Selective monofluorination: mechanistic studies and synthetic applications

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The introduction of fluorine into organic molecules is an important tool in modifying their physical, chemical and biological properties. This review briefly presents the different approaches which can be used for selective monofluorination. The strategies that we have developed for fluorination vicinal to unsaturated systems, paying attention to the regio- and stereo-control during the fluorination step are then discussed in detail. From these studies, two promising approaches emerge: the first employs transition metal complexes; the second uses tailor made fluorinated key building blocks. Some applications to the preparation of natural product analogues are also mentioned.

Introduction

It is well-known that introduction of a fluorine atom strongly modifies the physical, chemical and biological properties of organic molecules. This appears mainly to be due to the very unique properties of this atom (Figure 1): its van der Waals radius is only slightly larger than hydrogen (1.1 Å) while its electronegativity is the highest known. Furthermore, it forms very strong bonds to carbon, hydrogen and many other elements. Thus, exchange of hydrogen for fluorine induces the minimum of steric modifications together with the maximum of electronic perturbations. Similarly, the carbon-hydroxyl bond length (1.43Å) is very close to that of carbon-fluorine (1.39Å), with similar polarities. However, while the former can readily form hydrogen bonds, fluorine is only a weak hydrogen bond acceptor.

Although, fluorine chemistry has expanded in many directions it is probably in the field of bioorganic chemistry that the most spectacular developments have occurred during the last two decades (Figure 2). It has lead for instance to very useful enzyme inhibitors or mechanistic probes for biochemistry and there are already some fluorine containing drugs on the market. Selected examples of rationally designed molecules are shown in Figure 3. The gem difluoro compound 1 is a renin inhibitor active in nanomolar quantities. The presence of the two fluorine atoms ensures that the ketone exists mainly as the hydrate and therefore, is a very good transition state analogue for the hydrolysis of the peptide bond. In the eicosanoid family, introduction of two fluorine atoms in thromboxane A2 (compound 2) very strongly stabilises this, otherwise, extremely labile molecule by inhibition of the ring cleavage of the oxetane. Similarly, the electronic effect of the allylic fluoride strongly stabilises the enol ether function in the prostacycline analogue.

Numerous excellent studies have been devoted to the preparation of trifluoromethylated derivatives, as well as gem difluorocompounds. However the synthesis of monofluorinated molecules can be still considered as a challenging problem, especially if stereochemical control is a key issue in the target molecule. Studies dealing with the asymmetric synthesis of monofluorinated molecules are limited.

From a retrosynthetic point of view two basic disconnections, either a C-C or a C-F, can be envisaged. If we consider the C-C disconnection first, three different types of reactions can be envisaged (Figure 4). The electrophilic addition of R1 to a fluorinated carbon, or alternatively nucleophilic addition of anionic R1 to a fluorinated carbocation would provide the desired compound. Another alternative would be to consider radical type additions. This first C-C bond disconnection appears attractive, though the main problems to be solved would be the preparation of such fluorinated intermediates along with the control of their reactivity and the stereochemistry of the reactions.

The three above mentioned approaches will be considered sequentially. To the best of our knowledge, there is no example of asymmetric C-C
Why Fluorine?

<table>
<thead>
<tr>
<th>Halogen</th>
<th>Van der Waals' radius (Å)</th>
<th>Electronegativity</th>
<th>Bond Energy (Kcal/mol)</th>
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<tr>
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<td>I</td>
<td>2.15</td>
<td>2.4</td>
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Fluoro Bioorganic Chemistry

- Fluorine-containing Enzyme Inhibitors
- Fluorinated Analogues as Mechanistic Probes
- Anticancer agents
- Antiviral agents
- Antibiotics
- CNS agents

Examples

bond formation using alpha-monofluorinated radical of such a general type but this would be an interesting approach to develop in the future. From a retrosynthetic point of view, the most closely related reaction appears to be the asymmetric hydrogenation of fluorinated alkenes (Figure 5). This addition shows good enantioselectivity and, interestingly, gives the same (R)-enantiomer starting from either geometrical isomer of 4.

Another interesting process is the catalytic asymmetric photodeconjugation process (Figure 6).
Asymmetric Synthesis of Monofluorinated Molecules

Scope and Limitations

- Synthesis of the fluorinated intermediates:
- Reactivity and stereoselectivity problems.

Asymmetric Hydrogenation

Asymmetric Photodeconjugation

It is worthy to note that in the case of fluorinated compound 6 the yield of the reaction is good but the enantioselectivity is considerably lower for 7 than for the equivalent alkylated derivatives\(^1\). This is a confirmation of the effect of fluorine on the stereoselectivity of this process.

The reactions developed in Myers's group starting from chiral fluoro amides such as 8 occur with excellent stereoselectivities, yielding optically active alpha-fluoro acids\(^1\). Another attractive approach involves the aldol addition starting from fluorinated silyl ketene acetics 9 where both the syn and anti aldol adducts have been isolated with good e.e.'s\(^6\).

The second possible basic strategy is to make a C-F bond disconnection (Figure 8). Here again three
Asymmetric Synthesis of Monofluorinated Molecules

**Scope and Limitations**

- Development of efficient fluorinating agents.
- Reactivity and stereoselectivity problems.

different reaction types can be considered: either a) an «electrophilic fluorination» by addition of F⁺ to carbanions, or b) a «nucleophilic fluorination» by reaction of F⁻ with carbocations, and c) radical type additions.

In this strategy, the most challenging problems are the development of efficient fluorinating agents along with control of reactivity and stereoselectivity.

Enantioselective addition of monofluorinated radicals have not yet been reported, although the chemistry of trifluoromethyl and perfluoroalkyl radicals has been well-developed₁⁷. The reaction which is, at least formally, closest to the radical addition is the reaction of F₂. An interesting example of highly diastereoselective addition of molecular fluorine to the chiral-non-racemic lactone 10 had been reported (Figure 9)¹⁸. After saponification and cleavage, the fluorinated cyclohexanone 11 was obtained in optically pure form.

In contrast, the asymmetric electrophilic fluorination has been already studied in detail. One method is to start from a chiral enolate and to use
achiral fluorinating agents. This has been pioneered by Davis et al., using Evans’s oxazolidinones 12 as chiral auxiliaries (Figure 10)\(^9\). The e.e.’s obtained for the alpha fluorinated carboxylic acids 13 are good to excellent.

Lower d.e.’s were obtained using phenyl menthol derived chiral auxiliaries 14\(^{20}\). The use of SAMP hydrazones by Enders et al. was also successful for the synthesis of fluorinated ketones\(^{21}\).

The other option is to use a chiral fluorinating agent as illustrated in Figure 11. Sultam derived compounds such as 15 or 16 have been successfully developed by Differding\(^{22}\) and Davis\(^{23}\). Although the e.e.’s are already good (70-75%), further improvements can be expected in the future for such reactions.

Finally the last possibility is the nucleophilic fluorination and, specifically, the asymmetric dehydroxy-fluorination will be discussed (Figure 12)\(^9\).

The ideal pathway would be to start from a chiral-non-racemic alcohol, such as 17 and there are dozens of good methods to obtain such optically pure compounds. After transformation into a good leaving group (tosylate, triflate, etc...) a S\(_{N2}\) type nucleophilic substitution by F\(^-\) should give the target fluoride 18 in pure form with inversion of configuration. This ideal process is far from general since F\(^-\) is both a poor nucleophile and a strong base. Therefore, competitive processes frequently occur, particularly the reactions via a carbocation leading to racemic products via S\(_{N1}\) type processes. Neighbouring group participation is
Electrophilic Fluorination

Chiral fluorinating agent

1) NaH, ether
2) [chiral fluorinating agent]

Yield: 63% ee: 70%

Yield: 40% ee: 75%

Figure 11

Asymmetric Dehydroxy-Fluorination

Retention

Rearrangements

If β H

Elimination

1) Activation of Fluorinating Agent
2) SN2
3) SN1

Inversion

Racemic

Figure 12

also possible and the fluorination can occur with overall retention of configuration. Finally, rearrangements and (or) elimination processes, characteristic of carbocationic intermediates can also occur. It is important to note that all these pathways have indeed been observed, depending upon the nature of the starting alcohol. In particular, it can be easily recognised that, if at least one of the groups R1, R2 or R3 can stabilize a carbocationic intermediate, the corresponding pathway will be favoured and become strongly competitive with the desired reaction!

Such competition can be illustrated with a very simple example reported by Middleton in his seminal work on fluorination with Diethyl Amino Sulfur Trifluoride (DAST) (Figure 13):

The reaction of both regiosomeric allylic alcohols 19 and 20 led to the same (1:2) ratio of the corresponding fluorides 21 and 22. This can be explained by a classical competition between SN2 and SN2' and eventually S_Ni processes in such an allylic system. Many examples of this sort have subsequently been described.

Thus, based on these considerations, our goals in this field were as follows (Figure 14).

The first was to develop new methodologies to
perform regio-and stereo-selective monofluorination in all cases which are very challenging due to the potential generation of carbocationic intermediates. The most representative examples are allylic and polyenic systems as well as the fluorination in benzylic or propargylic position.

Starting from compounds prepared in this way it should be possible to perform selective synthesis of fluorinated analogues of some biomolecules. In this context, both natural product analogues and pharmacological tools were our second objective.

Very few studies have dealt with the effect of the C-F bond in the allylic position on the reactivity of neighbouring pi systems; furthermore, its effect on the diastereoselectivity of different type of reactions (cycloadditions, nucleophilic and electrophilic reactions, etc...) would be of great interest, both from a mechanistic and synthetic point of view. Regioselective access to molecules of this sort would greatly contribute to such studies.

At this stage, three different strategies toward these goals were investigated (Figure 15): the first, to be only briefly described here, relies on substituent effects to control the regioselectivity of fluorination; the second will take advantage of the known properties of some transition metal complexes to obtain a good regio- and stereo-control. We have pioneered this strategy in fluorine chemistry; the last will involve the preparation, and use in synthesis, of some selected fluorinated key building blocks.

Considering briefly the first strategy, around twenty examples of unsaturated and polysaturated allylic alcohols has been selected and subjected to DAST fluorination. The conclusion obtained both from our own and literature studies was the following: for secondary fluorides, such reactions give rise to the most conjugated, and probably also the most stable, compounds. This is illustrated by the following examples.

Allylic alcohols substituted in beta olefinic
Strategies

1. Substituents effects

2. Transition metal complexes

3. Fluorinated key building blocks

Figure 15

Substituent Effect (1)

Strategy 1:

EWG

\[
\begin{align*}
\text{HO} & \quad \text{Me} \\
\text{EWG} = \text{CO}_2\text{Me}; \text{COPh}; \text{CN} \\
\text{EtO}_2\text{C} & \quad \text{OH} \\
\text{EtO}_2\text{C} & \quad \text{Me} \\
\text{EWG} & \quad \text{F}
\end{align*}
\]

DAST

\[
\begin{align*}
\text{RT} & \quad 50-65\% \\
\text{RT} & \quad 55\%
\end{align*}
\]

Figure 16

position by electron withdrawing groups react cleanly with DAST to give exclusively the corresponding allylic fluorides 24 without transposition (Figure 16).

In contrast, the allylic alcohol 25 obtained by reaction of propenyl magnesium bromide with mesoxalate reacts with DAST to give the corresponding fluoride 26 with complete transposition of the double bond. In both cases, only the most conjugated derivatives have been isolated. Both series of compounds are useful key intermediates for our mechanistic studies dealing with the effect of allylic fluoride on reactivity and stereoselectivity 26.

The next example proved to be useful with regard to the preparation of fluorinated analogues of lipids (Figure 17) 27. 4-Hydroxynonenal 31 is a fatty acid metabolite with various potent biological properties, including cytotoxicity 28. Another derivative, 13 HODE (also called coriolic acid) 32 is a metabolite from linoleic acid (both in human and in plants) with several intriguing biological properties 29. For instance, it is an inhibitor of the adhesion of tumor cells on platelets, an important step during formation of solid tumors 30. Therefore, it appeared of interest to synthesise the fluorinated analogues of these derivatives.

The synthesis starts from the very easily accessible
The reaction of acetal of 4-hydroxynonenal 27\(^2\) with DAST is completely regiocontrolled, occurring without transposition to give 28. The hydrolysis of the ketal gave in good yield the fluorinated analogue of 4-hydroxynonenal 29. Starting from this derivative, a Wittig reaction led with a very good stereoselectivity to the target, the fluorinated analogue of 13-HODE 30.

In conclusion, this first approach proved to be useful since it is possible to gain access in very short sequences to allylic fluorides with a good regiocontrol in many cases. However, taking into account the probable mechanism of the reaction (allylic or polyunsaturated carbocations) this first approach cannot afford enantiocontrol. Therefore, other strategies were studied in parallel.

The second strategy is based on the use of transition metal complexes (Figure 18) and takes advantage of their well-known abilities to selectively complex various pi systems and then, act as protecting
Strategy 2: Metalloassistance Concept

The tricarbonyl iron moiety is well-known for bonding strongly to conjugated dienes. The corresponding complexes are easily accessible, even on a large scale and therefore have been extensively employed in synthesis \(^{32}\). We will use them first to illustrate the metalloassistance concept (Figure 19) and will then describe our results in this field.

Starting from an alcohol vicinal to the complex such as 33, transformation into a good leaving group (this occurs during reaction with DAST) should lead to a labile intermediate; indeed it is well-known that the iron carbonyl moiety helps to the departure of the leaving group and stabilises the intermediate ion. The addition of fluoride anion should then give the desired fluorinated compound 34, without any transposition due to the blocking effect of the transition metal. Furthermore, since this type of complex is chiral, it should also be possible to control the stereochemistry of the process. The possibility of a direct intramolecular fluorination, without going through the carbocation, could also be considered in this process.

The first results, shown in Figure 20, proved to be excellent\(^{33}\). Due to the chirality of this complex and the stereogenic center next to it, these molecules exist as a pair of stereoisomers, called psi-exo 33 and psi-endo 35\(^{34}\). The reaction has been performed on both derivatives, and in each case, on pure enantiomers. The reaction of psi exo alcohol with DAST was rapid and quantitative at \(-50^\circ C\) and gave exclusively the corresponding fluoride 34. The reaction occurred with overall retention of configuration. The very high stereoselectivity of this process (\(>97\%\)), established using high field \((^{19}F, ^1H, ^{13}C)\) NMR directly on the crude reaction mixture, is noteworthy. The reaction with the psi-endo stereoisomer 35 was also rapid but a little less selective since a (96: 4) ratio of isomers 36 and 34 was obtained. The major compound 36, corresponding again to overall retention of configuration, was isolated in 86\% yield.

Removal of the organometallic unit (Figure 21) was achieved in this case with trimethyl amine N-oxide and gave the corresponding free dienes (+)-37 and (-)-37. The moderate isolated yields which have been obtained are mainly due to the volatility of these derivatives and this is a well-known consequence (and everyday experience of chemist) resulting from introduction of fluorine into organic molecules!

These dienes have been isolated in optically pure form, as established by NMR in the presence of chiral groups. Furthermore, most of such complexes are chiral and accessible in optically pure form. They have already been established as excellent tools in organic synthesis for the stereo- and enantio-controlled preparation of various type of compounds including bioactive molecules\(^{31}\). Surprisingly, to the best of our knowledge, such an approach has never been used previously for stereoselective fluorination.

Relevant to our studies will be the complexes of iron, chromium, rhenium and cobalt which are able to selectively complex, in a stoichiometric manner, different pi systems.
shift reagents. However the role of the transition metal complex in this process now needed to be established. Therefore, the fluorination was carried out under the same conditions on the optically pure dienol (−)-38. As expected, the reaction proceeded with regiocontrol leading only to the most conjugate diene but this derivative was racemic. Therefore, was clearly demonstrated that the complex played key role in the stereochemical control of the fluorination.
More functionalised systems were also studied in order to ascertain the scope of the reaction (Figure 22).

Fluorination of the psi-exo derivatives 39a and 39b were again completely stereoselective but for the psi-endo complexes, the result was depending upon the nature of the substituent: a (3:1) ratio of retention versus inversion of configuration was obtained for the propargylic system and the ratio became (2:1) in the case of the allyl.

Would it be possible to extend the reaction to the more challenging problem of tertiary fluorides 35? This was in fact easily performed starting, in this case, from the complexed ketone 43, again in optically pure form (Figure 23).

The reaction of butyl lithium led stereoselectively to the tertiary alcohol 44 which reacted with DAST to give a (4:1) ratio of the corresponding fluorides 45 and 46. The major stereoisomer, isolated in 55% yield could be decomplexed to give the optically pure diene (+)-47 with the tertiary fluoride in allylic position. Similarly, the enantiomer (-)-47 was prepared starting from enantiomeric organometallic complex. To the best of our knowledge, these are the first examples of optically active tertiary fluorides vicinal to C-C double bonds.

A proposed mechanism for these reactions, based on the Newman projection along the carbon bearing the alcohol and the vicinal carbon of the organometallic complex and accounting for the stereochemistry is shown in Figure 24.

Starting from the first psi-exo complex there is no particular steric hindrance for the departure of the leaving group (OLG) assisted by the metal; no further steric effect is obvious during addition of the nucleophile, which occurs again anti to the bulky organometallic moiety. Therefore, the reaction occurs in every case easily and with a complete retention of configuration.

Data are completely different for the other psi-endo stereoisomer. A conformation similar to the preceding one and convenient for the metalloassisted process is probably not the ground state, which probably requires the smallest atom (hydrogen) to be close to the organometallic unit. Rotation around the C-C bond will introduce steric strain between the R group and the diene part of the complex. Similar effects will be observed at each of the ensuing steps: formation of the stabilized carbocation, fluorine addition and return to the ground state conformation. Therefore it is not surprising that, for these isomers, the reaction is only stereoselective (isomerisation may
Figure 23

Figure 24
Potential applications

![Figure 25](image)

occurs at the intermediate carboxylation stage) and also strongly dependent on the size of the R group.

Such a preparation of conjugated dienes or polyenes bearing a fluorine in allylic position may offer many opportunities in the synthesis of analogues of biomolecules. For example, we have reported earlier a formal synthesis of leukotriene B₄ and labelled derivatives starting from such organoiron complexes. Since the fluorination of these derivatives occurs under mild conditions, it should be possible to prepare, using a similar scheme, the 12-fluoro analogue of LTB₄ (Figure 25).

The next important question was whether we could extend this concept to other transition metal complexes. The answer was clearly positive since the same strategy could be used for fluorination in benzylic position, using chromium derivatives and in the allylic series using some rhenium complexes (Figure 26). The propargylic systems and the corresponding cobalt complexes will be discussed later.

The reaction of DAST with chromium substituted tetrads and indanols occurred smoothly to give the corresponding fluorides in good yields. The transition metal complex exerts impressive stereocontrol on the reaction: in every case, the fluoride added exclusively trans to the bulky Cr(CO)₅ group.

The cationic rhenium complexes appear interesting for two reasons. First, they are chiral at the metal centre and second, they selectively bind to two electron pi species. The two stereoisomeric complexes obtained from 2-butene-3ol again reacted readily with DAST and contrary to previous experiments in non-complexed series there was no allylic transposition in this case. Furthermore, the reaction giving were stereospecific and by analogy with results obtained with other nucleophiles, overall retention of configuration should be the favoured process.

In conclusion to this second part, we have demonstrated for the first time that such a strategy using transition metal complexes appears very attractive in the selective monofluorination process. Selection of the appropriate transition metal complex should allow the control of the regio-and the stereo-selectivity of fluorination, using its protective and stereoinducing properties. However, a drawback of this strategy is the preparation of the starting complexes, especially if optically active derivatives need to be used which in some cases require multistep (and time-consuming) sequences. Consequently, we were interested in also developing in parallel a third approach (Figure 27).

The basis of this strategy was to prepare small, chiral molecules which already contained the fluorine atom. Using alpha-fluorinated carbonyl compounds, for instance, Davis has already demonstrated the
usefulness of this approach\textsuperscript{39}. Taking into account the very high efficiencies of transition metal catalysed C-C bond formation\textsuperscript{40}, we selected for our purposes vinyl metal derivatives with the fluorine atom in the allylic position (general structure 54). Since the corresponding propargylic fluorides 53 can easily be recognised as the most direct precursors to such intermediates, both series of molecules have been studied (Figure 28).

The challenges that we now have to consider in both series are: the selective preparation (with a good regio-and stereo-control !) of the propargylic fluorides
and the corresponding vinyl metals (with proper choice of metal!); the reactivity of those derivatives. In particular, how will the fluorine atom influence the reactivity of neighbouring π systems?; the compatibility of the C-F bond, especially with regards to the hydrometallation step and the following transition metal catalysed C-C bond coupling.

A model with a C₉ chain was selected to minimise the volatility problems⁴¹. The preparation of this propargylic fluoride 56 proved to be straightforward (Figure 29).

The reaction of DAST with propargylic alcohol 55 led to the target fluoride, together with a small amount of enyne separated by chromatography on silica gel. It is interesting to note that, in this reaction, like in many others that we have done with fluorinated key intermediates

Strategy 3:

Problems:
- Synthesis
- Reactivity
- Compatibility of the C-F bond

Figure 28.

Fluorinated key intermediates

![Diagram](image)

Synthesis

H==MgBr + nC₉H₁₉CHO → THF, RT 80%

56

57

58

59

60

DAST + CH₂Cl₂, RT 50%

Figure 29.

Having in hand the propargylic fluoride, the reactivity of the acetylenic C-H bond was studied first (Figure 30).

We found no negative effects introduced by having a fluorine atom in the propargylic position. After metallation using butyl lithium, alkylation to 57 or esterification giving 58 occurred smoothly. Sonogashira type coupling gave the desired ketone 59. No decomposition of these propargylic fluorides were observed.

The reactivity of the triple bond was now studied in hydrometallation and, as expected, the propargylic fluoride proved to be more sensitive. Preliminary experiments in hydroalumination, as well as hydroboration led only to decomposition products. Although further experiments need to be done in this field it is possible to speculate that such (hard !) metals have a very high affinity for the fluorine atom leading preferentially to a C-F bond cleavage and to decomposition of these molecules. In contrast, fruitful results were obtained in the hydrostannylation process.
CH Reactivity

1) nBuLi
THF/HMPA
2) nC₅H₁₁Br
56%

56

Pd (PPh₃)₄ (0.1 eq.)
Cul (0.1 eq.)
PhCOCl
Et₃N
48%

58

nBuLi, THF
56%

59

57

Figure 30

(C=C) Reactivity

H-≡-SnBu₃ (1.1 eq.)
Bu₃SnH (1.1 eq.)
AIBN (cat)
90°C, 1 h.
77%

56

60

4

Figure 31

(Figure 31). Noteworthy is the fact that we are dealing here with a soft metal and furthermore, working under radical type conditions!

Under these conditions, a (4:5) ratio of the Z 60 and the E 61 isomers was obtained, along with 10% of the branched regioisomer 62. These derivatives could be separated by chromatography on silica gel. Palladium catalysed hydrostannylation led to a (1:1) mixture of the E and branched isomers while stannylecupration gave only decomposition products.

The reactivity of the carbon-tin of these new vinyl stannanes was studied next (Figure 32).

Stille coupling gave the desired products but only in low yields (20-30%), probably due to the sensitivity of the final products to the reaction conditions. On the contrary iodination gave, in good yields and in a stereospecific manner, the corresponding vinyl iodides 63 and 64 bearing an extra fluorine atom in allylic position. These novel derivatives are themselves attractive intermediates and therefore the carbon-iodine bond reactivity was studied next (Figure 33).

These molecules perform well in palladium catalysed coupling reactions. When subjected to the Heck reaction 42, under Jeffery's conditions 43, they gave in good yields and in a stereospecific manner both the E,E 65 and the E,Z 66 dienes. Similarly, the Sonogashira reactions 44, under Linstrumelle's conditions 45, gave the expected enynes 67 and 68 with a full control of the E or the Z stereochemistry of the double bond. Again, the carbon-fluorine bond appears compatible with such palladium catalysed reaction conditions.

Although the yields have still to be improved in some steps, this sequence (propargylic fluoride to vinylstannane then iodide and transition metal catalysed C-C bond formation) appears to be a new, short and versatile, sequence towards stereodefined polysaturated systems with a fluorine atom in allylic position. This novel approach would be of
much interest for the preparation of analogues in several families of natural products. However, a key question still remains to be resolved towards this goal: how can the absolute configuration at the stereocentre bearing the fluorine atom be controlled? Taking into account the general strategy developed this stereocontrol needs to be studied at the first fluorination step. Since essentially nothing was known about the stereochemical outcome of the propargylic fluorination, we developed studies based on three different, but structurally simple, models (Figure 34).

In the first propargylic alcohol 69 stereocentres in the form of a chiral dioxolane with a C₂ symmetry axis were introduced on the other side of the triple bond. This will of course lead to diastereoselectivity
Models

Stereoselectivity

Problems

- Stereoselective synthesis:
  - propargylic alcohols
  - cobalt complexes

- Stereochemical analysis

Figure 34

Figure 35

Studies. The two other models 70 and 55 have only the carbinol chiral stereocentre; therefore, optically active derivatives will be necessary in order to measure the enantioselectivity of this propargylic fluorination. Obviously, in both series we will have to solve the problems involved in the stereoselective synthesis of such alcohols, and corresponding cobalt-carbonyl complexes. We also require to develop the appropriate tools for the stereochemical analysis; this last problem will not be straightforward with such propargylic fluorides, as indicated later.

Starting with the first model\(^\text{16}\), we had to demonstrate that high field NMR allowed to discriminate between the two diastereoisomers, both at the propargylic alcohol stage and for the final fluoride. The synthesis of the target alcohol 69, as a (1:1) mixture of stereoisomers was straightforward (Figures 35 and 36).
After protection as a silyl ether, butynol is formylated and the aldehyde protected as a chiral dioxolane, using \((R,R)-2,3\)-butanediol. At this stage the two stereoisomers of 72 were easily differentiated using \(^{13}\text{C}\) NMR. Desilylation led to the target molecule as an equimolar mixture of stereoisomers.

The reaction with DAST, at \(-35^\circ\text{C}\), was rapid, quantitative and completely regiocontrolled (Figure 36) with the propargylic derivatives 73 being the only fluorinated compounds obtained and again, the two stereoisomers readily characterised using \(^{19}\text{F}\) NMR. Starting from the alcohol, the corresponding cobalt complex 74 was also easily prepared using standard procedures and again the stereoisomers easily differentiated by high field NMR. The fluorination with DAST gave, quantitatively, the corresponding cobalt-complexed propargylic fluoride 75, as a (1:1) mixture of isomers readily characterised by NMR.

Having secured both the fluorination process and the analytical method, it became possible to study its stereoselectivity. For this purpose, pure diastereoisomers of propargylic alcohols needed to be prepared and subjected to fluorination (Figure 37).

The same synthetic scheme was followed, starting from (S)-butynol and gave the desired propargylic alcohol 76 in a 94% d.e. Under previously described conditions the reaction with DAST led to the corresponding fluoride 77 with a 92%d.e.; this value could be further confirmed by NMR of the derived complex 78. Thus fluorination occurred with a very high degree of stereocentrol in this derivative.

The reaction of the corresponding propargylic alcohol complexed to cobalt-carbonyl 79 gave very interesting results:

First, there was a strong temperature dependence in this process: the d.e. increased from 40% at room temperature to 86% at \(-80^\circ\text{C}\). Therefore, this reaction still has a high stereocentrol, but only at very low temperature.

All the NMR data clearly indicated that the major compound 80 obtained in this fluorination was different from previous one 78. In agreement with the mechanism generally accepted for reaction with DAST, inversion of configuration can be assumed for the fluorination of the free propargylic alcohol, while an overall retention of configuration was observed in the case of corresponding complex. Therefore, we have here an interesting example of a stereodivergent process.

The same reactions were repeated on the other diastereoisomeric alcohol (starting in this case with \((R)-\)butynol) and exactly the same results and the same diastereoselectivities were observed. This result was important as it, therefore, excluded any effect from the remote stereocentres in the dioxolane on the stereoselectivity of the fluorination.

The overall retention of configuration in the case of the cobalt carbonyl derivative was easily explained
using the same metalloassistance process as described previously (Figure 38).

The departure of the leaving group anti to the cobalt is followed by the addition of fluoride from the same side. Interestingly, the temperature effect observed in this reaction gave some indication about the diastereoisomerisation process, i.e., the rotation barrier around the carbon-carbon bond in this stabilised carbocation and with our complexes, the process should be slow at $-80^\circ$C.
In fact this reaction is nothing more than the first reported extension to fluorination of the well-known Nicholas reaction. However, this result introduced new questions about the mechanism of these reactions and the exact nature of the fluorinating agent (Figure 39).

The fact that fluoride anions can decomplex the cobalt-carbonyl derivatives has been known for a long time and this method has been reported recently as a mild and chemioselective process for such a purpose. Therefore, in order to explain the excellent results obtained in our reactions with DAST at least two proposals could be made:

The DAST reaction is almost instantaneous, even at low temperatures, while decomplexation is slower and consequently the kinetics could favour fluorination in this instance. Alternatively, another fluorinating agent could be involved in this reaction. These observations could be consistent with Shellhammer’s proposal that, after reaction with DAST, an ion pair is formed and the corresponding anion could react with the carbocation to give the fluoride directly. It should be noticed also that reaction of fluoride anion with the pentadienyl cations complexed to a Fe(CO)₅ unit or with arene chromium carbonyl cations gave only decomposition products and none of the expected fluoride. Therefore, further mechanistic studies will be necessary to give support to the above proposals.

The next models designed for our study were propargylic alcohols with a single stereogenic centre and therefore had to be prepared in optically active form. The first having a n-pentyl chain on the triple bond (-)-70, was easily prepared from optically pure butynol (-)-71 and reaction with DAST was again regiocontrolled, leading exclusively to the propargylic fluoride 82 (Figure 40).

However at this stage, a difficult problem arose since none of the usual tools employed for the analysis of optically active compounds (chiral GC, chiral HPLC, chiral NMR shift reagents, etc...) allowed us to differentiate between the two enantiomers of this propargylic fluoride! This is probably due to the very special properties of this type of compound which are both volatile and very non-polar. Therefore, we had to use another, recently introduced, technique of NMR in chiral liquid crystalline solutions (Figure 41).

In this method, the chiral derivative is dissolved in a solution of a peptide (polybenzyl glutamate) in, for instance chloroform. This peptide makes a chiral nematic phase which is oriented in the magnetic field of the NMR. In this «solvent» the two enantiomers may have different orientations and/or different interactions with the chiral environment and this will affect all the order dependent NMR interactions and it becomes possible to observe different signals for each enantiomer. This technique proved to be very fruitful, especially for the most difficult cases such as isotopic chirality. Furthermore, several types of nuclei can be used : proton decoupled deuterium NMR, proton-coupled ¹³C NMR, as well as proton-decoupled ¹³C NMR. Since this last method was known to be more efficient in the case of sp-hybridised carbon, it appeared to us the method of choice for our propargylic fluorides. Indeed, this gave excellent results with the fluoro nonyne (Figure 42).

The racemic derivative (+/-)-82 was isolated in 65% yield by reaction of nonynol (+/-)-70 with DAST. The proton decoupled ¹³C NMR in chiral
Problem: Stereochemical analysis!

Chiral Discrimination using NMR in Poly-$\gamma$-Benzyl-L-Glutamate Liquid Crystalline solutions

liquid crystalline solution gave a excellent differentiation for the sp carbon close to the stereogenic center. Although less discriminated, the other sp carbon also gave different signals for both enantiomers. Obviously, this was a key result allowing us to start the stereochemical study of the fluorination process.

The reaction sequence was then repeated starting from the optically active (e.e $> 95\%$) (+)-nonytol (+)-70 (Figure 43).

Here again the reaction showed a strong temperature dependence. The e.e. of the propargylic fluoride (+)-82 was only 45% for a reaction at -55°C but it was raised to 75% for fluorination at -95°C. In this particular case, it is possible to speculate that the pentyl group donates electrons and could better stabilise intermediate carbocations and this should ultimately facilitate the competitive $S_N1$ process. Consequently, by working at a very low temperature, it was possible to achieve good (75%) stereocontrol on this fluorination.

The last model studied was the fluoro-dodecyne 56 which was a very important example since this compound was the starting material for our preparation of polyunsaturated systems, as described earlier.
**Selectivity Monofluorination: Mechanistic Studies and Synthetic Applications**

**Figure 42**

(±) Nonynol

![NMR spectrum for (±) Nonynol](Image)

- DAST in CH$_2$Cl$_2$
- 65% yield

**Figure 43**

(R)-Nonynol

![NMR spectrum for (R)-Nonynol](Image)

- DAST in CH$_2$Cl$_2$
- 65% yield

- e.e. > 95%
- e.e. = 75±5%
- e.e. = 45±5%
The results obtained are shown in Figure 44. The starting propargylic alcohol (+)-55 was synthesized (90% e.e.) by Alpine Borane reduction of corresponding ketone 83. Although less sensitive than in the previous case, the reaction with DAST was still temperature dependent. Using both $^{13}$C and $^{19}$F NMR in chiral liquid crystalline solvents, an increase in the e.e.'s was observed (65% at room temperature to 80% at $-35^\circ$C and 88% at $-50^\circ$C) for (-)-56. Therefore, an excellent stereocontrol (> 97%) was observed for the fluorination of this key intermediate and this allowed us to draw several conclusions from this model and hence our general strategy towards fluorinated analogs of biomolecules with unsaturated systems (Figure 45).

Starting from easily accessible propargylic
alcohols, a very short and versatile sequence towards the target molecules was developed with only four steps (fluorination, hydrostannylation, iodination and palladium catalysed C-C coupling) being necessary. Furthermore, the first step can be enantiocontrolled, while the second gives both the E and Z (in a separated form), and the two last steps are stereospecific. Therefore, we hope that it will prove to be a very flexible approach towards fluorinated analogues of biomolecules. Various types of natural products could be considered for that purpose, and let us mention briefly two representative examples.

Many polyunsaturated fatty acid metabolites (for instance in the arachidonic cascade) have structures relevant to this general type. For example, the two leukotriene B₄ analogs (the 5-fluoro 84 and the 12-fluoro 85) would be very interesting molecules in order to determine the effect of the hydroxyl groups on binding to the receptor for this important mediator. A possible approach is indicated in Figure 46.

Taking into account the previous model studies, it appears possible to design as key intermediates, both a Z and an E vinyl iodide, with the fluorine atom in allylic position. Such molecules, with the appropriate chains, should be accessible via the propargyl fluoride strategy, as described above. These syntheses are currently under study in our laboratory.

A last example has been chosen from the field of pheromones. The disparlure is a well-known pheromone of the Gypsy Moth. Elegant studies by Prestwich et al., have established that the 9,9 difluoroanalogue had a strong inhibitory effect towards the epoxide hydrolase of this insect. Therefore, it would be interesting to prepare the two stereoisomers of the monofluorinated analogue 86 in order to obtain better structure activity relationships for this molecule. This could be easily achieved again, starting from the previously described propargyl fluoride 56 (Figure 47).

A three step sequence of alkylation followed by Lindlar’s semihydrogenation and epoxidation led to the target molecule. This last step gave a (1:1) mixture of the syn and anti stereoisomeric epoxides, separated by chromatography on silica gel.

Extension to the preparation of corresponding enantiomers is under study, since the starting propargyl fluoride 56 has already been prepared in optically active form, as demonstrated above.

As a general conclusion from these studies on the
preparation of monofluorinated compounds, several important points should be noted:

The main rules governing the regioselectivity of monofluorination vicinal to unsaturated or polyunsaturated systems have been determined.

The use of appropriate transition metals allows good control in the regio- and stereo-selectivity of fluorination. Even though more mechanistic studies are necessary to fully understand the mechanism, we have demonstrated for the first time that the reaction of DAST with alcohols complexed to transition metals is a very powerful methodology in this field.

The strategy starting from propargylic fluorides appears to be the shortest and the most versatile for the preparation of derivatives with polyunsaturated systems. This methodology will probably be of much interest for the stereoselective synthesis of analogues of polyunsaturated fatty acid metabolites for instance.

Finally, some of these new allylic fluorides have allowed us to do some fundamental studies dealing with the influence of the C-F bond in an allylic position on the regio- and stereo-selectivity of reactions on the vicinal double bond. Such studies, combining experimental and high level computational studies will help to establish the relative roles of the steric and electronic effects of the fluorine atom on these reactions. These studies will be reported in due course.

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References


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