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α-FLUOROCARBONYL COMPOUNDS AND RELATED CHEMISTRY

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A. INTRODUCTION

Although elemental fluorine was first prepared by Moissan almost a century ago, research in organic fluorine chemistry during the next fifty years was focused primarily on simple aliphatic (Swarts, Bockemüller, Henne) and aromatic (Balz–Schiemann) compounds. A watershed for fluoroorganic chemistry came during the "Manhattan Project" of World War II, which posed demands for

developing extremely stable organic materials. After it was found that perfluoro compounds could meet these demands, hundreds of such materials, including polymers, were developed. Another important field in which fluorine plays a very distinctive role is the chemistry of biologically-active compounds. In the early 1950s, the discovery that fluorosteroids can, in some cases, surpass naturally occurring hormones in their biological activity,[1] boosted enormously the research dealing with the introduction of fluorine at specific sites in compounds of potential biological interest. In many cases there was a need to develop methods for the synthesis of compounds possessing an α-fluorocarbonyl moiety. In this review we present recent chemistry, synthetic routes, and reagents which have been utilized or specifically developed for the construction of this function.

There are many instances where the chemistry of this moiety is similar to that of general fluorine-containing compounds. Only such cases relevant to α-fluorocarbonyl derivatives will be reviewed. Usually, we will not deal with perfluoro compounds which are covered in other publications, such as the excellent Specialist Periodical Reports Vols 1–3 of the Chemical Society. Neither will the chemistry of the acyl fluorides be presented, since, in most cases, they serve as intermediates for fluorine-free compounds.

For the sake of brevity and clarity, only a representative example of each case will generally be cited. Also, we will not deal with the numerous patents and other publications which are not published in the open scientific literature.

B. REACTIONS WITH NUCLEOPHILIC FLUORINE

Since fluorine is the most electronegative element, it is natural that the most widely used fluorinating reagents are the ones which possess nucleophilic fluorine. They exist in several variations: as metal fluorides, hydrogen fluoride, and compounds which possess, for example, S—F, N—F, and halogen—F bonds and in which the fluorine clearly behaves as a nucleophile. Most of the reactions are based on nucleophilic substitution by S_N1 or S_N2 mechanisms.

I. *Metal and tetraalkyl ammonium fluorides*

Swarts treated AgF with methyl iodoacetate to produce the extremely toxic methyl fluoroacetate (**1**).[2] The reaction of KF with methyl chloroacetate in an autoclave at 220° gave **1** in 54% yield.[3]

$$I{-}CH_2COOMe + AgF \longrightarrow FCH_2COOMe$$

1

In order to avoid the inconvenient autoclave, substitution reactions were later performed with potassium fluoride in polar solvents. Other fluorides, such as NaF or NH_4F, which are insoluble in these solvents, did not react. Another condition to be met was the use of dry reagents and solvents. Otherwise, fluoride ion loses most of its nucleophilic power because of hydration. One of the first solvents used was acetamide and the relatively volatile α-fluoroesters were distilled, as formed, from the

$$RCHXCOOR^1 + KF \xrightarrow{MeCONH_2} RCHFCOOR^1$$

R = Me, Et; X = Br, OTs

reaction mixture. This method was also used for preparing ^{14}C-methyl fluoroacetate,[4] but was limited to low boiling α-fluoroesters, since at higher temperatures, the acetamide is too volatile and part of it is carried over with the distillate.[5,6] This problem was overcome by employing amides instead of esters, thus permitting the use of high boiling alcohols such as diethylene glycol (D.E.G.), which dissolves

$$RCHXCONR_1R_2 \xrightarrow[125°, 2hr]{KF/D.E.G.} RCHFCONR_1R_2\ (45-70\%)$$

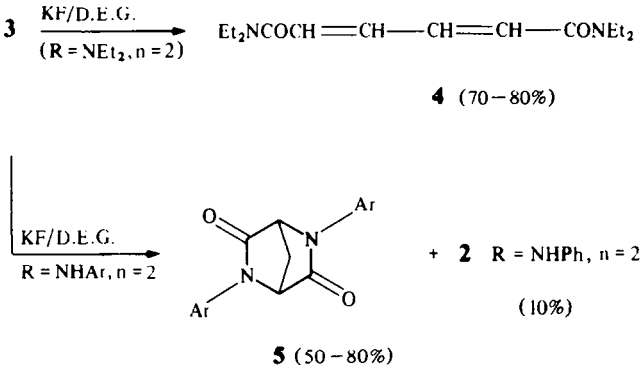
R = H, Alk, Ph; $R_1 = R_2$ = Et, R_1 = H, R_2 = Ar; X = Cl, Br, OTs

about 15% KF, without an undesirable trans-esterification reaction.[7] This method was also applied to the synthesis of α,α′-difluorodicarboxylic acids **2** (R = OH), obtained by hydrolysis of the

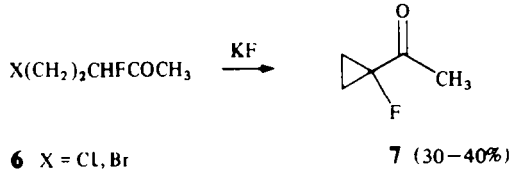
$$RCOCHBr(CH_2)_nCHBrCOR \xrightarrow{KF/D.E.G.} RCOCHF(CH_2)_nCHFCOR \xrightarrow{^{+}H^{+}} \mathbf{2}\ (R = OH)$$

3 **2** (40–50%)

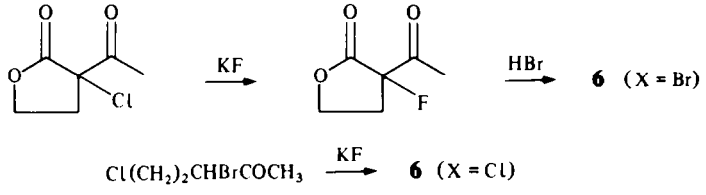
corresponding α,α′-difluoroanilides **2** (R = NHPh). Thus, α,α′-difluoroazelaic (**2**, R = OH, n = 5), sebacic (**2**, R = OH, n = 6), and docosandioic (**2**, R = OH, n = 18) acids were obtained.[8] Fluoride ion, however, is not only a nucleophile, but a strong and versatile base.[9] If a diethylamide **3** (R = NEt_2, n = 2) was employed, mainly *trans*-muconic acid diethyl amide (**4**) was produced, but if various anilides were used, a unique heterocyclic bicyclic system **5**, was formed. In both these reactions, where HBr elimination occurred, the potassium fluoride acted as a base rather than as a nucleophile.[10] The basicity



of KF was also demonstrated in yet another cyclization via enolates of 5-halo-3-fluoro-2-pentanones (**6**), leading to 1-fluorocyclopropyl methyl ketone (**7**). The starting fluoro ketones were prepared by



halogen–fluorine exchange, using KF.[11]



Fluoride preferentially replaces halogen α to carbonyl, as demonstrated in its reaction with ethyl α,β-dihalo-β-phenyl-propionates. No vicinal difluoro compounds were formed, although the second

$$PhCHXCHXCOOEt \xrightarrow{KF} PhCHXCHFCOOEt$$

X = Cl, Br **8** (60%)

halogen in **8** can be replaced by radioactive iodine using $Na^{131}I$ in boiling acetone for 6 hr.[12] Only bromine was replaced in α-bromo-α-chloro ketones **9**, when treated with the more reactive HgF_2 to produce α-chloro-α-fluoro ketones **10**. Under more forcing conditions or if α-bromo-α-fluoro ketones were treated with HgF_2, usually 1,2-dicarbonyl compounds were formed by an, as yet, unclear mechanism. Only in the case of gem-dihalopropiophenone **10**, **11** (R = Ph, R_1 = Me) were the

$$RCOCBrClR_1 + HgF_2 \longrightarrow RCOCFClR_1$$

9 **10**

$$\textbf{10} \text{ or } RCOCBrXR_1 + HgF_2 \longrightarrow RCOCOR_1$$

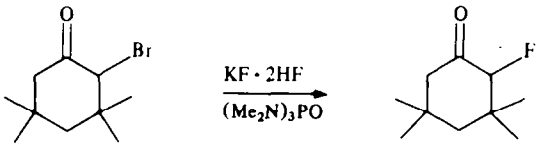
11 X = Br
12 X = F

corresponding gem-difluoro derivatives isolated in high yield.[13] The fluoride salts may be

$$\textbf{11,12} + HgF_2 \longrightarrow PhCOCF_2CH_3$$

R = Ph

accompanied in some cases by HF without losing their nucleophilic power and α-bromo ketones were thus converted to the corresponding α-fluoro derivatives.[14] The use of metal fluorides in protic solvents



(75%)

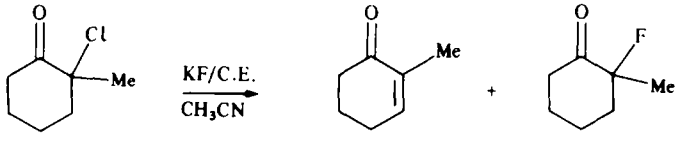
or with HF suffers from the strong tendency of fluoride ion towards solvation, mainly through hydrogen bonding.[9] Interesting quantitative data on such bonds are provided by a study of the X-ray structure of the $KF \cdot (CH_2CO_2H)_2$ complex.[9a] Its nucleophilic and basic powers are markedly reduced. A partial answer to this problem was provided by replacing the metal with a bulky tetraalkyl ammonium cation, which cannot form coordinate bonds with fluoride ion. Thus, less tight ion pairing is achieved. Tetracthyl and tetrabutylammonium fluorides were thus used to replace halogens[15] or tosylates[16] α to carbonyls. While some tetraalkyl ammonium fluorides are commercially available, or

$$RCHXCOOEt + R_4'NF \xrightarrow[\text{or } CH_3CN]{HMPT} RCHFCOOEt$$

R = Me, R' = Et, X = Br (60%)
$R = CH_3(CH_2)_{15}$, R' = Bu, X = OTs (75%)

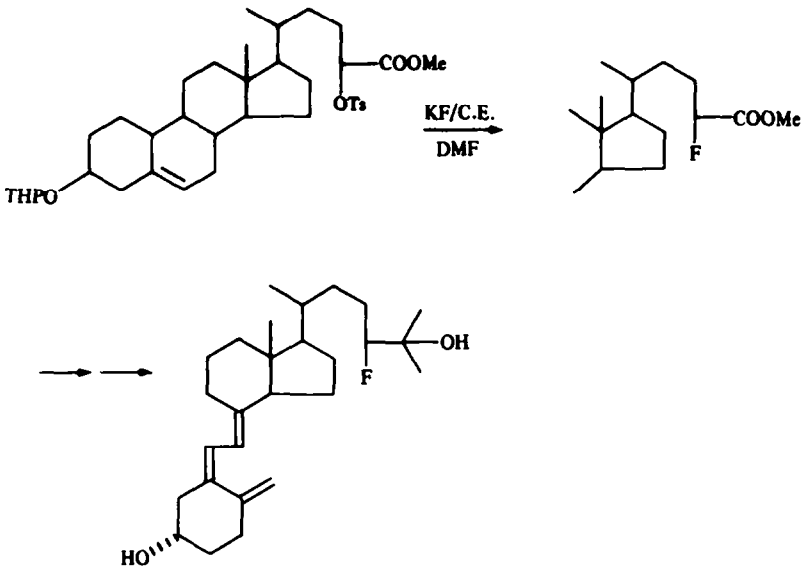
$$PhCOCH_2Br + Et_4NF \longrightarrow PhCOCH_2F \quad (30\%)$$

quite simple to prepare by titration of the corresponding hydroxides with aqueous HF, they are efficient only when very dry and this requirement is extremely difficult to meet,[17] although procedures for drying such salts are available.[17a] The introduction of crown ethers (C.E.) as complexing agents for potassium ion in KF reduced considerably the need for tetraalkyl ammonium fluorides. It has been found that KF can be solubilized in acetonitrile, benzene or other solvents containing catalytic amounts of 1,4,7,10,13,16-hexaoxacyclooctadecane (18-crown-6), thus leaving an unsolvated fluoride, termed by Liotta as "naked" fluoride,[18] which behaves as a base as well as a nucleophile under mild conditions. Thus, while the tertiary chloride in 2-chloro-2-methylcyclohexanone reacts very slowly with dry KF in acetonitrile, the addition of small amounts of 18-crown-6 brings the reaction to completion in a very short time. We have repeated this reaction and have found no evidence of the



(69%) (31%)

tertiary fluoro ketone. The sole product was the α,β-unsaturated ketone.[19] Severe steric restrictions should preclude facile displacement of a cyclohexyl *tertiary* chloride. If, indeed, the fluoro compound is formed, an electrophile-assisted ionization process would seem to be required. Kobayashi used KF in DMF containing 18-crown-6 for one of the most important steps in his multistep synthesis of 24-fluoro-25-hydroxy vitamin D_3 (**13**).[20] The replacement of several halogen atoms attached to one carbon was



13

also investigated and while the chloroacetate of benzyl alcohol **14** reacted cleanly with KF/C.E. to produce the corresponding fluoroacetate **15**, the dichloroacetate **16** produced, along with the expected difluoro compound **17**, products resulting from C—O and C—C cleavage. These were the only compounds isolated when the trichloroacetate **18** reacted under the same conditions.[21] Another

$$\underset{\textbf{14}}{BzOCOCH_2Cl} \xrightarrow[\text{Sulfolane}]{\text{KF/C.E.}} \underset{\textbf{15}}{BzOCOCH_2F}$$

$$BzOCOCHCl_2 \xrightarrow[\text{Sulfolane}]{\text{KF/C.E.}} \underset{\textbf{17}}{BzOCOCHF_2} + PhCH_2F + CH_2Cl_2 + PhCH_2Cl$$

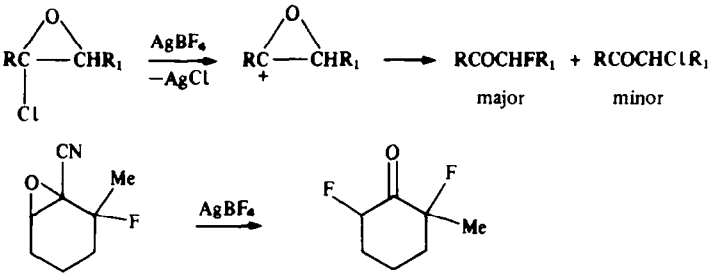
$$\underset{\textbf{18}}{BzOCOCCl_3} \xrightarrow[\text{Sulfolane}]{\text{KF/C.E.}} PhCH_2Cl + PhCH_2F + CHCl_3$$

technique for achieving unsolvated dry fluoride ions was developed recently by Ishikawa[22] and consisted of "spray dried" KF. Thus, an aqueous potassium fluoride solution is sprayed and dried by a stream of heated air (300–500°) resulting in a bulky mass which is less hygroscopic than the usual dried KF and easier to handle. This dry salt replaces halogen by fluorine in efficient and high yield reactions, e.g.

$$BuCOCl \xrightarrow[\text{MeCN, R.T.}]{\text{KF}} BuCOF \ (92\%)$$

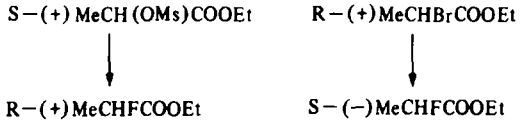
$$ClCH_2COOEt \longrightarrow FCH_2COOEt \ (47\%)$$

Although less frequently used, silver tetrafluoroborate can also be utilized as a fluorinating agent, mainly when a halogen[23,24] or a cyano group[25] is situated α to the oxirane function.



II. *Ion exchange*

Ion exchange is an excellent technique which combines the advantage of performing a reaction on a solid phase, under phase transfer conditions, resulting usually in clean substitution via an S_N2 mechanism. A further advantage is that fluoride ion exhibits the lowest affinity toward resins while the latter has high affinity for the leaving group X^-. However, this technique appears to offer little advantage over R_4NF or KF–C.E. Colonna[26] worked with tertiary amino resins $P—CH_2\overset{+}{N}Me_3F^-$ and was able to replace various bromine atoms and methanesulfonates situated on asymmetric carbon atoms. This technique was also used extensively for introduction of radioactive ^{18}F into organic

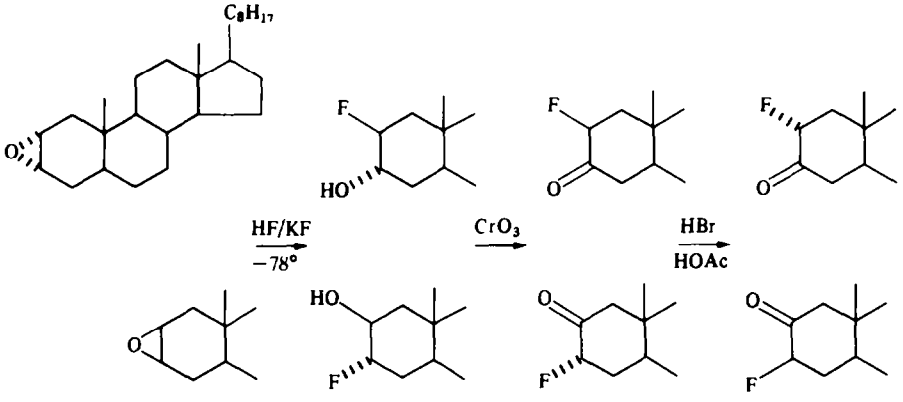


molecules. Thus, gas[27] or liquid chromatographic columns were packed with Dowex[28] or Amberlyt A26[29] resins treated with $^{18}F^-$ to produce, for example, ethyl (^{18}F) fluoroacetate from ethyl bromoacetate. Fluorine-18 containing compounds were also synthesized through substitution reactions with free K ^{18}F and with $Et_4N\ ^{18}F$.[30] Such compounds are potential radiodiagnostic agents, especially as tracers for rapid dynamic metabolic functions.

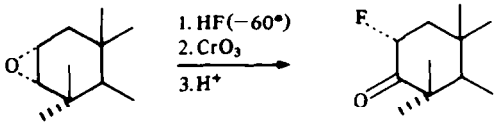
III. *Fluorinations with* HF

One of the main routes to α-fluoro carbonyl compounds starts with an olefin which is epoxidized and the resulting oxirane reacts with HF, followed by oxidation of the fluorohydrin moiety.

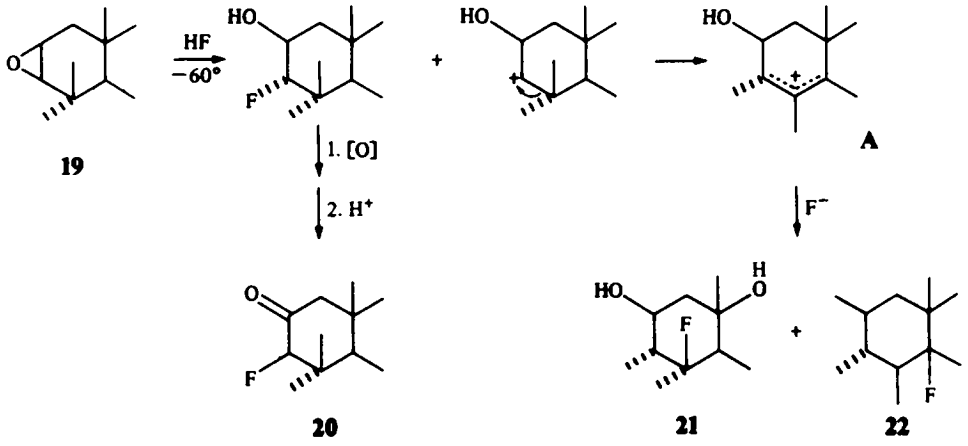
Steroid chemistry, in particular, used this approach prior to the introduction of various electrophilic fluorinating agents. Levisalles[31] used the 2,3-α, and -β, epoxides of cholestane to introduce equatorial fluorine in the 2 and 3 positions, respectively, according to the following scheme. The



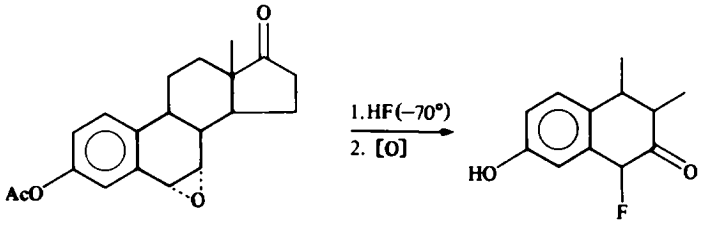
opening of the epoxides proceeded in good yield (80–90%) in the expected *trans*, diaxial mode. This produced the somewhat thermodynamically less stable axial fluorine derivatives which, after acidic treatment of the oxidized fluoro ketones, rearranged to the more stable equatorial isomers. Similiar results were obtained when 2,3-α-epoxides of 4,4-dimethyl steroids[32,33] underwent reaction. The



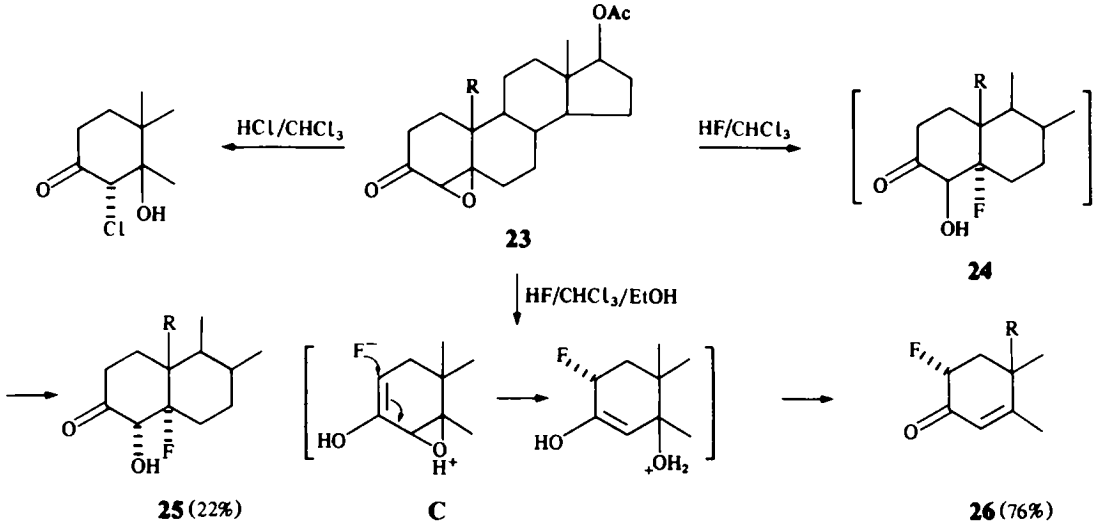
situation is somewhat different when 2,3-β-epoxy-4,4-dimethyl steroids **19** are considered. Only low yields of the expected fluoro ketones-**20** (0–30%) were obtained, together with considerable amounts of rearranged products of type **21**, **22**, which arise from the cationic intermediate **A**. Epoxides in ring **B**

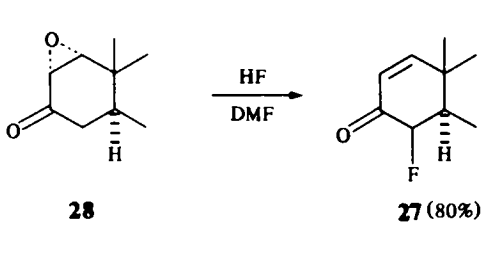


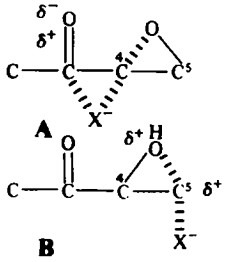
were also opened by HF, in a *trans* diaxial mode,[34] producing the biologically important 6-fluoro derivatives without affecting other functions in the molecule. The opening of epoxides α,β to carbonyl



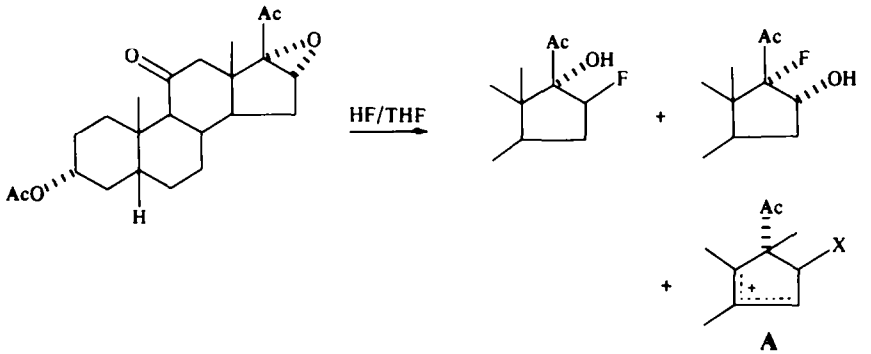
were carefully studied and present some interesting results. Neeman[35] compared the reactions of 4,5β-epoxy-17 β-hydroxyandrostan-3-one acetate (**23**) with HX (X = F, Cl, Br) in chloroform or in more solvating media like chloroform–ethanol or DMF.



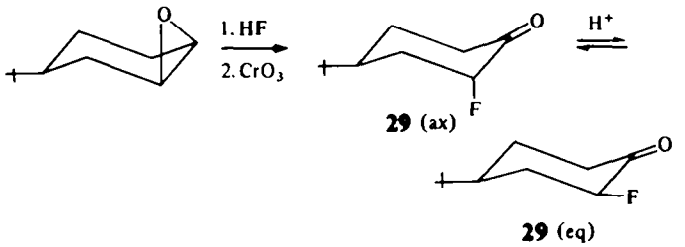


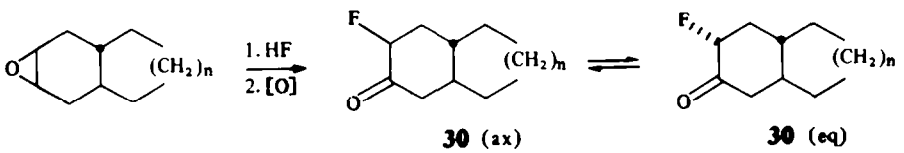


Fluoride, in contrast to chloride, is a small ion and therefore can approach the hindred C-5. Since it has a very low polarizability and cannot form bridged intermediates like **A**, attack occurs via transition state **B** of the protonated oxirane, bearing a partial positive charge at C-5. Fluoride can be more readily accommodated at C-5 than at C-4 which is adjacent to the positive end of the carbonyl dipole. It is believed that the initial product is the *trans* diaxial 4β-hydroxy-5α-fluoro derivative **24**, which readily epimerizes to the 4α-hydroxy isomer **25** (R = Me). When, however, the HF is strongly solvated ($CHCl_3$–EtOH), fluoride cannot approach the C-5 position. The so-called "cine" fluorination takes place, producing the 2α-fluoro steroid **26** (R = Me). A mechanism involving fluorine migration was proposed,[36] which seems unlikely, since it has been contradicted by other experiments.[35b] The intermediate proposed for cine fluorination is the enol form of the keto-epoxide **C**. This fluorination was also exploited in the regiospecific synthesis of 2α-fluoro-10β-hydroxysteroids **26** (R = OH), a key intermediate in the synthesis of 2-fluoroestrones.[37] The above considerations also led to a regiospecific fluorination at C-4 in **27** when 1,2α-epoxy-3-one steroids **28** were employed.[35a,36] Fluorination of steroidal epoxides vicinal to carbonyls were also performed on ring **D**. Two fluorohydrins were isolated along with several other compounds through the intermediate **A**.[38]

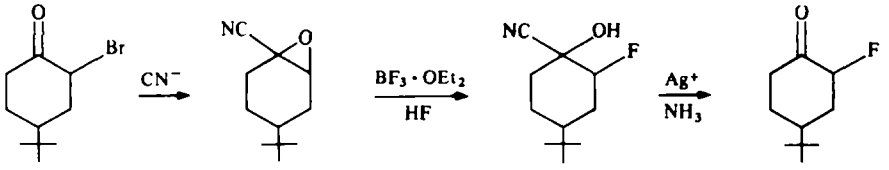


Various other non-steroidal epoxides also reacted with HF with subsequent oxidation to the corresponding α-fluoro ketone. The following two examples[39–41] are representative of many. A

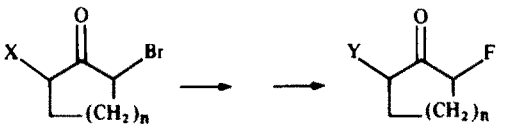




somewhat similar method enabled replacement of halogen α to a carbonyl by fluorine. Treatment of such an α-haloketone with cyanide produced an epoxy nitrile which was opened by $HF/BF_3 \cdot OEt_2$. The resulting α-fluorocyanohydrin was easily oxidized, usually by ammoniacal silver salts, to the corresponding α-fluoroketones such as **29**,[42,43] to α,α'-difluoroketones **31**[44] and, in the appropriate cases, to α-fluoroaldehydes,[43] or 3-fluoro-2-ketoacids.[43a]



29 (*cis* and *trans*)



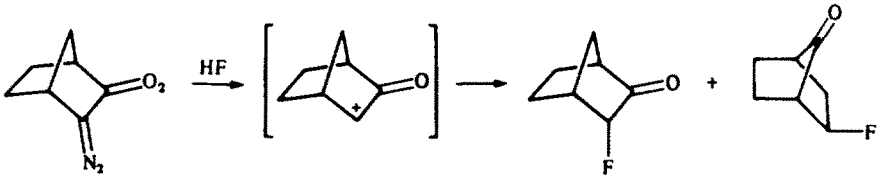
n = 1,2,3; X = H
n = 2; X = Br

31 n = 1,2,3; Y = H
n = 2; Y = F

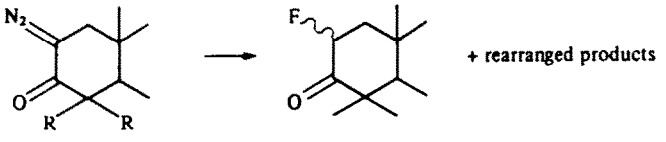
$C_5H_{11}CHBrCHO \longrightarrow\longrightarrow C_5H_{11}CHFCHO$

When strongly acidic conditions are applied to cyclohexyl fluoroketones, an equilibrium between axial and equatorial fluorine is achieved. The epimerization proceeds through the corresponding enols. The fluorine atoms impose two opposite effects, increasing the acidity of the adjacent proton, thus aiding the first stage of the enolization process, but concurrently decreasing the basicity of the carbonyl, so that only strong acids, such as HCl, should be used for the epimerization.[39–46] The equilibrium constants of some fluoroketones have also been calculated and compared with the experimental values and the differences attributed to orbital interactions of the equatorial fluorine with nearby atoms.[47] It has been observed that under neutral conditions the amount of the equatorial conformer increases with the dielectric constant of the solvent.[48] This is in accord with the finding that the dipole moments of α-haloketones are practically independent of the nature of the halogen, but depend on its axial–equatorial conformation.[49] Apart from IR and PMR, the stereochemistry of the α-fluoroketones and some of their hydrates[50] can easily be determined by a ^{13}C-NMR technique.[15,41,51,52]

Hydrofluoric acid reacts with α-diazocarbonyls to give the respective fluorinated compounds. This reaction, however, is not widely used since the starting diazo compounds are usually not readily accessible and because the reaction proceeds through a carbocation α to carbonyl, which is responsible for several side reactions. Thus, diazonocamphor (**32**) gave 30% of the expected fluoride **33** and 52% of the rearranged **34**.[53] The same situation was observed in steroids as with the cholestanone derivative **35**. While 2α-fluorocholestanone (**36**) was obtained in 30–40% yield,[54a] the reaction with 4,4-dimethyl cholestanone **35** (R = Me) gave only 5% of the 2α-fluoro derivative **37**.[54b] Since these reactions also proceeded through carbocations, several by-products arising from ring contractions and opening of ring A were observed. Anhydrous HF has also been employed in carbohydrate chemistry. Through



32 **33** **34**

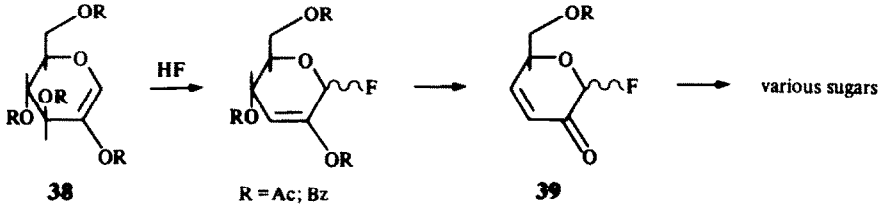


+ rearranged products

35 R = H, Me

36 2α–F, R = H
37 2β–F, R = Me

several additions and eliminations of the elements of HF, the enol esters **38**, were converted to α-fluorocarbonyl-containing sugars **39**, which served as useful intermediates for synthesis of other carbohydrate systems.[55]



38 R = Ac; Bz **39**

IV. *Fluorinations with* HF/*pyridine complex*

Anhydrous hydrogen fluoride is one of the most inexpensive fluorinating agents. However, it is quite inconvenient to handle, due to its low boiling point (19.6°). This problem was overcome mainly through the work of Olah, who introduced in 1960 the pyridinium fluoride reagent, obtained by the reaction of pyridine with formyl fluoride and decarbonylation of the intermediate N-formylpyridinium fluoride.[56] This procedure was inconvenient and Olah later showed that pyridinium poly hydrogen fluoride (30% Py. 70% HF),[57] a stable storable liquid, can be conveniently prepared from pyridine and HF at low temp. This complex can generally replace anhydrous HF and many examples were presented in Olah's full report.[58] Thus, $Py(HF)_x$ was used in the synthesis of α-fluoro carboxylic acids through deaminative fluorination of amino acids, in the fluorination of diazoketones, or in replacement of halides by fluorine in α-haloketones, using HgO as a catalyst. These reactions usually proceed in 40–80% yields. The

$$RCH(NH_2)COOH \xrightarrow[NaNO_2]{Py(HF)_x} [RCH(N_2^+)COOH] \longrightarrow RCHFCOOH$$

R = Me, Et, Pr, i−Pr, Bu, t−Bu, etc.

$$RCOCHN_2 \xrightarrow{Py(HF)_x} RCOCH_2F$$

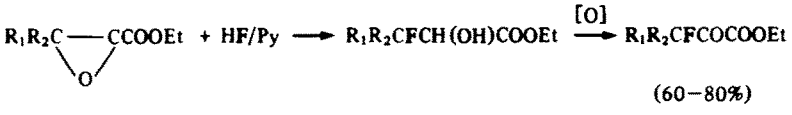
$$RCOCHN_2 \xrightarrow[NY]{Py(HF)_x} RCOCHFY$$

NY = N - halosuccinimides R = Ph, C_6H_{11}, Et, EtO

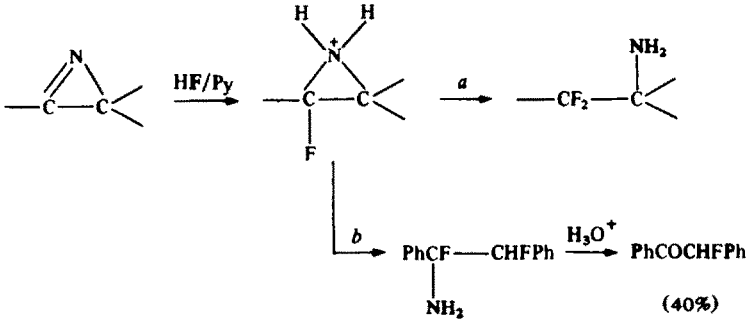
$$CH_3CH(X)COR \xrightarrow[Py(HF)_x]{HgO} CH_3CHFCOR$$

R = Et, Ph, OH

hydrogen fluoride–pyridine complex was also utilized for opening epoxides α to the carboxylic moiety, forming, after oxidation, pyruvic acid derivatives in high yields.[59] The reaction of HF/Py with another small ring system, I-azirine derivatives, was also studied, but the main products in this reaction were β,β-difluoroamines (Path *a*) and only in certain cases, α-fluoroketones were obtained[60] (Path *b*).

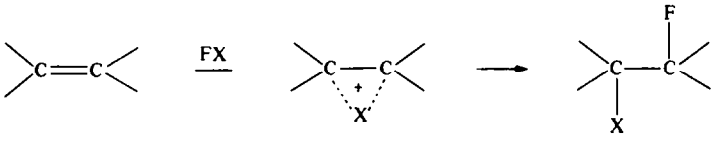


R_1R_2 = H, various Alk, Ar and alicyclic.



V. *Reactions with halogen fluorides*

Addition of the elements of XF (X = Cl, Br, I) across double bonds is usually achieved by two routes, viz. an indirect approach consisting of reaction of olefins with a mixture of anhydrous HF and a source of "positive" halogen like N-haloimides[61] and via a "true" halogen fluoride, synthesized from the elements, followed by its addition to double bonds.[62] Usually, both methods give similar results. Only a few examples are found, however, for the addition of these elements to double bonds to produce α-fluoro carbonyl derivatives. Understandably, such reactions are slower and more difficult than those with a more electron-rich double bond, but both proceed via the same bridged halonium ion, followed by attack of nucleophilic fluorine in a *trans* fashion. Methyl acrylate (**40**, X = H) reacted with a mixture



of either hexachloromelamine (HCM) or Cl_2 and anhydrous HF to yield both Markovnikov and anti-Markovnikov adducts **41** and **42** (X = H) in the ratio of 1 : 4,[63] while methyl methacrylate (**40**, X = Me) gave mainly Markovnikov adducts (**41**, X = Me).[64] Chlorofluorination of dimethyl maleate and

$$CH_2{=}C(X)COOMe \xrightarrow[HF]{HCM \text{ or } Cl_2} CH_2ClCXFCOOMe + CH_2FCHClCOOMe$$

40 X = H, Me — **41** X = H (10%), **41** X = Me (50%) — **42** X = H (40%)

fumarate (**43**, R = Me, *cis* and *trans*, respectively) was also achieved and fully stereospecific *trans* addition was observed.[65] The same pattern was found when the elements of [BrF] were added to various esters of fumaric and maleic acids.[66] Many such adducts were tested for antifungal properties

$$ROOCCH{=}CHCOOR \xrightarrow{XF} ROOCCHXCHFCOOR$$

43 R = Me — X = Cl, Br — **44** *threo* or *erythro*

$$\xrightarrow[-HF \text{ or } HBr]{B^-} ROOCCX{=}CHCOOR$$

45

and the *threo*-ethyl 2-bromo-3-fluorosuccinate (**44**, *threo*, R = Et, X = Br) appeared to be the most active. A mixture of compounds were obtained, which included in addition to the bromo-fluoro adduct, fluoro- and bromoolefins (**45**—X = F, Br, both *trans*). It is known that **44** eliminates HF preferentially to HBr in the ratio of 2 : 1 in slightly basic solutions.[67] Chlorine monofluoride, prepared from Cl_2 and F_2, can also be used to displace bromine by fluorine, including bromine vicinal to carboxylic functions. If excess ClF is used, two bromines in the same molecule can be replaced.[68]

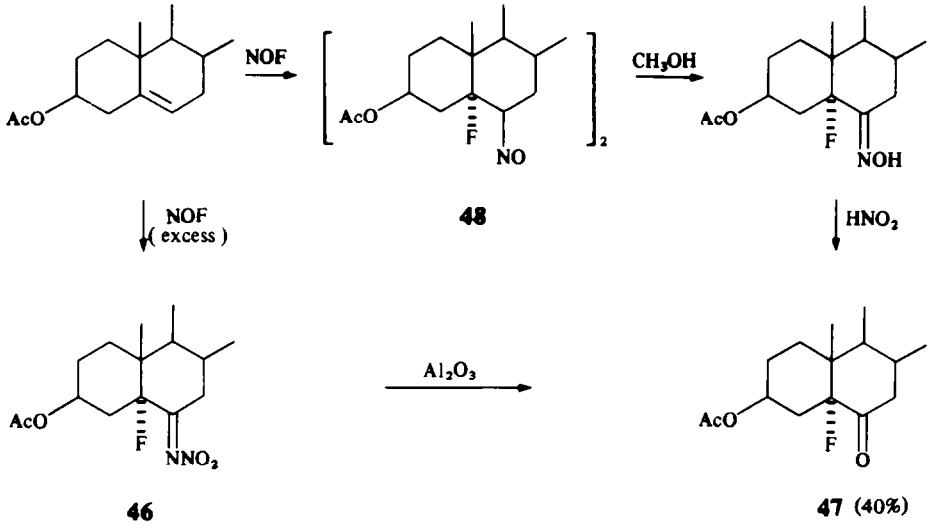
$$CH_2BrC(CH_3)BrCOOMe \xrightarrow{ClF} CH_2XC(CH_3)FCOOMe$$

X = Br, mol/eq of ClF, 68%
X = F, 2 mol/eq of ClF, 93%

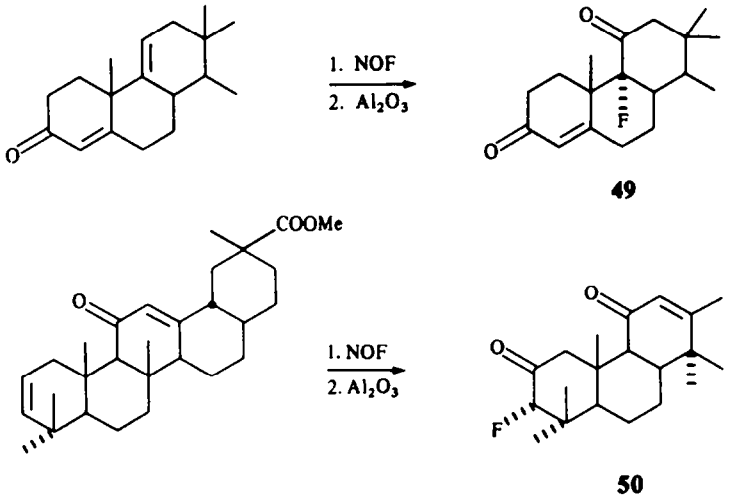
VI. *Reactions with nitrosyl fluoride*

While the chemistry of nitrosyl chloride is well established, only a few examples are recorded of reactions with NOF, mainly in the steroidal field. Boswell[69,70] was the first to investigate this reagent, which converts double bonds in two steps to fluoroketones. When NOF reacted with a 5,6-steroidal olefin, two intermediates were formed : a 5α-fluoro-6-nitrimino steroid-**46** (excess of NOF), which can be hydrolyzed, usually on alumina, to a 5α-fluoro-6-one steroid-**47**, and the dimer of 5α-fluoro-6-

nitroso steroid-**48** (insufficient amount of NOF). The latter, on treatment with methanol and deamination with nitrous acid, produced the same fluoroketone **47**. This method was also used with



Δ9,11 steroids to give the important 9α-fluoro-11-one steroid-**49**,[71] and with methyl 3-deoxo-2,3-ene-glycyrrhetate to produce the 3α-fluoro-2-one derivative **50**.[72] In both cases, the other conjugated system did not interfere with the reaction.

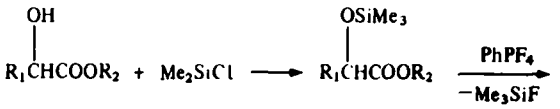


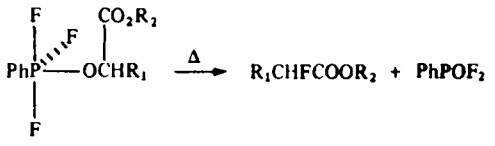
VII. *Reactions with reagents possessing a* P—F *bond*

Alkyl α-hydroxy carboxylates can be silylated and then treated with $PhPF_4$ to form compounds of type **51** with a phosphorus–oxygen bond. The driving force for the formation of these intermediates is the high affinity of the fluorine for the silicon atom. The unstable **51** was then decomposed thermally to produce the corresponding α-fluoro esters.[73] Similarly, Bu_3MePF serves as a fluorinating agent by opening halo epoxides. Such reagents replace halides with inversion of configuration, indicating an S_N2 mechanism.[74]

VIII. *Fluorinations using* SF_4 *and* DAST

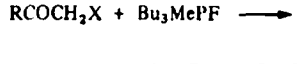
Sulfur tetrafluoride has long been known for its ability to react with carbonyls and hydroxyls.[75] Since it reacts faster with hydroxyls, several studies were performed on hydroxycarbonyl compounds. Diesters of tartaric acid are probably the most favorable substrates of this kind. When dimethyl tartrate (**52**) of unspecified configuration reacted with SF_4 in the presence of HF at 100°, about 38% of dimethyl 2,3-difluorosuccinate (**53**) was obtained, while at 25° only monofluorination took place.[76] Hudlicky[77]



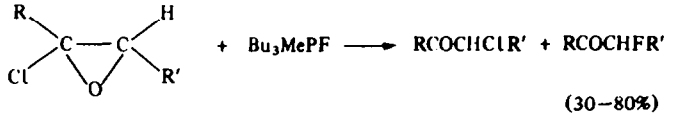


51 (20–80%)

R_1 = H, Me, F; R_2 = Me, Et



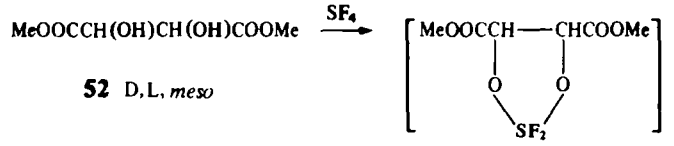
R = Ph, t–Bu, NMe_2; X = Br, Cl



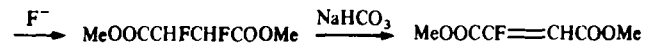
(30–80%)

R = t–Bu, Ph; R' = H, Me

studied the stereochemistry of the reaction and found that inversion of configuration occurred at only one carbon, which led him to propose a cyclic intermediate **54**. Thus, both (–)-D and (+)-L dimethyl tartarates (**52**) gave meso-**53**, while meso-**52** produced the racemic mixture of **53**. The same conclusions were also derived by Yagupolskii[78] who actually isolated several adducts and raised the yield of **53** to 95% by using an excess of HF. Basic treatment of **53** gave fluorofumarate in 50% yield.[76]

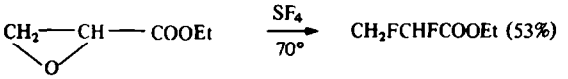


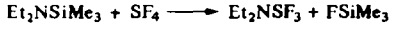
52 D,L, *meso* **54**



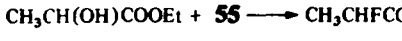
53 *meso*, (D+L) *trans*

Sulfur tetrafluoride reacts also with oxiranes to produce mainly vicinal difluoro derivatives. When the oxirane is situated vicinal to a carboxylate group, the reaction usually requires more severe conditions, but eventually, α,β-difluorocarboxylates are formed in good yields.[79] These reactions are



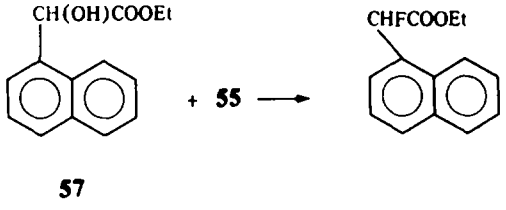


55 (DAST)



56

inconvenient, however, since SF_4 is a very toxic gas, the reactions require high pressure equipment and tars are formed. These difficulties were overcome by preparing the SF_4 analogue, diethylaminosulfur trifluoride (DAST-**55**) which is a stable, storable liquid which reacts similarly to SF_4.[80] Middleton[81] fully developed the reaction of DAST with carbonyls, and more importantly, with hydroxyl groups, which results in clean substitution by fluorine. Even with sensitive alcohols, which cannot survive the reaction conditions of SF_4, relatively small amounts of elimination and rearranged products were observed. Hydroxyls α to carbonyl groups, as in ethyl lactate (**56**) or in ethyl 1-naphthyl-glycolate (**57**), were exchanged by fluorine in 78 and 60% yields, respectively. Lowe showed that such substitution occurred with inversion of configuration.[82] Esters of α-oxoarylacetic acids reacted with DAST to give high yields of α,α-difluoroarylacetic derivatives, including **58** (X = F) and **59** (X = F). It is noteworthy that while **58** (X = H) is an antiinflammatory drug and **59** (X = H) a plant growth regulant, the fluoro analog **58** (X = F) is essentially inactive, but that of **59** (X = F) retains its biological activity.[83]



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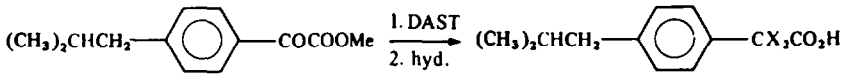

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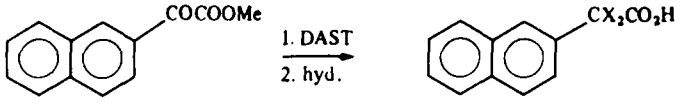
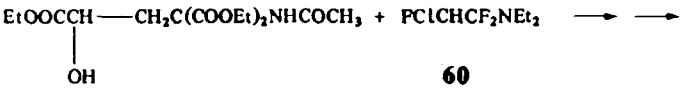


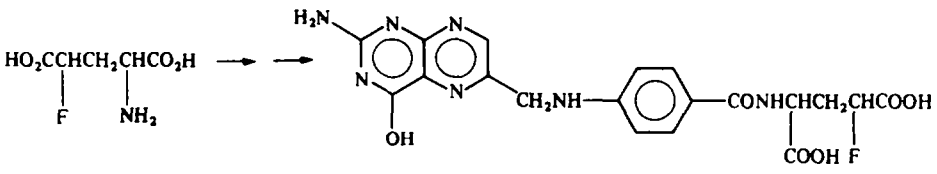
59

IX. *Reactions of* 2-*chloro*-1,1,2-*trifluoroethyl-diethylamine* (**60**) *and its analogs*

This reagent, which was developed and used extensively in the early 1960s for replacing steroidal hydroxyl groups with fluorine,[84] was also employed by Bergmann[85] for the synthesis of α-fluoro carboxylic acid derivatives from the corresponding α-hydroxy esters. The reaction proceeds with inversion of configuration. Apart from the preparation of α-fluorophenylacetic acid derivatives and methyl α-fluoroisobutyrate, this reagent was also used for the synthesis of γ-fluoroglutamic acid **61** which serves as a starting material for the synthesis of fluorofolic acid (**62**).[86]



60



61 **62**

Subsequently, analogous reactions were described. The addition of diethylamine to trifluorostyrene, followed by hydrolysis, produced N,N-diethyl-α-fluorophenylacetamide **63**.[87] Similar addition to perfluoropropene gave a mixture of the adduct **64a** and the unsaturated amine **64b**. This reagent,

developed by Ishikawa,[88] proved to be a fluorinating agent superior in some respects to **60**, and is more stable and easier to store. When **64** was hydrolyzed, N,N-diethyl-1,2,2,2-tetrafluoropropionamide (**65**) was obtained and by Grignard arylation and treatment with alcoholic alkali, α-fluoro-β-ketoesters (**66**) were ultimately isolated in good yields.[89] Perfluoroacyl fluorides (**67**), free of HF, were prepared in 59–

$$PhCF{=}CF_2 \xrightarrow[2.\,H_2O]{1.\,HNEt_2} PhCHFCONEt_2$$

63

Ishikawa reagent **64**

$$CF_3CF{=}CF_2 \xrightarrow{HNEt_2} CF_3CHFCF_2NEt_2 + CF_3CF{=}CFNEt_2$$

64a **64b**

$$\mathbf{64a} + H_2O \longrightarrow CF_3CHFCONEt_2 \xrightarrow{ArMgBr} ArCOCHFCF_3$$

65

$$\xrightarrow[2.\,H^+(-2HF)]{1.\,RO^-/ROH} ArCOCHFCOOR$$

66

91% yields by heating perfluorocarboxylic acids with **64**, in the presence of sodium fluoride.[89a] Ethyl

$$R_fCO_2H + \mathbf{64} \xrightarrow{NaF} R_fC(=O)F$$

67

mandelate was readily converted to ethyl α-fluorophenyl acetate[88] (**68**) and benzoin to the ketone (**69**).[89b]

$$PhCHOHCO_2Et + \mathbf{64} \longrightarrow Ph{\cdot}CHF\,CO_2Et \quad \mathbf{68}$$

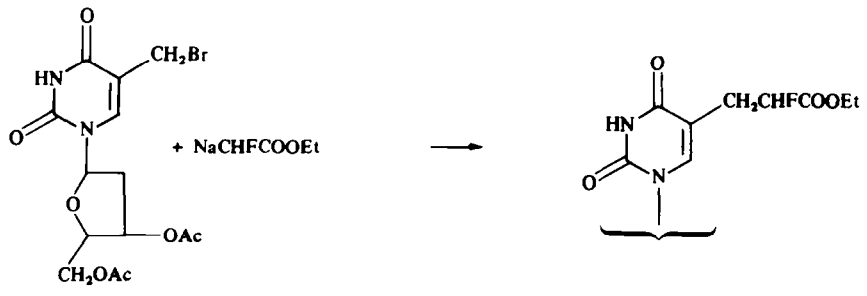
$$PhCHOHCOPh + \mathbf{64} \longrightarrow Ph{\cdot}CHF\,CO\,Ph \quad \mathbf{69}$$

C. SYNTHESIS OF FLUOROCARBONYL DERIVATIVES FROM FLUORINE-CONTAINING MOLECULES

I. *Reactions on a carbon atom attached to fluorine*

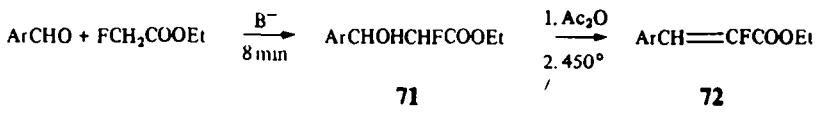
Such reactions are usually performed on α-fluorocarbonyl derivatives and utilize the enhanced acidity of the hydrogen adjacent to the fluorine and carbonyl groups. Ethyl fluoroacetate, for example, is a reactive substrate. Direct alkylation with simple alkyl bromides[90] and with the biologically important uracyl derivatives **70**[91] have been attempted, but the yields were quite poor.

$$CH_2F\,COOEt + BuBr \xrightarrow[(Me_2N)_3PO]{NaH} BuCHFCO_2Et \quad (10\%)$$

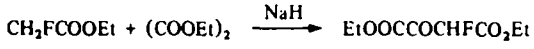


70

Fluoroacetates readily condense with various aromatic aldehydes in good yields. Yields are drastically reduced when an electron-withdrawing group is situated in the *para* position.[92] The *erythro* fluorohydrin (**71**), the major component of this aldol condensation, can be acetylated and pyrolyzed to *cis*-ethyl fluorocinnamate (**72**). The *threo* isomer of **71** gave the *trans* isomer of **72**.

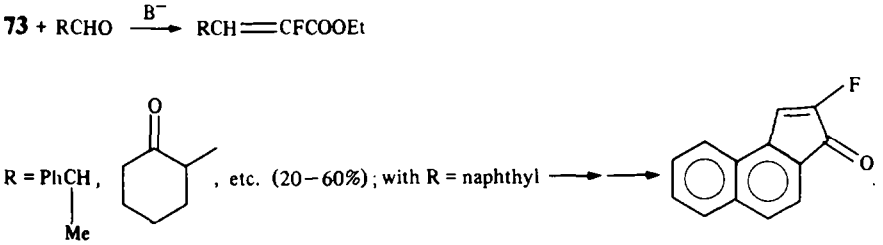


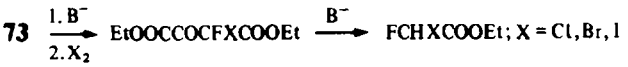
71 **72**

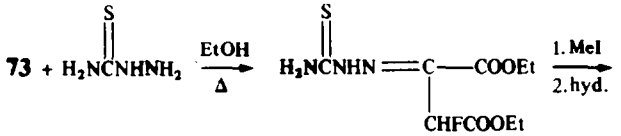


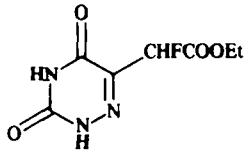
73

Diethyl fluorooxaloacetate **73**, which was first prepared by Bergmann from ethyl fluoroacetate and ethyl oxalate,[93] possesses a more acidic hydrogen than the fluoroacetate. In basic media, **73** reacted readily with aldehydes to produce, eventually, α-fluoro-unsaturated acids, some of which undergo cyclization reactions.[94] Compound **73** reacted with halogens to give fluorohaloacetates,[95] with thiosemicarbazide under neutral conditions to construct the biologically interesting 6-azauracil derivatives **74**,[96] and with paraformaldehyde in the synthesis of methyl α-fluoroacrylate (**75**). The latter can be readily polymerized under a variety of conditions.[97]









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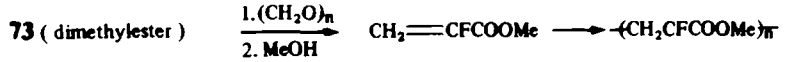
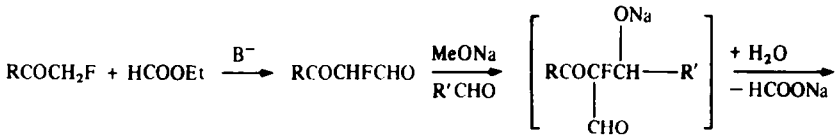
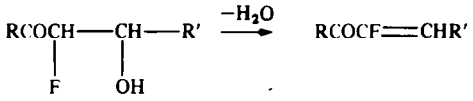


75 (35%)

Fluorocarbonyls react with ethyl formate to form α-fluoro α-formyl ketones and esters in 50–70% yields.[98] These compounds also condense with aldehydes and following loss of sodium formate from

the resulting intermediates, give the corresponding fluorohydrins **76**. Compound **76** can be dehydrated to the α-fluorovinylic carbonyls (**77**).[99]



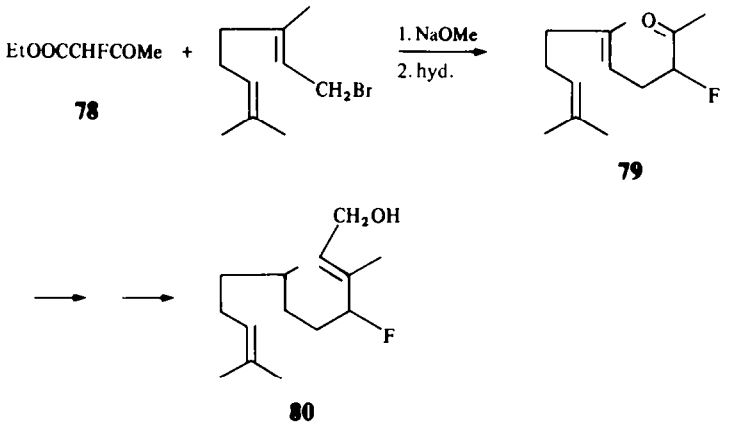


76 **77**

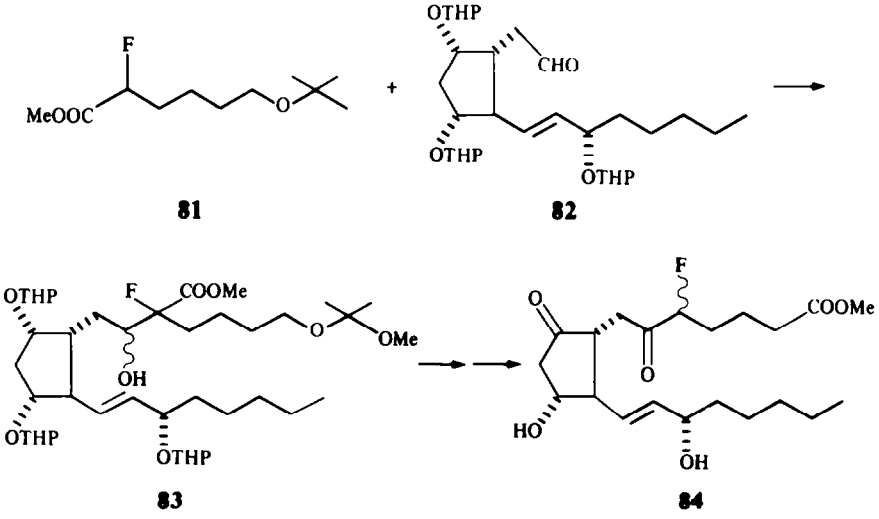
R = Ph, OEt; R' = H, Me, Et, i−Pr

Fluoroacetoacetate **78**[100] was alkylated with bromide to give 3-fluorogeranylacetone **79**, which was converted eventually to 4-fluorofarnesol (**80**). Such fluorine-containing isoprenyl derivatives are potential insect juvenile hormone substitutes, hyperlipidemic drugs and cancer chemotherapeutic agents.[101]

Fluoroprostaglandins are also of great biological interest. When the α-fluoroester **81** was treated with lithium diisopropylamide and the aldehyde **82**, the fluoro derivative **83** was obtained and converted ultimately to 5-fluoro-6-keto-PGE1 methyl ester **84**. This compound is 10 times more potent in uterine contraction activity (in rats) and in inhibition of stress ulcers than PGE1 itself.[102]

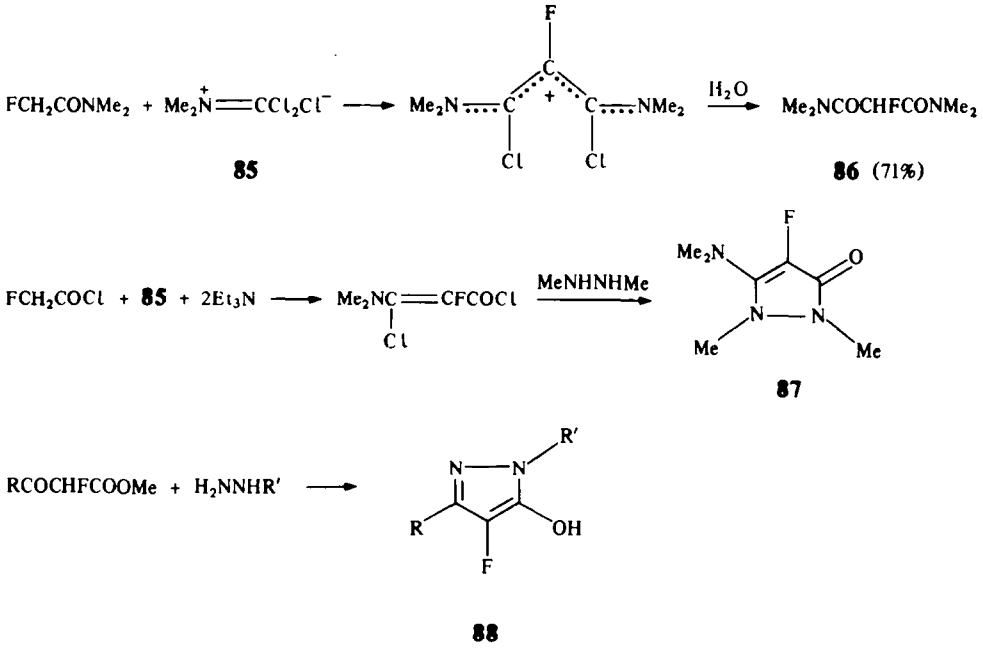


78 **79** **80**



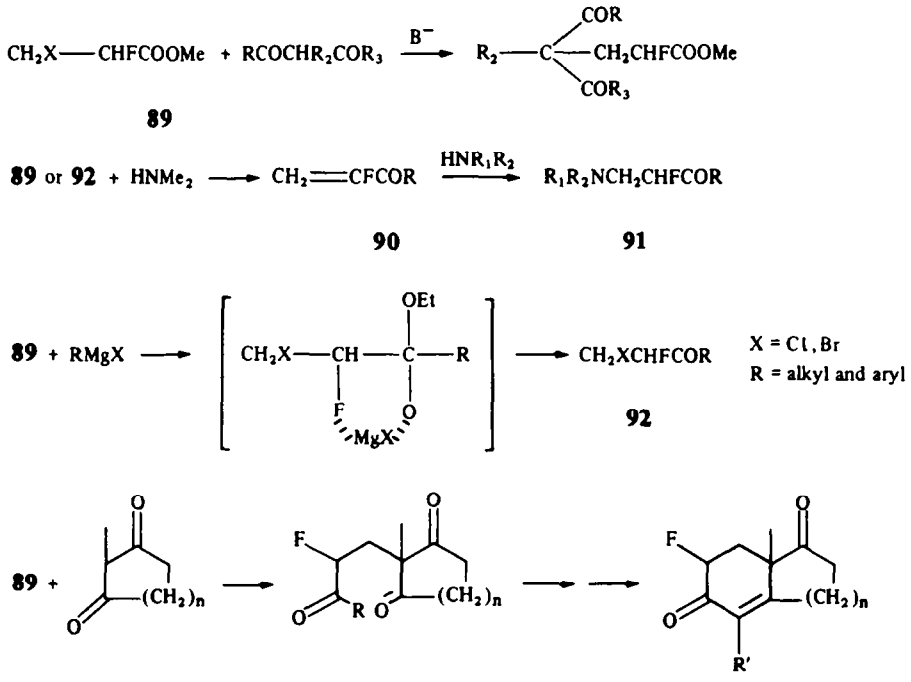
81 **82** **83** **84**

Another type of condensation involving the active hydrogens of fluoroacetate derivatives was described by Viehe,[103] who used the phosgeniminium chloride **85** to form fluoromalonate amides **86** and a large number of fluorine-containing heterocyclic systems. These include compounds containing the fluorocarbonyl group, such as 4-fluoropyrazolin-5-one **87**. Cyclizations of fluoroacetoacetates with hydrazines lead to similar heterocyclic systems, e.g. **88**.[104]



II. *Reactions on carbon β to the fluorine*

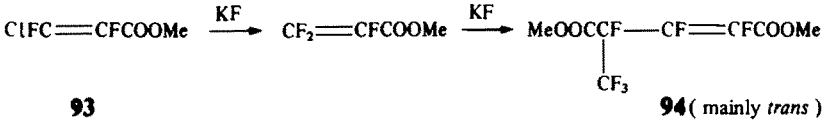
The fact that chloride and bromide are better leaving groups than fluoride was used by Elkik for regioselective nucleophilic substitution in the presence of neighboring fluorine. Thus, α-fluoro-β-halopropionates (**89**) were treated with anions of various 1,3-dicarbonyl derivatives and only the α-halogen was displaced.[105] Similar behavior was observed when **89** reacted with amines. One mole-equivalent of dimethylamine gave the α-fluoroacrylate (**90**, R = OMe). Various amines could then be added to **90** to produce the corresponding β-amino-α-fluoropropionates (**91**, R = OMe).[16a,b,107] When

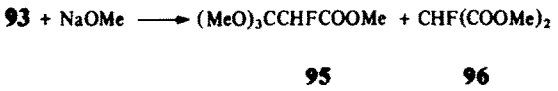


89 reacted with Grignard reagents, only α-fluoro-β-haloketones (**92**) were obtained, in good yields. These ketones (**92**) and dimethylamine readily formed **90** and **91** (R = Et, Bu, Ph, $PhCH_2$). The enones **90** reacted with various 1,3-dicarbonyls as a part of a total steroid synthesis.[106c,d]

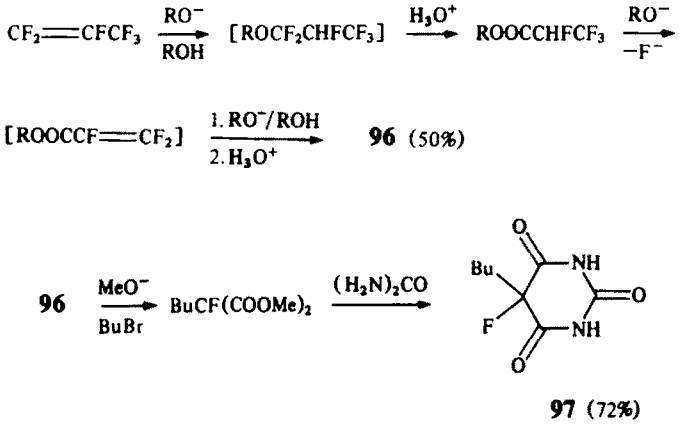
III. *Reactions of polyfluorinated compounds*

The reaction of chlorodifluoropropenoates **93** with KF produced the highly reactive methyl trifluoroacrylate, which underwent dimerization of *trans* **94**.[108] Treatment of **93** with other bases, such as NaOMe, led to displacement of chloride ion with formation of methyl β,β,β-trimethoxy α-fluoropropionate (**95**), accompanied by the important dimethyl fluoromalonic acid (**96**).[109] A better

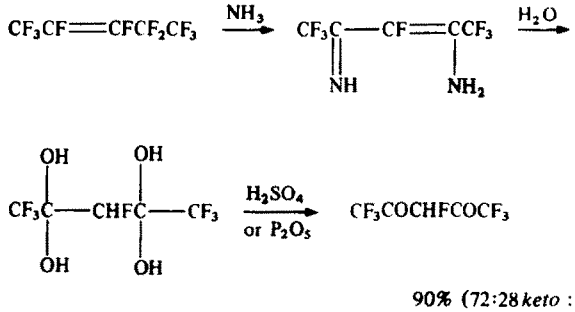




synthesis of fluoromalonates (**96**) was developed recently by Ishikawa, who treated commercial perfluoropropene with alkoxide. The fluoromalonate was then alkylated with BuBr and treated with urea to form 5-butyl-5-fluorobarbituric acid **97**.[110] Similar addition of bases like alkoxides,[111] amines



or ammonia[112] to perfluorinated olefins, with subsequent hydrolysis, also produced fluorocarbonyl compounds, e.g.



Aqueous ammonia was added to perfluoropropene in dioxane to form the very stable, useful intermediate, α-hydrotetrafluoropropionitrile (**98**). With strong electrophiles which are also strong Lewis acids, e.g. $AlCl_3$, the nitrile moiety of **98** is reactive and eventually forms α-fluoroketones, as shown.[113] Aluminum chloride and $FeCl_3$ are useful Friedel–Crafts catalysts for the condensation of

$$CF_3CF{=}CF_2 + NH_3,H_2O \longrightarrow CF_3CHFCN \xrightarrow{AlCl_3} CF_3CHFC^{+}{=}N\bar{A}lCl_3$$

98

$$\xrightarrow[2.\ HCl]{1.\ C_6H_6} CF_3CHFC(Ph){=}NH \xrightarrow{H_2O} CF_3CHFCOPh$$

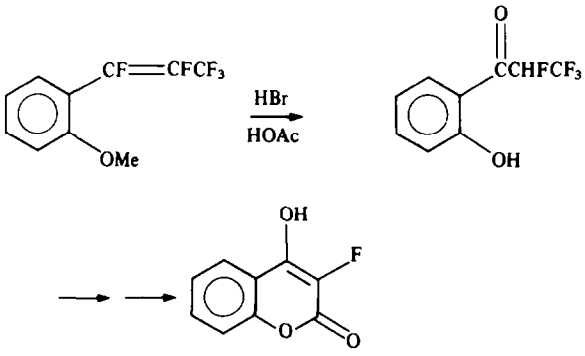
polyfluoroalkenes, such as trifluorethylene, with various acyl halides. The products can be easily converted to α-fluoro-β-ketoesters **99**.[89,114]

$$R{-}COCl, + CHF{=}CF_2 \xrightarrow{AlCl_3} RCOCHFCF_2Cl \xrightarrow[-HCl]{B^-} [RCOCF{=}CF_2]$$

$$\xrightarrow[2.\ H^+(-2HF)]{1.\ R'O^-/R'OH} RCOCHFCOOR'$$

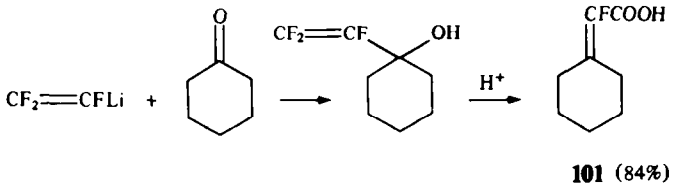
99 (88%)

Acidic treatment of perfluorinated olefins also leads to the α-fluorocarbonyl moiety as demonstrated by the reaction of 1-(*o*-methoxyphenyl) pentafluoropropene with HBr–HOAc. Ultimately, in this case, 3-fluoro-4-hydroxycoumarin (**100**) was obtained.[114a]



IV. *α-Fluorocarbonyls via organometallic intermediates*

While there are many examples of fluorine-containing organometallic compounds, they are usually stable only at low temperatures, because of their tendency to eliminate the elements of metal fluoride. In



101 (84%)

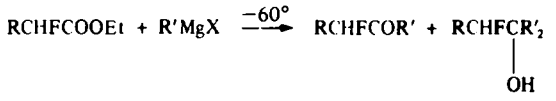
$$R_1R_2CO + CF_2{=}CFLi \longrightarrow R_1R_2C(OH){-}CF{=}CF_2 \xrightarrow{R_3Li} R_1R_2CCHFCF_2R_3 \xrightarrow{H^+} R_1R_2C{=}CFCOR_3$$

102 **103**

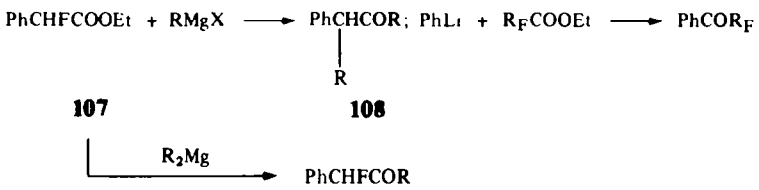
$$\xrightarrow[2.\ H_3O^+]{1.\ LiAlH_4} R_1R_2C(OH){-}CF{=}CFH \xrightarrow{H^+} R_1R_2C{=}CFCHO$$

104

cases where elimination does not occur readily, fluoroorganometallics can be manipulated with relative ease. Trifluorovinyllithium reacted with cyclohexanone to form cyclohexylidenefluoroacetic acid (**101**) in 84% yield.[115] Similarly, the readily formed 1,1,2-trifluoro-3-hydroxy-1-alkenes (**102**) were converted to fluorovinylic ketones **103**.[116] If, however, the intermediate **102** was reduced and treated with sulfuric acid, unsaturated α-fluoroaldehydes **104** were obtained in good yields. Grignard or organolithium reagents react with α-fluoroesters under several conditions. If the reaction temperature was kept below −60°, the main product was an α-fluoroketone (**105**), accompanied by only a small amount of the corresponding alcohol (**106**). Aryl α-fluoroacetates (**107**), however, form fluorine-free ketones (**108**), a problem which was overcome by replacing RMgX with R_2Mg.[117–119]

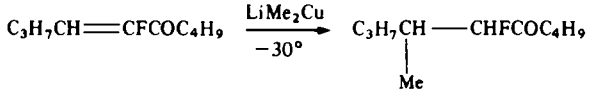


105 (60%) **106** (5–10%)

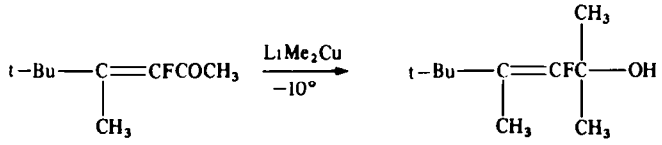


When the temperature of the reaction was raised to room temperature or slightly higher, mainly the alcohols **106** were obtained.[119,120]

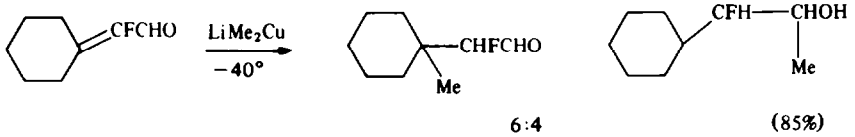
α-Fluoroenones, aldehydes, ketones and esters react with lithium dimethylcuprate without affecting the fluorine atoms. Both 1,2- and 1,4-additions were observed, the ratios depending only on the steric hindrance at the β-position. When steric factors were minimal, 1,4-addition prevailed, while, 1,2-addition predominated when the 4-position was crowded.[121]



(80%) 100% 1,4



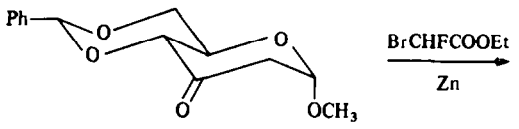
(50%) 100% 1,2



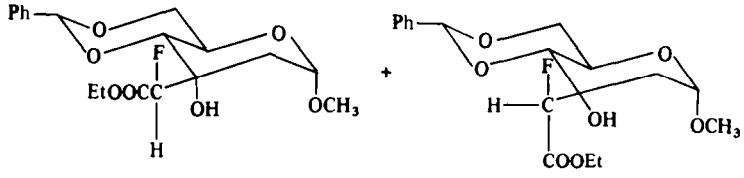
6:4 (85%)

Reagents for the Reformatsky reaction can be derived from fluorine-containing compounds and those react without affecting the strong carbon–fluorine bond. Ethyl bromofluoroacetate was treated with Zn and then with ketone **109**, which can be regarded as a masked oxaloacetate. The reaction is stereoselective and the fluoroacetate moiety was found to possess only the equatorial conformation. Two isomers **110** and **111** were formed. These could be degraded in a single step to substituted

fluorocitric acids (**112** and **113**, respectively). It has been determined that the absolute configuration of **112** is (1*R*, 2*S*) and of **113** (1*S*, 2*S*). The inhibitory isomer of fluorocitric acid which is formed in the citrate synthase reaction with fluoroacetyl-CoA is neither **112** nor **113**. Thus, an unequivocal assignment of the 1*R*, 2*R* configuration—**114**, can be made for this toxic substance.[122]

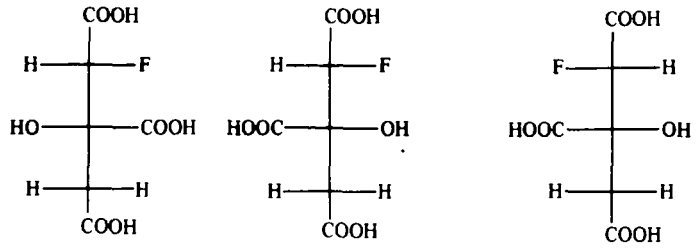


109



110 (14%) **111** (47%)

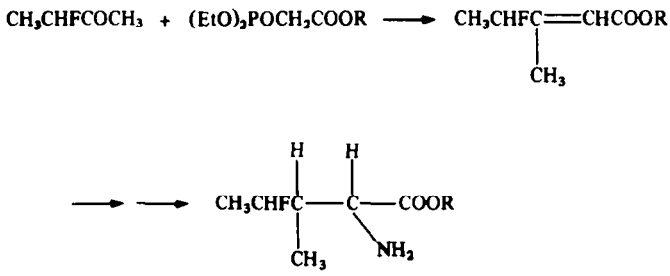
1. H_3O^+
2. $KMnO_4/OH^-$
3. H_3O^+



114 **112** **113**

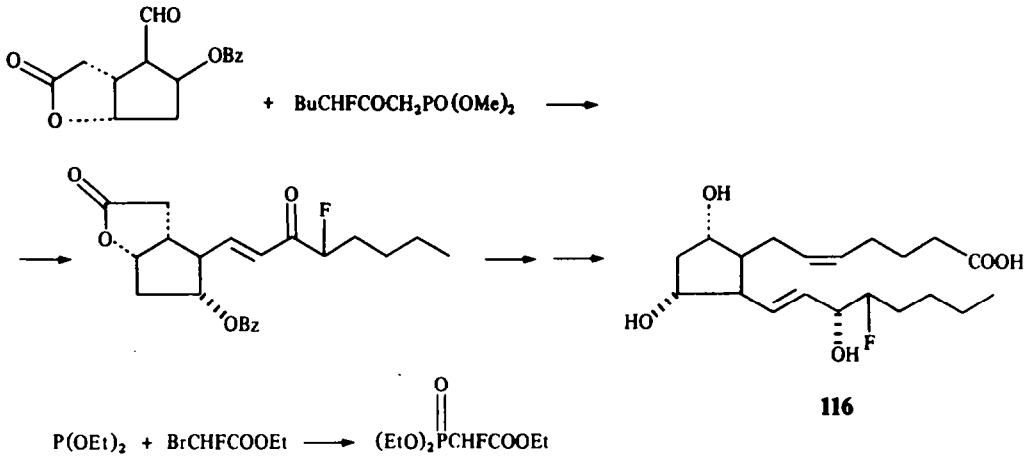
V. *Wittig type reactions with α-fluorocarbonyl compounds*

α-Fluorocarbonyl derivatives react with Horner–Wittig reagents without affecting the fluorine atom. Usually, fluorocarbonyls were treated with ethyl diethylphosphonoacetate to give olefins in good yields.[123,124] α-Fluoroisoleucine (**115**) was synthesized by this route.[124] Carbonyls react readily



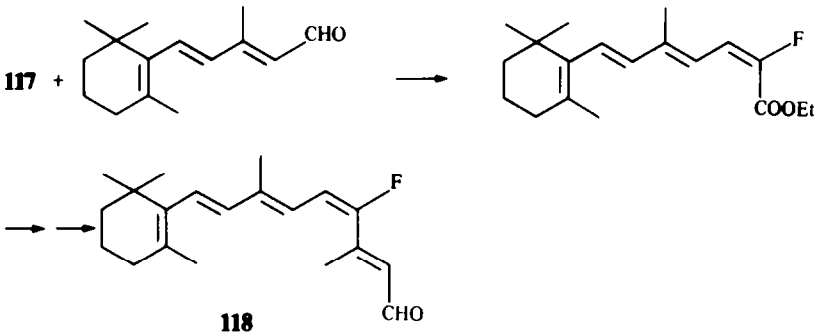
115

with fluorine-containing phosphonates, mainly for synthesis of biologically interesting compounds. Fluoroprostaglandins, e.g. **116**, a potent pregnancy inhibitor in hamsters,[125,126] and fluororetinals such as **118**,[127] are two such examples. In general, this approach is excellent for the synthesis of fluoroolefins since ethyl diethylphosphonofluoroacetate (**117**) can be prepared in high yield.[128]



116

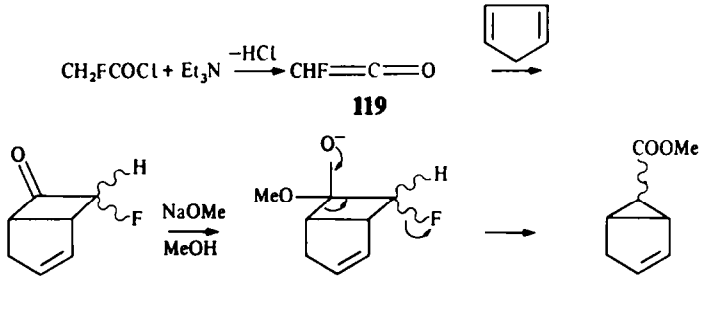
117 (85%)



118

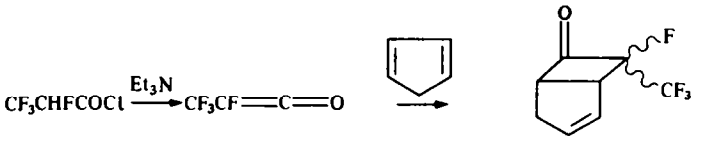
VI. *Cyclization reactions involving the α-fluorocarbonyl moiety*

Brady[129,130] was the first to prepare monofluoroketen **119** and to react it with olefins. Compound **119** was obtained by dehydrochlorination of fluoroacetyl chloride with Et_3N at $-78°$. At this low



119

120 (40%) **121**

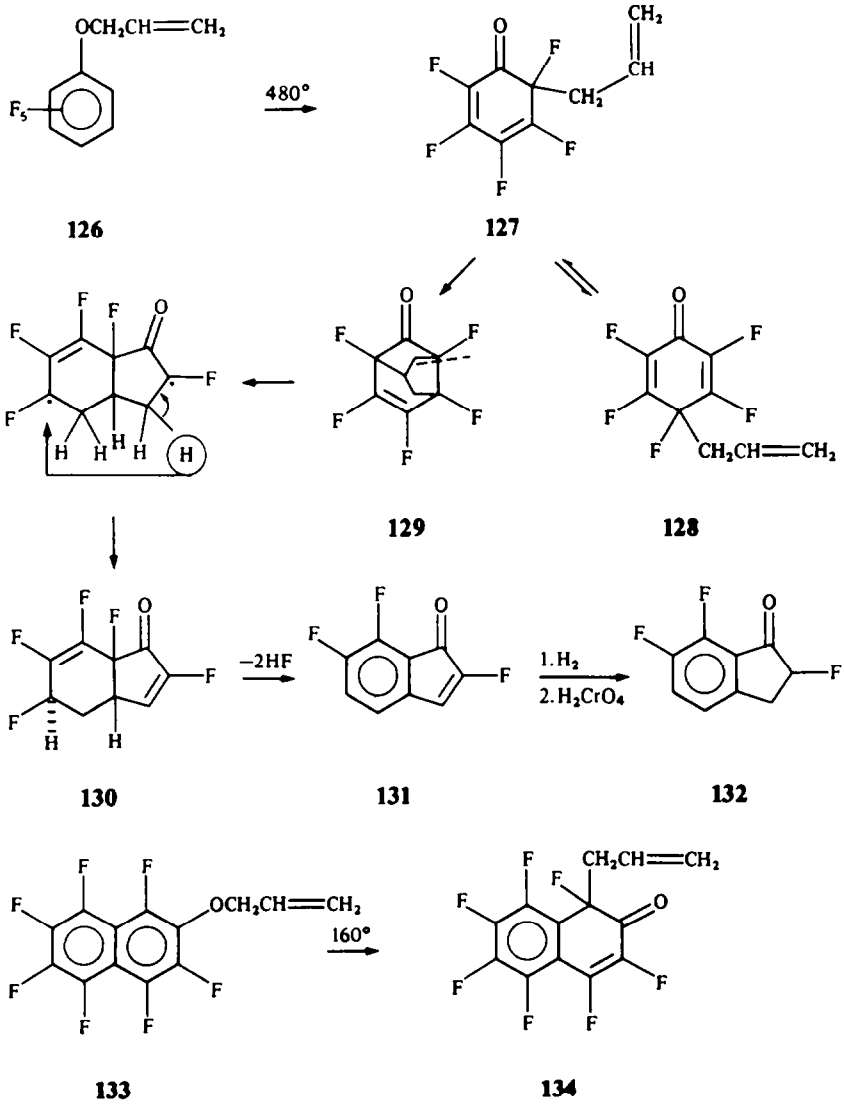


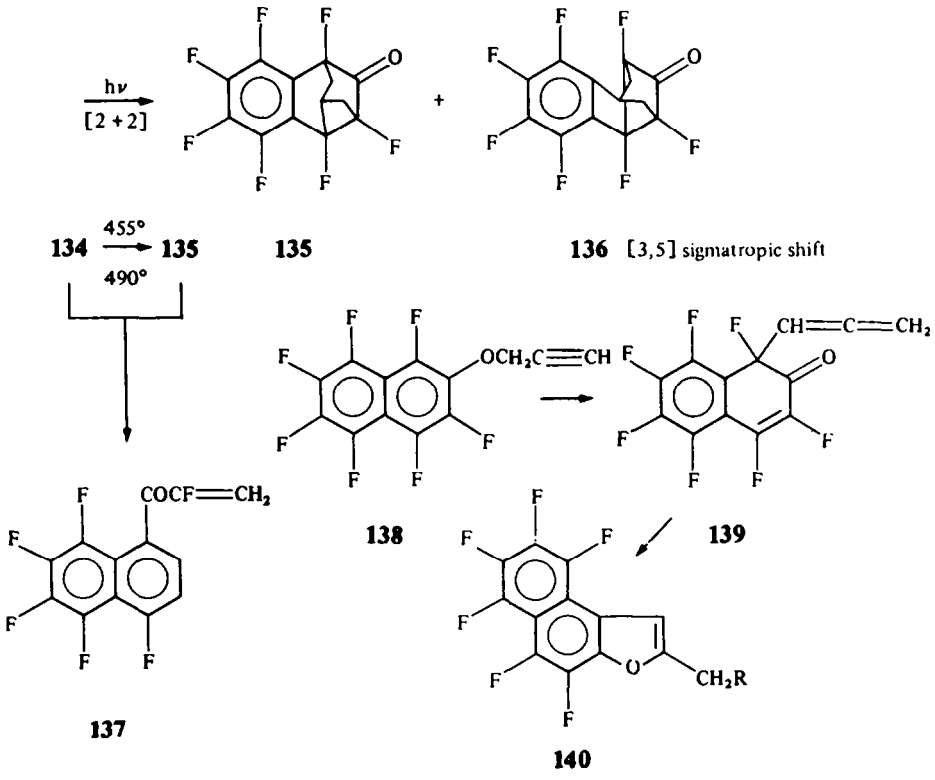
122 **123** (60%)

124 (R = i-Pr) **125** (40%)

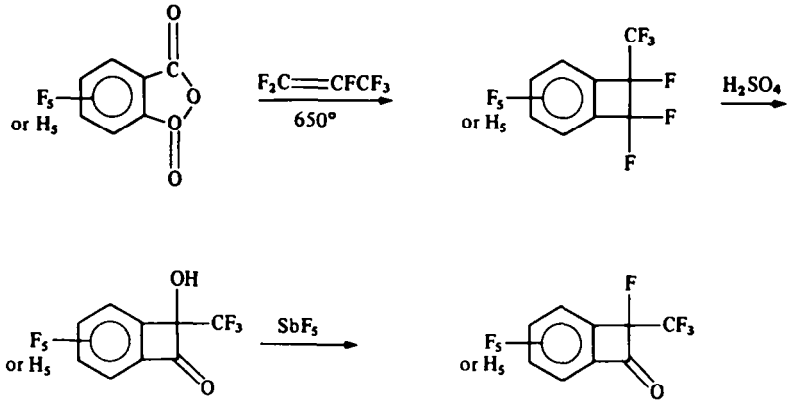
temperature, **119** was quite stable for prolonged periods of time and it reacted with cyclopentadiene, by 1,2-cycloaddition, only upon warming to room temperature. The bicyclo adduct **120** was formed in 40% yield. Similarly, reaction with trifluoromethylfluoroketene (**122**) led to the same system, **123**, in good yield.[131] Under strongly basic conditions, **120** lost fluoride and rearranged to the cyclopropane derivative **121**, but since the fluorine is usually a poor leaving group, the yield in this step was only 10%.[132] The ketene **119** reacted with N,N-diisopropylcarbodiimide (**124**) to produce the corresponding azetidine **125**. Bartlett[133] established the stereochemistry of the adducts of the reaction of **119** with cyclopentadiene and found that the minor component was the *exo*-7-fluorobicyclo[3.2.0]hept-2-en-6-one (**120**) and the major one its *endo* isomer. Dreiding and Ghosez[134] established recently that under various conditions both isomers of **120** can be equilibrated to an *endo*:*exo* ratio of 89:11.

Brooke[135–137] described some interesting thermal and photochemical internal Diels–Alder reactions and 3,5-sigmatropic rearrangements. When pentafluorophenyl-prop-2-enyl ether (**126**) was pyrolyzed at 480°, a thermally induced, symmetry allowed, sigmatropic rearrangement took place, forming **127**. The author proved that this dienone is in equilibrium with **128**, an isomer resulting from *ortho–para* rearrangement of the allyl group in **127**. Through an internal Diels–Alder reaction, **127** was converted to **129**, followed by cleavage of a carbon–carbon bond to give the relatively stable diradical, which by hydrogen migration formed **130**. Dehydrofluorination could lead to the unstable inden-1-one derivative **131** which was hydrogenated and oxidized to the stable **132**. Reactions proceeding through similar intermediates with the naphthyl derivative **133** were also described. Thus, **134** was formed by a

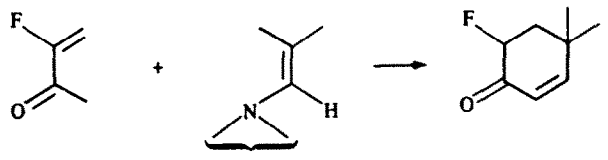




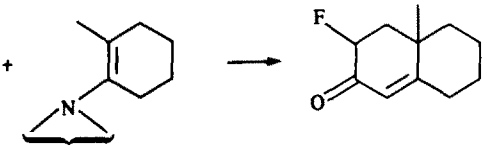
sigmatropic rearrangement, then photolyzed to **135** by [2+2] addition. The fluoroketone **136**, an allowed photochemically induced [3.5] sigmatropic rearrangement product, was found as a by-product. The transformation **134** → **135** could also be induced thermally and, at higher temperatures, both compounds gave the same fluoroketone, **137**. Brooke[138,139] has also carried out similar rearrangements with the acetylenic ether **138**. The allenic derivative **139** was obtained, which then could be converted to various furan derivatives of type **140**. Another thermolytic conversion of organic compounds to α-fluorocarbonyls was described by Yakobson[140] who treated phthalic or perfluorophthalic anhydride with hexafluoropropene at 650°.



Condensation of fluorovinyl methyl ketone (**141**) with enamines led to various α-fluorocyclic enones, such as 6-fluoro-4,4-dimethylcyclohexanone (**142**) or the fluorine-containing steroid percursor **143**.[141] The conjugated fluoroenone **142** and its 5-membered analogue **144** were the subject of photochemical cycloaddition studies using 2,3-dimethyl-2-butene or cyclopentadiene. When **142** was irradiated at 336 nm in isooctane the major product was the corresponding oxetane **145**, but when acetonitrile was used, the major product was the cyclobutane derivative **146**. With the 5-membered ring **144**, mostly oxetane formation, leading to **147**, was observed.[142] These results are somewhat in contrast to the

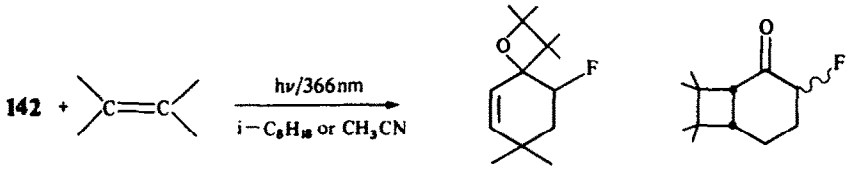


141 **142** (65%)

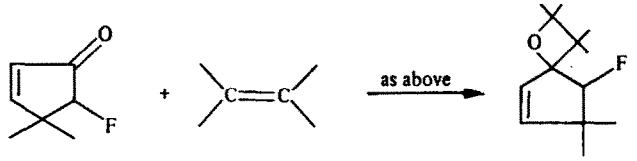


141 **143** (48%)

case of the corresponding chlorocycloenones which usually yield more of the cyclobutane than the oxetane derivatives.[143]



142 **145** **146**

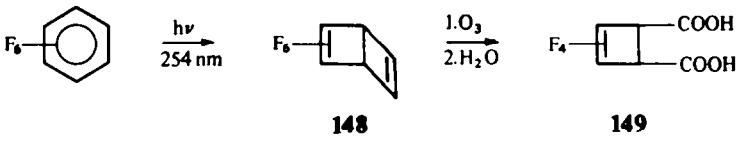


144 **147**

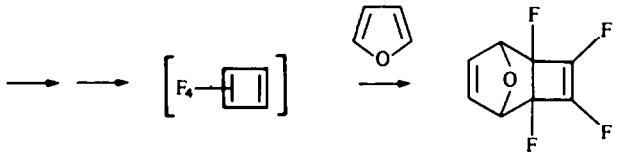
D. PHOTOCHEMICAL, RADICAL, CARBENE, AND ELECTROCHEMICAL REACTIONS

I. *Photochemistry*

Except for a few examples, some of which were described previously, photochemical reactions of α-fluoro carbonyl compounds do not differ appreciably from their fluorine-free analogues. It is other differences, mainly the relative stability of the fluorocarbons compared to the hydrocarbons, which occasionally have been taken into consideration. Lemal[144] photoisomerized hexafluorobenzene at 245 nm, converting it to hexafluoro Dewar benzene **148** and then to tetrafluorocyclobutene-3,4-dicarboxylic acid **149**. The latter compound served as an intermediate for the synthesis of the short-lived tetrafluorocyclobutadiene **150** which could be trapped with dienophiles to form **151**, and dimerized to the tricyclic **152** or to octafluorocyclooctatetraene (**153**). The differences in stability and electron density at sites near fluorine or hydrogen was also demonstrated by comparing the photoabstraction of γ-hydrogen from ketones and fluoroketones, using 4,6,8,8,8-pentafluoro-3-octanone—$CH_3CH_2COCHFCH_2C\underline{H}RCH_2CF_3$ (**154**, R = F). It has been found that there is a larger fraction of the triplet reaction product using **154** (R = F) than with the corresponding 3-octanone. This is due to the increased energy required for the abstraction of the hydrogen in question (the underlined H in **154**) by the excited carbonyl group, because of its lower electron density. Consequently, an intersystem crossing from the excited singlet to the excited triplet states is possible. The fluorine-substituted radical **155** was also expected to be more stable than its hydrogen analog, a fact that again explains the different ratios of products due to "type I" and "type II" processes resulting from the



148 149



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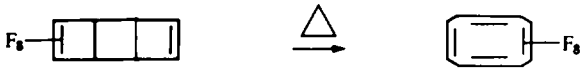
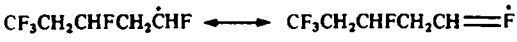
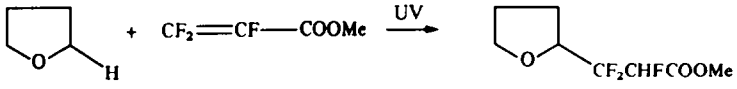


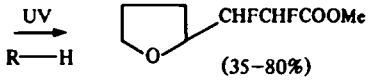
152 153

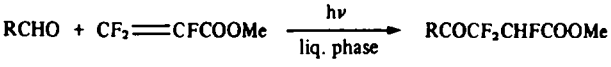


155

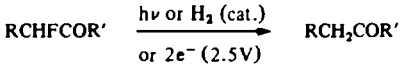
photolysis of **154** (R = F and R = H).[145] The photochemical addition of methyl trifluoroacrylate to ethers[146] and aldehydes[147] was also studied. The reactivity of various ethers, which reacted exclusively at the α-position, was found to be in the order THF > Et_2O > 1,4-dioxane.







In contrast to other fluorine atoms in a molecule, fluorine α to carbonyl, as well as allylic or vinylic fluorine, undergo hydrogenolysis under photochemical,[148] electrochemical[149] or catalytic[150] conditions. The solvent employed was found to be of importance and various mechanisms for the reductions were proposed.



II. *Radical fluorinations*

Usually, radical fluorinations are not selective processes and produce complex mixtures of fluorine-containing compounds. Tatlow[151] used $KCoF_4$ to fluorinate some short chain esters, including propionates, acrylates and succinates to obtain polyfluoro acid fluorides of various degrees of fluorination. It was observed, however, that as chain branching increased, fluorination proceeded with increasing difficulty until pivaloyl fluoride could not be fluorinated by this method. Another source of

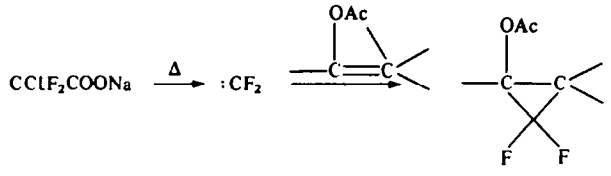
fluorine atoms is elemental fluorine. Fluorine reacted at room temperature with representative acyl fluorides to give a complex mixture of many partially fluorinated compounds, including α-fluorocarboxylic acid derivatives.[152] Lagow perfected this technique and, with the aid of a multizone cryogenic reactor, conducted a direct fluorination of oxygen-containing compounds using varying concentrations of elemental fluorine in helium for long periods.[153] In this way, perfluorinated products were obtained which were either new or had been previously prepared in only minute amounts. Some examples are given below.

$$CH_3COOCH_2CH_3 \xrightarrow[-78°]{F_2} \underset{(5\%)}{CF_3COOCF_2CF_3} + \underset{(20\%)}{CF_3COOCHFCF_3}$$

$$(CH_3)_3CCOF \xrightarrow[-78°]{F_2} \underset{(52\%)}{(CF_3)_3CCOF} + \underset{(20\%)}{(CF_3)_2(CF_2H)CCOF}$$

III. *Fluorocarbenes*

Another route which leads to α-fluorocarbonyl compounds is the action of difluorocarbene on compounds containing electron-rich double bonds, such as enol acetates or enamines. Crabbe[154] generated difluorocarbene by pyrolysis of the sodium salt of chlorodifluoroacetic acid and added it to cyclic enol acetates to form 2,2-difluorocyclopropane-1-one acetate derivatives (**156**). This reaction was applied to the enol acetate of tetralone (**157**), resulting in the difluorocyclopropane derivative **158** in 60% yield. Crabbe's detailed studies on the opening of the cyclopropane ring under basic conditions showed that only the bond not adjacent to the difluoromethylene moiety was cleaved. It seems that because the fluorine is a rather poor leaving group, a non-concerted mechanism of type **A** leads to anion **B**. This can either be protonated to produce difluorobenzosuberone (**159**) or can expel fluoride ion to form a fluoro enone **160**. Under basic conditions, the latter was converted quantitatively into the corresponding fluorine-free tropone system **161**. It is noteworthy, however, that once the difluoroketone **159** was formed, it could not be transformed to **161** under the reaction conditions.



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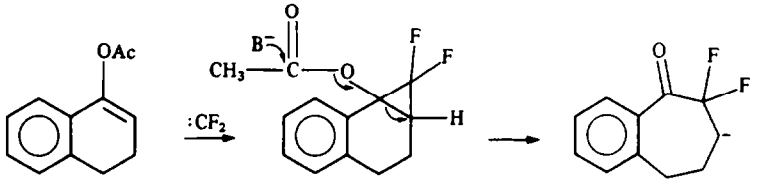
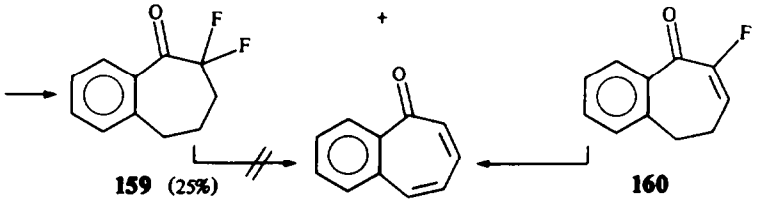
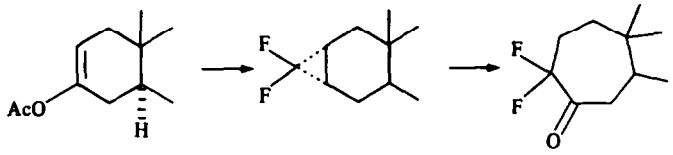


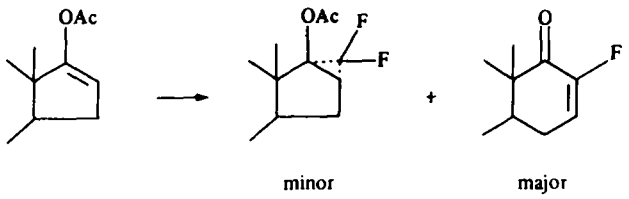
157 **158** (60%) **A** **B**

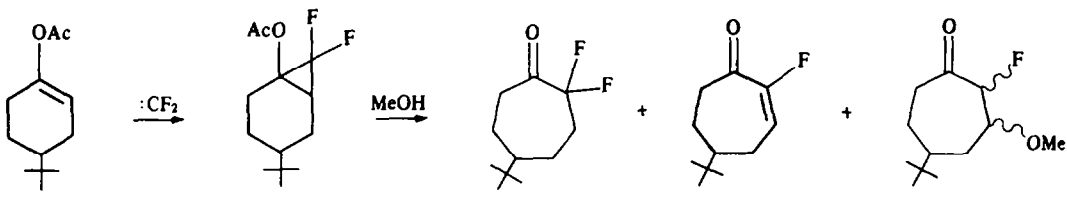


159 (25%) **161** **160**

Crabbe applied this reaction to steroidal enol acetates in rings **A**, **B** and **D**. Usually, ring expansion occurred to produce fluorosteroids, as shown below. Kobayashi[155] applied this reaction to the enol

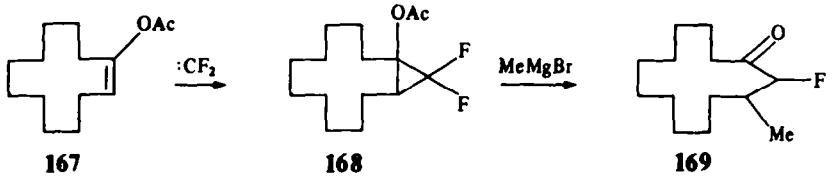




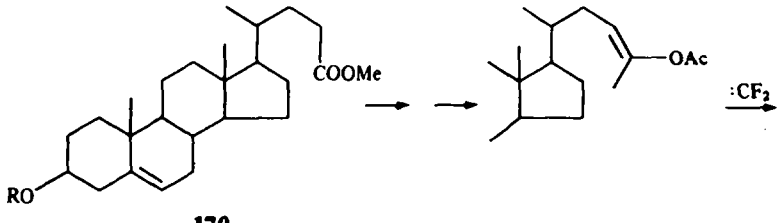


162 **163** **164** **165** **166**

acetate of 4-t-butylcyclohexanone (**162**) and obtained the adduct **163**, which, by hydrolysis with MeOH or other nucleophiles, afforded the α,α-difluoroketone **164** along with the corresponding α-fluoro enone **165** and the fluoroether **166**. The enol acetate of cyclotridecanone (**167**) also reacted and the difluorocyclopropane (**168**) thus obtained was treated with MeMgBr in the presence of CuBr. The 3-membered ring was cleaved and 2-fluoro-3-methylcyclotridecanone **169** was obtained, probably via



167 **168** **169**



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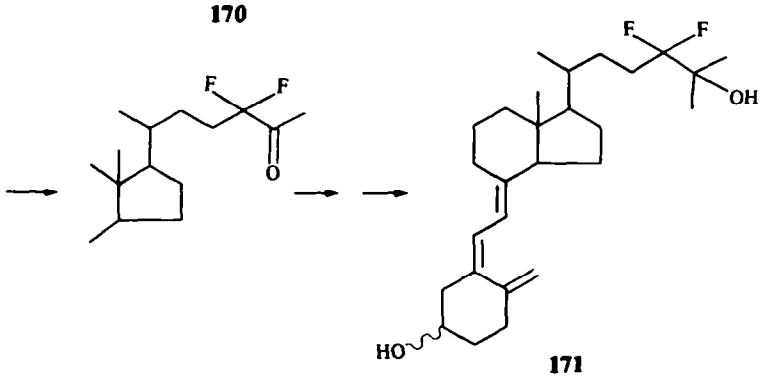
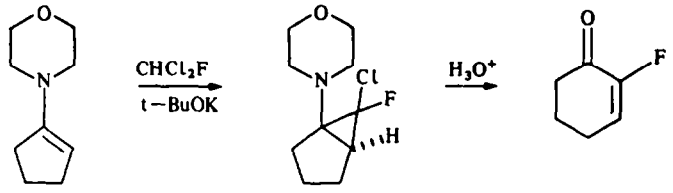
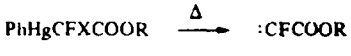


171

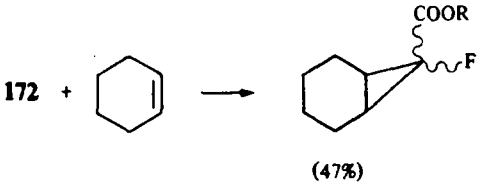
1,4-addition of the Grignard reagent to the resulting fluoro enone. The addition of the fluorocarbene to an electron-rich double bond served as a key step in the synthesis of 24,24-difluoro-25-hydroxyvitamin D_3 (**171**) from the bile acid **170**.[120] Fluorochlorocarbene: CFCl, was obtained by the action of strong base on dichlorofluoromethane[156] or by thermal decomposition of phenyl (dichlorofluoromethyl) mercury.[157] This carbene reacted with various enol acetates and enamines to produce α,α-chlorofluorocarbonyl or α-fluoro enone derivatives. Similarly, fluorocarboalkoxycarbenes (**172**),



obtained from their mercury precursors **173**, reacted with isolated double bonds to yield cyclopropanyl α-fluorocarboxylic acid derivatives **174**. The stereochemistry of the reaction was studied and usually, both epimers were obtained.[158]



173 (X = Br, Cl; R = Me, Et) **172**



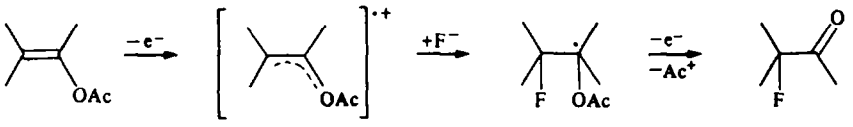
174 (40%)

IV. *Electrochemical fluorinations*

This technique, like the radical fluorinations, is difficult to employ when a selective fluorination is desired. Hence, relatively few studies have been published in the last decade dealing with electrochemical fluorinations involving α-fluorocarbonyl derivatives. Work on the fluorination of methyl 3-methoxypropionate is characteristic.[159] The distillation fraction with boiling point up to 50° consists of at least 15 polyfluoroacyl fluorides.

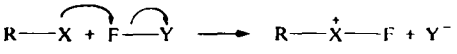
$$CH_3OCH_2CH_2COOMe \xrightarrow[\text{fluor.}]{\text{elec. chem.}} \text{many polyfluorinated products.}$$

A recent paper[159a] described a new route to α-fluoroketones by anodic oxidation of enol acetates in the presence of $Et_3N \cdot 3HF$, which served as the fluorinating agent and supporting electrolyte.



E. ELECTROPHILIC FLUORINATIONS

The concept of electrophilic fluorination has been the subject of considerable debate and controversy, since the process appears to require the removal of a pair of electrons from fluorine, the most electronegative element. It is unnecessary, however, that electrons be formally removed from the fluorine prior to reaction with a nucleophile. It would be sufficient to initiate nucleophilic attack on the fluorine atom, with concerted displacement of a good leaving group, so that a deficiency of electrons need never develop about the fluorine atom.



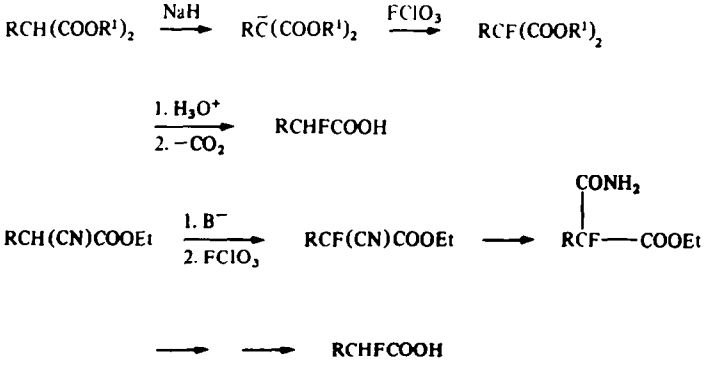
One cannot exclude, however, the possibility of radical or electron-transfer reactions from certain reagents in this category, if high concentration, electron-poor substrates and other radical-favoring conditions are present. Since we will review only reactions of an ionic nature, we use the term "electrophilic fluorine", to indicate a fluroine atom susceptible to attack by various nucleophilic moieties, such as electron-rich olefins or carbanion centers.

There are currently at least four commercial reagents which may be considered as a source of electrophilic fluorine: perchloryl fluoride, $FClO_3$, xenone difluoride, XeF_2, fluoroxytrifluoromethane, CF_3OF (or trifluoromethyl hypofluorite) and F_2 itself. A few other fluoroxy compounds are known, e.g. SF_5OF, $CF_2(OF)_2$, and $F(CF_2)_nOF$. They are rather difficult to obtain and little work has been done with them, usually with results similar to those obtained with CF_3OF. However, elemental fluorine can be used for *in situ* synthesis of various other fluoroxy reagents, such as CF_3CF_2OF or acetyl hypofluorite, CH_3COOF. All of these compounds can be employed for the construction of α-fluorocarbonyl derivatives.

There are a number of excellent reviews, although several are already quite outdated, which deal with some of the above reagents. Djerassi[61] has a special chapter on reactions of $FClO_3$ with steroids. Filler[160] reviewed organic reactions involving the interesting xenon fluorides, while Hesse[161] has done the same with CF_3OF. An additional review deals mainly with the preparation and properties of some fluoroxy compounds.[162]

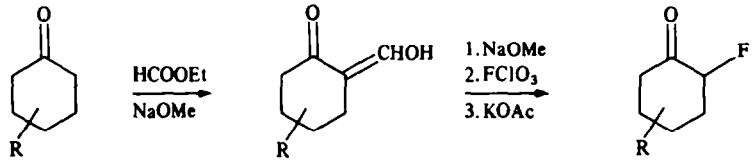
I. *Perchloryl fluoride*—$FClO_3$

Perchloryl fluoride, one of the earliest electrophilic fluorinating agents, does not always react as an electrophile, since the ligand attached to the fluroine possesses unoccupied *d* orbitals which can facilitate either nucleophilic attack upon that ligand or electron-transfer. This sometimes results in chlorinated and/or oxygenated products rather than those containing fluorine.[163] Moreover, $FClO_3$ transfers fluorine only to very reactive nucleophiles, such as enamines or anionic centers. The use of this reagent has declined dramatically in recent years, primarily owing to difficulty in handling. On a number of occasions, serious explosions have occurred, which have been attributed to admixture of organic solvents with the chlorates produced. Nevertheless, perchloryl fluoride has been very useful for the synthesis of many fluorine-containing carbonyl derivatives. α-Fluorocarboxylic acids have been synthesized using malonic esters. These were treated with strong base, then reacted with $FClO_3$, hydrolyzed and decarboxylated.[164–167] Gershon[168] prepared similar compounds starting with C-alkylated ethyl cyanoacetates, which were converted to amides and then to α-fluorocarboxylic acids.

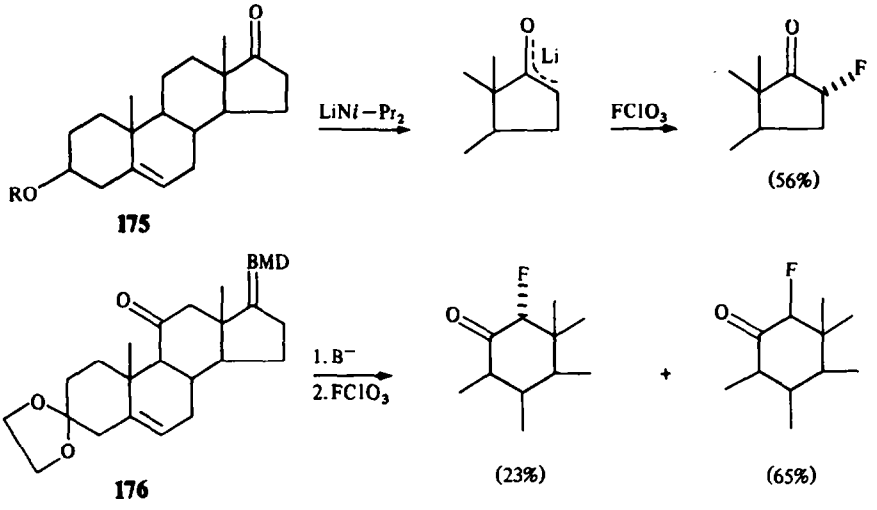


The toxicity of these acids and amides was tested on various animals and found to be as expected (high toxicity with even number, low with odd number carbons). The antifungal properties of α-fluorocarboxylic acids were determined against several fungi. The highest activity was found with acids at chain lengths of C_8—C_{14}.[169]

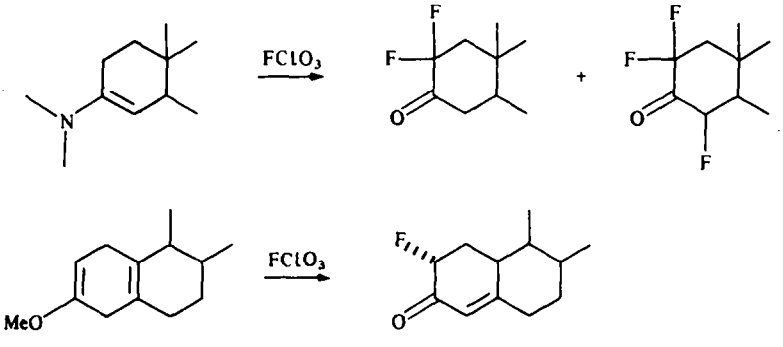
A similar approach was used for introducing fluorine α to carbonyl. Reaction of ketones with ethyl formate produced α-hydroxymethylene derivatives which could then be treated with base and $FClO_3$ as shown. α-Hydroxymethylene ketones are tautomers of 1,3-dicarbonyl compounds and other



examples of the latter can be fluorinated in a similar way.[142b,170–172] Fluorine can also replace the metal in enolates, although extra precautions should be exercised in such reactions. The lithium enolate of androst-5-ene-17-one (**175**)[173] or the sodium enolate of pregn-5-ene-3,11-dione (**176**) derivative[174] serve as examples. The strongly nucleophilic enamines and enol ethers (although only rarely, enol



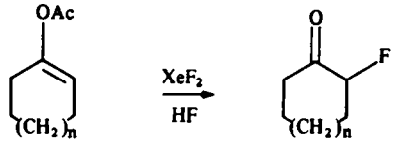
acetates) react successfully with $FClO_3$. There are many such examples cited by Djerassi,[61] so we present only two instances from steroid chemistry which have been published in the last decade. The reactions were not always straightforward, as mono, di, and even trifluorination occurred,[175] especially when enamines were the substrates.[176]



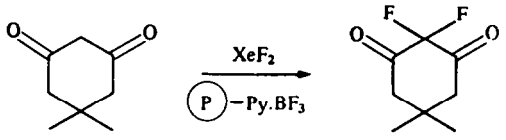
II. *Reactions with xenon fluorides*

Filler's review[160] sheds light on some of the reactions of organic compounds with xenon fluorides, especially with the most available xenon derivative, XeF_2. Some of the studies with this compound have

been devoted to the synthesis of α-fluorocarbonyl derivatives. Zupan[177] investigated the reaction of enol acetates and 1,3-dicarbonyl compounds with XeF_2. Hydrogen fluoride, $BF_3 \cdot OEt_2$ and especially, the insoluble cross-linked polystyrene-4-vinylpyridine complex with BF_3, serve as catalysts. Under these conditions, the enol acetates **177** afforded monofluoroketones **178** in 60–85% yields, while 1,3-diketones, such as **179**, usually gave difluoro products, e.g. **180**, in good yields.

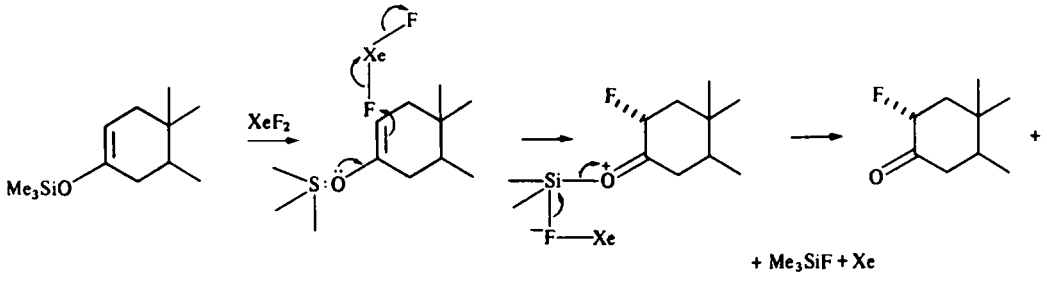


177 **178** (60–85%)

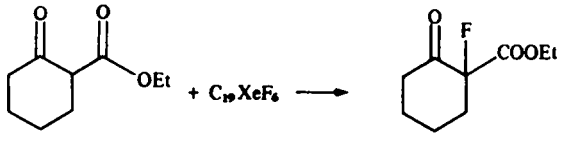


179 **180** (80%)

Trimethylsilyl enol ethers of cycloalkanones are more reactive than enol acetates or enamines toward XeF_2.[19] With a trace of pyridinium polyhydrogen fluoride at 0°, 70–90% yields of 2-fluorocycloalkanones were obtained. Similarly, the silyl enol ether of ethyl benzeneacetate was smoothly converted to ethyl 2-fluorobenzeneacetate. No catalyst was needed when XeF_2 reacted with various steroid silyl enol ethers to give good yields of α-fluoroketones.[178] Mechanistic studies showed that this reaction is an electrophilic one.



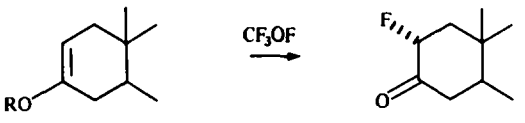
As mentioned, most of the reactions of xenon fluoride compounds in organic chemistry employ the relatively stable XeF_2, since XeF_4 or XeF_6 are much too reactive and tend to explode violently. Graphite intercalates of xenon fluorides were found to be more gentle reagents than the parent fluorides.[179] This observation was used by Kagan[180] to react the lamellar $C_{19}XeF_6$ with various 1,3-dicarbonyl derivatives like **181**, which gave the corresponding 2-monofluoro compounds (**182**). However, simple ketones and even enol acetates do not react with the intercalate $C_{19}XeF_6$.



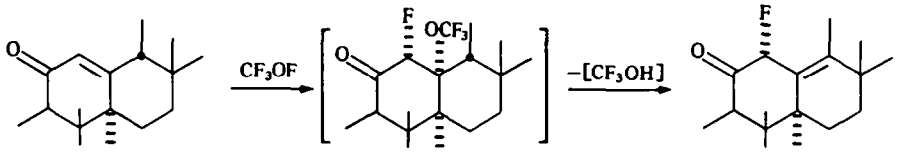
181 **182** (60%)

III. *Fluoroxytrifluoromethane*—CF_3OF

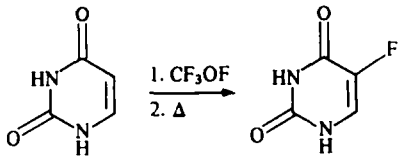
About 15 years ago, Barton and Hesse[181] introduced trifluoromethyl hypofluorite (fluoroxytrifluoromethane), CF_3OF, to organic chemistry. This compound had been prepared previously.[182] They demonstrated that under conditions infavorable to radical reactions, this reagent acts as a much more potent electrophile than $FClO_3$, without the danger associated with the latter. CF_3OF was used for the synthesis of α-fluoroketones from the corresponding enol acetates and enol ethers. It added to various double bonds and reacted with some aromatic compounds to form fluoro derivatives, accompanied, usually, by substantial amounts of α,α-difluoroketones. Most of the

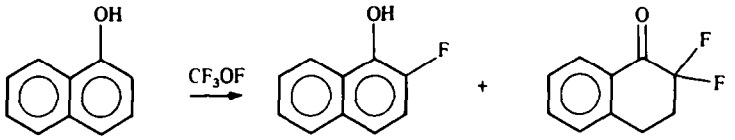


R = Ac, Me (various steroids)

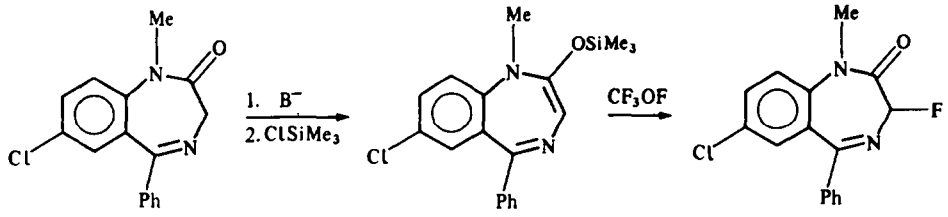


methyl 3 - acetyl glycyrrhetate



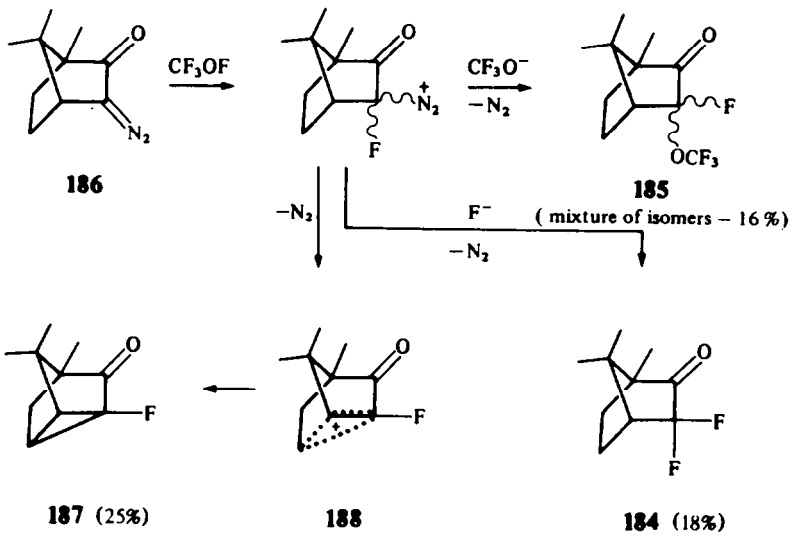


chemistry of CF_3OF, up to 1977, is covered in the comprehensive reviews by Hesse[161] and Barton,[183] which detail the evidence for the electrophilicity of its oxygen bound fluorine. Mechanistic studies of its reactions were also covered. Later, Middleton[184] treated trimethylsily enol ethers of aldehydes, ketones, amides, esters and acids with CF_3OF, to obtain the corresponding α-fluoro derivatives. The reaction is usually clean, since the main by-products, COF_2, and $FSiMe_3$, are gases. The synthesis of 3-fluorodiazepam (**183**) serves as an example. Wakselman[185] fluorinated diazoketones with CF_3OF in



+ CF_2O + $FSiMe_3$ **183** (80%)

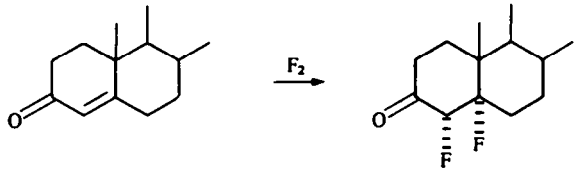
low to moderate yields, producing mainly α,α-difluoroketones, **184** and α-fluoro-α-trifluoromethoxy ketones, **185**. The initial electrophilic attack on the diazo group is followed by nucleophilic attack of F^- or CF_3O^-. The origin of the fluoride seems to be the unstable anion CF_3O^- which tends to decompose rapidly to carbonyl fluoride and F^-. In the case of 3-diazobornan-2-one (**186**) a third tricyclic compound, **187**, was also formed as a result of the rearrangement of the exo diazonium ion, leading to the intermediate ion **188**.



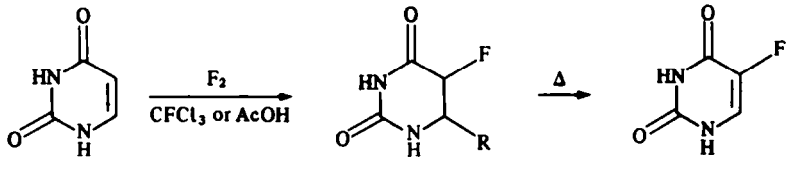
186 **185** **187** (25%) **188** **184** (18%)

IV. *Selective fluorinations with* F_2

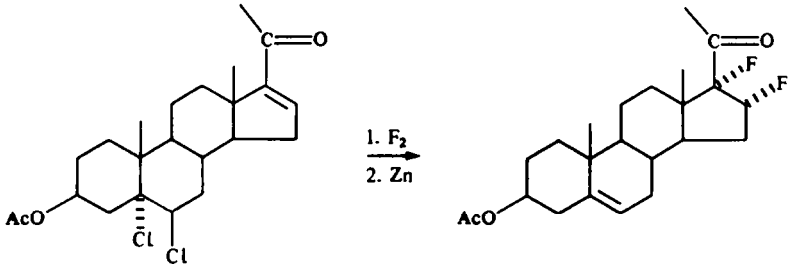
Up to several years ago it was commonly held that "fluorination by fluorine is unlikely to be used in normal organic synthesis".[186] This attitude, however, is changing gradually and it has been shown that direct fluorination under appropriate conditions can achieve surprising results both in new reaction patterns and in high selectivity.[187–190] However, there are still only a few examples of employing elemental fluorine directly with organic substances to form α-fluorocarbonyl derivatives. In 1966, Merritt reported a successful *cis* addition of F_2 to cholest-4-ene-3-one (**189**).[191] Later, it was shown[192–194] that F_2 can be added across the double bond of the uracil system to form, in good yield, the important cancer chemotherapeutic agent 5-fluorouracil (**190**) and its derivatives. Recently, elemental fluorine was added to an enone system in the steroidal ring D of **191**. The products were 16α,17α-difluoropregnenolone (**192**, *syn* addition), accompanied by some rearranged products.[195]



189 (60%)

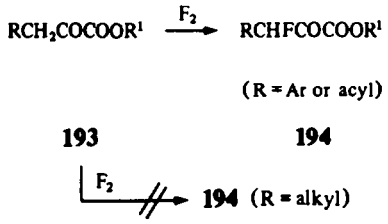


190 (60–90%)

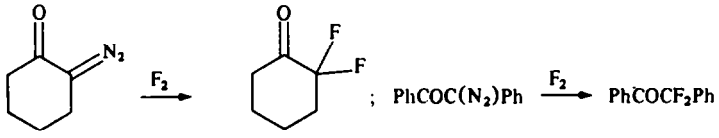


191 **192** (40%)

Direct fluorination of pyruvic acid derivatives, **193**, was also attempted. When the ketomethylene moiety possesses substantial enol character (**193**, R = Ar or R″CO), fluoropyruvates **194** were obtained in moderate to good yield. However, in the case of low enol character, as in **193** (R = alk), a

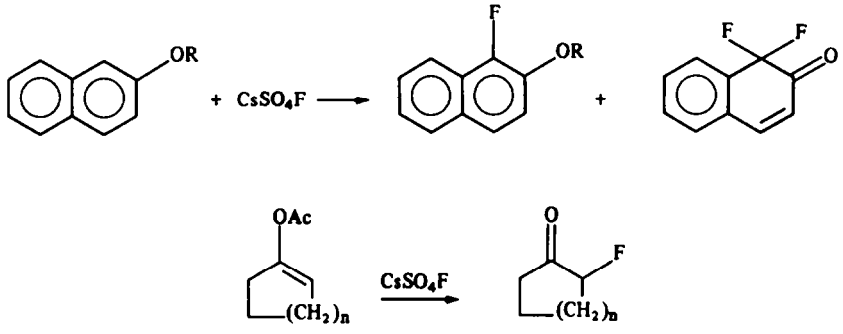


complex mixture of products was formed.[196] Patrick[197] isolated the difficult to obtain gem-difluorocarbonyls by reaction of diazoketones with elemental fluorine. The results were better than in the parallel reaction with CF_3OF, which is described in Section DIII above.



V. *Fluorinations with* $CsSO_4F$

Appelman recently developed and identified a new, interesting solid electrophilic fluorinating agent, cesium fluoroxysulfate, $CsSO_4F$, which was prepared from Cs_2SO_4 and F_2.[198] Appelman[199] and Zupan[200] demonstrated that this reagent could be used as an aromatic fluorinating agent, but in certain cases, as with 2-methoxynaphthalene, fluoroketones were also formed. Zupan also used this



reagent for the preparation of α-fluoroketones from the corresponding enol acetates, which strongly suggested the electrophilic character of the reagent.[201] While $CsSO_4F$ is a potentially very promising reagent, especially since it can be isolated and stored, caution should be exercised, since it tends to explode under certain conditions.[200]

VI. *Fluorinations with reagents prepared* in situ *with* F_2

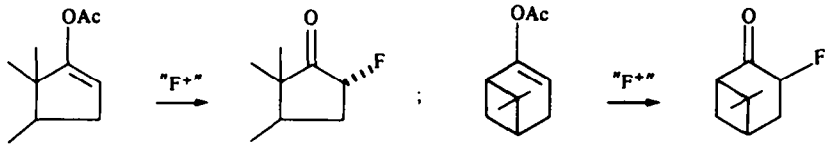
All the reagents described up to this point are either commerically available or should be isolated and purified prior to use. CF_3OF and XeF_2 are quite expensive and not easy to obtain in most places outside of the United States. Perchloryl fluoride possesses serious safety problems and $CsSO_4F$, although a very promising reagent, is not yet widely used and still has to prove itself. Elemental fluorine can serve as a source for electrophilic fluorine in some reactions involving selective delicate fluorinations,[187–190] but when reacted with electron-rich double bonds, it produces only tars, among which no α-fluorocarbonyl derivatives could be detected.

Recently, however, a new approach to this problem has emerged.[202] It has been found that F_2 reacts with a suspension of sodium trifluoroacetate in fluorotrichloromethane at −78° to form an oxidizing solution. The oxidizing power originates from compounds possessing the weak oxygen–fluorine bond. Two such reagents were detected and identified through their products, viz.

fluoroxypentafluoroethane—CF_3CF_2OF (**195**) and trifluoroacetyl hypofluorite—CF_3COOF (**196**). These two main compounds are accompanied by other oxidizing materials. However, all the oxidants in the reaction mixture have one feature in common, the oxygen-bound fluorine. Rozen[203] has shown that this is an electrophilic fluorine and the whole mixture of fluoroxy compounds produced *in situ* can react as a single homogeneous reagent. Without any isolation or purification, the mixture reacts with steroidal and other enol acetates to produce high yields of α-fluoroketones. Two examples are shown.

$$CF_3COONa + F_2 \longrightarrow CF_3CF_2OF + CF_3COOF + Rf(OF)_n$$

195 **196**



" F^+"= a mixture of fluoroxy compounds acting as an electrophilic fluorinating agent.

Under certain conditions, the reaction of F_2 with CF_3COONa could be directed to produce mainly the hypofluorite (**196**). This compound was added to some olefins to form fluorohydrins after mild hydrolysis.[204] The fluorohydrins, in turn, could be oxidized to the corresponding α-fluoroketones (see Section AIII). The reaction of **196** with diphenylacetylene is a special case in which α-fluoro-α-phenylacetophenone **197** and benzil are the only products formed. Fluorine also reacted with acetic

$$ArCH{=}CHAr' + CF_3COOF \longrightarrow \underset{\displaystyle OCOCF_3\ \ F}{ArCH{-}CHAr'} \xrightarrow{B^-}$$

196

$$\underset{\displaystyle OH\ \ F}{ArCH{-}CHAr'}$$

$$PhC{\equiv}CPh + \mathbf{196} \longrightarrow \underset{\displaystyle F\ \ \ OCOCF_3}{PhC{=}CPh} \xrightarrow{hyd.} PhCHFCOPh$$

197

$$\mathbf{196} \rightarrow \left[\underset{\displaystyle OCOCF_3\ \ F}{\overset{\displaystyle F\ \ \ \ OCOCF_3}{PhC{-}C{-}Ph}}\right] \longrightarrow PhCOCOPh$$

acid salts to form the previously unknown acetyl hypofluorite **198**. This is the first example of a compound possessing an OF group attached to a hydrocarbon radical.[205] Such compounds were considered previously only in theoretical papers.[206] Acetyl hypofluorite was added, in a stereoselective *syn* addition, to unsaturated esters such as *trans* and *cis* methyl cinnamate **199**, to form, respectively, *threo* and *erythro* α-fluorocarboxylic acid derivatives **200**. Being a much milder electrophilic reagent

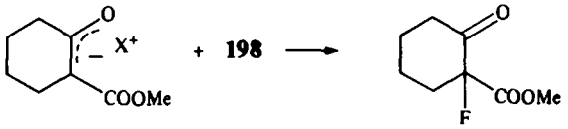
$$PhCH{=}CHCOOMe + CH_3COOF \longrightarrow \underset{\displaystyle OAc\ \ F}{PhCH{-}CHCOOMe}$$

199 **198** **200**

trans *threo*

cis *erythro*

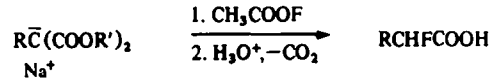
than F_2, CF_3OF or CF_3CF_2OF, acetyl hypofluorite is able to react, although in only moderate yields, with 1,3-dicarbonyl compounds possessing considerable enolic character. This is demonstrated with 2-carbomethoxycyclohexanone (**201**, X = H), which was converted to the 2-fluoro derivative **202**. However, when the enol contribution is small, as in dimethyl malonate, no reaction took place. The results were much better and yields dramatically higher, when the sodium enolates of any type of 1,3-dicarbonyl compounds reacted with acetyl hypofluorite. Such reactions were not successful with the other known fluoroxy reagents since they are too reactive and produce tars.[207]



201 **202**

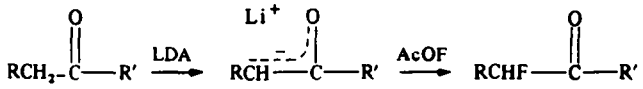
X = H (30%)
X = Na (75%)

X = H 0%
X = Na 92%



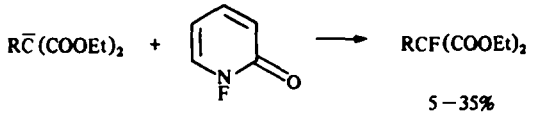
77%

It has now been shown that CH_3COOF reacts quite cleanly with metal enolates, which are usually more reactive than 1,3-dicarbonyl enolates. This reaction offers a shorter route for converting carbonyls to their corresponding α-fluoro derivatives.[207a]

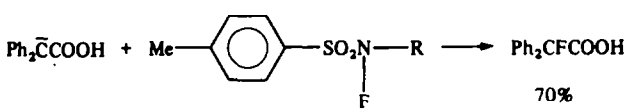


VII. *Fluorinations with reagents containing the* N—F *bond*

Recently, a new class of agents which are able to fluorinate enolates, has been introduced. The common feature of these reagents is the reactive N—F bond. Purrington[207b] synthesized 1-fluoro-2-pyridone using F_2. This reagent reacted with several malonate anions to produce various α-fluoromalonates. Barnette[207c] prepared a series of N-fluoro-N-alkylsulfonamides, again using elemental fluorine. These relatively stable N-fluoro compounds can react with various anions including enolates, cleanly and efficiently, to produce the α-fluorocarbonyl moiety in good yields.



5–35%

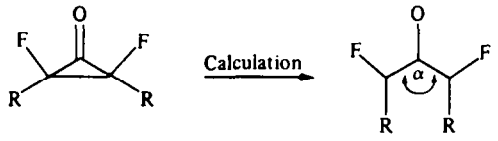


70%

F. THEORETICAL STUDIES

There have been few theoretical studies concerning the α-fluorocarbonyl moiety. The works of Allinger[208,209] and Meyer[209,210] are probably the most noteworthy. The stabilities and dipole moments of some rotational isomers of certain fluoroketones were calculated by the CNDO/2 method. The effect of solvation on conformational equilibria was studied mainly by the molecular mechanics method. The results are comparable to the experimental data. Studies are continuing for the updating of the molecular mechanical force field (MM2) of organic halides including the α-fluorocarbonyl moiety, and although improvements are still needed, much progress has been made.

Semiempirical MO methods, including INDO and MINDO, for the ring opening of fluoro substituted cyclopropanones, such as **203**, were compared with the parallel *ab initio* treatment. The predictions of the semiempirical calculations are in the same direction and magnitude as the *ab initio* ones (fluorine appears to enhance the ring opening), but the numerical values are incorrect and of little use.[211] Rotational isomerism in fluoroacetones was also studied by NMR and the results were



203

compared with some MO calculations, but full agreement with the experimental results does not always exist.[212]

G. BIOLOGICAL ACTIVITY STUDIES

Since the discovery that fluoroacetic acid and fluorocortisone have different, but nevertheless very potent biological activities, a plethora of studies have been conducted in order to upgrade such activities or develop new biologically-active compounds by introducing fluorine into various molecules. Attempts have also been made to delineate the mechanisms by which fluorine-containing molecules affect living organisms. A full description of this research is, of course, beyond the scope of this review and the reader should refer to the appropriate reviews, monographs, and books, the latest published by Filler and Kobayashi.[213] We have, however, mentioned on several occasions some biological aspects of certain α-fluorocarboxyl derivatives and in this section, we present briefly a few additional biologically interesting activities of this category of fluoroorganic compounds.

Naturally, the toxic fluoroacetic acid has attracted much attention. It was esterified, for example, with cholesterol and other sterols and alcohols, thus acquiring a delayed toxicity action (up to 14 days) towards red fire ants.[214] Certain vegetation growing near phosphate processing plants, which release a considerable amount of HF, developed the ability to produce fluoroacetates and fluorocitrates which were detected and identified by GC techniques.[215] These toxic compounds, which may damage the local water supply, can be removed by filtration through granular activated carbon.[216] Some species even developed special enzymes which were found to cleave the strong C—F bond in fluoroacetates (but not in other fluorine containing compounds).[216] There have been numerous studies dealing with the action of fluorine-containing compounds on enzymes which utilize the non-fluorinated analogs as substrates in various biological processes. Fluoroacetyl-CoA was shown to react with citrate synthase to produce 1*R*, 2*R* fluorocitrate.[218,219] Fluorooxaloacetic acid is an inhibitor of malate[220] and succinate[221] dehydrogenases. There are cases where an enzyme from a mammalian source would not interact with a fluorine-containing compound while the same enzyme from a bacterial source would be entirely deactivated.[222] This observation might be used for developing drugs against certain microorganisms. Further enzymatic studies were conducted with fluoropyruvic acid, including the shikimate pathway,[223,224] with fluoroglutarates in the nervous system,[225] with fluorosugars,[226,227] or with fluorine-containing prostaglandin precursors.[228] Usually, it was found that the relevant enzymes were partially inhibited by the respective α-fluorocarbonyl derivative. In some cases, the fluorine atom is not essential for a specific biological activity. Amides of phenylfluoroacetic acid showed coronary vascodilatory activity which was not changed significantly when the fluorine was replaced by Cl or Br.[229] Some fluoro quinazolinones are potent muscle relaxants. High activities were retained after

additional fluorine substitution or repositioning the fluorine atom. Other structural modifications, however, including replacement of the fluorine by O, N or S substituents resulted in loss of activity.[230] The same is true for vinyl fluoroacetate, which exhibits antineoplastic effects and inhibits mammary gland tumors, while vinyl acetate itself shows no such activity.[231] Finally, we reiterate the significant role of 5-fluorouracil (5FU) and its many derivatives, which have been so effective as antitumor agents.[232]

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