24)-C(24)-C(25)-C(33)	58.3(14)
C(23)-C(24)-C(25)-C(33)	-178.5(11)
C(22)-O(21)-C(26)-C(25)	-61.6(13)
C(22)-O(21)-C(26)-C(36)	174.9(10)
C(24)-C(25)-C(26)-O(21)	56.2(13)
C(33)-C(25)-C(26)-O(21)	-177.2(10)
C(24)-C(25)-C(26)-C(36)	175.9(10)
C(33)-C(25)-C(26)-C(36)	-57.5(14)
O(21)-C(22)-C(27)-C(28)	-178.2(11)
C(23)-C(22)-C(27)-C(28)	-57.0(17)
O(21)-C(22)-C(27)-C(32)	7.0(17)
C(23)-C(22)-C(27)-C(32)	128.3(12)
C(32)-C(27)-C(28)-C(29)	-1.5(19)
C(22)-C(27)-C(28)-C(29)	-176.5(12)
C(27)-C(28)-C(29)-C(30)	3.7(19)
C(28)-C(29)-C(30)-C(31)	-3.8(19)
C(28)-C(29)-C(30)-N(30)	179.5(11)
C(29)-C(30)-N(30)-O(30)	-26.2(17)
C(31)-C(30)-N(30)-O(30)	157.1(12)
C(29)-C(30)-N(30)-O(31)	156.8(12)
C(31)-C(30)-N(30)-O(31)	-19.9(18)
C(29)-C(30)-C(31)-C(32)	2(2)

N(30)-C(30)-C(31)-C(32)	178.4(12)
C(30)-C(31)-C(32)-C(27)	0.5(19)
C(28)-C(27)-C(32)-C(31)	-0.6(18)
C(22)-C(27)-C(32)-C(31)	174.4(12)
C(26)-C(25)-C(33)-C(34)	55.3(14)
C(24)-C(25)-C(33)-C(34)	179.1(10)
C(25)-C(33)-C(34)-C(35)	-56.3(13)
C(33)-C(34)-C(35)-C(36)	57.0(13)
O(21)-C(26)-C(36)-C(35)	179.5(10)
C(25)-C(26)-C(36)-C(35)	57.7(14)
C(34)-C(35)-C(36)-C(26)	-56.1(14)

X-ray structure of *N*-(Tosyl)-2-(4-bromophenyl)-4-fluoropiperidine 196b



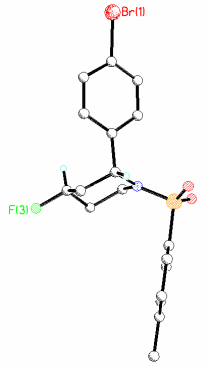


Table 1. Crystal data and structure refinement for gldh4.

Identification code	gldh4	
Empirical formula	C18 H19 Br F N O2 S	
Formula weight	412.31	
Temperature	93(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 13.454(3) Å	α= 90°.
	b = 9.5255(19) Å	β= 94.451(18)°.
	c = 13.714(3) Å	γ = 90°.
Volume	1752.2(6) $Å^3$	
Z	4	
Density (calculated)	1.563 Mg/m^3	
Absorption coefficient	2.485 mm^{-1}	
F(000)	840	
Crystal size	0.120 x 0.120 x 0.120 mm^3	
Theta range for data collection	2.61 to 25.34°.	
Index ranges	-16<=h<=16, -11<=k<=10, -16<=l<=16	
Reflections collected	15768	
Independent reflections	3180 [R(int) = 0.1111]	
Completeness to theta = 25.00°	99.5 %	
Absorption correction	Multiscan	
Max. and min. transmission	1.0000 and 0.9129	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3180 / 0 / 219	

Goodness-of-fit on F^2	1.219
Final R indices [I>2sigma(I)]	R1 = 0.0685, wR2 = 0.1472
R indices (all data)	R1 = 0.0731, wR2 = 0.1504
Largest diff. peak and hole	0.468 and -1.099 e.$Å^{-3}$

Table 2. Bond lengths [Å] and angles [°] for gldh4.

N(1)-C(2)	1.470(6)
N(1)-C(6)	1.485(6)
N(1)-S(1)	1.611(4)
C(2)-C(7)	1.533(6)
C(2)-C(3)	1.548(7)
C(3)-C(4)	1.505(7)
F(4)-C(4)	1.425(5)
C(4)-C(5)	1.506(7)
C(5)-C(6)	1.516(7)
C(7)-C(8)	1.395(6)
C(7)-C(12)	1.399(6)
C(8)-C(9)	1.374(7)
C(9)-C(10)	1.382(7)
C(10)-C(11)	1.377(7)
C(10)-Br(10)	1.898(5)
C(11)-C(12)	1.391(6)
S(1)-O(1)	1.439(3)
S(1)-O(2)	1.444(3)
S(1)-C(13)	1.770(5)
C(13)-C(18)	1.387(7)
C(13)-C(14)	1.397(7)
C(14)-C(15)	1.395(7)
C(15)-C(16)	1.389(7)
C(16)-C(17)	1.400(8)
C(16)-C(19)	1.509(7)
C(17)-C(18)	1.384(7)

C(2)-N(1)-C(6)	116.6(4)
C(2)-N(1)-S(1)	122.4(3)
C(6)-N(1)-S(1)	120.4(3)

N(1)-C(2)-C(7)	110.5(4)
N(1)-C(2)-C(3)	109.7(4)
C(7)-C(2)-C(3)	114.6(4)
C(4)-C(3)-C(2)	109.7(4)
F(4)-C(4)-C(3)	108.6(4)
F(4)-C(4)-C(5)	108.9(4)
C(3)-C(4)-C(5)	111.1(4)
C(4)-C(5)-C(6)	109.2(4)
N(1)-C(6)-C(5)	111.4(4)
C(8)-C(7)-C(12)	118.0(4)
C(8)-C(7)-C(2)	122.0(4)
C(12)-C(7)-C(2)	119.9(4)
C(9)-C(8)-C(7)	121.1(5)
C(8)-C(9)-C(10)	120.2(4)
C(11)-C(10)-C(9)	120.1(4)
C(11)-C(10)-Br(10)	119.6(4)
C(9)-C(10)-Br(10)	120.2(4)
C(10)-C(11)-C(12)	119.7(4)
C(11)-C(12)-C(7)	120.8(4)
O(1)-S(1)-O(2)	119.3(2)
O(1)-S(1)-N(1)	107.4(2)
O(2)-S(1)-N(1)	107.0(2)
O(1)-S(1)-C(13)	107.9(2)
O(2)-S(1)-C(13)	107.2(2)
N(1)-S(1)-C(13)	107.5(2)
C(18)-C(13)-C(14)	120.9(4)
C(18)-C(13)-S(1)	120.2(4)
C(14)-C(13)-S(1)	118.8(4)
C(15)-C(14)-C(13)	118.3(5)
C(16)-C(15)-C(14)	122.1(5)
C(15)-C(16)-C(17)	117.6(5)
C(15)-C(16)-C(19)	121.1(5)
C(17)-C(16)-C(19)	121.2(5)
C(18)-C(17)-C(16)	121.7(5)
C(17)-C(18)-C(13)	119.2(5)

Symmetry transformations used to generate equivalent atoms:

Table 3. Torsion angles [°] for gldh4.

C(6)-N(1)-C(2)-C(7)	76.5(5)
S(1)-N(1)-C(2)-C(7)	-111.8(4)
C(6)-N(1)-C(2)-C(3)	-50.8(5)
S(1)-N(1)-C(2)-C(3)	121.0(4)
N(1)-C(2)-C(3)-C(4)	53.7(5)
C(7)-C(2)-C(3)-C(4)	-71.3(5)
C(2)-C(3)-C(4)-F(4)	179.7(4)
C(2)-C(3)-C(4)-C(5)	-60.5(5)
F(4)-C(4)-C(5)-C(6)	179.8(4)
C(3)-C(4)-C(5)-C(6)	60.1(5)
C(2)-N(1)-C(6)-C(5)	51.6(5)
S(1)-N(1)-C(6)-C(5)	-120.3(4)
C(4)-C(5)-C(6)-N(1)	-53.6(5)
N(1)-C(2)-C(7)-C(8)	-158.9(4)
C(3)-C(2)-C(7)-C(8)	-34.4(6)
N(1)-C(2)-C(7)-C(12)	26.3(6)
C(3)-C(2)-C(7)-C(12)	150.8(4)
C(12)-C(7)-C(8)-C(9)	2.8(7)
C(2)-C(7)-C(8)-C(9)	-172.1(4)
C(7)-C(8)-C(9)-C(10)	0.4(8)
C(8)-C(9)-C(10)-C(11)	-3.6(7)
C(8)-C(9)-C(10)-Br(10)	174.4(4)
C(9)-C(10)-C(11)-C(12)	3.5(7)
Br(10)-C(10)-C(11)-C(12)	-174.6(4)
C(10)-C(11)-C(12)-C(7)	-0.1(7)
C(8)-C(7)-C(12)-C(11)	-3.0(7)
C(2)-C(7)-C(12)-C(11)	172.1(4)
C(2)-N(1)-S(1)-O(1)	26.0(4)
C(6)-N(1)-S(1)-O(1)	-162.5(3)
C(2)-N(1)-S(1)-O(2)	155.3(4)
C(6)-N(1)-S(1)-O(2)	-33.3(4)
C(2)-N(1)-S(1)-C(13)	-89.8(4)
C(6)-N(1)-S(1)-C(13)	81.6(4)
O(1)-S(1)-C(13)-C(18)	161.1(4)
O(2)-S(1)-C(13)-C(18)	31.4(4)
N(1)-S(1)-C(13)-C(18)	-83.4(4)

O(1)-S(1)-C(13)-C(14)	-20.3(4)
O(2)-S(1)-C(13)-C(14)	-150.0(4)
N(1)-S(1)-C(13)-C(14)	95.2(4)
C(18)-C(13)-C(14)-C(15)	-0.5(7)
S(1)-C(13)-C(14)-C(15)	-179.1(3)
C(13)-C(14)-C(15)-C(16)	0.9(7)
C(14)-C(15)-C(16)-C(17)	-1.0(7)
C(14)-C(15)-C(16)-C(19)	178.5(5)
C(15)-C(16)-C(17)-C(18)	0.7(7)
C(19)-C(16)-C(17)-C(18)	-178.8(5)
C(16)-C(17)-C(18)-C(13)	-0.3(8)
C(14)-C(13)-C(18)-C(17)	0.2(7)
S(1)-C(13)-C(18)-C(17)	178.8(4)