Synthesis of terminal monofluoro olefins

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1 Introduction

The small and highly electronegative fluorine atom has found many applications in synthetic and physical organic chemistry.[1] Several fluorinated monomers are of importance in polymer synthesis.[2] In enzyme substrate analogues, fluorine may be found as a substitute for hydrogen (on steric grounds), as a hydroxy analogue (though its capacity to accept hydrogen bonds is smaller than expected), or as an α-substituent in phosphate mimics (with a CFH or CF_2 group replacing an oxygen atom).[3] With fluorinated analogues readily accepted by the target enzymes, much work has been aimed at the synthesis of mono-[4] and difluorinated[5] substrates. Especially interesting is the use of fluorinated substrates as suicide inhibitors.[6] The development of new, mild fluorinating agents is of great interest[1,7] because the production of several halofluorocarbons, used in numerous synthetic routes, is being restricted according to the Montreal Protocol.[8]

In our work on the Horner–Wittig synthesis of fluoro olefins, the question came up of what methods were known to prepare such products, and how generally applicable these were. The aim of this review is to provide an answer to these questions. The focus will be on the formation of terminal monofluoro olefins of the general structure $R^1R^2C{=}CHF$ in which R^1 is a carbon substituent and R^2 a carbon substituent or a hydrogen atom†. These will be referred to as fluoro olefins. For clarity, the term vinyl fluoride will only be used for fluoroethene ($CH_2{=}CHF$). Generally, only routes with synthetic potential will be discussed. Stereoselective routes towards fluoro olefins will be emphasised, as separation of (*E*)- and (*Z*)-isomers often is problematic. Another point of special interest is the applicability of a method to the preparation of poly-unsaturated systems, as only few routes towards such compounds have been described.

While further transformation of compounds already containing a fluoromethylene group will usually not be treated, possible side reactions occurring during formation or isolation of such products will be mentioned when necessary.

Parts of the material presented here have been discussed in other reviews. Fluoro olefins, including di- and trifluoro olefins, which showed mechanism-based enzyme inhibition were treated in 1991 by Bey *et al.*[6] The reactivity of fluoroallene was summarised by Dolbier in 1991, with emphasis on its mechanistic implications.[9]

Fluorinated ylides and related compounds, and their use in the synthesis of fluorinated alkenes were reviewed by Burton *et al.* in 1996.[10]

2 Elimination reactions of saturated compounds

Many of the early routes towards fluoro olefins proceeded through fluorinated alcohols, or polyhalogenated compounds containing at least one fluorine atom. Recent advances have sparked off new interest in these compounds. They can be converted into fluoro olefins through a variety of elimination reactions like dehydration, dehydrohalogenation or dehalogenation.

† In some illustrative cases, these side-chains may be (poly)fluorinated.

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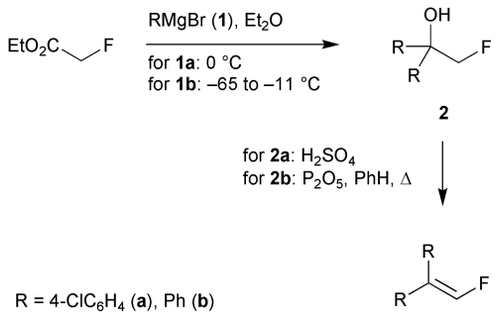
2.1 Dehydration and dehydrohalogenation routes *via* α-fluoro-β-heteroalkanes

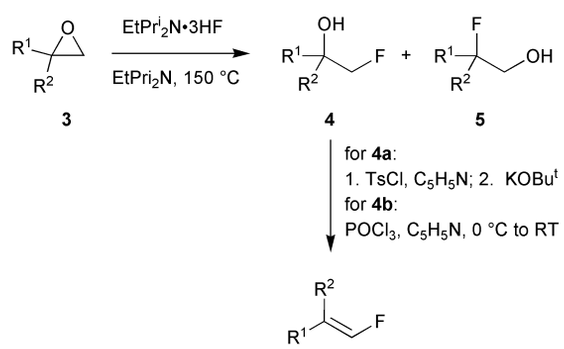
Reaction of ethyl fluoroacetate with excess arylmagnesium bromides **1** afforded carbinols **2**, which could be dehydrated under harsh conditions to yield 2,2-diaryl-1-fluoroethenes in a straightforward approach with an overall yield of 23–31% (Scheme 1).[11]



Scheme 1

In order to identify an error in the literature, 2-fluoro-1,1-diphenylethanol has also been converted into 1,2-difluoro-1,1-diphenylethane. Heating this *vic*-difluoride was reported to yield 1,1-diphenyl-2-fluoroethene, but no yield was given.[12]

Heating terminal epoxides **3** with a 1 : 1 ethyldiisopropylamine–HF complex led to regioselective formation of fluorohydrins **4**, with the ratio of isomers **4** : **5** shown to be > 9 : 1 for a number of epoxides.[13] The alcohol function was removed through tosylation and treatment with base,[13] or *via* chlorination in pyridine[14] to give fluoro olefins in overall yields up to 86% (Scheme 2).

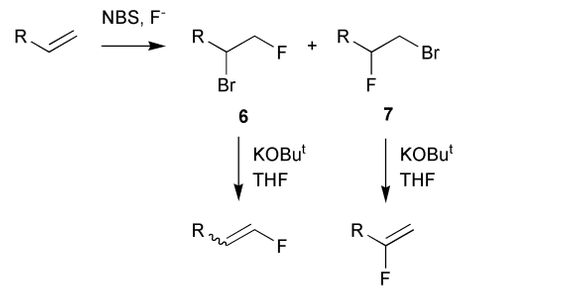


R[1], R[2] = n-C_8H_{17}, H (**a**); -CH_2CH(n-C_6H_{13})CH_2- (**b**)

Scheme 2

For the conversion of olefins into fluoro olefins, the halofluorination reaction has found some application. A halonium donor and a fluoride source were used to introduce X–F to a carbon–carbon double bond.[15] The predominant Markovnikov-type regiochemistry makes this method less suited for the synthesis of terminal fluoro olefins, unless an electron-withdrawing substituent is present.[16] Still, in some cases with electron-withdrawing substituents in the allylic or homoallylic position, precursors **6** of terminal fluoro olefins were formed in amounts equal to or higher than isomers **7**, yielding 2-fluoroalkenes.[15a,17] Fluoro olefins were formed by treatment with base (usually $KOBu^t$), with (*E*)-isomers predominant.[17,18] Examples with a high 1-fluoroalkene yield are shown in Scheme 3. Overall yields were generally under 25%, with product mixtures demanding laborious chromatographic work-up. Another method using halofluorination is treated in Section 2.3.

Bromofluorination was the key step in preparing GABA-aminotransferase inhibitor **8** (Fig. 1).[17a,b]



6 + **7**: R = 5-(2-oxopyrrolidinyl), F^- = C_5H_5N•9HF; Et_2O
R = 2-(*N*-carbobenzyloxypyrrolidinyl), F^- = TBAF•2HF; CH_2Cl_2
R = 2-hydroxy-1-(phenylmethyl)propyl, F^- = $C_5H_5N_9$•HF; Et_2O

Scheme 3

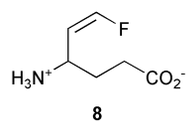
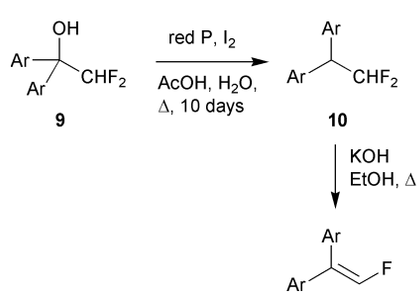


Fig. 1

2.2 Dehydrohalogenation of geminal fluorohaloalkanes

Geminal difluorides have the obvious advantage over α-fluoro-β-chloroalkanes that no competitive dehydrofluorination towards 2-chloroalkenes can occur. In other halofluorides, loss of HBr or HI seems sufficiently favorable over dehydrofluorination to be interesting synthetically.

2,2-Difluoro-1,1-diarylethanols **9** were obtained from ethyl difluoroacetate and Grignard reagents in 40–64% yields. Deoxygenation to 1,1-difluoro-2,2-diarylethanes **10** and dehydrofluorination by KOH were accomplished in overall yields of around 80% (Scheme 4).[19]



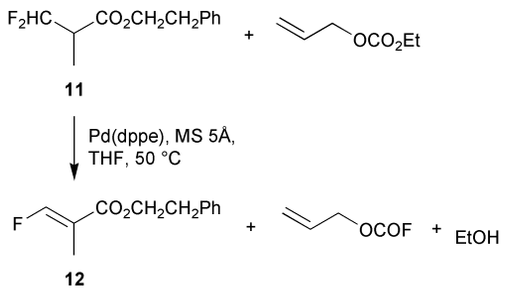
Scheme 4

In similar fashion, difluoroacetic acid was transformed into 1,1-difluoro-2-arylethanes,[20] which were converted to β-fluorostyrenes with one equivalent of $KOBu^t$.[20,21] No yields were provided, but similar treatment of 1,1-difluoro-2-(*p*-nitrophenyl)-ethane, obtained in 39% yield by action of sulfur tetrafluoride on *p*-nitrophenyloxirane, gave a 54% yield of (*E*)-β-fluoro-*p*-nitrostyrene.[22]

Both sulfur tetrafluoride[23] and the more convenient diethylaminosulfur trifluoride (DAST)[24] have been applied for the conversion of aldehydes into difluorides, which underwent dehydrofluorination through thermolysis.

Attempted palladium-catalysed allylation of 3,3-difluoro-2-methylpropionate **11** failed because of competitive dehydrofluorination, resulting in 3-fluoromethacrylate **12** in 71% yield (Scheme 5).[25] No substitution of the fluoride by ethoxide was noted, although such reactions have been reported.[11b]

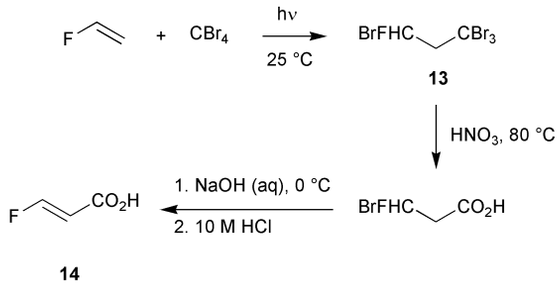
Radical additions of halofluoroalkanes to vinyl fluoride[26] or 1-fluoropropene[23] were applied to prepare fluoro olefins carrying fluorinated side chains. In a somewhat more elaborate reaction scheme, radical addition of tetrabromomethane to vinyl fluoride under UV-irradiation afforded 1,1,1,3-tetrabromo-3-fluoropropane **13** in 36% yield. Conversion of the tribromomethyl group into a carboxylic acid, and basic



dppe: diphenyldiphosphinoethane

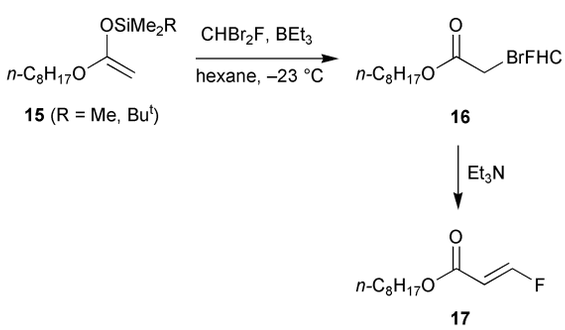
Scheme 5

dehydrobromination yielded (*E*)-β-fluoroacrylic acid **14** with good selectivity in 38% yield (Scheme 6).[27]



Scheme 6

The fluorine atom can also be present in the radical added to the olefin moiety. Triethylborane-promoted radical addition of dibromofluoroethane to ketene silyl acetals **15** to give α-bromofluoromethyl-substituted ester **16**,[28] followed by treatment with triethylamine, gave (*E*)-β-fluoroacrylate **17** in 80% yield (Scheme 7).[28b]

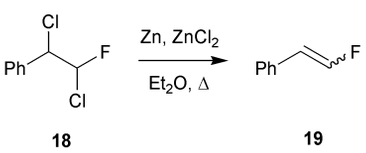


Scheme 7

2.3 Reductive elimination from β-heterosubstituted α-fluoro-α-haloalkanes

1-Fluoro-1,2-dihaloalkanes can be dehalogenated to yield fluoro olefins. In the earliest examples, at the start of the twentieth century, vinyl fluoride was prepared in this way by using zinc,[29] phenylmagnesium bromide,[30] or alcoholic KI[30] as reductants. Zinc has remained the reagent of choice in dehalogenations.

Reaction of 1,2-dichloro-2-fluoro-1-phenylethane **18** with zinc dust gave the desired β-fluorostyrene **19** in 65% yield (Scheme 8).[31] Debromination of 1,2-dibromo-2-fluoro-1-phenylethane and its *p*-nitro analogue were successfully achieved with sodium iodide.[32]

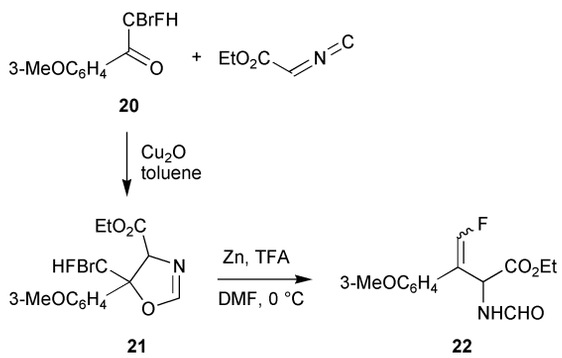


Scheme 8

Halofluorination of a β-chloromethacrylate took place both regio- and stereoselectively.[16] Dehalogenation proceeded in 90% yield to give the 3-fluoroacrylate an 85 : 15 (*E*) : (*Z*) ratio.[33]

By using 1,1-difluoro-2-chloroalkanes, formation of undesired vinyl halogenides is prevented. Such compounds were accessible in 32–50% yield over three steps from difluoroacetic acid derivatives,[34] or in 66% yield by fluorination of a 2-chloroaldehyde.[35]

The β-heteroatom can also be an oxygen atom. α-Bromo-α-fluoroacetophenone **20** was transformed into 5-(bromofluoromethyl)oxazoline **21**, which yielded protected β-fluoromethylene-*m*-tyrosine derivative **22** by zinc reduction as a mixture of (hard to separate) (*E*)–(*Z*)-isomers in 74% overall yield (Scheme 9).[36]



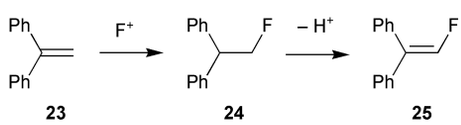
Scheme 9

3 Electrophilic fluorination reactions

The extreme electronegativity of fluorine makes compounds capable of releasing positive fluorine potent reagents for the fluorination of nucleophilic compounds. Electron-rich alkenes and anionic vinyl compounds have served as starting materials.

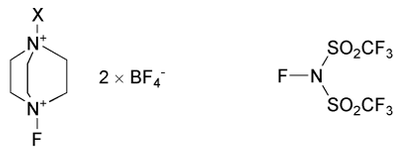
3.1 Addition–elimination reactions of F^+-donors with 1,1-diphenylethene

Formal addition of F^+ to an alkene, followed by elimination of H^+, is a potential way to produce fluoro olefins. 1,1-Diphenylethene **23** has been the prime substrate for these reactions, as the intermediate cation **24** is stable enough to prefer loss of a proton to form fluoro olefin **25** over rearrangement or addition of the anion generated by the F^+-source (Scheme 10).



Scheme 10

With fluorine at −78 °C, 78% of fluoro olefin **25** was obtained, along with small amounts of di- and trifluorinated by-products.[37] Higher temperatures only led to, originally misidentified,[38] rearranged products.[12,19] Use of fluorooxytrifluoromethane led to complex mixtures with both 1,1-diphenylethene[39] and styrenes.[40] Better results were obtained with caesium fluorooxysulfate ($CsSO_4F$),[41] and commercially available 1,4-diazabicyclo[2.2.2]octane derivatives Accufluor™ **26a** and Selectfluor™ **26b** (Fig. 2),[42] with yields of up to 74% before isolation. *N*-Fluorobis[(trifluoromethyl)sulfonyl]-imide **27** could only be used in the presence of a large excess of alkene, as otherwise dimeric and trimeric products prevailed.[43]



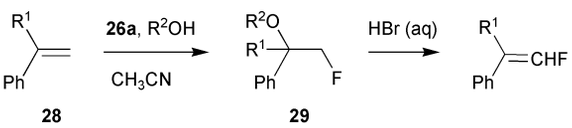
26a: X = OH: Accufluor™
26b: X = CH_2Cl: Selectfluor™

27

Fig. 2

3.2 Two-step synthesis of fluoro olefins *via* electrophilic fluorination of alkenes

Trapping of the intermediate cation, by treatment of phenyl-substituted alkenes **28** with Accufluor™ **26a** in the presence of protic solvents, gave Markovnikov-type addition products **29** in 90–95% yields.[44] These were reportedly transformed into terminal fluoro olefins in good yields by treatment with aqueous HBr (Scheme 11).



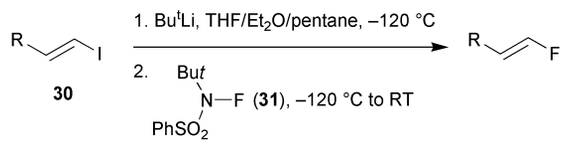
28 **29**

R^1 = H, Me, Ph; R^2 = H, Me

Scheme 11

3.3 Reaction of alkenyl-lithium, -tin, -silicon and -boron reagents with F^+-donors

The use of F^+-donors has been expanded by reaction with anionic vinyl compounds. (*E*)-Vinyl iodides **30** were converted into the analogous fluorides in 71–80% yields through lithiation and reaction with *N*-*tert*-butyl-*N*-fluorobenzenesulfonamide **31** (Scheme 12); protonation of the lithiated intermediate was the



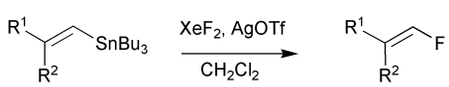
30

R = *n*-C_6H_{13}, Ph, 17-(5α-androstanyl)

Scheme 12

main side reaction.[45] No (*Z*)-vinyl iodides were examined, and most compounds lacked additional functionalities. More reactive fluorinating agents gave only traces of the desired products with alkenyllithiums or analogous mercurials.[45b]

Readily accessible vinylstannanes **32** were converted into fluoro olefins by xenon difluoride in the presence of a silver salt (Scheme 13).[46] Silver triflate was found to give the highest yields,



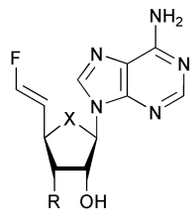
32

R^1, R^2 = (1-hydroxycyclodocecyl)methyl, H (**a**); $-CH_2CH_2CH(Ph)CH_2CH_2-$ (**b**); *n*-$C_{10}H_{21}$, H (**c**); Ph, Ph (**d**); $-(CH_2)_{11}-$ (**e**); 2-$C_{10}H_7$, Me (+ isomer) (**f**); $-CH_2CH_2N(CO_2Et)CH_2CH_2-$ (**g**)

Scheme 13

up to 70%.[46c] The configuration of the double bond usually is maintained during the reaction. The main by-products stem from proteolysis of the stannane.

The reaction has been applied to synthesise fluorohomovinyl analogues of adenosine **33a**,[47] 3′-deoxyadenosine **33b**,[48] and aristeromycin **33c** (Fig. 3),[49] with crude yields of around 60%. Synthesis of an ^{18}F-labelled deoxyuridine derivative, using

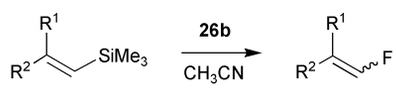


33a: R = OH, X = O
33b: R = H, X = O
33c: R = OH, X = CH_2

Fig. 3

elemental fluorine in the destannylation step, proceeded in 7% yield.[50]

Fluorodestannylation of tributyl(2,2-diphenylvinyl)stannane **32d** has been achieved in 71% yield with Selectfluor™ **26b**.[51] With the same reagent, vinylsilanes **34** were converted into fluoro olefins in 32–57% isolated yield, with some double-bond isomerisation (Scheme 14).[52] Likewise, (*E*)-vinylboron tri-

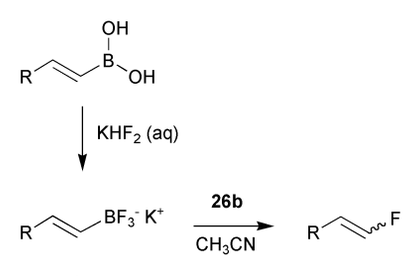


34

R^1, R^2 = Ph, H; *n*-C_6H_{13}, H; Et, Ph

Scheme 14

fluorides **35** were transformed into fluoro olefins in 58–89% yield, with complete loss of stereochemistry (Scheme 15).[53]



35

R = Ph (**a**), 4-MeC_6H_4 (**b**), 4-ClC_6H_4 (**c**), Bu^n (**d**)

Scheme 15

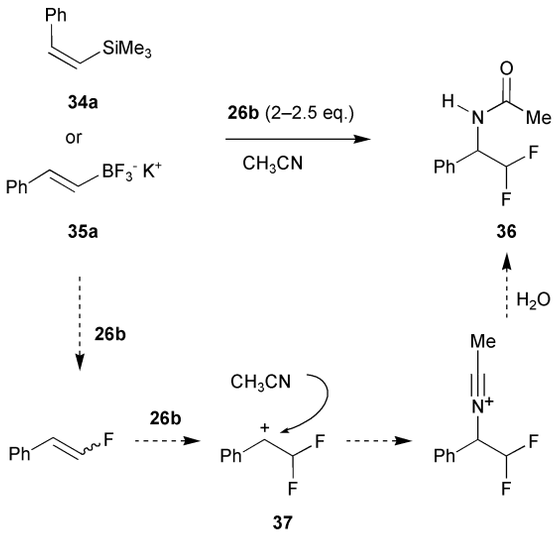
With excess Selectfluor™ **26b**, difluoromethyl-substituted amides such as **36** were formed in acetonitrile;[52,53] alcohols[52] and water[52,53] could also be trapped by the intermediate difluorinated cation **37** (Scheme 16).

4 Nucleophilic fluorination reactions

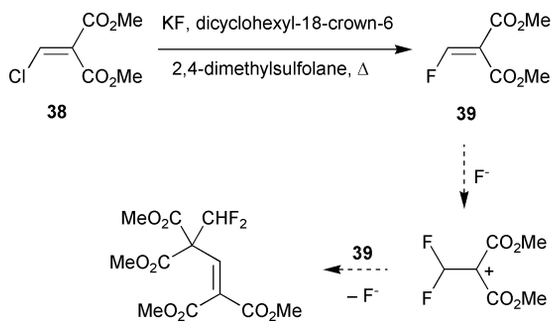
While for electrophilic fluorination quite expensive reagents are needed, nucleophilic substitution of a halogenide by fluoride would present one of the cheapest means for the introduction of fluorine. Some examples of nucleophilic addition reactions have already been presented in Section 2, namely ring-opening of an epoxide and halofluorination. However, these reactions required an additional elimination step. The reactions treated in this Section give fluoro olefins directly, or after isomerisation.

4.1 Nucleophilic fluorinations directly yielding fluoro olefins

Direct conversion of vinyl chlorides into vinyl fluorides has been performed with electron-poor alkenes through addition–elimination reactions. Heating 2-benzoyl-1-chloroprop-1-ene with KF led to formation of the fluoro olefin, which was purified by GC.[54] Likewise, chloromethylenemalonate **38** gave the fluorinated analogue **39** in 23% yield.[55] The product was immediately distilled out of the reaction mixture to prevent fluoride-induced dimerisation (Scheme 17).[55b]

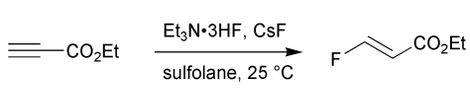


Scheme 16



Scheme 17

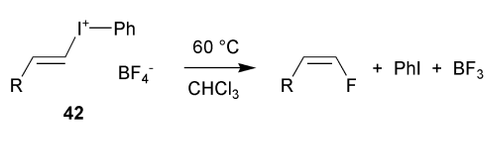
Michael-type addition of fluoride to ethyl propiolate **40** afforded (*E*)-β-fluoroacrylate **41** stereoselectively in 51% yield (Scheme 18).[56]



40 **41**

Scheme 18

Thermolysis of alkyl-substituted (*E*)-alkenyl(phenyl)-iodonium tetrafluoroborates **42** in chloroform gave the corresponding (*Z*)-fluoro olefins as the main products. Although an addition–elimination sequence appears likely at first sight, the authors suggest an S_N2 mechanism (Scheme 19).[57]



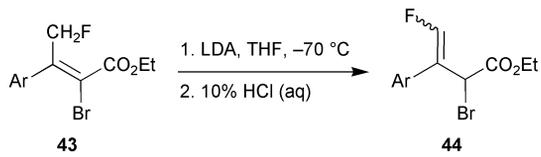
R = Me, Bu^t, n-C_8H_{17}

Scheme 19

4.2 Isomerisation of allylic fluorides

Fluoro olefins can be obtained from allyl fluorides through migration of the double bond. The most simple example of such a reaction is the conversion of allyl bromide into 1-fluoropropene by heating with KF, and subsequent iodine-catalysed equilibration.[58]

Base-induced conversion of allylic fluorides into fluoro olefins is most easily achieved if the allylic protons are more acidic than those geminal to the fluorine, as in 4-fluorocrotonates. With nucleophilic fluorination (by KF[59] or KHF_2)[60] as a key step, 4-fluorobut-2-enoate **43** was prepared. This was deconjugated into 4-fluorobut-3-enoate **44** using LDA, with 70% conversion (Scheme 20). Interpretation of the results was hampered by extensive formation of by-products in successive steps.[61] The yield of the initial fluoro olefin amounted to about 55%.

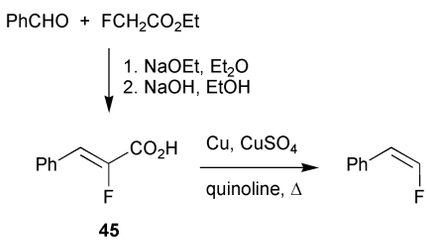


Scheme 20

5 Decarboxylative procedures

5.1 Decarboxylation of α-fluorocinnamic acid and related reactions

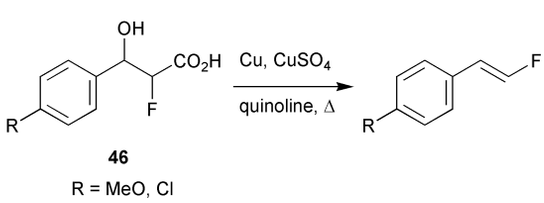
α-Fluorocinnamic acid **45** was converted into β-fluorostyrenes with *retention of configuration*, by heating in the presence of copper, in 75% yield (Scheme 21).[62] Decarboxylation of α-



Scheme 21

fluorocinnamic acid proceeded much faster for the (*E*)-isomer than for the (*Z*)-isomer.[62b] Various *para*-substituted (*Z*)-β-fluorostyrenes were prepared in the same manner.[62c] A route for the conversion of α-fluoroacrylic acids into fluoro olefins with *inversion of configuration* will be treated in Section 7.3.

Some *para*-substituted (*E*)-β-fluorostyrenes were not accessible through the related cinnamic acids. However, treatment of α-fluoro-β-hydroxyacids **46** with copper gave the desired products with 85–90% (*E*)-stereoselectivity (Scheme 22).[62c]

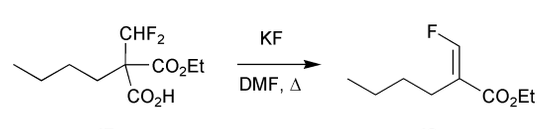


R = MeO, Cl

Scheme 22

5.2 Decarboxylative dehydrofluorination

Malonates can be alkylated with chlorodifluoromethane to form difluoromethylmalonates. In the synthesis of fluorinated prostaglandin derivatives, decarboxylation of malonic acid monoethyl ester **47** under basic conditions was accompanied by defluorination to yield β-fluoroacrylic acid **48** almost quantitatively (Scheme 23).[63] This method has also been applied in routes towards fluoroallylamines[64] and 3-fluoro-2-methylprop-2-enyl acetate.[65] Dimethyl difluoromethylmalonates can be decarbalkoxylated with loss of fluoride by use of lithium iodide in DMF.[66]



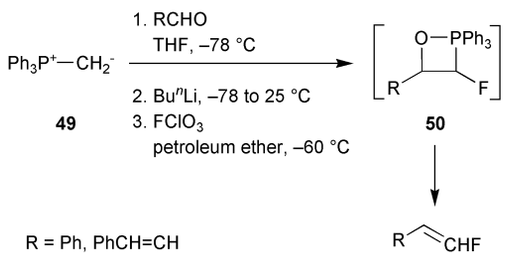
Scheme 23

6 Wittig-type reactions

The most widely applied reaction for the formation of carbon–carbon double bonds from carbonyl compounds must be the Wittig olefination employing phosphonium ylides, and the related Horner reactions using phosphine oxide or phosphonate anions. Indeed, these reactions have been popular as key-steps in the formation of fluoro olefins. Attention will first be focused on Wittig-type reactions in which fluoro olefins are formed accompanied by loss of the oxidised phosphorus moiety. Much of this work has already been included in a review.[10]

6.1 Fluorination of Wittig intermediates

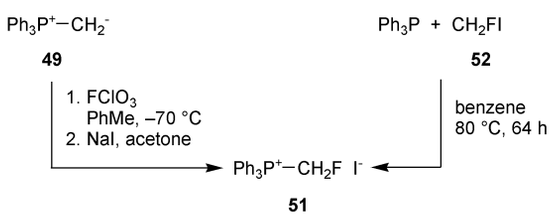
In the first synthesis of monofluoro olefins (and dienes) through a Wittig reaction, the fluorine atom was introduced *after* reaction of ylide **49** with the aldehyde. The intermediate[67] obtained after reaction with the aldehyde was deprotonated, and treated with the hazardous reagent perchloryl fluoride ($FClO_3$) to give fluorinated intermediate **50**, yielding the fluoro olefin in 25–60% yield (Scheme 24).[68]



Scheme 24

6.2 (Fluoromethyl)triphenylphosphonium salts

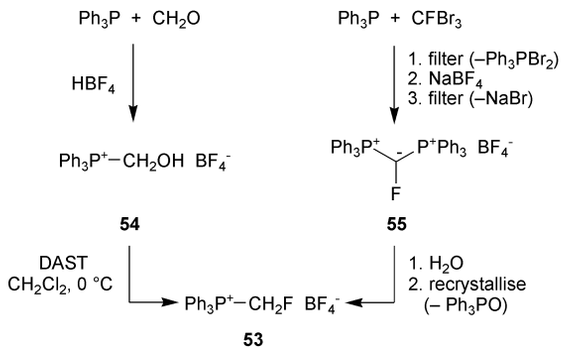
Initial routes towards (fluoromethyl)triphenylphosphonium iodide **51** were not attractive, because they used either perchloryl fluoride,[69] or fluoroiodomethane **52**[70] (which is difficult to prepare), even though yields were 80 and 86% respectively (Scheme 25).The deuterated Wittig salt has been prepared by treatment with basic D_2O.[71]



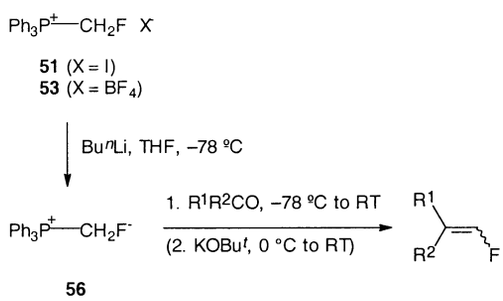
Scheme 25

A major synthetic improvement was the preparation of (fluoromethyl)triphenylphosphonium tetrafluoroborate **53**. Two high-yielding routes were reported: one based on fluorination of hydroxymethylphosphonium salt **54** with DAST (88% yield); the other on hydrolysis of bisphosphonium species ('phosphoranium salt') **55**, obtained from triphenylphosphine and tribromofluoromethane (80–90% yield) (Scheme 26).[72]

Deprotonation of phosphonium salt **51**[69–71] or **53**[73] with *n*-butyllithium to form ylide **56**, followed by addition of the carbonyl compound gave fluoro olefins with (*E*) : (*Z*) ratios invariably near unity. Yields were improved by addition of KOBu^t after betaine formation (Scheme 27),[70,74] or by a cunning simultaneous generation of benzaldehyde and ylide **56**.[75] Yields of up to 91% have been obtained.[74,75] Prolonged exposure of fluoro olefins to *tert*-butoxide to complete the Wittig reaction was reported to lead to a lowering of the yield.[70]



Scheme 26



reaction conditions, R^1R^2CO:
from **51**, without KOBu^t:
3-tetrahydropyranyloxy-Δ^5-androsten-17-one, benzaldehyde, 3-trifluoromethylbenzaldehyde, 3-chlorobenzaldehyde, *n*-hexanal
from **51**, with KOBu^t:
α,α,α-trifluoroacetophenone, acetophenone, benzophenone, cycloheptanone, *n*-heptanal
from **53**, without KOBu^t:
(2*S*)-methyl *N*-(*tert*-butoxycarbonyl)-4-oxoprrolidine-2-carboxylate
from **53**, with KOBu^t:
3-*n*-hexylcyclobutanone, 3,3-di(ethylthio)cyclobutanone, 2-dimethylaminomethyl-1-oxo-1,2,3,4-tetrahydronaphthalene

Scheme 27

This Wittig reaction has not been used to prepare 1-fluoro-1,3-dienes directly, but it was recently applied as a key step in a multi-step synthesis towards such compounds.[76]

As well as the pure Wittig salt **53**, a 1 : 1 'instant ylide' mixture of tetrafluoroborate **53** and KH, generating the ylide when dissolved in methyl *tert*-butyl ether, can be stored at −25 °C without decomposition for extended periods of time.[77]

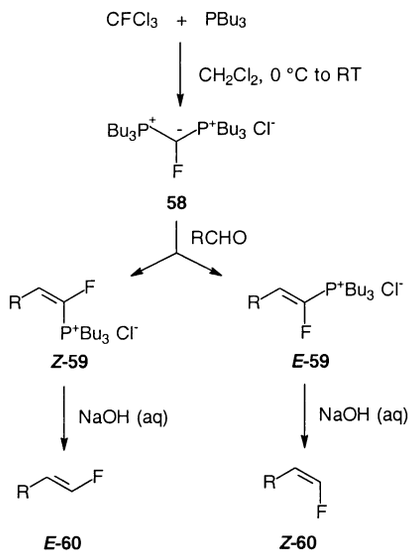
6.3 Fluoroiodomethyl(triphenyl)phosphonium iodide

Before the fluoromethylphosphonium salt was available through an attractive route, (fluoroiodomethyl)triphenylphosphonium iodide **57** was developed as an alternative. Dehalogenation with zinc–copper couple yielded ylide **56** (Scheme 28), which appeared to be less reactive than when generated from the fluoromethyl salt. It gave slightly higher yields in a few cases.[70]

Scheme 28

6.4 Bis(tributylphosphonio)fluoromethyl chloride

By reacting trichlorofluoromethane (CFC-11) with three equivalents of tributylphosphine, bis(tributylphosphonium) ('phosphoranium') salt **58** was formed.[78] Addition of aldehydes provided α-fluorovinylphosphonium species **59** in yields of 75–90%.[79] Basic hydrolysis yielded, as expected,[80] the corre-



R = *n*-C_6H_{13} (**a**), *n*-C_7H_{15} (**b**), *n*-C_9H_{19} (**c**), *c*-C_6H_{11} (**d**), 3,4-$(MeO)_2C_6H_3CH_2$ (**e**), $Br(CH_2)_4$ (**f**), Ph (**g**), 3-MeC_6H_4 (**h**), 4-MeC_6H_4 (**i**), 4-$MeOC_6H_4$ (**j**), 4-FC_6H_4 (**k**) 4-ClC_6H_4 (**l**), 3-$CF_3C_6H_4$ (**m**), 2-MeC_6H_4 (**n**), 2-$MeOC_6H_4$ (**o**), 2-ClC_6H_4 (**p**), 3,4-$(OCH_2O)C_6H_3$- (**q**), 4-$Me_2NC_6H_4$ (**r**), PhCH=CH- (**s**) (see text for stereochemical details)

Scheme 29

sponding olefins (Scheme 29). Formation of intermediates **59** and fluoro olefins **60** occurred with excellent selectivities,‡ resulting in sole formation of (*Z*)-olefins ***Z*-60a–f** from aliphatic aldehydes,[79,81] and predominantly (*E*)-olefins ***E*-60g–q** from benzaldehydes,[79,81c–e] with isolated yields up to 77%.[79,81]

The selectivity was explained by proposing that for formation of intermediates **59**, energetically favourable transition states **61** were governed by steric factors for aliphatic aldehydes (**61-*trans***), while with aromatic aldehydes, the other isomer (**61-*cis***) was favoured because of an intramolecular charge-transfer complex between the benzene ring and a phosphonium group (Fig. 4).[79] A curious exception was 4-dimethylaminobenzalde-

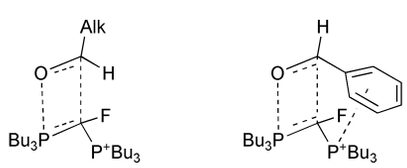


Fig. 4

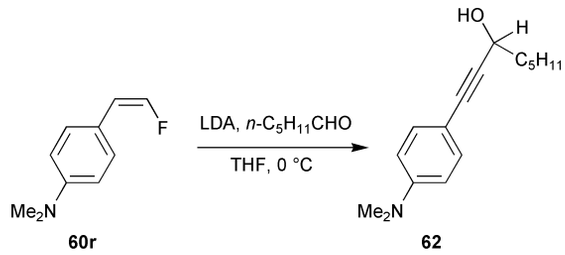
hyde, which afforded the (*Z*)-β-fluorostyrene ***Z*-60r**.[81c] The (*E*) : (*Z*) ratio of the unstable cinnamaldehyde derivative **60s**, only analysed by GC, was unknown.[81d]

The use of CFC-11 in this reaction, followed by transformation of the fluoro olefins into propargylic alcohols such as **62** by reaction with LDA and an aldehyde, has been proposed as a decomposition method of this controlled substance (Scheme 30).[81c,d] To the best of our knowledge, bis(triphenylphosphonium) species **55**[72] has not been used as such for the synthesis of fluoro olefins.

6.5 Dialkyl fluoromethylphosphonates

Phosphonates without electron-withdrawing α-substituents tend either to lack reactivity or to resist losing the phosphorus moiety. With diisopropyl fluoromethylphosphonate, diastereo-

‡ The stereochemistry of intermediates **59** has not always been investigated, but in all cases reported the vinylphosphonium salt and olefin had related configurations.

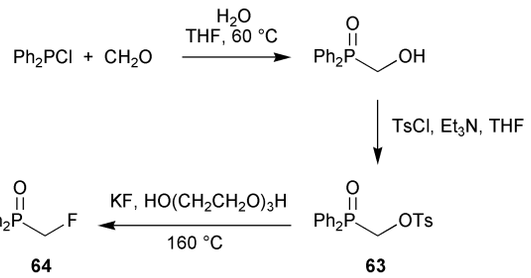


Scheme 30

meric mixtures of α-fluoro-β-hydroxyalkylphosphonates were prepared in low yields. Upon heating to 50 °C, fluoro olefins were formed; no yields were provided.[82] Much higher reactivity was found for the related phosphine oxide, which is treated next.

6.6 (Fluoromethyl)diphenylphosphine oxide

Heating toluene-*p*-sulfonate **63** with KF gave (fluoromethyl)diphenylphosphine oxide **64** in 80% yield (Scheme 31).[83]



Scheme 31

Addition of a wide range of carbonyl compounds (including α,β-unsaturated and enolisation-sensitive examples) to deprotonated **64**, and quenching of the reaction with NH_4Cl, led to isolation of α-fluoro-β-hydroxyalkylphosphine oxides **65** as diastereoisomeric mixtures in 45–94% yield. These (usually) stable and crystalline compounds were often separable. Treatment with sodium or potassium base yielded the fluoro olefins stereoselectively in yields up to 91% (Scheme 32). Highest yields were found for the formation of (*Z*)-isomers, and for compounds carrying electron-donating β-substituents, while competition by formation of phosphinoyl epoxides or ketones was responsible for the lower yields found in some cases.[83]

An earlier report[84] on (fluoromethyl)diphenylphosphine oxide **64** was shown to be erroneous.[83]

7 Reductions of polyfluorinated alkenes

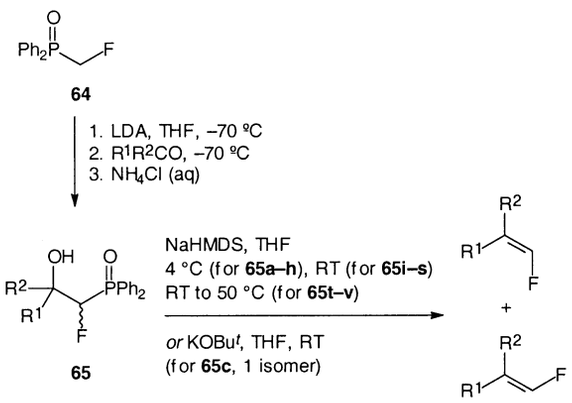
Polyfluorinated alkenes are often more easily accessible than fluoro olefins. This makes it interesting to find selective reductions to transform the former into the latter.

7.1 Reduction of allylic trifluorides

After polyfluoroalkenes containing an allylic trifluoromethyl group had already been reduced to fluoro olefins,[85] sodium 2-(trifluoromethyl)acrylate **66** was reduced with excess $LiAlH_4$ at −78 °C through the intermediate β,β-difluoromethacrylic acid **67** to β-fluoromethacrylic acid **68** in 46% yield (Scheme 33).[86]

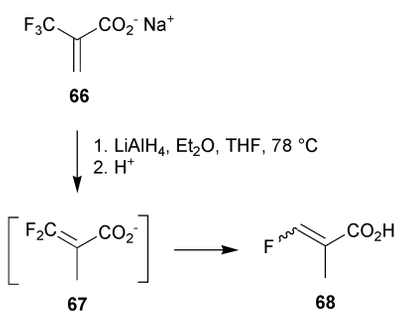
7.2 Reduction of 1,1-difluoromethylene groups

Obviously, reduction of 1,1-difluoroalkenes[5,10] could be a powerful tool to obtain fluoro olefins. Various hydride donors have been applied, the choice of which is governed by the other functional groups present in the molecule. Generally, high yields and (surprisingly) high stereoselectivities were obtained.



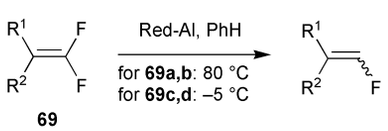
R1R2CO = *p*-dimethylaminocinnamaldehyde (**a**), cyclododecanone (**b**), 2-phenylcyclohexanone (**c**), 4-*t*-butylcyclohexanone (**d**), acetophenone (**e**), 9-fluorenone (**f**), (*R*)-carvone (**g**), 2-adamantanone (**h**), decanal (**i**), benzaldehyde (**j**), 2-chlorobenzaldehyde (**k**), 4-methoxybenzaldehyde (**l**), 4-biphenylcarboxaldehyde (**m**), 4-nitrobenzaldehyde (**n**), 2-pyridinecarboxaldehyde (**o**), 3-(2-furanyl)acrolein (**p**), benzyloxyacetaldehyde (**q**), 3-phenylpropionaldehyde (**r**), *Ent*-Garner's aldehyde (**s**) 1-phenylcyclopropylcarboxaldehyde (**t**), α,α,α-trifluoroacetophenone (**u**), methyl benzoylformate (**v**)

Scheme 32



Scheme 33

Sodium bis(2-methoxyethoxy)aluminium hydride (Red-Al) in benzene was found to be more reactive than $LiAlH_4$ in THF for the conversion of unfunctionalised difluoroalkenes **69** into fluoro olefins, in 71–96% yield (Scheme 34).[87] Reflux conditions

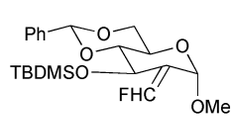


69

R^1, R^2 = *n*-C_6H_{13}, H (a); *n*-$C_{10}H_{21}$, H (b); Ph, H (c); Ph, Me (d)

Scheme 34

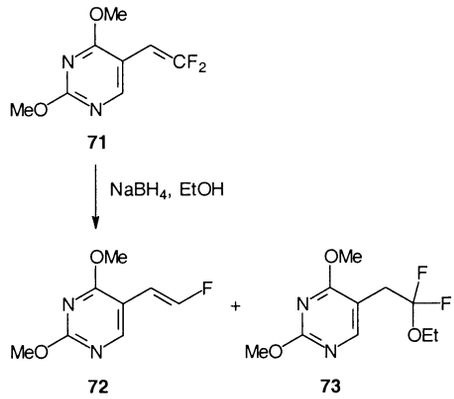
were needed for reduction of compounds **69a**,**b**, while phenyl-substituted **69c**,**d** were readily converted at −5 °C. This method was shown to be readily applicable to obtain 2-fluoromethylene 2-deoxyglucose derivative **70** as a single isomer (Fig. 5).[88]



70

Fig. 5

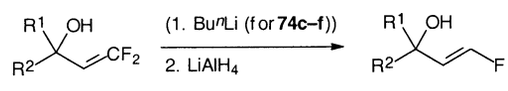
Difluorovinylpyrimidine **71** was selectively reduced with borohydride to the (*E*)-monofluoro derivative **72** in 57% yield. Addition of ethanol to the double bond produced major side product **73** (Scheme 35).[89]



Scheme 35

Difluoromethylene groups are much more prone to reduction if they are part of a 3,3-difluoroallyl alcohol or 3,3-difluoroacrylate, probably because of activation of the reducing agent by complexation with the oxygen.

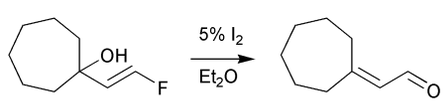
The reduction of 3,3-difluorinated allyl alcohols **74** to monofluorinated **75** was performed with high (*E*)-selectivity (Scheme 36).[90] The reaction occurred through an addition–



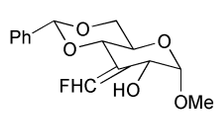
R^1,R^2 = Me_2C=$CHCH_2CH_2C$(Me)=$CHCH_2CH_2$-, Me (**a**); -CH_2-*o*-C_6H_4-CH_2CH_2- (**b**); *n*-C_6H_{11}, H (**c**); -$(CH_2)_6$- (**d**); 2-thienyl, H (**e**); (*E*)-*n*-$C_5H_{11}CH$=CH-, H (**f**)

Scheme 36

elimination reaction.[90a] Competitive S_N2' substitution of the hydroxy group, as reported for the reaction with $NaBH_4$, was avoided by prior deprotonation.[90b,c] Fluoroallyl alcohols **75c–f** were stored in dilute form, as they were reported to undergo a variety of allylic migrations.[46c,90b,c] This reactivity was applied in the formation of α,β-unsaturated aldehydes such as **76**, in a reaction catalysed by iodine (Scheme 37).[90b] 3-Fluoromethylene 3-deoxyglucose derivative **77** (Fig. 6) was obtained as a 3 : 2 isomeric mixture by reduction with Red-Al.[91]



Scheme 37

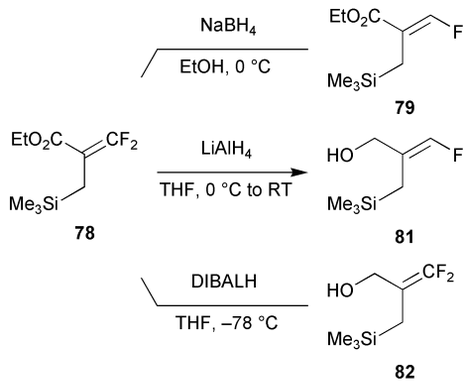


77

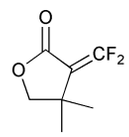
Fig. 6

The action of various reducers has been investigated for α-difluoromethylene ester **78** (Scheme 38).[92] It was converted into monofluoromethylene ester **79** in 97% yield with good stereoselectivity (*E* : *Z* = 12 : 88) by reduction with $NaBH_4$ (which is too weak to reduce the ester function).[92b] Likewise, α-(difluoromethylene)lactone **80** (Fig. 7) was reduced stereoselectively without reduction of the ester functionality.[93]

With the stronger reducer $LiAlH_4$, (*Z*)-3-fluoroallyl alcohol **81** was formed, probably through reduction of the ester function to the difluoroallyl alcohol, followed by defluorination (note that the reverse order was suggested by the authors).[92a] The compound was isolated as the acetate ester in 60% yield.[92b]



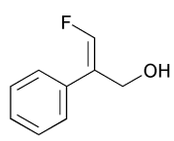
Scheme 38



80

Fig. 7

While DIBAL-H was able to reduce the ester, the difluoromethylene group was kept intact, resulting in alcohols **82**.[92] However, along with 34% of the difluorinated alcohol, monofluorinated (*E*)-2-phenylallyl alcohol **83** was formed in 28% yield by DIBAL-H reduction of a difluorinated ester precursor (Fig. 8).[94]

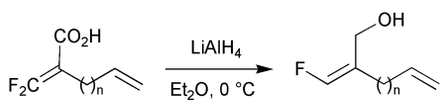


83

Fig. 8

The stereoselectivity found for the reduction of **78** by $NaBH_4$ and $LiAlH_4$ was explained by an Si ··· F interaction.[92] Note, however, that $NaBH_4$ reductions of pyrimidine **71**[89] and lactone **80**[93] also occurred stereoselectively, and that the hydroxymethylene and fluorine groups are found in a *trans*-position in 3-fluoroallylic alcohols **75**[90] and **83**[94] as well.

As an exception to this rule, reduction of 2-(difluoromethylene)-(ω − 1)-alkenoic acids **84** with $LiAlH_4$ at 0 °C was reported to afford (*Z*)-fluoro olefins **85** preferentially (Scheme 39).[95] The reason for this selectivity was assumed to be



84 *n* = 1,2 **85**

Scheme 39

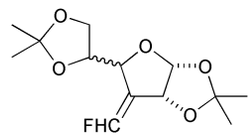
a favourable interaction between the fluorine atom and the hydroxy group. A more likely explanation is that the difluoromethylene group is reduced first (*cf.* Section 7.1), with (*Z*)-selectivity induced by favourable interactions of both the carboxylate and the fluorine with the aluminium ion.[96]

7.3 Reduction of other 1-halo-1-fluoromethylene compounds

1-Bromo- and 1-chloro-1-fluoroalkenes have been reduced to yield the corresponding fluoro olefins. New methods towards 1-bromo-1-fluoroalkenes may revive interest in these reductions.[97] Generally, the reactions are stereoselective, but obtaining stereochemically pure starting compounds may be challenging.

Lithiation of (*E*)- or (*Z*)-1-bromo-2-phenyltetrafluoropropene with Bu^nLi yielded the anion, which was protonated by water to give the corresponding fluoro olefin in 80–92% high yield.[98]

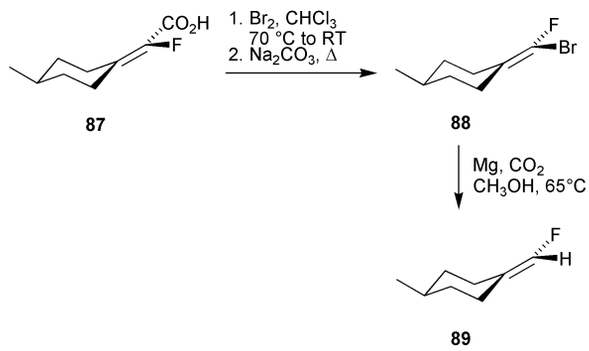
Chlorofluoromethylene-containing sugars were reduced in 37–57% yields to the fluoromethylene compounds **86** (Fig. 9) using $LiAlH_4$.[99]



86

Fig. 9

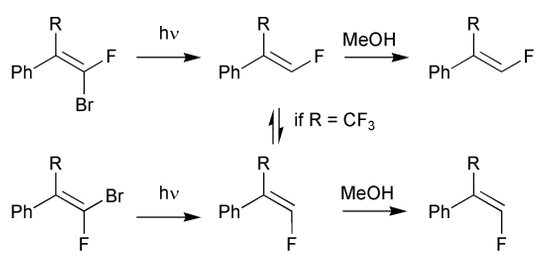
To synthesise an enantiomerically pure fluoroalkene, α-fluorinated α,β-unsaturated acid **87** was converted into 1-bromo-1-fluoroalkene **88** in 55% yield by means of a bromination–decarboxylative dehydrobromination procedure. Bromofluoro olefin **88** could be reduced with magnesium in methanol to give fluoro olefin **89** with inversion of the configuration with respect to the acid, in 69% yield (Scheme 40).[100]



87 **88** **89**

Scheme 40

Reductions through α-fluorovinyl radicals usually occur stereoselectively.[101] In kinetic studies, Bu_3SnH–AIBN in benzene[101a] and irradiation at 248 nm in methanol[101c] were used to convert both isomers of β-bromo-β-fluorostyrene **90a** stereoselectively into β-fluorostyrene **92a** (Scheme 41). Isomerisation was only noted when radical **91** was destabilised, as in the case of β-bromo-β-fluoro-α-(trifluoromethyl)styrene **90b**.[101c] Stereoselective reduction with Bu_3SnH–AIBN of ethyl β-bromo-β-fluoroacrylate proceeded in 85% yield.[101b]



90 **91** **92**

R = H (**a**), CF_3 (**b**)

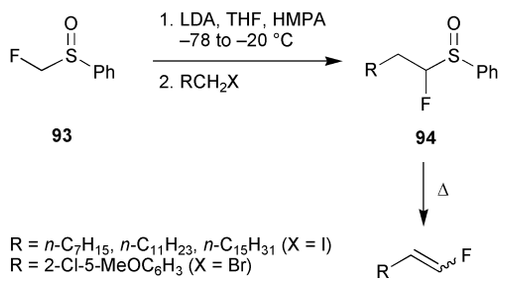
Scheme 41

8 Syntheses involving α-fluoroalkyl sulfur compounds

α-Fluoroalkyl sulfur compounds have found broad application in the synthesis of fluoro olefins. However, elimination of the sulfur moiety to yield the fluoro olefin is not trivial. The methods developed to deal with this problem will be treated here.

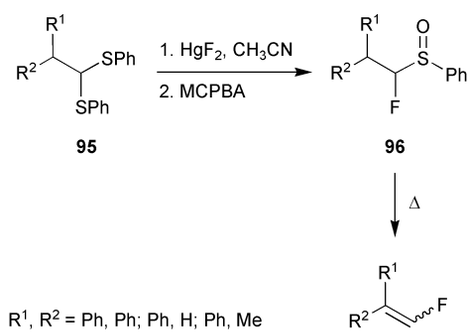
8.1 Thermal sulfoxide eliminations

The synthesis of α-fluoroalkyl sulfur reagents was very dependent on high-yielding routes towards α-fluoroalkyl sulfides. The original synthesis of α-fluoromethyl phenyl sulfide used nucleophilic substitution of chlorine by fluorine.[102] Fluoromethyl phenyl sulfoxide **93**, obtained by mono-oxidation, was alkylated to give α-fluoroalkyl sulfoxides **94** in 60–85% yield, offering fluoro olefins through pyrolysis in 73–95% yield (Scheme 42).[103]



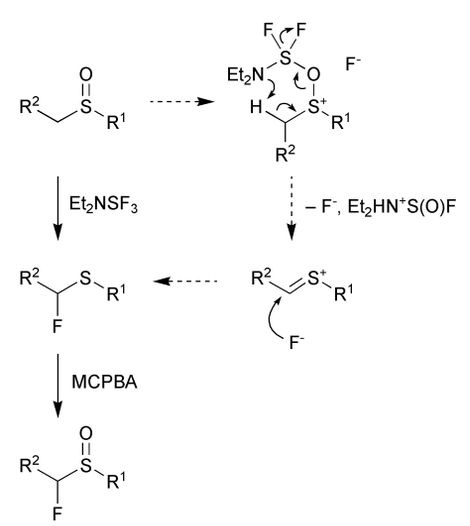
Scheme 42

From dithioacetals **95**, α-fluoroalkyl sulfoxides **96** were obtained in 48–86% yield through treatment with HgF_2 and mono-oxidation. Pyrolysis gave fluoro olefins in yields of 38–80% (Scheme 43).[104]



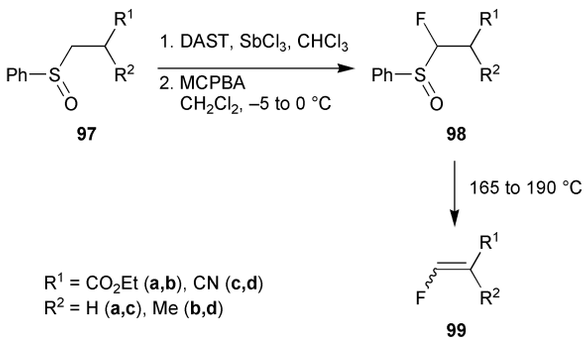
Scheme 43

The most high-yielding synthesis of α-fluorinated sulfides is the deoxygenative fluorination of alkyl sulfoxides with DAST (Scheme 44).[105] Use of a Lewis acid catalyst, like zinc iodide[105] or especially antimony trichloride,[106] was often (but not always) advantageous. Consecutive mono-oxidation provided the sulfoxides in yields of up to 100%.



Scheme 44

While pyrolysis was usually conducted in a sealed tube,[103–105] such forcing conditions were not always required. For example, sulfoxides **97** could be converted to fluorinated derivatives **98**, which afforded β-fluoroacrylate derivatives **99** in 67–85% yield by immediate distillation from the reaction mixture (Scheme 45).[107] Aristeromycin analogue **100** (Fig. 10) was obtained as a 1 : 1 *E*–*Z*-mixture by thermolysis in the presence of ethyldiisopropylamine.[108]



Scheme 45

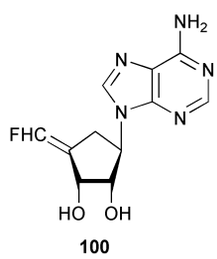
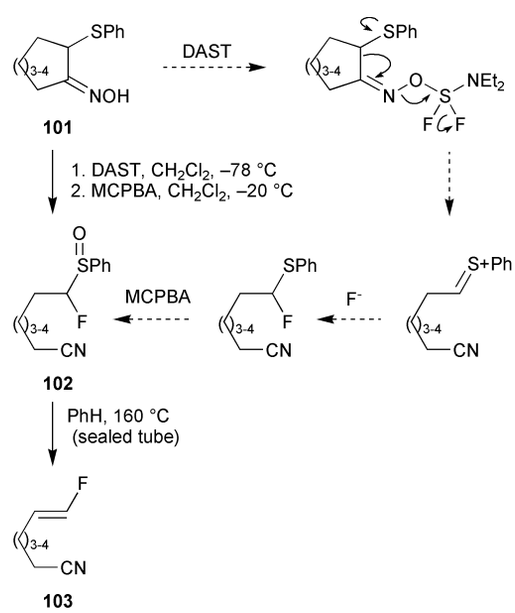


Fig. 10

Deoxygenative fluorination of α-phenylthiocycloalkanone oximes **101** was accompanied by ring-opening, yielding cyanoalkyl sulfoxides **102** after mono-oxidation. Pyrolysis proceeded cleanly to afford ω-cyanoalkenyl fluorides **103** in 46–73% yield over three steps (Scheme 46).[109]

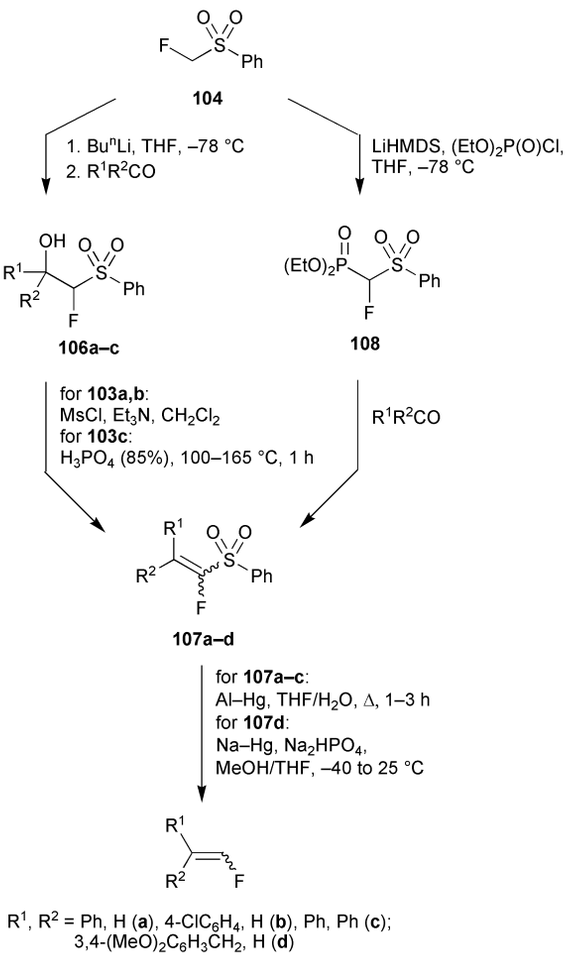


Scheme 46

8.2 Amalgam-promoted desulfurisations

To avoid the high temperatures needed for sulfoxide elimination, fluoromethyl sulfone **104**[110] and fluoromethyl sulfoximine **105**[111] were developed, both prepared through the DAST protocol.

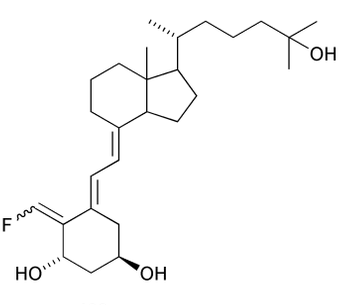
Initially, fluoromethyl sulfone **104** was condensed with carbonyl compounds to yield β-hydroxy compounds **106**, which were converted into 1-fluorovinyl sulfones **107a**–**c** in 67–92% overall yield by mesylation in the presence of base or acidic dehydration.[110a] More recently, sulfone **104** was converted into phosphonate reagent **108** to react with carbonyl compounds in a two-step, one-pot procedure to form α-fluorovinyl sulfones **107c**,**d**.[81a,110b] Yields of up to 100% have been achieved.[112] Reduction of (*E*)-fluorovinyl sulfones ***E*-107a**–**c** with aluminium amalgam produced fluoro olefins in 90% yield, as 1 : 1 *E*–*Z*-mixtures.[110] With sodium amalgam, fluoro olefins were obtained in 70% yield from isomeric mixtures of **107d**, with *E*-isomers apparently somewhat favoured (Scheme 47).[81a] A



Scheme 47

more efficient route based on 1-fluorovinyl sulfones **107** will be treated in Section 8.3.

Recently, vitamin D analogue **109**, a fluorinated triene (Fig. 11), was prepared by sodium amalgam reduction of an α-hydroxy-β-sulfonyl intermediate as the key step, after synthesis *via* reduction of a 1-fluorovinyl sulfone had failed.[113] Yields

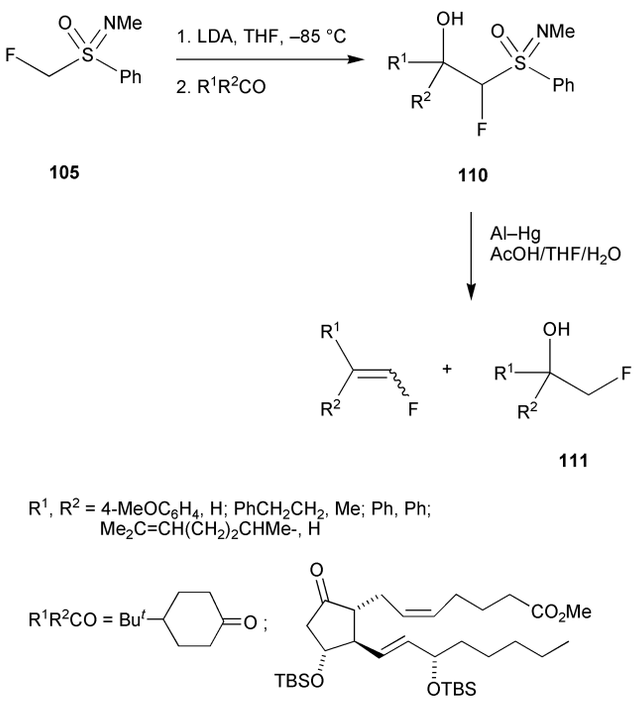


109

Fig. 11

of such reductions were low (24–32%), because of competing formation of fluorohydrins. This reactivity is similar to that of fluoromethyl sulfoximine **105**, which will be described next.

Reaction of sulfoximine **105** with carbonyl compounds yielded β-hydroxy adducts **110**. These could be converted into fluoro olefins in one step, in up to 92% yield, by reduction with aluminium amalgam. Yields were reduced by competing formation of fluoro alcohols **111**, in up to 36% yield (Scheme 48).[111]



Scheme 48

8.3 Tributylstannylation of α-fluorovinyl sulfones

Stannylation of α-fluorovinyl sulfones **107**, prepared from the *in situ* synthesised phosphonate **108**, provides one of the highest-yielding routes to fluoro olefins. The protonated form of intermediate **108**[114] was isolated for a two-pot procedure.[115] In an AIBN-initiated reaction with tributyltin hydride, α-fluorovinylstannanes **112** were formed stereoselectively from ketone derivatives,[112,115,116] but with steric mixing for aldehyde derivatives.[81a,112,117] Yields were typically 72–96%. Treatment of stannanes **112** with base (sodium methoxide,[112,116a,c,d] ammonia–methanol or ammonia–methanol–CsF,[112,116a,b] TBAF–THF[81a,116d,117]) afforded the corresponding fluoro olefins in 64–100% yield without a change in the isomeric ratio. Typical examples[112] of the reaction sequence are given in Scheme 49.

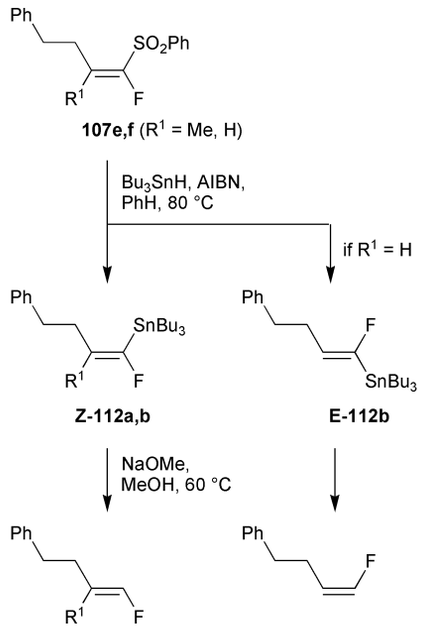
Fluorinated di- and trienes are apparently not accessible by this route;[114] 1-fluoroethenyl phenyl sulfone lost its fluorine atom instead of the sulfonyl group.[112]

(*E*)-Fluoromethylene-2′-deoxy-2′-cytidine (MDL 101,731) **113**, a potent anti-tumour agent,[115,116a,b] as well as acyclic nucleoside analogues **114**[116d] have been prepared in this way (Fig. 12).

8.4 Other sulfoxide eliminations

Diethyl difluoromethyl(α-methylsulfinyl)malonate **115** yielded unstable fluoromethylenemalonate **116** upon treatment with triethylamine, probably initiated by deprotonation of the methyl sulfoxide (Scheme 50).[118]

Chlorofluoromethyl phenyl sulfide **117**, obtained from dichlorofluoromethane and thiophenol, has been used to prepare various α-fluorinated sulfoxides. α-Chloro-α-fluoroalkyl sulfoxides **118** reacted with Grignard reagents to give *cis* fluoro olefins,[119] while desulfinylation of α-fluorovinyl sulfoxides



Scheme 49

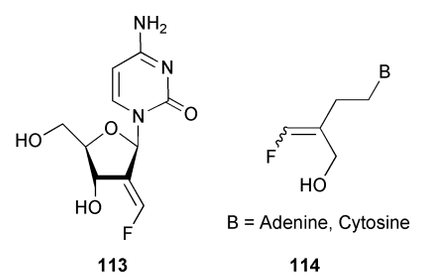
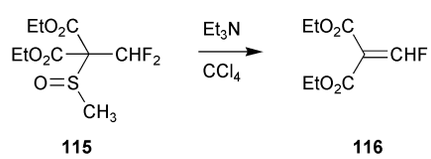


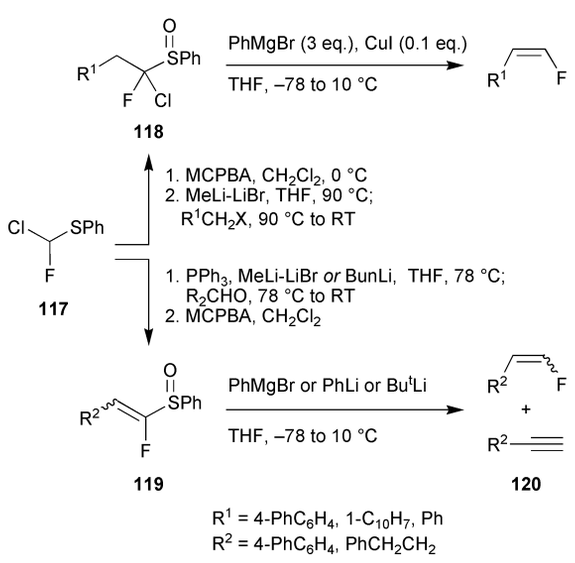
Fig. 12



Scheme 50

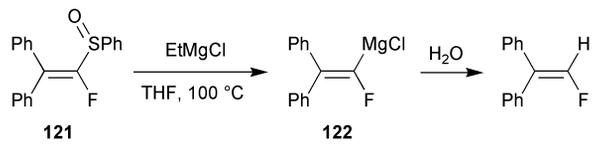
119[120] gave mixtures of fluoro olefins as minor products, with formation of alkynes **120** being favoured (Scheme 51).[119b]

1-Fluoro-2,2-diphenyl-1-(phenylsulfinyl)ethene **121** could be converted to α-fluorovinylmagnesium chloride **122**. Proteolysis



Scheme 51

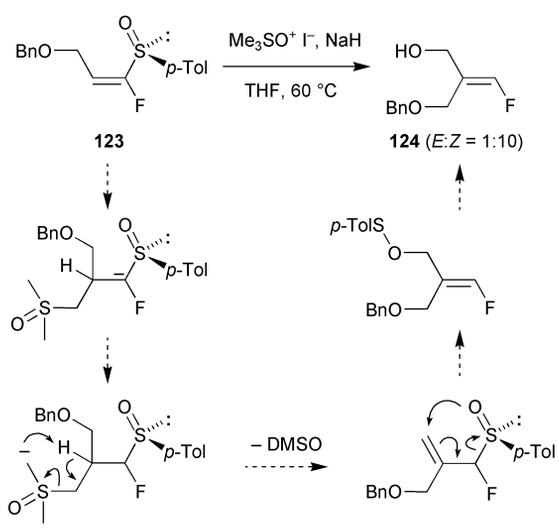
gave the fluoro olefin in 88% yield (Scheme 52).[121] This reaction failed for the corresponding cyclopentadecanone derivative.



Scheme 52

Finally, 1-fluorovinyl sulfoxides can also be desulfurised electrochemically. 1-Fluoro-2-arylvinyl sulfoxides gave the corresponding fluoro olefins in up to 70% yield.[122]

The allyl sulfoxide ⟶ allyl sulfenate rearrangement could also be a possibility for removal of the sulfoxide function. This likely was the decisive step in the unexpected transformation of 1-fluorovinyl sulfoxide **123** into 3-fluoroallyl alcohol **124** by treatment with dimethyl sulfoxonium methylide, which occurred in 59% yield (Scheme 53).[123]



Scheme 53

8.5 Retro-cycloaddition of fluorinated sulfones

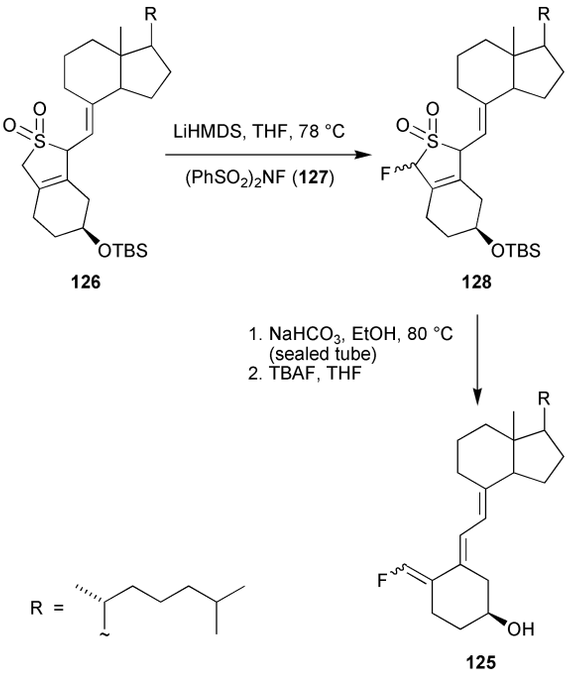
A different approach involving sulfones has been used in the synthesis of fluorinated vitamin D analogue **125**. Sulfur dioxide adduct **126** was regioselectively deprotonated, and fluorinated with *N*-fluorobenzenesulfonimide (NFSI) **127** to give compound **128** in 51% yield. Sulfur dioxide was readily expelled through thermolysis, restoring the, now fluorinated, triene function (Scheme 54).[124]

9 Fluoroallene cycloadditions[9]

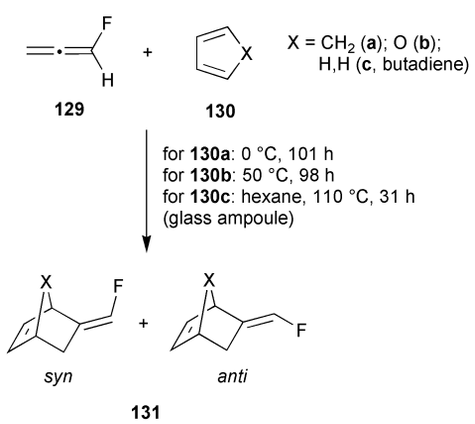
A large number of compounds containing exocyclic fluoromethylene groups have been synthesised by cycloadditions of (mono)fluoroallene **129** (MFA), which was prepared in five steps from dibromofluoromethane and ethene in 8.5% overall yield.[125] MFA will engage in [4+2], [2+2] and [3+2] cycloadditions. Regioselectivity was in favour of fluoro olefin formation in most cases (*i.e.* cycloaddition took place at the non-fluorinated double bond). Although MFA is an interesting tool for the synthesis of fluoro olefins, it should be noted that many of these compounds, especially the heterocyclic ones, are unstable.

Treating MFA with a ten-fold excess of dienes **130** gave 46–90% yields of the Diels–Alder adducts **131**, with slight *syn*-selectivity (Scheme 55).[125,126]

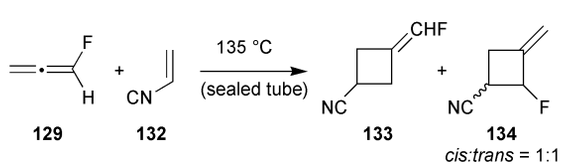
The non-concerted [2 + 2] cycloaddition of MFA with a 20-fold excess of acrylonitrile **132** to produce fluoromethylenecyclobutane **133** proceeded in only 31% yield and was accompanied by formation of fluorocyclobutanes **134** in 14% yield (Scheme 56).[127]



Scheme 54



Scheme 55

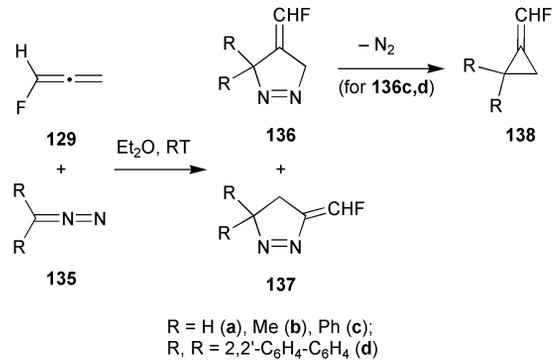


Scheme 56

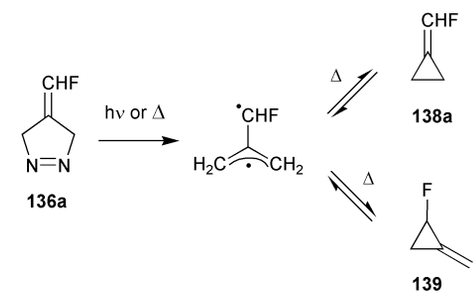
[3+2] Cycloaddition of a slight excess of MFA with diazomethane **135a** gave only unstable 4-fluoromethylene-4,5-dihydro-3*H*-pyrazole **136a** in 95% yield,[128] but with substituted diazo compounds **135b–d** 5-fluoromethylene products **137** were favoured.[129] Loss of nitrogen from adducts **136** occurred readily at room temperature, leading to fluoromethylene cyclopropanes **138** (Scheme 57).[128,130] Cyclopropane **138a**, obtained by thermolysis or photolysis of **136a**, rearranged at temperatures over 220 °C to give 1-fluoro-2-methylenecyclopropane **139** (Scheme 58).[128a,130]

Nitrile oxides **140** gave unstable isoxazoles **141** with high regio- and stereoselectivity for R = Mes, but for R = Ph, a mixture also containing isoxazole **142** was obtained (Scheme 59).[129]

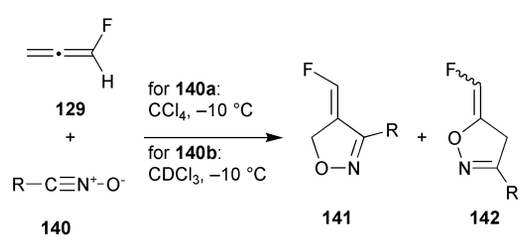
Synthetically most interesting is the reaction of MFA with nitrones **143**, which gave stable fluoromethylene isoxazolidines **144** in 83–99% yields with good *syn*-selectivity (*syn* : *anti* ratios of 3–6 : 1) (Scheme 60).[126,129,131]



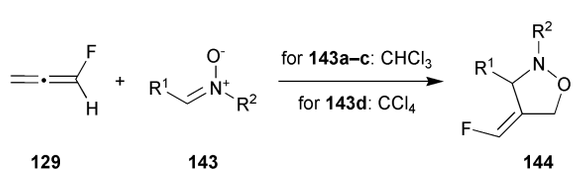
Scheme 57



Scheme 58



Scheme 59



Scheme 60

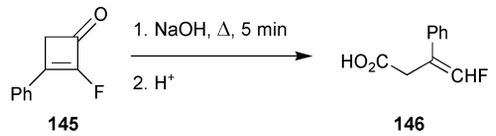
10 Ring-opening reactions and other rearrangements

Many fluoro olefins have been formed through rearrangements, but only a few cases may be synthetically useful: in many cases the synthesis of starting compounds was arduous, yields were low, or the products could be obtained with more ease by other synthetic routes. However, because of the interesting chemistry involved in quite a few cases, we have tried to give a broad overview. Some examples may indeed show the synthetic potential of these reactions.

10.1 Ring-opening of cyclic ketones

An early example of a ring-opening reaction leading to a fluoro olefin was presented in the alkaline hydrolysis of 2-fluoro-3-phenylcyclobut-2-enone **145** affording 4-fluoro-3-phenylbut-3-enoic acid **146** in 33% yield after crystallisation (Scheme 61).[132]

Photolysis of α-fluorocyclohexanone in Bu^{t}OH gave 6-fluorohex-5-enal in 8% yield, along with a larger amount of *tert*-butyl 6-fluorohexanoate (30%). The configuration of the double bond was not determined. In other solvents, no fluoro olefin was formed at all.[133]

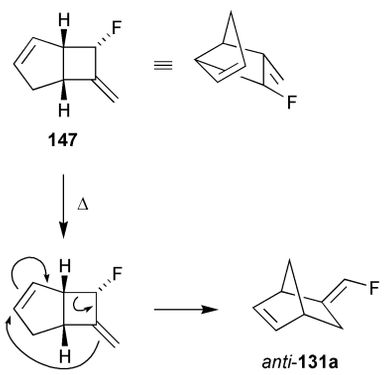


145 146

Scheme 61

10.2 Pericyclic reactions

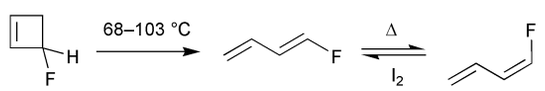
Cope-rearrangement of *endo*-7-fluoro-6-methylenebicyclo-[3.2.0]hept-2-ene **147**, synthesised in two low-yielding steps from cyclopentadiene and fluoroketene, gave (*E*)-(fluoromethylene)bicyclo[2.2.1]hept-2-ene *anti*-**131a** as the major product at low conversion (Scheme 62).[134] This compound was



Scheme 62

more easily accessible *via* cycloaddition of fluoroallene **129** to cyclopentadiene **130b** (*cf.* Scheme 55).[125]

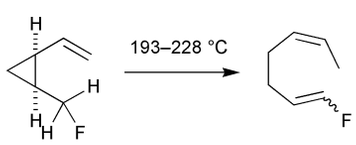
3-Fluorocyclobutene **148**, obtained through an arduous synthetic route, was pyrolysed to give (*E*)-1-fluorobuta-1,3-diene **149** as the sole product through electrocyclic ring-opening (Scheme 63). Equilibration of this compound by heating with iodine showed the (*Z*)-isomer to be somewhat more stable.[135]



148 149

Scheme 63

cis-1-(Fluoromethyl)-2-vinylcyclopropane **150** was prepared in low yield from the parent alcohol by a tosylation/fluorination procedure. Pyrolysis led to a clean mixture of dienes **151** through a 1,5-hydrogen shift (Scheme 64).[35]



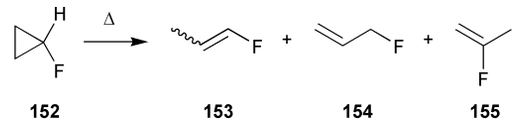
150 151

Scheme 64

10.3 Fluorocyclopropane ring-openings

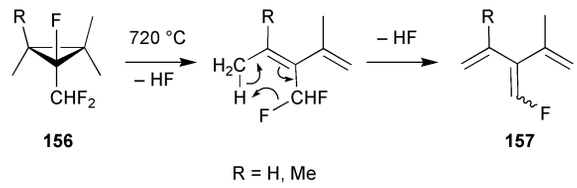
Fluorocyclopropane **152** yielded a mixture of all of the other four isomers of C_3H_5F on pyrolysis at temperatures over 400 °C, of which the 1-fluoroprop-1-enes **153** were the main products, making up 72–95% of the reaction mixture, along with allyl fluoride **154** and 2-fluoropropene **155** (Scheme 65).[136]

1-Difluoromethyl-1-fluorocyclopropanes **156**, carrying multiple methyl groups, gave trienes **157** containing a fluoromethylene group in up to 47% yields on pyrolysis. The presence of a methyl group was necessary for the final dehydrofluorination step to occur. This was explained by a concerted mechanism (Scheme 66).[137]



152 153 154 155

Scheme 65



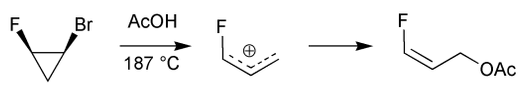
156 157

R = H, Me

Scheme 66

10.4 Rearrangements *via* cations

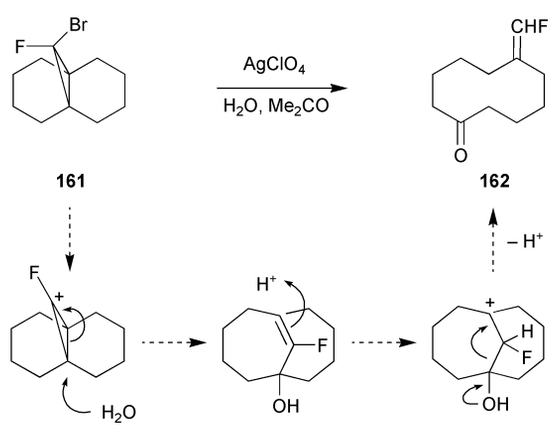
Heating *cis*-1-bromo-2-fluorocyclopropanes **158** in acetic acid led to formation of fluoroallyl cation **159**, which was trapped to give (*Z*)-3-fluoroallyl acetate **160** in 75% yield with good stereoselectivity (Scheme 67). The *trans*-cyclopropane likewise afforded the (*E*)-isomer.[138]



158 159 160

Scheme 67

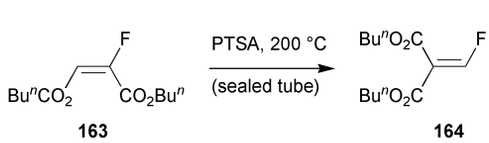
Silver perchlorate-assisted solvolysis of 11-bromo-11-fluorotricyclo[4.4.1.0^{1,6}]undecane **161**, available through a low-yielding synthesis, gave a mixture of products. The main product, formed in 28% yield, was found to be 6-fluoromethylenedecanone **162** (Scheme 68).[139]



161 162

Scheme 68

Dibutyl fluoromaleate **163** was reported to rearrange to fluoromethylenemalonate **164** upon heating with acid (Scheme 69).[140] Little evidence for its formation was presented, which is not surprising in view of the lack of stability of these compounds (*cf.* Section 4.1).[55b,118]



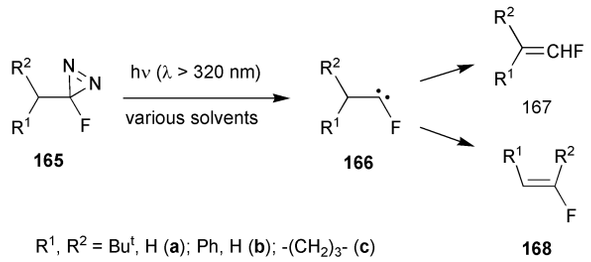
163 164

Scheme 69

10.5 Rearrangements of carbenes

Photolysis of substituted 3-fluorodiazirines **165** gave α-fluorocarbenes **166**. These rearranged to terminal fluoro olefins **167** through a 1,2-hydrogen shift. However, ring-substituted

diazirine **165c** reacted preferentially through ring expansion to give fluorocycloalkenes **168** (Scheme 70).[141]



Scheme 70

Fluoro olefins with polyfluorinated sidechains have been obtained by 1,2-hydrogen shift in an α-fluorocarbene,[142] and by 1,2-fluoride shift in a β-fluorocarbene.[143]

Conclusion

In this review, we have tried to give a broad overview of the reactions that lead to the formation of terminal monofluoro olefins. Emphasis has been put on methods that have been proven to be synthetically useful, but methods which could turn out to be routes to new synthetic procedures have also been discussed. The picture that emerges can be briefly described as follows.

In the search for pharmaceutically interesting compounds, as well as in physical organic chemistry, for comparative reasons the synthesis of both (*E*)- and (*Z*)-isomers of fluoro olefins is of interest. This may be most easily achieved *via* the Horner–Wittig route, which provides access to easily separable isomeric mixtures. On the other hand, the synthesis of single isomers in high yields is more readily achieved through the fluorinative ring-opening of epoxides, by reduction of difluoromethylene compounds, or through 1-fluorovinyl sulfone chemistry. All these routes avoid compounds which are affected by the Montreal protocol, and new routes towards fluoro olefins should be devised bearing this in mind as well.

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