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Xenon Difluoride in Synthesis

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Contents

1. Introduction

Our interest in the general problem of introducing fluorine into organic molecules prompted us to develop a method for the synthesis of vinyl fluorides starting from vinyl stannanes. An examination of the various commercial sources of fluorinating agents suggested that we consider the use of XeF_2. Xenon difluoride seems an improbable reagent for organic synthesis and, as it turns out, an interesting one as well. This interest has led to the present overview of the reactions of XeF_2.

A brief discussion of the discovery and the properties of XeF_2 is in order. The first stable compounds derived from a noble gas are due to Neil Bartlett who reported in 1962 the synthesis of what he believed to be $[Xe]^+[PtF_6]^-$.[1] This was a red, crystalline solid which he obtained by allowing Xe to react with PtF_6. Bartlett's material was probably $[FXe]^+[PtF_6]^-$ or $[FXe]^+[Pt_2F_{11}]^-$.[2] Earlier, his team had prepared $[O_2]^+[PtF_6]^-$.[3] The ionization enthalpy of O_2 nearly matched that of Xe, which suggested that the reaction with Xe would also take place. Also in 1962, scientists working independently at Argonne National Laboratories prepared XeF_4 by heating the elements, in their correct proportions, for 1 h at 400 °C in a nickel canister.[4] These researchers found evidence for the formation of a lower fluoride of xenon in their reaction. This lower fluoride was almost certainly XeF_2. Two groups, working independently, have since described practical, room temperature syntheses of XeF_2. Mixing xenon and fluorine in a 1:2 ratio in either a quartz or in a fused silica vessel, and subjecting the mixture to discharges from an induction coil,[5] or to light from a high-pressure mercury arc,[6] produced the desired difluoride. The initial quantum yield for the photochemical process was ca. 0.3, indicating an efficient reaction. In both syntheses the product was condensed from the reaction medium, therefore these

methods can be adapted for a continuous process. Recent refinements in the design of the apparatus and of the method have resulted in a process which is suited for the production of kilogram lots of XeF_2.[7,8] By always maintaining a small excess of Xe over F_2 during the process one can avoid co-producing XeF_4. This is an important consideration from the standpoint of safety (*vide infra*).

Xenon difluoride is also available from a number of commercial sources.[9] Although the material is not cheap, neither is it prohibitively expensive, particularly when one considers the molar cost. Some of the reactions that XeF_2 mediates can also be carried out with elemental fluorine. For an occasional user, XeF_2 will probably be the more attractive reagent, in spite of the cost. The hazards associated with elemental fluorine, either neat or as a dilute solution in nitrogen gas, require safety precautions for measuring and transferring, and for conducting the reactions.[10] Xenon difluoride, by contrast, is a colorless crystalline solid (mp 129 °C), which can be weighed and transferred in air. Most reactions with XeF_2 can be conducted in glass apparatus with no apparent diminution in yield. Reasonable care in handling XeF_2 is advisable, since it sublimes readily (4.55 Torr vapor pressure at 25 °C);[11] it has a pungent odor similar to that of chlorine at low concentration. Xenon difluoride can be thought of as a tamer version of F_2; nevertheless, it is a highly reactive substance. Recent work has shown that XeF_2 reacts with several solvents in which it was previously thought to be inert.[12] In particular, with CH_2Cl_2 and $CHCl_3$ reaction takes place and leads to products of fluorine-chlorine and fluorine-hydrogen exchange (eq 1, 2). The reactions with both these solvents are complete within 2 days at room temperature. It has been noted that the reaction of XeF_2 with wet, impure CH_2Cl_2 can be violently explosive, even at low temperature.[12] This behavior is probably due to the autocatalytic nature of the decomposition, in which the HF produced from the reagent accelerates the process. This factor should be considered whenever reactions are scaled up. For example, even though XeF_2 reacts with CCl_4 much more slowly than with either CH_2Cl_2 or $CHCl_3$, small amounts of HF lead to complete decomposition of the reagent within 1 h at room temperature. On the other hand, XeF_2 reacts very slowly with CH_3CN and with FCl_2C-CF_2Cl. In the case of CH_3CN, <4% of CFH_2CN and HF could be observed after ca. 6 weeks, whereas in FCl_2C-CF_2Cl, the complete decomposition of XeF_2 requires ca. 20 days at room temperature.

$$XeF_2 + CH_2Cl_2 \longrightarrow \underset{24.4\%}{CH_2FCl} + \underset{25.6\%}{CHFCl_2} + \underset{37\%}{HF} + \text{others} \qquad [1]$$

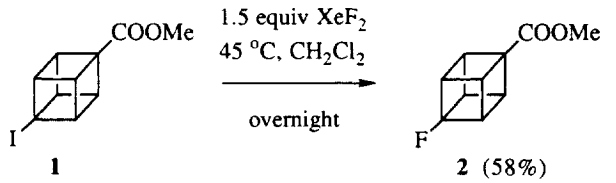
$$XeF_2 + CHCl_3 \longrightarrow \underset{67.1\%}{CHFCl_2} + \underset{13.9\%}{CHFCl_2} + \underset{17.8\%}{HF} + \underset{1.2\%}{CHF_2Cl} \qquad [2]$$

The higher fluorides of xenon (XeF_4 and XeF_6) are more reactive than XeF_2 and also present a greater hazard, since their hydrolytic decomposition products are shock-sensitive xenon oxides. Therefore, contamination of XeF_2 even by modest amounts of XeF_4 may lead to the production of explosive XeO_3 at the end of a reaction.

In the discussion that follows, the emphasis will be on reactions that are preparatively useful and also on findings that provide mechanistic insight. Results of the past ten years or so will be reviewed. Excellent overviews of the earlier work have been published,[13-15] as well as discussions of alternative reagents and methods for introduction of fluorine into organic molecules.[16-20]

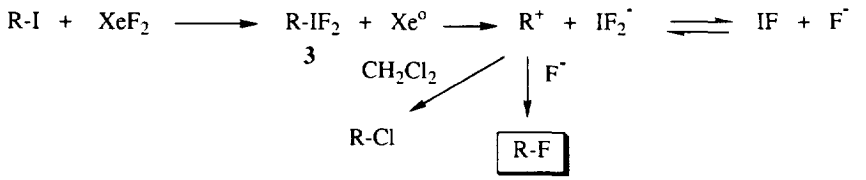
2. *Fluorodeiodination*

An interesting reaction takes place between iodides and XeF_2 in which exchange of fluorine for iodine occurs (eq 3). Della and Head have converted methyl 4-iodocubanecarboxylate **1** to fluorocubane carboxylate **2** in 58% yield upon exposure to a modest excess of XeF_2 at 45 °C overnight in CH_2Cl_2.[21] The process

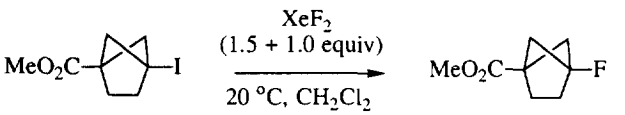


1 **2** (58%) [3]

apparently involves a cationic intermediate,[22] and can be thought of in terms of the following mechanistic scheme:

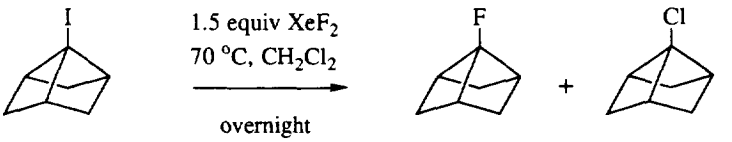


Oxidation of the iodide to difluoride **3** takes place with loss of xenon gas. Heterolytic cleavage of **3** in the subsequent step gives rise to a carbocation, along with IF_2^-, which is in equilibrium with F^- and IF. The carbocation is trapped by F^- to produce the alkyl fluoride. The carbocation may also undergo reaction with the solvent to give the alkyl chloride. Typically, the more stable cations give rise to fluorides exclusively, whereas the more highly energetic bridgehead cations are indiscriminate in their reactivity. This method is well suited for generation of bridgehead cations that are difficult or impossible to access in other ways. For example, eq 4 represents the first time that the 1-bicyclo[2.1.1]hexyl cation has been trapped.[21] In this instance, addition of



4 **5** (5%) [4]

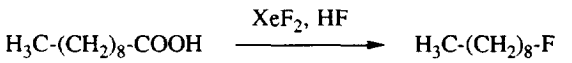
another full equivalent of XeF_2 was necessary in order to consume iodide **4** completely. In this case, as in eq 3, the excess of reagent is required to make up for losses due to the decomposition of the reagent. Equation 5 illustrates a striking example of the generation of a highly energetic bridgehead carbocation.[23] The more drastic reaction conditions reflect the instability of the 6-tricyclo-[3.1.1.$0^{3,6}$]heptyl carbocation. The proportion of bridgehead chloride in the product mixture was found to correlate strongly with the calculated energies for a series of carbocations. The fluorodeiodination reaction can also be accomplished with F_2.[24]



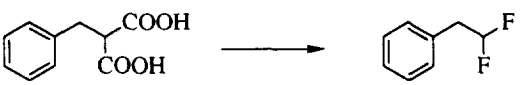
6 **7** (72/28) **8** [5]

3. Fluorodecarboxylation

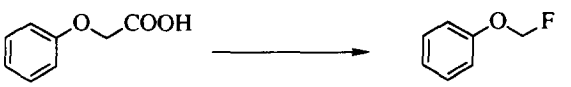
The bridgehead iodides referred to in the section above are conveniently prepared through oxidative decarboxylation of the corresponding bridgehead carboxylic acids with I_2 and lead tetraacetate in benzene. A conceptually related oxidative decarboxylation takes place when carboxylic acids are treated with XeF_2 (eq 6).[25]



9 **10** (54%) [6]

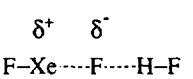


11 **12** (68%) [7]



13 **14** (64%) [8]

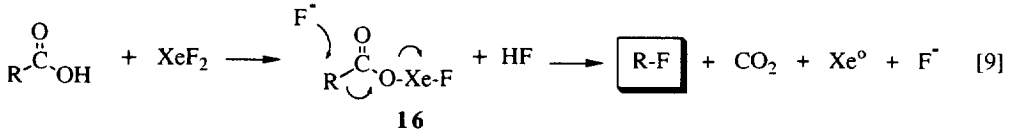
This transformation is essentially a Hunsdiecker reaction, and it is applicable to the preparation of a wide variety of fluorides. Substituted malonic acid **11** (eq 7) led to *gem*-difluoride **12** in good yield, whereas phenoxyacetic acid **13** led to fluoromethyl ether **14** (eq 8).[25] In these reactions, fluorination of the aromatic ring by XeF_2 did not compete with fluorodecarboxylation. Amino acids and hydroxy acids do not participate in this reaction and lead to recovered starting material.[26] Benzoic acid produced benzoyl fluoride in 20% yield. These reactions, and many others involving XeF_2, are catalyzed by HF. Presumably, this catalysis is due to a hydrogen bonding interaction between HF and one of the fluorine atoms on XeF_2 which polarizes the Xe-F bond (cf. **15**). The net effect is to increase the electrophilicity of the fluoroxenon fragment. This effect is not limited to HF.[27] Since the fluorodecarboxylation reaction produces HF, it is also autocatalytic.

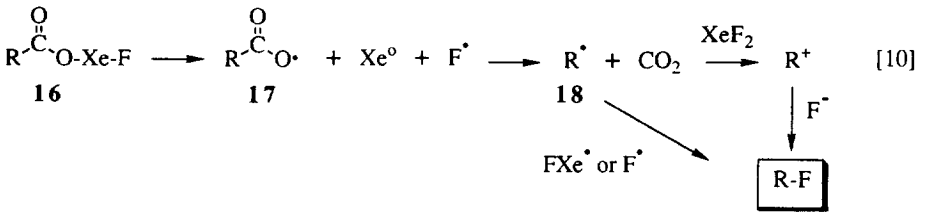


15

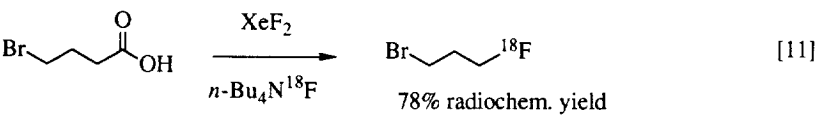
Consideration of the mechanistic possibilities leads to two distinct pathways, which are summarized in eqs 9 and 10. The first step in both schemes is the acid-catalyzed formation of fluoroxenon ester **16**. This

intermediate is not unlikely: DesMarteau has isolated and characterized the fluoroxenon ester of trifluoroacetic acid.[28] Nucleophilic attack of fluoride anion on **16** (eq 9) leads to the observed alkyl fluoride, CO_2, xenon gas

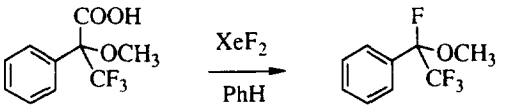




and fluoride anion. There is evidence for this pathway from the following ^{18}F radiochemical labelling experiment: 4-Bromobutanoic acid underwent fluorodecarboxylation with XeF_2 in the presence of n-$Bu_4N^{18}F$ to produce 1-bromo-3-fluoropropane in 78% radiochemical yield (eq 11).[26] This result suggests that the mechanism, which is summarized in eq 9, involves nucleophilic attack by fluoride at C2. It is clear that exchange to generate ^{18}F-Xe-^{19}F was not taking place, since complete exchange could lead to a maximum radiochemical yield of only 50%. Furthermore, a control experiment showed that no exchange of the label occured under the reaction conditions. The evidence does not exclude the pathway in which loss of CO_2 from **17** generates radical **18** (eq 10), which then undergoes electron-transfer in a subsequent step to generate a carbocation. Also, since the fluorodecarboxylation is an efficient process for carboxylic acids bearing fully substituted α-carbons, it is likely that the electron transfer mechanism of eq 10 is valid in some cases.

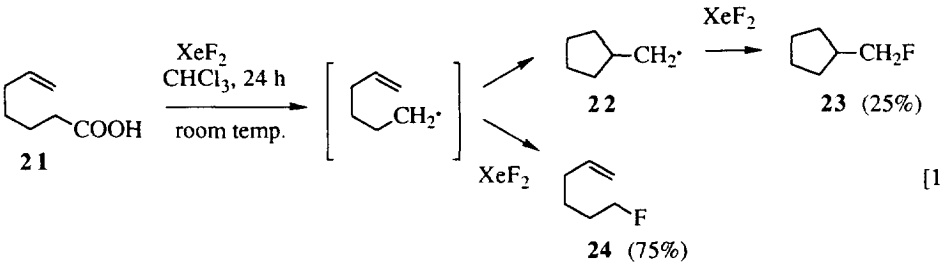


Fluorodecarboxylation of optically active Mosher's acid **19** (eq 12) took place in high yield to produce optically inactive tertiary fluoride **20**. Loss of optical activity in this case provides strong evidence for a trivalent intermediate (radical or cation). When the reaction was run in the presence of n-$Bu_4N^{18}F$, the radiochemical yield of **20** was 65%, suggesting that fluoride is incorporated via a cationic pathway. Further evidence in support of an ionic mechanism was provided by the fluorodecarboxylation of phenylacetic acid. No 1,2-diphenylethane was detected in the reaction products, as would have been expected had benzyl radicals been generated.[26]



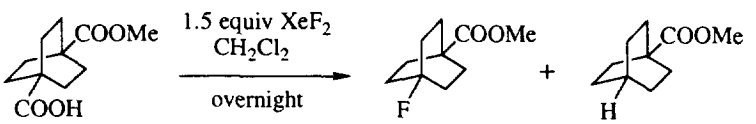
19 **20** (95%) [12]

In 1993 Patrick and coworkers performed a definitive experiment that proved the intermediacy of radicals in the fluorodecarboxylation reaction.[29] 6-Heptenoic acid **21** (eq 13) was treated with XeF_2 at room temperature in $CHCl_3$ for 24 h. The minor product, (fluoromethyl)cyclopentane **23**, provides good evidence for the intermediacy of radical **22**. 1-Fluorocyclohexane was not observed as a product, neither was it converted to **23** or to **24** under the reaction conditions. Fluorides **23** and **24** were also subjected to the reaction conditions in separate experiments and did not undergo interconversion. From the same series of experiments, the second-order rate constant for fluorine abstraction from XeF_2 was determined to be $k_{(abs,\ 25\ ^oC)} = 1.1 \times 10^6\ M^{-1}s^{-1}$; therefore XeF_2 very efficiently transfers a fluorine atom.[29]



21 **22** **23** (25%) **24** (75%) [13]

Additional evidence for the intermediacy of radicals during the fluorodecarboxylation was provided by the reaction of 4-carbomethoxybicyclo[2.2.2]octane-1-carboxylic acid **25** (eq 14).[21] 1-Carbomethoxybicyclo-[2.2.2]octane **27** was isolated in 12% yield, along with 77% of bridgehead fluoride **26**. The appearance of reduced product **27** is most easily explained by a postulate of H atom abstraction from the solvent by a radical intermediate. Also, had the reaction proceeded through a cationic species, one would have expected some of the bridgehead chloride in the product. Patrick has shown that this process can be used for introducing a bridgehead deuterium.[29] Since the separation of **26** from **27** is difficult, it is fortunate that **25** can also be converted to **26** by fluorodeiodination of the corresponding bridgehead iodide (cf. eq 3). The fluorodeiodination reaction proceeds via the carbocation, rather than the radical, and may give rise to some of the chloride in the product. Typically, separation of the alkyl fluoride from the corresponding chloride is easily accomplished.



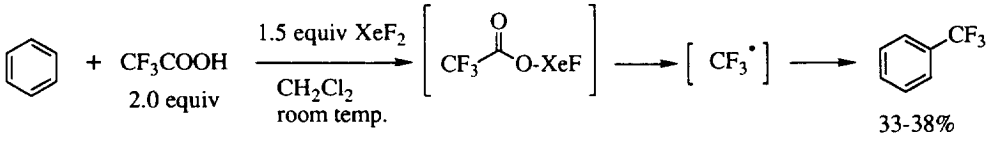
25 **26** (77%) **27** (12%) [14]

The preceding discussion is paradigmatic for XeF_2: the conversion of starting materials to products takes place along two pathways simultaneously, one of which is an electron-transfer process. Minor variation

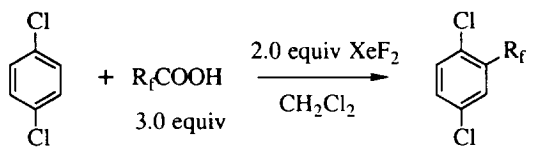
in the structure of the substrate shifts the reaction to a different mechanistic manifold. Caution is indicated in any attempt to draw overly broad mechanistic conclusions from a limited number of examples.

4. Perfluoroalkylation

The fluorodecarboxylation reaction discussed in the preceding section also provides a straightforward approach for the introduction of perfluoroalkyl groups into aromatic rings. An example of this process is provided in eq 15.[29,30] Treatment of a solution of benzene in CH_2Cl_2 with modest excesses of trifluoroacetic acid and XeF_2 provided trifluoromethylbenzene in 33-38% yield. The reaction presumably took place through the intermediacy of the fluoroxenon ester, which collapsed to give trifluoromethyl radicals. This process works best for electron-poor aromatics. In aromatics bearing activating groups (alkyl, alkoxy), ring fluorination competes effectively with perfluoroalkylation.



[15]

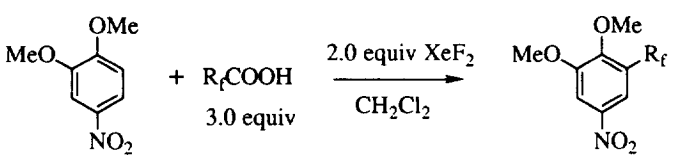


$R_f = CF_3$ 72%
C_2F_5 62%
C_3F_7 55%

[16]

28

The perfluorodecarboxylation reaction is not limited to trifluoroacetic acid. *p*-Dichlorobenzene (eq 16) underwent efficient alkylation with perfluoropropanoic and perfluorobutanoic acids, as well as with trifluoroacetic acid.[30] The modest excesses of the reagent used in these reactions serve to compensate for the loss of perfluoroalkyl radicals to dimerization and to other side reactions. Equations 17 and 18 illustrate an application of the method for the synthesis of moderately substituted aromatics. Perfluoroalkylation of **29** (eq 17) provided a single regioisomeric product **30**;[30] in the case of **31** (eq 18) the reaction was essentially non-selective.[30] The acetamido hydrogen in **31** apparently had no effect on the reaction, indicating that the reaction of XeF_2 with the perfluorocarboxylic acid took place much more rapidly than any process involving the NH.



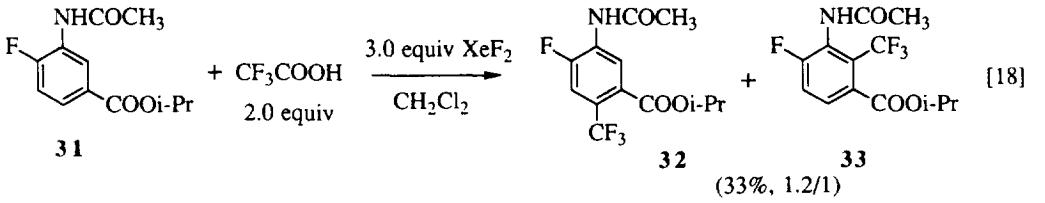
$R_f = CF_3$ 52%
C_2F_5 43%

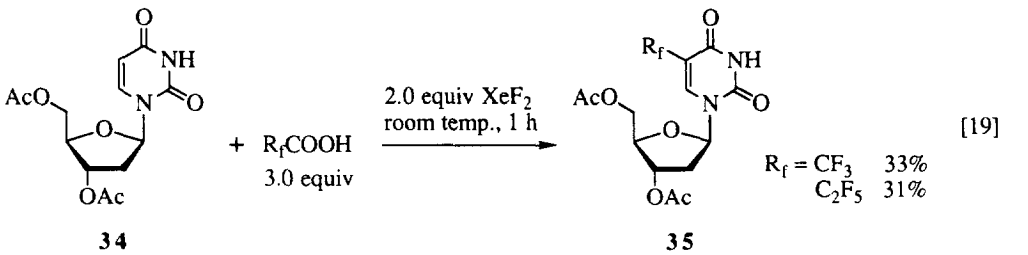
[17]

29 **30**

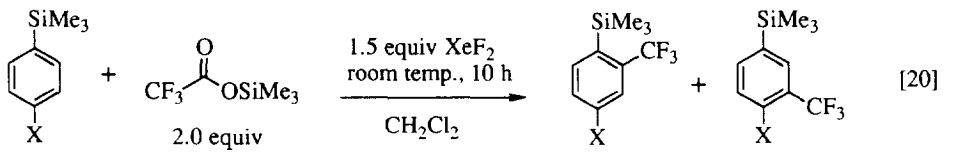
Neither is the perfluoroalkylation limited to aromatic carbocycles. 3',5'-Di-*O*-acetyl-2'-deoxyuridine **34** was perfluoroalkylated at C5 in modest yield (eq 19).[30] This outcome attests to the mildness of the reaction

conditions. The low yields are offset by the convenience of a procedure that introduces the perfluoroalkyl group in a single step.





A potentially significant extension of the method involves the perfluoroalkylation of trimethylsilyl arene derivatives (eq 20).[30] Since these substrates would not be expected to survive even brief treatment with perfluorocarboxylic acids, the trimethylsilyl carboxylate was used in place of the free acid. For example, trifluoromethylation of **36** and **37** produced mixtures of regioisomeric products **38** and **39**, respectively. Significantly, no products of *ipso*-desilylation were observed, although the perfluoroalkylation in this instance was appreciably slower. The absence of any catalysis by acid (cf. **15**) in this reaction explains the diminution in the rate. The expedient of using the trialkylsilyl ester in place of the free perfluorocarboxylic acid broadens the scope of this reaction.

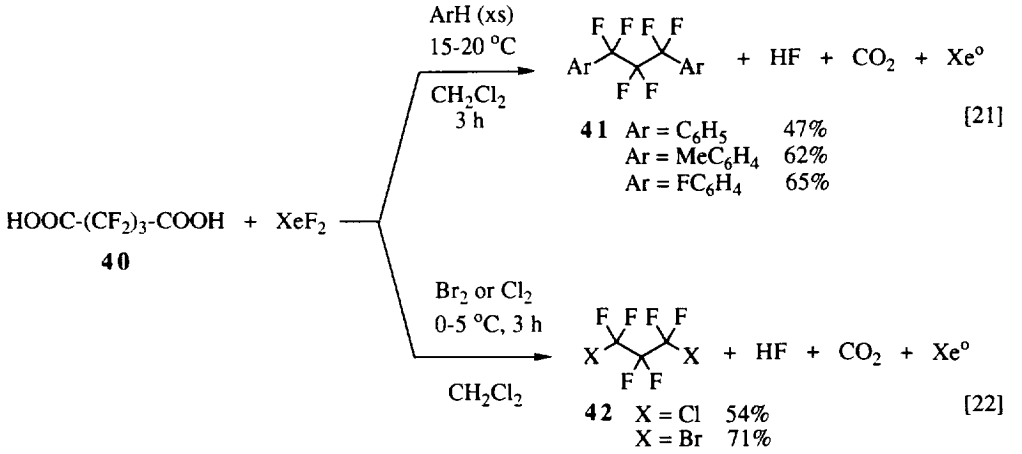


36 X = Cl
37 X = NHAc

38o,m	X = Cl	1/4	43%
39o,m	X = NHAc	1/3.5	37%

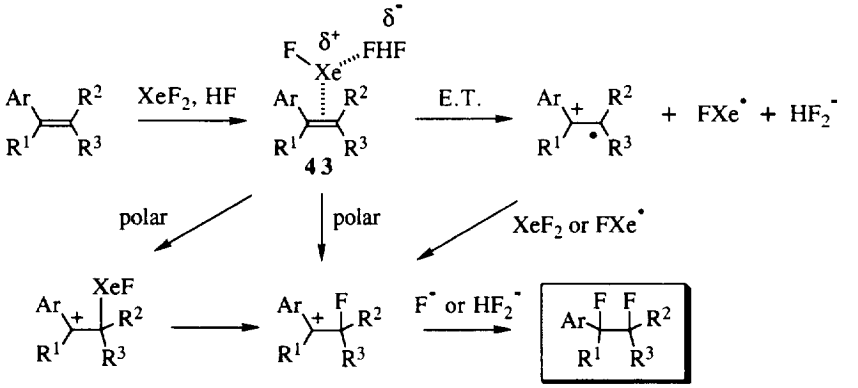
In a closely related process, perfluoroalkylation of hexafluoroglutaric acid **40** took place with XeF_2 in benzene to produce **41** (Ar=Ph) in 47% yield (eq 21).[31] The same reaction with toluene or fluorobenzene was also successful; however, in these cases the product (**41**) was isolated as an *o*, *m* and *p* regioisomeric mixture. The intermediate from the transformation of **40** can be trapped by halogen, when the reaction is conducted in the presence of molecular chlorine or bromine. 1,3-Dichloro- and 1,3-dibromohexafluoropropanes **42** were produced in good yield (eq 22).[31] This is another XeF_2 mediated version of the Hunsdiecker reaction. In the

conversions shown in eqs 21 and 22 a 1:1 molar ratio of hexafluoroglutaric acid to XeF_2 was used. Therefore this represents a remarkably efficient process in which each XeF_2 oxidizes two carboxylate groups.



5. Reactions with Alkenes

The conversion of alkenes to vicinal and geminal difluorides has been described.[32,33] The acid catalyzed difluorination of phenyl substituted alkenes is often preparatively useful.[34] Two mechanisms can be considered for this reaction: one an electrophilic polar process; the other an electron transfer (E.T., eq 23).[34] Direct attack of F^+ is unlikely because of the extremely high heat of formation for this species; therefore an interaction between the alkene and the reagent, as shown in **43**, has been postulated.[34] One would predict that an increase in the electron density (i.e. a decrease in the ionization potential, IP) at the C=C should increase the rate of an electrophilic process. Provided that steric encumbrance of the transition state for electrophilic attack

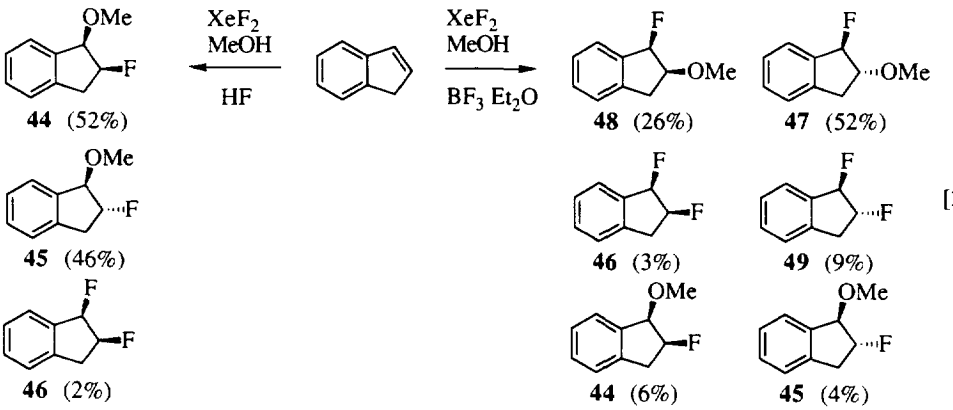


is not an issue, a linear relationship between the IP and log K_{rel} would be predicted, if the rate determining step involves electron donation from the alkene to the reagent (i.e. **43**). This outcome is exactly what was observed for a series of phenyl substituted alkenes.[34] On the basis of this result, no distinction could be made

between the two pathways of eq 23. These fluorinations are non-stereospecific and do not take place in the absence of acid catalysts (HF or BF_3); it is therefore likely that more than one pathway is involved.

In the presence of alcohols the reaction of XeF_2 with phenyl substituted alkenes takes a different course. Indene reacted with methanol and XeF_2 in the presence of HF to produce fluoroether **44** as the major product, along with the diastereoisomer **45** (eq 24).[35,36] Small amounts of vicinal difluoride **46** were also produced. When $BF_3{\cdot}Et_2O$ was used in place of HF to catalyze the addition, the major products were fluoroethers **47** and **48**. In the HF catalyzed reaction, production of a fluoronium ion equivalent appears to have taken place, whereas in the presence of $BF_3{\cdot}Et_2O$, the major products appear to be derived from an oxonium intermediate. The crossover products in the $BF_3{\cdot}Et_2O$ case may be explained by the presence of small amounts of HF from the decomposition of XeF_2. In both reactions, initial formation of MeOXeF has been postulated. The production of methyl hypofluorite (MeOF) would require F_2, a much stronger oxidant than XeF_2.[37] Also, the reaction was shown to be zero order in alkene with 1 equiv each of XeF_2, indene and BF_3; therefore XeF_2 was not combining directly with indene in the rate determining step. The researchers proposed that proton transfer from HF to the oxygen of MeOXeF, followed by loss of MeOH, led to FXe^+ (a fluoronium ion equivalent). In the BF_3 case, an oxygen electrophile was postulated to form by polarization of the XeF bond in MeOXeF. The reaction of indene with XeF_2 in aqueous 1,2-dimethoxyethane apparently takes place directly, i.e. the initial interaction is between indene and XeF_2, rather than between XeF_2 and water.[38] This transformation does not appear to have preparative utility.

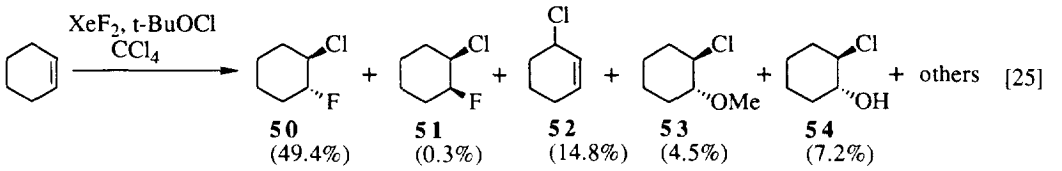
The multiplicity of products in the XeF_2/MeOH reaction (eq 24), and the lack of stereospecificity, again suggests the simultaneous involvement of more than one mechanism. Moreover, it has been shown that small variations in the structure of the organic molecule or in the reaction conditions, can alter the course of the reaction.[39] For these reasons, its preparative utility will be somewhat limited.



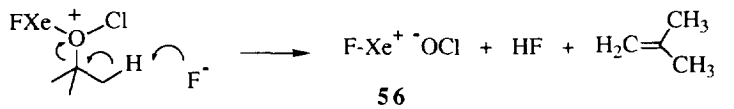
[24]

Two additional reactions are known in which alkenes combined with XeF_2 in the presence of some auxiliary reagent. In the first, *tert*-butyl hypochlorite and XeF_2 in CCl_4 reacted with cyclohexene to produce *trans*-1-chloro-2-fluorocyclohexane **50** as the major product (eq 25).[40] The conversion took place in the absence of acid catalysts, and no reaction could be observed when either of the two reactants was added separately to cyclohexene. Based on this observation, and on the following lines of evidence, the initial

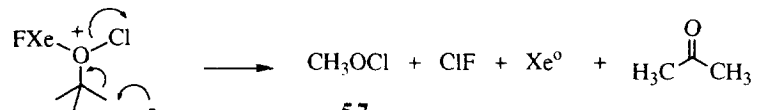
formation of the 1:1 complex **55** was postulated. Isobutylene was evolved, and *trans*-chlorohydrin **54** (eq 25) was isolated. Neither of these two products was observed when cyclohexene was allowed to react with *n*-Bu_4NF or with *tert*-butyl hypochlorite in the absence of XeF_2. Equation 26 summarizes the postulated pathway to the alkene and the chlorohydrin. Fluoride, acting as a base, abstracts a proton from one of the methyl groups of **55**, fragments the complex into isobutylene and fluoroxenon hypochlorite **56**, and produces HF. The combination of hypochlorite (presumably from **56**) and HF produces hypochlorous acid (HOCl), which adds to cyclohexene and leads to **54**.



50 (49.4%) **51** (0.3%) **52** (14.8%) **53** (4.5%) **54** (7.2%) [25]



55 **56** [26]

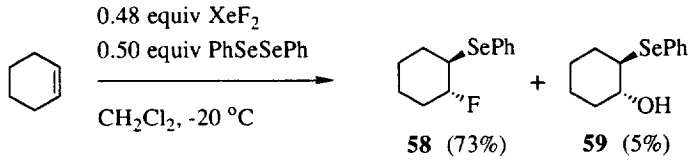


55 **57** [27]

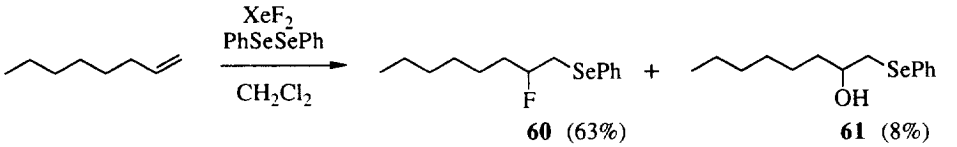
Equation 27 rationalizes the appearance of **53** in the product mixture. Hypochlorite can attack one of the methyls of **55** in a nucleophilic process to give methyl hypochlorite **57** and chlorine monofluoride. Chlorine monofluoride leads to the major product **50**, whereas **57** gives rise to **53**. Methyl hypochlorite was not found in the reaction of tert-butyl hypochlorite with $Ca(OCl)_2$ in THF, implying that complex **55** is required for the formation of **57**.[41] Chlorine monofluoride could be swept from the reaction with a nitrogen stream, without carrying XeF_2 or *tert*-butyl hypochlorite. Trapping with cyclohexene gave **50**. These results suggest considerable preparative utility for this process; however the scope and limitations remain to be defined.

With phenyl diselenide and alkenes, XeF_2 leads to fluoroselenation (eq 28).[42,43] By allowing XeF_2 to react at -20 °C in CH_2Cl_2 with a 5% molar excess of phenyl diselenide, Uneyama and Kanai obtained a reagent with the chemical behavior and spectroscopic properties expected for phenyselenyl fluoride (PhSeF). The reaction took place violently at -20 °C, with vigorous gas evolution. The reagent was thermally unstable, and underwent rapid decomposition at 20 °C. The reaction of cyclohexene with a small deficiency of the reagent produced *trans*-fluoroselenide **58** in good yield, along with a small amount of hydroxyselenide **59**. The fluoroselenide products of this reaction were hydrolytically unstable and underwent partial hydrolysis to hydroxyselenides during chromatographic purification on silica gel. The participation of both fluorine atoms of XeF_2 in forming the reagent suggests that its stoichiometry is PhSeF, rather than $PhSeF_3$. The addition

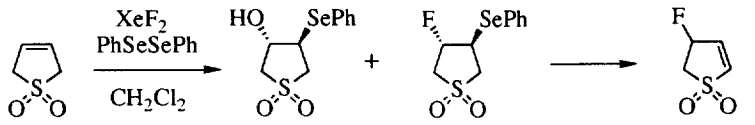
regiochemistry is predominantly Markovnikov. For example (eq 29), 1-octene gave fluoroselenide **60** and hydroxyselenide **61**.[42] Oxidative deselenation of the products with hydrogen peroxide led to allylic, rather than vinyl, fluorides. For example (eq 30) 2,5-dihydrothiophene-1,1-dioxide underwent fluoroselenation to produce **62** as the major product. Separation and oxidative deselenation of **62** gave 4-fluoro-4,5-dihydrothiophene-1,1-dioxide **64** in 82% yield.[42]



58 (73%) **59** (5%) [28]



60 (63%) **61** (8%) [29]

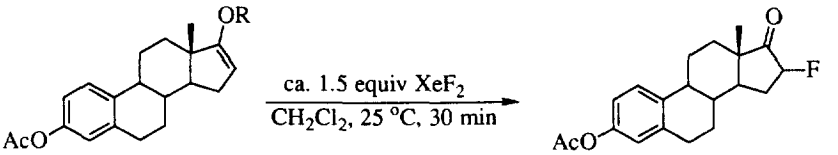


63 (22%) **62** (43%) **64** (82%) [30]

Several alternative strategies exist for converting alkenes to fluoroselenides, but none of them make use of XeF_2.[44-46] The XeF_2/PhSeSePh method has an advantage with electron-deficient alkenes that fail to react in some of the other protocols.[42]

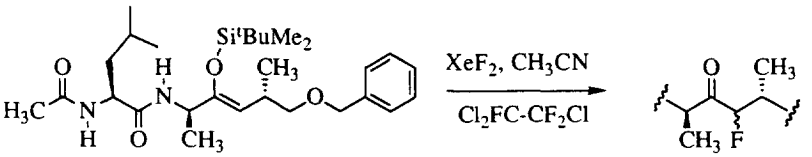
6. Fluorination of Enol Derivatives

Enol trialkylsilanes and enol acetates are efficiently converted to the corresponding α-fluorocarbonyl derivatives by XeF_2.[47] Estrone-derived enol acetate **65a** (eq 31) treated with a ca. 50% molar excess of XeF_2 at room temperature provided α–fluoroketone **66** in nearly quantitative yield.[48] The reaction was selective for the α diastereomer. The fluorination of **65a** took place with other reagents as well (viz. $CsOSO_3F$, CF_3OF, F_2/N_2), however, in all cases the yields were inferior. Enol trialkylsilanes have been reported to be more reactive in the XeF_2 process than the corresponding enol acetates or even the enamines,[49-51] therefore it is surprising at first glance that enol trimethylsilane **65b** produced **66** in only 44% yield.[48] This outcome can most easily be understood in terms of the much greater hydrolytic lability of the enol trimethylsilanes compared to the corresponding enol acetate derivatives.[52] Also, the observation that *tert*-butyldimethylsilyl enol ethers react with XeF_2 in a cleaner fashion, and produce the α–fluoroketones in higher yields than the corresponding trimethylsilyl derivatives, supports this hypothesis.[53] The α-fluorination of enol acetates is strongly catalyzed by HF, so it is essential to exclude water from the reaction.[54,55]



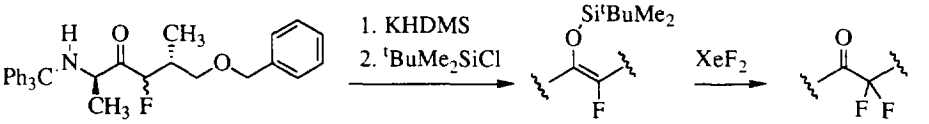
65a R = Ac
65b R = $SiMe_3$

66 99% (from **65a**; α/β = 9/1) [31]



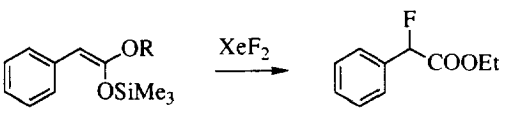
67 **68** (71%, 1/1) [32]

Exposure of *tert*-butyldimethylsilyl enol ether **67** to XeF_2 in a mixture of acetonitrile and 1,1,2-trichlorofluoroethane led in 71% yield to a 1:1 mixture of α–fluoroketone diastereoisomers **68** (eq 32).[53] Note that no fluorination of the aromatic ring took place in **65a**, **65b** or in **67**. The monofluoroketone **68** was designed as a peptide isostere. α–Fluoroketones are thought to form stable hemiketals upon reaction with the active site serine of serine proteases and can function as protease inhibitors. Evidently, the fluorination can be repeated (eq 33).[53] Thus, exposure of **69** to strong base, followed by *tert*-butyldimethylsilyl chloride, produced fluoroenol silane **70**, treatment of which with XeF_2 led to α,α–difluoroketone **71** in unspecified yield.



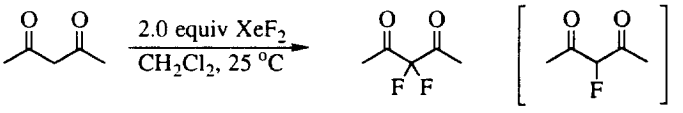
69 **70** **71** [33]

This fluorination method is not limited to the enol derivatives of ketones. Ketene acetal **72a** (R=Et) reacted with XeF_2 to produce α–fluoroester **73** in 75% yield (eq 34).[49] The same treatment of **72b** (R=TMS) led only to non-fluorinated product, presumably as a consequence of the vastly greater susceptibility of **72b** toward protiodesilylation.

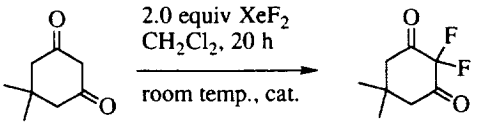


72a R = Et
72b R = $SiMe_3$

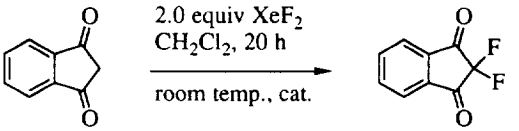
73 (75% from **72a**) [34]



74 (70%) 75 [35]



76 (85%) [36]

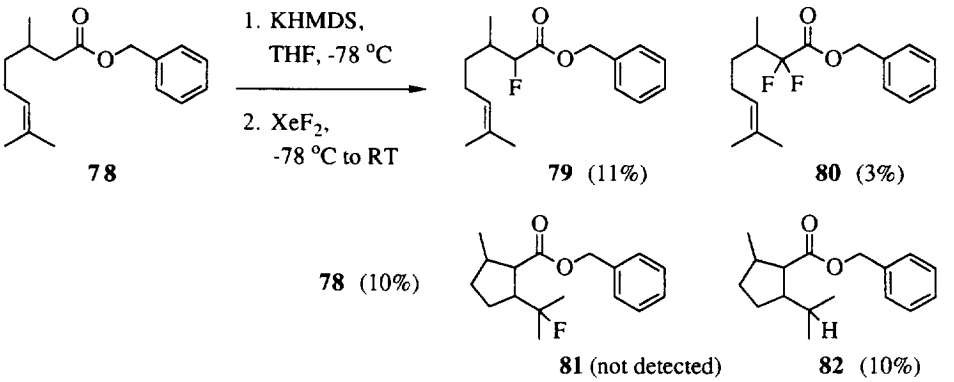


77 (80%) [37]

Highly enolic 1,3-diketones also undergo acid catalyzed fluorinations with XeF_2.[54,55] 2,4-Pentanedione reacted with 2 equiv XeF_2 at room temperature in CH_2Cl_2 to produce difluoride **74** in 70% yield (eq 35). When 1 equiv XeF_2 was used, difluoride **74** was the sole product, indicating that introduction of the second fluorine was faster than the first. At higher dilution, and by use of sub-stoichiometric amounts of XeF_2, low yields of monofluoride **75** were obtained.[54] This reaction offers an efficient approach to difluorodiketones. Dimedone was converted to difluoride **76** in 85% yield with 2 equiv XeF_2 (eq 36).[54] The transformation is effectively catalyzed by a mixture of insoluble, crosslinked polystyrene-4-vinylpyridine and the BF_3 complex of this polymer. Under these conditions 1,3-indanedione was converted in good yield to difluoride **77** (eq 37).[54,55] Nafion-H® has also been used to catalyze these reactions.[55]

The mechanism for the reaction of XeF_2 with enol acetates and with enol silanes is probably ionic, since the stereochemistry of the products is the same as when CF_3OF,[56] $FClO_3$[57] or CH_3CO_2F[58] serve as the source of fluorine. These reagents are thought to react by an ionic pathway.[59] Circumstantial evidence in favor of an ionic mechanism for the XeF_2 case is also provided by the fact that neither the rate nor the reaction products are affected by the presence of molecular oxygen. The additional fact that silyl enol ethers are much more reactive than enol acetates also supports an ionic pathway.[52] Nevertheless, electron transfer processes are common with XeF_2, as has been discussed earlier in this review. Quite often in mechanistic discussions, the distinction is lost between electron transfer processes (which lead to fluorinated products) and those that lie on a completely separate reaction manifold and lead to unfluorinated products. Differding and Rüegg illustrated this point for the reaction of the potassium enolate of benzyl citronellate **78** with XeF_2 (eq 38).[60] They obtained a modest amount of the monofluoroester **79**, along with a small quantity of difluoroester **80**. Significantly, no cyclic fluoride **81** was identified in the product mixture, although the corresponding non-fluorinated cyclic product was isolated. Difluoride **80** arose from the deprotonation of **79** by unchanged enolate, followed by reaction with additional fluorinating agent. The absence of **81** from the mixture indicated that a radical with a half-life *greater* than that of a 1-hexenyl radical was not an intermediate in the manifold

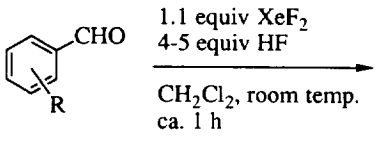
leading to fluorinated products (cf. eq 13). Had a radical been formed through loss of an electron from the enolate of **78**, ring closure would have taken place, as shown by the cyclization of benzyl α-bromocitronellate to **82** with *n*-Bu_3SnH. The occurrence of **82** in the product shows that XeF_2 oxidized the enolate, but the fluorinated and non-fluorinated products of eq 38 lie on separate pathways.[60] These results suggest a pathway to **79** and **80** that does not involve electron transfer, but the results do not preclude an initial electron transfer, followed by a fluorine atom transfer that is faster than cyclization.



[38]

7. Reactions with Aryl Aldehydes and Ketones

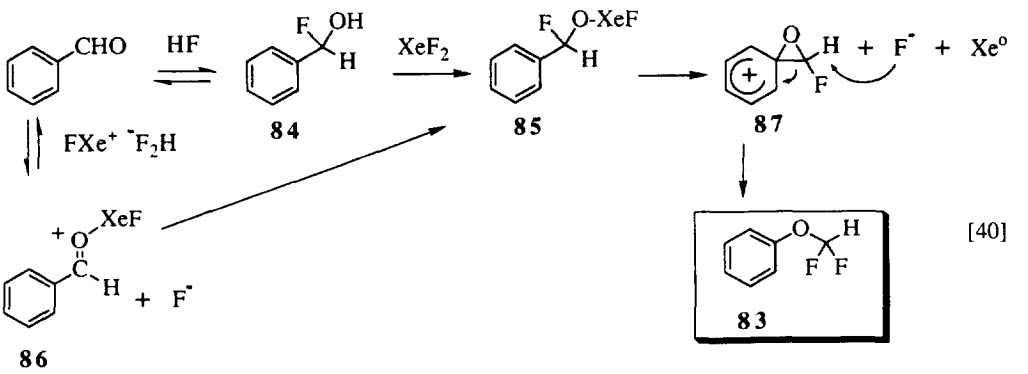
Fluorination of aryl aldehydes or ketones with XeF_2 is accompanied by skeletal rearrangement. This process is illustrated for aryl aldehydes in eq 39,[61] and several features are noteworthy. The highest yields of difluoromethyl ethers were realized when 4 or 5 equiv HF were present. Also, for benzenes substituted by strongly electron-donating groups (such as methoxy or acetamido) fluorination of the aromatic ring competed with the reaction leading to difluoromethyl ether, and some polymerization also took place. At the time of this writing, mechanistic details of the mechanism had not been published, but the rationalization summarized in eq 40 will be tentatively proposed.[61] The rearrangement presumably takes place through the intermediacy of alkoxyfluoroxenon **85**. This compound has been postulated to arise from interaction of fluorohydrin **84** with XeF_2.[61] The fluorohydrin, in turn, is formed reversibly from the direct addition of HF to the aldehyde. Alternatively, activation of XeF_2 by HF, followed by transfer of fluoroxenon cation to the aldehyde carbonyl oxygen, leads to **86**. Attack of **86** by fluoride leads to tetrahedral intermediate **85**. Collapse of **85** to phenonium ion **87** takes place with loss of elemental xenon and formation of fluoride anion. Nucleophilic attack of fluoride on **87** provides difluoromethyl ether **83**.



83

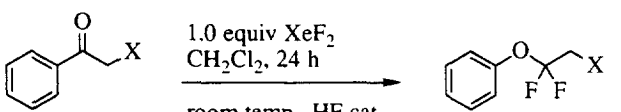
R = H	68%
R = p-Me	78%
R = o-NO_2	83%
R = p-Cl	85%

[39]



[40]

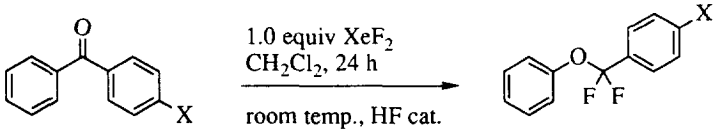
Fluorination with XeF_2 takes a similar course with aryl ketones.[55,62,63] Zupan and Zajc converted acetophenone (**88**a, eq 41) to 1,1-difluoroethyl phenyl ether **89**a in low yield.[62] Considerable acetophenone was recovered from the reaction mixture. The yield was much better for the case of α-fluoroacetophenone **88**b (eq 41). Benzophenone (**90**a, eq 42) was converted to α,α-difluorobenzyl phenyl ether **91**a in 21% yield with 62% recovery of the starting material.[62] Fluorination of 4-nitrophenyl phenyl ketone **90**b led exclusively to **91**b.[62] No α,α-difluorobenzyl-4-nitrophenyl ether was produced, a result that can be understood by consideration of the mechanism, which is summarized in eq 40. 2-Fluoro-1-indanone **92** (eq 43) dissolved in hydrogen fluoride-pyridine mixture was treated for 2 h at room temperature with 1 equiv XeF_2.[62] The major products were 2,2,3-trifluoro-3,4-dihydro-2*H*-1-benzopyran **93** and 2,2,3,6-tetrafluoro-3,4-dihydro-2*H*-1-benzopyran **94**. This latter compound apparently arose from the acid catalyzed aromatic ring fluorination of **93**. 2,2-Difluoro-1,3-indanedione **77** was converted in modest yield to **95** (eq 44).[55] Although the reactions, which are summarized in eqs 41-44, proceed in modest yield, they provide ready access to materials that would be very difficult to prepare in any other way. A major competing process in all these cases is fluorination of the aromatic ring, which is also catalyzed by HF.



88a X = H
88b X = F

89a X = H (23%) + **88a** (65%)
89b X = F (52%) + **88b** (24%)

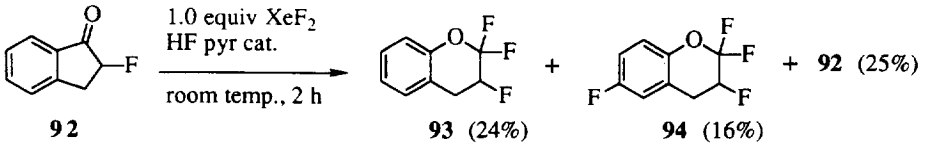
[41]



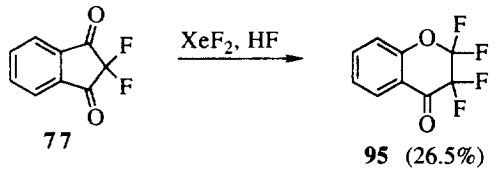
90a X = H
90b X = NO_2

91a X = H (21%) + **90a** (62%)
91b X= NO_2 (20%) + **90b** (67%)

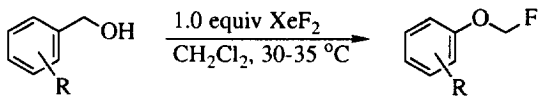
[42]



[43]



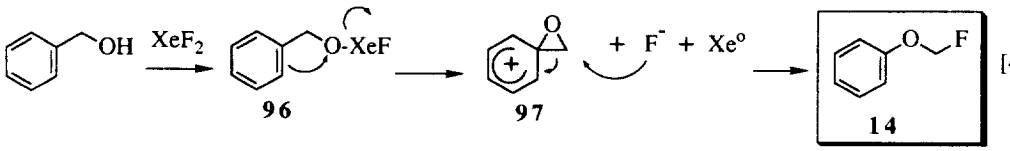
[44]



14 R = H (70%)
R = o, m, p-NO_2,
p-CH_3 or m-F (75-85%)

[45]

Fluoromethyl aryl ethers are also obtained from the treatment of benzyl alcohols with XeF_2 (eq 45).[64] Exposure of benzyl alcohol to an equivalent of XeF_2 in CH_2Cl_2 at 30-35 °C led to the evolution of gas, presumably Xe, and the formation of fluoromethoxybenzene **14** in 70% yield, along with some benzaldehyde and starting material. Electron-withdrawing substituents on the benzene ring improved the yields of the derived fluoromethyl ethers (eq 45). Electron-donating substituents had the opposite effect. *p*-Methylbenzyl alcohol led to the fluoromethyl ether in only 20% yield from a tarry and complicated reaction mixture. Substitution by even more strongly electron-donating groups (HO-, RO-, RNH-) did not provide useful results.

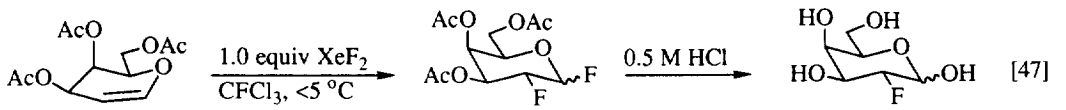


[46]

It is likely that the reactions of aryl aldehydes and benzyl alcohols proceed through similar mechanisms. Treatment of benzyl alcohol with XeF_2 in all likelihood leads to alkoxyfluoroxenon intermediate **96** (eq 46). Collapse of **96** to phenonium ion **97** (cf. **87** in eq 40), followed by nucleophilic attack by fluoride, leads to the observed product **14**. The formation of **96** can be expected to be catalyzed by HF, therefore the overall process is likely to be autocatalytic. The failure of this reaction for benzyl alcohols bearing electron-donating groups is probably due in large part to aromatic ring fluorination, as well as to side reactions taking place from a benzyl carbocation.

8. Fluorosugars

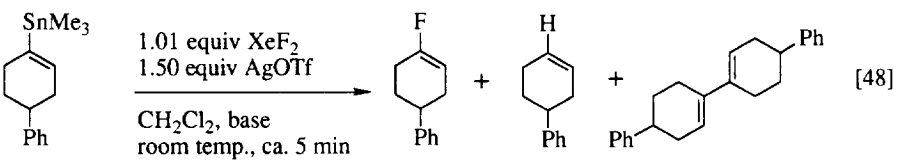
Exposure of tri-*O*-acetyl-D-galactal (**98**) to XeF_2 provided 2-deoxy-2-fluoro-D-galactose (**100**) after hydrolysis and purification (eq 47).[65] The intermediate anomeric fluoride **99** is a potentially useful fluorogalactosyl donor. Selectively fluorinated hexoses have been used to probe biochemical mechanisms but often require tedious synthesis. The preparation of **100**, which is summarized in eq 47, is noteworthy, since the process requires neither catalysis nor a polar solvent and provides only the C2 equatorial fluoride. No rearranged or fluorine-containing side products were isolated. Neither was 2-deoxy-D-galactose, the product of acid catalyzed hydrolysis, seen in the product. Earlier work described the $BF_3{\cdot}Et_2O$ catalyzed addition of XeF_2 to D-glucal, D-galactal, and D-fucal.[66,67] In each instance small amounts of the C2 epimeric fluorides were obtained in the product mixture. The mechanism that was postulated[65] for the conversion of **98** to **99** does not involve HF catalysis; however, since no acid scavenger was present, catalysis may have taken place. It is likely that for electron-rich alkenes such as **98**, the uncatalyzed fluorination is fast enough to compete with the decomposition of XeF_2.



98 **99** α/β = 49/51 **100** (63% overall) [47]

9. Vinyl Fluorides from Vinyl Stannanes

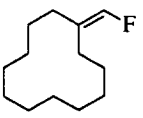
Vinyl stannanes and vinyl silanes can be converted to the corresponding iodides, bromides, or chlorides by treatment with the appropriate halogen electrophile. The analogous process for fluorides was not known until recently.[68-70] Exposure of vinyl stannane **101** to 1.5 equiv of silver(I)triflate and 1.01 equiv of XeF_2 in CH_2Cl_2 containing 0.1 equiv of 2,6-di-*tert*-butyl-4-methylpyridine led to a rapid reaction in which vinyl fluoride **102** was the major product. Silver(I)hexafluorophosphate and silver(I)tetrafluoroborate also



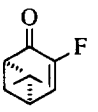
101 **102** (79%) **103** **104** [48]

catalyzed the reaction; however, yields were inferior with these reagents. In the absence of the pyridine base, significant amounts of alkene **103** accompanied **102** in the mixture. Separation of **102** from **103** was difficult. In the absence of the silver salt and the amine base a very slow reaction (2-3 days at 25 °C) took place between **101** and XeF_2 to produce small quantities of fluoride **102**. The major product under these conditions was alkene **103**, although small amounts of **104** were also observed. Presumably, reaction of XeF_2 with the solvent led to HF, and protiodestannylation gave **103**. Treatment of **101** with 1.1 equiv of

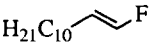
AgOTf in the absence of XeF_2 led to dimer **104** in 79% yield. A silver mirror was observed at the end of this reaction. The fluorination reaction is general, and tolerates functionality: ketone, ester, carbamate, ketal, ester, ether, phenol, and tertiary alcohol were not affected. Vinyl fluorides **105-109**[71,72] were prepared in this way in the indicated yields from the corresponding trimethylstannanes.



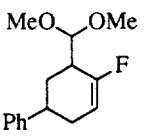
105 (70%)



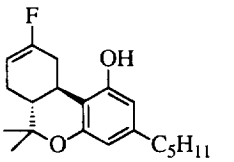
106 (20%)



107 (39%)

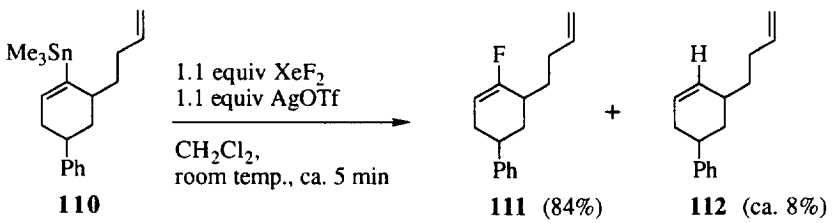


108 (53%)

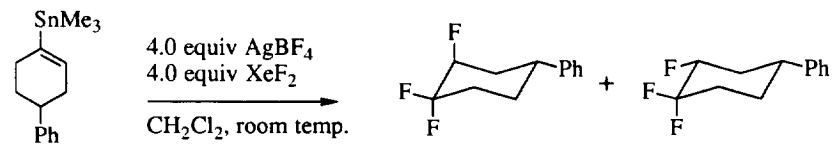


109 (52%)

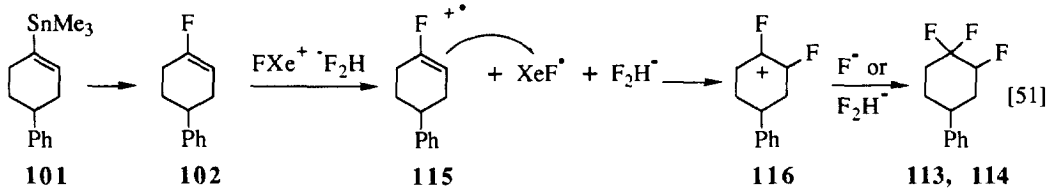
The mechanism for this conversion apparently does not involve radicals, since **101** in neat 1,1-dichloroethylene produced **102** in 76% yield.[72] Had the reaction proceded via a vinyl radical, trapping by the solvent would have taken place. The transformation, which is summarized by eq 49, provides additional evidence against the intermediacy of a radical. Treatment of **110** with XeF_2 and AgOTf in CH_2Cl_2 afforded a high yield of vinyl fluoride **111** in a very rapid reaction (eq 49). Had a vinyl radical been present as an intermediate, the formation of cyclic products likely would have been observed.[60,73] Although the appearance of dimer **104** in eq 48 may suggest a radical, it is not clear whether vinyl fluoride **102** and **104** share a common intermediate.



110 **111** (84%) **112** (ca. 8%) [49]



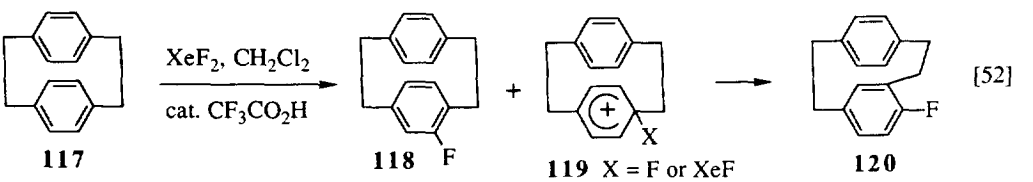
101 **113** (3/2 51%) **114** [50]



An unusual outcome resulted when we exposed **101** to an excess of $AgBF_4$ and XeF_2 (eq 50).[71] Diastereomeric trifluorides **113** and **114** were formed in 51% yield. We obtained a much higher overall yield of trifluorides by conducting the reaction in two steps. First, stannane **101** was converted to vinyl fluoride **102** according to eq 48. Then exposure of **102** to 3.0 equiv of $AgBF_4$ and 1.2 equiv of XeF_2 provided the same mixture of **113** and **114**, this time in 90% yield. Formation of the trifluorides was completely suppressed by addition of 10 equiv of 2,6-di-*tert*-butyl-4-methylpyridine. These results all suggest that the conversion of **102** to **113** and **114** was catalyzed by the traces of HBF_4 present in the $AgBF_4$. Indeed, the HF catalyzed addition of XeF_2 to alkenes, which produces vicinal difluorides, has been described (*vide supra*).[74] A similar reaction probably took place with **102** (eq 51). Radical cation **115** is formed through an electron transfer process which simultaneously generates fluoroxenon radical and bifluoride. Radical recombination with loss of elemental xenon produces fluorine-stabilized carbocation **116**,[75-77] which is trapped by fluoride or bifluoride to give the observed products. The two-step process is more efficient because vinyl stannane **101** was not exposed to HBF_4 during the first step. In the direct process protiodestannylation leads to a diminution of the overall yield.

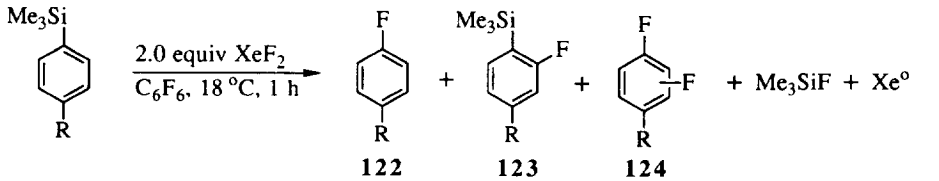
10. Aromatic Ring Fluorination

Electrophilic fluorination of activated phenyl rings by XeF_2 in general requires acid catalysis. Cyclophane **117** did not react with XeF_2 in the absence of CF_3COOH, or when the reaction was conducted in a Teflon® flask (eq 52).[78] In the presence of CF_3COOH, or in glass apparatus, fluorides **118** and **120** were observed. The reaction of XeF_2 (or HF) with the glass produces fluorosilicates that can function as catalysts. For both **118** and **120** electron transfer to form an aryl radical cation seems likely (*vide infra*). *Ipso*-substitution led to **119**, which rearranged to **120**.



Similar reactivity is exhibited by aryltrimethylsilanes.[79] Arylsilanes **121** reacted with 2 equiv of XeF_2 to produce preparatively useful yields of monofluoride product **122** (eq 53). Minor amounts of monofluoro arylsilanes **123** and difluorides **124** were also observed; fluorotrimethylsilane was detected in the product by ^1H nmr spectroscopy. The proportion of difluoride might have been diminished through the use of a smaller

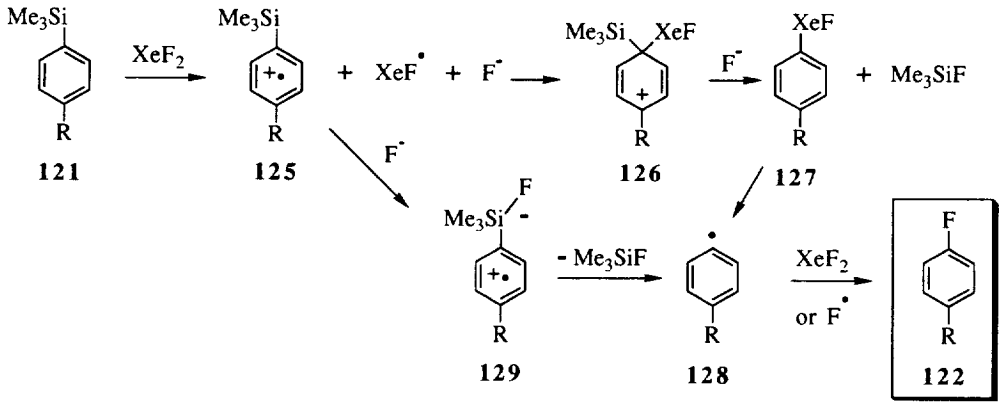
excess of XeF_2; however, the excess was found to be necessary for complete fluorodesilylation of the starting material. The product distribution from **121c** (R=OMe) sheds light on the mechanism: 4-Fluoroanisole (**122c**) was the major product, with smaller quantities of 3-fluoro-4-methoxyphenyltrimethylsilane **123c**; whereas when **121c** was treated with cesium fluoroxysulfate, a reagent presumed to react by way of an



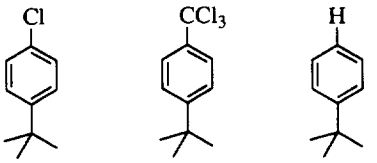
[53]

121 a R = H — 65.2 / 0 / 0 (+ 34.8 p-difluorobenzene)
b R = t-Bu — 86.3 / 7.6 / 6.1
c R = OMe — 61.4 / 38.6 / 0
d R = Cl — 82.1 / 11.5 / 6.4

electrophilic mechanism,[80] the relative proportions of **122c** and **123c** were reversed (2:5). Consequently in eq 53 substitution by a fluorine electrophile seems unlikely. The mechanisms summarized in eq 54 have been proposed to rationalize these observations.[79] Electron transfer to XeF_2 produces radical cation **125**, fluoroxenon radical, and fluoride. Radical combination affords pentadienyl cation **126**. Fluorodesilylation gives arylxenon intermediate **127**, which undergoes homolysis to aryl radical **128**. Combination with XeF_2 (or F·) leads to the fluoroaromatic product. An alternative pathway that cannot be ruled out involves fluoride attack on **125** to produce zwitterionic radical **129**. Loss of fluorotrimethylsilane from **129** leads again to **128**. Good evidence for the intermediacy of radical **128** was provided by the reaction of **121b** in $CHCl_3$. In addition to **122b**, chlorides **130** and **131**, along with *tert*-butylbenzene **132** were identified in the reaction mixture, suggesting that 4-*tert*-butylphenyl radical was an intermediate of the reaction.[79]

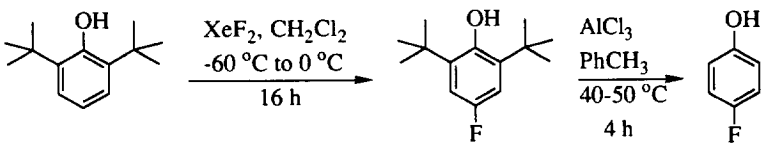


[54]



130 **131** **132**

ortho-Substitution is normally favored in fluorination of phenols with XeF_2. It is possible to overcome this limitation through blocking groups. 2,6-di-*tert*-Butylphenol **133** underwent fluorination at low temperature to produce monofluoride **134** in moderate yield (eq 55).[81] Transfer of the two *tert*-butyl groups of the product to toluene in a Lewis acid catalyzed Friedel-Crafts process gave *p*-fluorophenol **135** in good yield. Fluorination of phenols can also be accomplished conveniently and in high yield with N-fluoropyridinium triflate.[82,83]

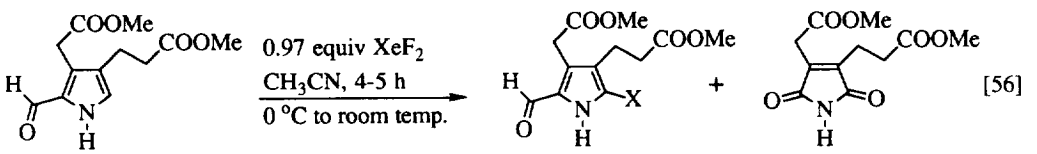


[55]

133 **134** (49.1%) **135** (85.4%)

Benzene has been reported to undergo conversion to phenol upon treatment with XeF_2 and water. This reaction may take place by means of HOXeF through an electron transfer process.[84]

Pyrrole **136** was converted to fluoride **137** in low yield, along with a substantial amount of imide **138**, by exposure to a small deficiency of XeF_2 in CH_3CN (eq 56).[85] In CH_2Cl_2 24% of chloride **139** was isolated. The appearance of the chloride was attributed to formation of FCl from the reaction of XeF_2 with the solvent. Significantly, of the several sources of fluorine that were examined, XeF_2 proved to be the best for the fluorination of pyrroles bearing electron withdrawing groups.



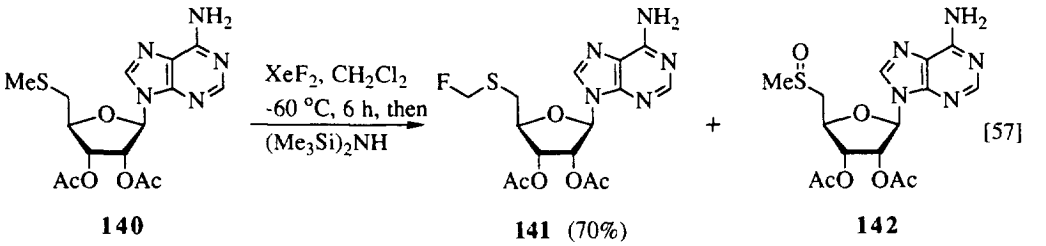
[56]

136 **137** (X = F, 32%) **138** (20%)
139 (X = Cl)

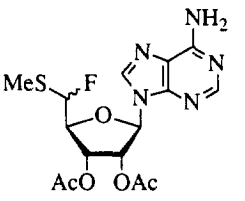
11. Fluorination of Thioethers

A process conceptually related to the Pummerer reaction takes place when alkyl thioethers are exposed to XeF_2 at low temperature. The first step is probably the formation of the corresponding sulfur(IV) difluoride. Treatment of 2',3'-di-*O*-acetyl-5'-*S*-methyl-5'-thioadenosine (**140**) at -60 °C in CH_2Cl_2 with XeF_2, followed by a quench at the same temperature with hexamethyldisilazane, led to fluoromethyl product **141**, along with minor quantities of sulfoxide **142** (eq 57).[86] The sulfoxide probably arises through

hydrolysis of the sulfur (IV) intermediate. Note that in this instance fluorination took place exclusively at the methyl group. Fluorination of **140** under slightly different conditions (-25 °C, followed by warming to room

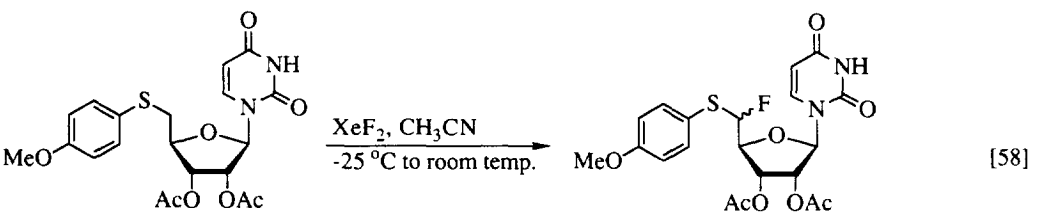


140 **141** (70%) **142** [57]



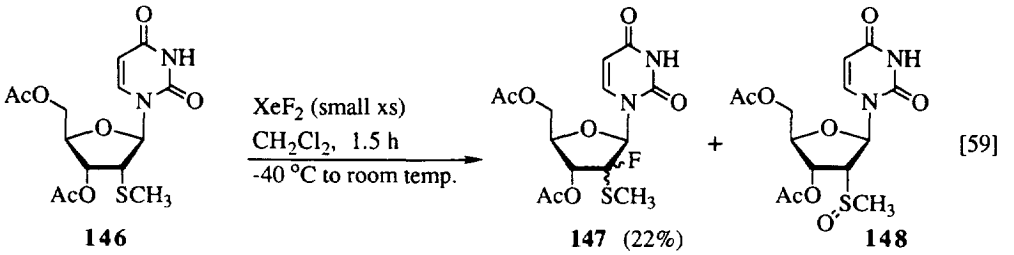
143

temperature, instead of -60 °C) led in 59% yield to a 39:61 mixture of fluorides **143** and **141** after a quench with aqueous $NaHCO_3$.[87] Fluoride **143** was formed as a 1:1 mixture of diastereoisomers. This lack of regiospecificity may be the result either of the higher reaction temperature or of the base responsible for mediating rearrangement of the sulfur(IV) intermediate. It is likely that this intermediate is stable at -60 °C, but decomposes at elevated temperatures. In the regioselective process, the hindered amine base is able to select



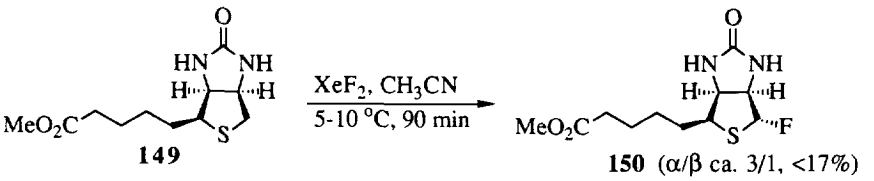
144 **145** (91%) [58]

between the methyl and methylene carbons.[88] If fluorination at the 5' carbon of a nucleoside is desired, an aryl thioether can be used. For example, exposure of thiouridine derivative **144** to XeF_2 in CH_3CN led to the 5'-fluorinated product **145** in excellent yield (eq 58).[89] Interestingly, fluorination of the activated phenyl ring did not compete with this process.



146 147 (22%) 148 [59]

The fluoromethyl thioethers (e.g. **141**) are relatively stable, but as the fluorine-bearing carbon becomes more highly substituted this is no longer the case. Thiouridine derivative **146** (eq 59) reacted with XeF_2 to give fluoride **147** as a diastereomeric mixture in low yield.[90] Sulfoxide **148** was also produced during this reaction. Fluoride **147** underwent slow decomposition on standing, but rapid (5 min) decomposition took place on silica gel at room temperature.

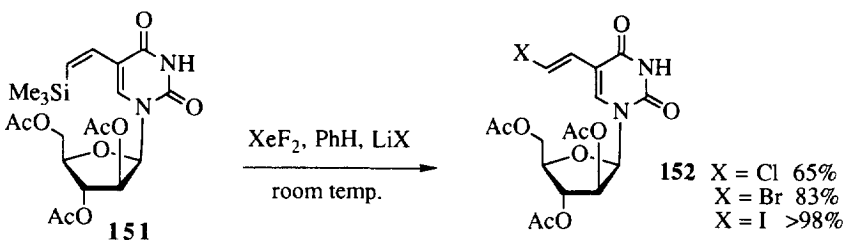


149 150 (α/β ca. 3/1, <17%) [60]

The fluorination of thioethers is certainly not limited to thionucleoside derivatives. Biotin methyl ester **149** was converted in low yield to fluoride **150** (eq 60).[91] The reason for the low yield is not clear, but it is probably due in part to losses that took place during purification of the product. It is also likely that conducting the reaction at lower temperature would improve its efficiency.

12. Miscellaneous Reactions

The xenon difluoride mediated halogenation of vinyl silanes offers convenient, as well as efficient access to vinyl halides (eq 61).[92] Robins and Manfredini presume the reaction proceeds by an oxidative conversion of a lithium halide to a halonium fluoride (XF), which, in turn, converts the vinyl silane to the corresponding vinyl halide with inversion of double bond geometry via the usual mechanism. Many alternative procedures for these types of transformations exist; however, this method promises to be very convenient for radiohalogenations, in which small quantities of halide are used.[92]



151 152 X = Cl 65%, X = Br 83%, X = I >98% [61]

The reaction of XeF_2 with Grignard reagents is evidently not preparatively useful (eq 62).[93] In this situation XeF_2 functions primarily as an oxidant, and the major products are derived from single electron transfers involving the solvent.

$$RMgBr + XeF_2 \xrightarrow{Et_2O} \underset{\mathbf{153}}{\overset{R}{\underset{CH_3}{O}}\!\!\diagup\!\!\diagdown CH_3} + RH + R\text{-}R \ (+ \text{ others}) \qquad [62]$$

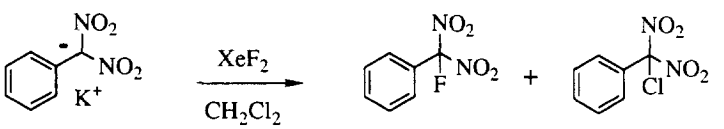
153 R = n-$C_{10}H_{21}$ 2/3/1
R = Ph 3/10/1

The reaction of XeF_2 with perfluoroimine **154** (eq 63) would appear to take place by means of a fluorine atom transfer, although a plausible polar mechanism can also be written.[94] Hydrazine **155** was produced in excellent yield.

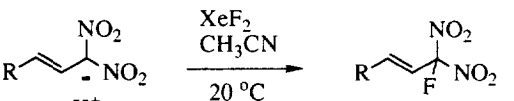
$$XeF_2 + 2\ CF_3\text{-}N{=}CF_2 \xrightarrow{\text{bomb tube}} \underset{\mathbf{155}\ (85\%)}{F_3C(F_3C)N\text{-}N(CF_3)CF_3} + Xe^o \qquad [63]$$

154

Potassium nitronate anion **156** reacted with XeF_2 in CH_2Cl_2 to produce fluoride **157** as the major product in good yield, along with minor quantities of chloride **158** (eq 64).[95] Similar product compositions have been detected in electrochemical oxidations of **156**. Potassium nitonate **159** underwent fluorination to **160** in high yield in a similar manner (eq 65). It is noteworthy that no products arising from F_2 addition to the double bond were observed when the reaction was performed in normal (silicate) glass vessels. When the reaction was conducted in a Teflon® reactor, product mixtures were observed. These results suggest that the F_2 addition, which is catalyzed by HF, was suppressed in the presence of silicate glass which effectively removes the HF from solution.[96]



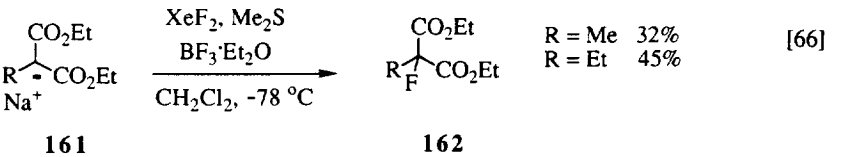
156 **157** (72%) **158** (3%) [64]



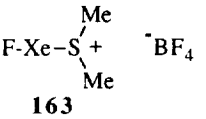
159 **160**

R = CN 71%
R = $CONH_2$ 63% [65]

Sodium diethylmalonate **161** was converted to fluoride **162** in modest yield by exposure to XeF_2 in the presence of one equivalent each of dimethylsulfide and BF_3·Et_2O at low temperature (eq 66).[97] The reaction is mechanistically interesting, and appears to proceed through the intermediacy of fluoroxenon sulfonium ion **163** which was characterized by ^{19}F nmr.

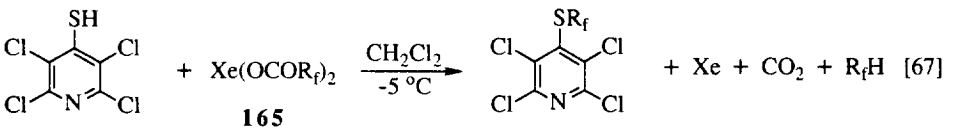


161 **162**



163

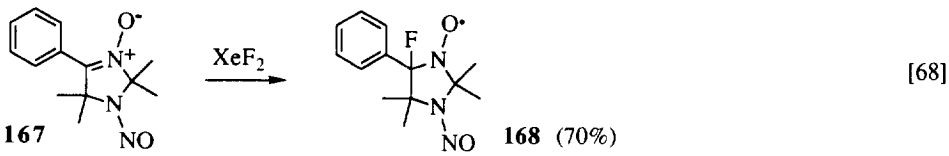
Chloropyridine thiol **164** underwent S-perfluoroalkylation with xenon perfluoroalkane carboxylates **165** (eq 67).[98] The chloropyridine disulfide was also isolated in all reactions. This observation suggests an electron transfer process for eq 67 involving the generation of perfluoroalkyl radicals.



164 **165**

166 Rf = CF_3 36%
Rf = C_2F_5 85%
Rf = C_3F_7 85%

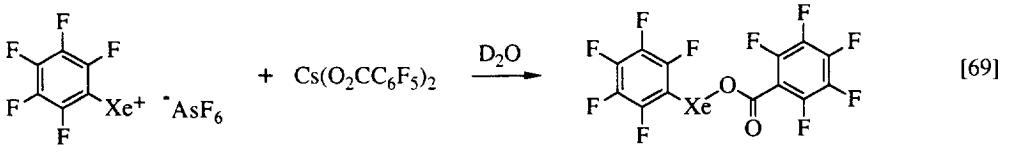
Phenyl nitrone **167** was converted in high yield to stable nitroxyl **168** in a reaction that may be general (eq 68).[99] Exposure of **168** to ammonia (or methylamine) in a subsequent step led to products of nucleophilic substitution of fluorine by nitrogen.



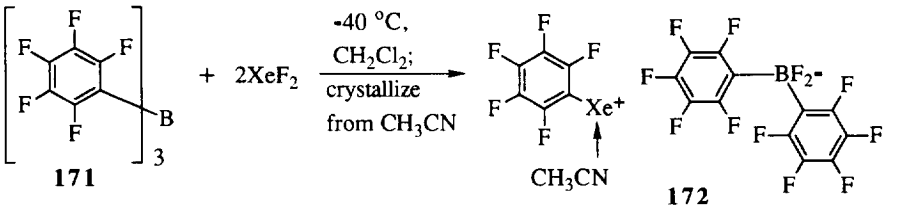
167 **168** (70%)

One of the exciting recent developments in the preparation of compounds with Xe-C bonds deserves attention.[100] Arylxenon ester **170** (eq 69)[101] was prepared in excellent yield from cesium perfluorobenzoate and arylxenon salt **169**. The product was recrystallized from CH_2Cl_2 and was characterized by X-ray crystallography. Exothermic decomposition of **170** took place around 85 °C, but at lower temperature the material was kinetically stable. No decomposition was observed even after 5 days at room temperature. Arylxenon salt **172** was prepared from XeF_2 and perfluorotriphenyl boron **171** as shown in eq 70.[102] Salt **172** was characterized by X-ray crystallography. Exposure to AsF_5 at low temperature gave **169**. The stable organoxenon compounds can be characterized through ^{129}Xe nmr.[103] Large coupling constants to fluorine are

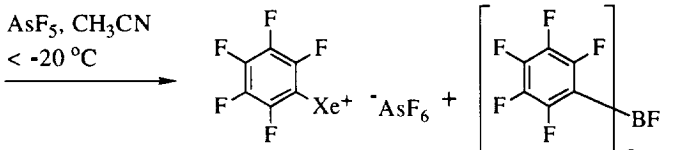
typically observed. For example, in **170** the xenon is coupled to the *ortho* fluorines with a coupling constant of 84 ± 6 Hz.[101]



169 **170** (80%) [69]



171 **172** [70]



169 **173**

Finally, a discussion of the chemistry of XeF_2 would not be complete without mentioning the availability of ^{18}F radiolabelled XeF_2.[104] An improved preparation produces reagent of high specific activity (450 mCi/mmol) in good yield.[105] Significantly, the radiolabelled material can be prepared within approximately one half-life of ^{18}F ($t_{1/2}$ ca. 110 min). This unstable isotope of fluorine is a positron emitter, and its incorporation into pharmaceuticals makes it possible to visualize transport and metabolic processes in real time by positron emission tomography (PET). Because of the very short half-life of ^{18}F, only the most rapid reactions of XeF_2 are useful for ^{18}F-labelled synthesis.

Conclusion

Xenon difluoride participates in a variety of synthetically useful reactions and mediates some startling organic transformations. This review has attempted to summarize some of the rich and unusual chemistry of XeF_2, and to provide the mechanistic insight required for the incorporation of these processes into synthetic planning.

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