A BUILDING BLOCK APPROACH TO MONOFLUORINATED ORGANIC COMPOUNDS

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Dedicated to Professor Oldřich Paleta on the occasion of his 70th birthday in recognition of his outstanding contributions to the area of organofluorine chemistry.

Building blocks for the synthesis of monofluorinated organic compounds are reviewed. The synthetic potential of polyhalomethanes, sulfur- and phosphorus-containing building blocks, difluoroethene, polyhaloethanes, fluoroacetic acid derivatives, and other compounds are described. Pericyclic reactions involving fluorinated compounds and application of the methodology of building blocks to the synthesis of monofluorinated pharmaceuticals and analogs of natural compounds are considered. The review with 317 references covers mainly the literature from 1996 through 2007.

Keywords: Fluorinated building blocks; Fluorinated organic compounds; Synthesis design.

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1. INTRODUCTION

Partially fluorinated organic compounds attract much attention when developing new drugs[1,2a] and agrochemicals[2], as well as in studying biochemical processes[3]. Thus, it is estimated that about 20% of pharmaceuticals on the market and 20–25% of drugs in the pharmaceutical pipeline contain at least one fluorine atom[1e,4]. A large number of handbooks, textbooks and monographs on this topic can serve as further evidence of significance of organofluorine compounds[5]. The high interest in fluorinated organics in drug design is explained by the possibility of modulating the pharmacological profile of the drug by introduction of fluorine atoms into the molecule, due to the deep influence of fluorine on the processes of absorption, distribution, recognition and interaction with the biological target as well as on the metabolism of the drug[1a,g]. Thus, fluorinated organics often exhibit increased metabolic stability and bioavailability[4a,1b] compared with their non-fluorinated analogues. In addition, fluorinated groups are often isosteric or isopolar to certain non-fluorinated functional groups[1a,6]. Fluorinated compounds can therefore mimic non-fluorinated counterparts in the processes of interaction with biological macromolecules[1a]. For example, C=CF is known to be an excellent mimic of the amide group[6a,f–h], while C–F mimics fragments C–OH[6c,e] and C–H[6e] or an oxygen atom in phosphonates[6d,e]. In addition, the compounds labeled by ^{18}F can be used to study biochemical transformations, drug pharmacokinetics and pharmacodynamics by the PET technique[1b,f,7]. Fluorinated organics also find application in ^{19}F NMR based physiology and pharmacology *in vivo* studies, such as gene activity investigation, determination of pH and metal ions concentrations, oxygen tension, etc.[3c].

The growing interest in fluorinated organics makes the development of synthetic procedures leading to such compounds highly desirable. This task is often rather complicated due to the difficulties of the incorporation of fluorine atom into organic molecules. One of the approaches to the synthesis of fluorinated organics implies development of methods for fluorination

of organic compounds by various fluorinating agents, both electrophilic (diluted with inert gas F_2, $FClO_3$, CF_3OF, *N*-fluoropyridinium triflate, Selectfluor, etc.), and nucleophilic (HF, $BF_3{\cdot}OEt_2$, BrF_3, XeF_2, AgF, DAST, SF_4, $R_3N{\cdot}n$HF, etc.)[8]. The main drawback of this approach is often the high price and/or toxicity of the fluorinating agent. Another approach consists in the application of simple commercially available compounds, such as halofluorocarbons, as building blocks[9], and the design of new building blocks as well. Such blocks must possess both a C–F moiety and a functional group, which can be used for the incorporation of the C–F fragment into a target molecule. The main problem of the latter approach is that the reactivity of fluorinated organics often differs seriously from that of non-fluorinated counterparts and this makes a priori predictions of their behaviour rather difficult.

A great number of original articles and reviews are devoted to the synthesis of fluorinated organic compounds. The literature up to 1997 is reviewed in the fundamental review of Percy[9]. Some examples of application of the building block methodology to the synthesis of various classes of monofluorinated compounds can be found in the reviews of Prakesch et al.[3a] (unsaturated fatty acids), Sutherland and Willis[10a], Qiu, Meng and Qing[10b] (amino acids), van Steenis and van der Gen[11a] (terminal monofluoroalkenes), Dolbier and Battiste[12a], Taguchi and Okada[12b], Fedoryński[12c] (fluorocyclopropanes). The synthesis of fluorinated organics using fluorinated organometallics has been reviewed by Shimizu and Hiyama[13a] and by Burton and Lu[13b]. The rearrangements of fluorinated compounds have been thoroughly reviewed by Percy and Prime[14]. Some examples of asymmetric synthesis of monofluorinated organics are presented in the reviews of Iseki[15], Mikami, Itoh and Yamanaka[6c]. An interesting approach towards the synthesis of fluorinated compounds based on the synthesis and application of multifunctional fluorinated carbon compounds is described in the review by Fujiwara and Takeuchi[16].

However, numerous examples of synthesis of monofluorinated organics, that appeared during the last decade, have not yet been reviewed from the point of view of application of the methodology of building blocks to the synthesis of such compounds. Such a review would be quite valuable for the evaluation of the methodology of building blocks in the synthesis of monofluorinated organics. The present review is organized in a manner that allows tracing gradual accomplishment of fluorinated units from the simplest, especially commercially available products, to quite complicated monofluorinated organics, representing potentially biologically active compounds, which would reveal the synthetic potential of the starting fluori-

nated building blocks. According to this, the review deals with compounds that are either commercially available or can be easily synthesized by the use of common laboratory techniques and that can be used as building blocks for the synthesis of monofluorinated organics. More complicated building blocks that are synthesized from such compounds are described together with their precursors. So, the synthetic potential of polyhalomethanes, sulfur- and phosphorus-containing building blocks, difluoroethene, polyhaloethanes, fluoroacetic acid derivatives and other compounds will be described. The pericyclic reactions which include the participation of fluorinated compounds will be considered as well. In addition, the application of the building block methodology to the synthesis of monofluorinated pharmaceuticals and analogues of natural compounds will be exemplified. The review covers, mainly, the literature from 1996 through 2007.

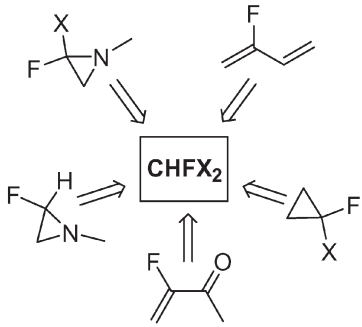
2. SYNTHETIC APPLICATIONS OF ONE-CARBON FLUORINATED BUILDING BLOCKS

One-carbon fluorinated building blocks include fluorinated halomethanes, such as $CHFCl_2$, $CHFBr_2$, $CHFI_2$, $CFCl_3$, $CFBr_3$ and CF_2Br_2, and fluorinated sulfur- and/or phosphorus-containing compounds, such as $PhSO_2CH_2F$, $(PhSO_2)_2CHF$, $PhSO_2CHFP(O)(OEt)_2$, $Ph_2P(O)CH_2F$.

Halomethanes $CHFCl_2$, $CFBr_3$ and CF_2Br_2 are commercially available. $CHFBr_2$ can be obtained in the laboratory from $CHBr_3$ and SbF_3 using a standard Swarts technique. Another way to this compound is described in ref.[17]. $CHFI_2$ can be prepared by the reaction of $CHFBr_2$ with NaI [18]. $(PhSO_2)_2CHF$ can be obtained by fluorination of $PhSO_2CH_2SO_2Ph$ with fluorine or with Selectfluor[19]. $PhSO_2CHFP(O)(OEt)_2$ can be obtained from $PhSO_2CH_2F$ and $(EtO)_2POCl$ [20a], or by fluorination of $PhSO_2CH_2P(O)(OEt)_2$ with $FClO_3$ [20b]. $Ph_2P(O)CH_2F$ can be obtained by reaction of Ph_2PCl with formaldehyde followed by tosylation and substitution of the TsO group by fluorine with KF [11a,21].

2.1. Polyhalofluoromethanes

Synthetic applications of dihalofluoromethanes (Scheme 1) utilize predominantly their ability to serve as halofluoro- or monofluorocarbene precursors. The reaction of halofluorocarbene with a C=C bond results in halofluorocyclopropane formation (monofluoro-[18a,22], chlorofluoro-[23], bromofluoro-[23d,g,24], and iodofluorocyclopropanes[18b,25]). This topic has been reviewed by many authors[9,12a,c,26].

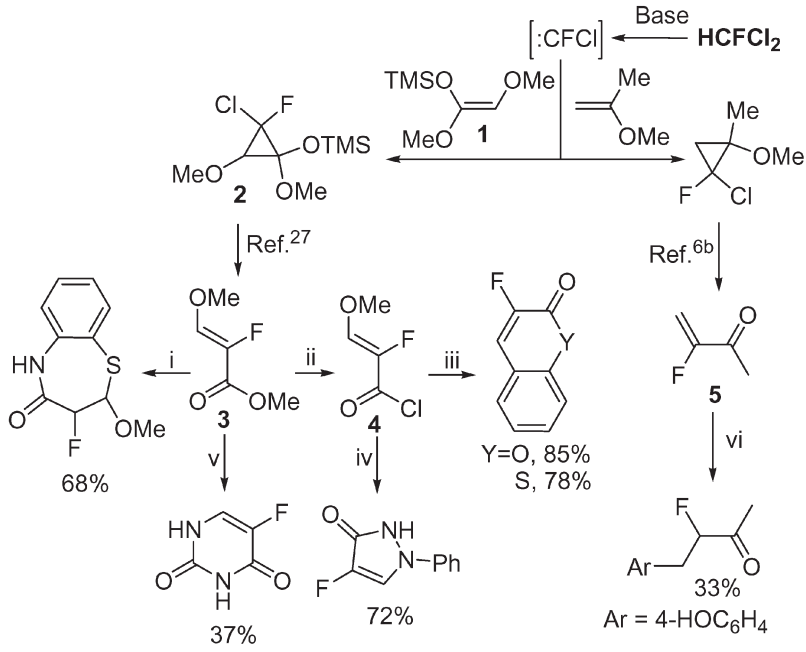


SCHEME 1

Chlorofluorocyclopropanes can be transformed into α-fluoro-α,β-unsaturated carbonyl compounds and into fluorinated dienes. The synthetic applications of α-fluoro-α,β-unsaturated carbonyl compounds are based, on the one hand, on their reduction to fluoroallylic alcohols and their reactions. The application of chlorofluorocyclopropanes in the synthesis of α-fluoro-α,β-unsaturated carbonyl compounds and α-fluoroallylic alcohols[9], as well as the rearrangements of the latter, were reviewed by Percy[9,14]. On the other hand, α-fluoro-α,β-unsaturated carbonyl compounds are able to enter Michael reaction with nucleophiles, and that allows them to be used in the synthesis of various monofluorinated compounds. Thus, the reaction of chlorofluorocarbene with alkene **1** led to chlorofluorocyclopropane **2**, which was solvolyzed to methyl 2-fluoro-3-methoxypropenoate (**3**)[27]. The reaction of **3** or the corresponding acyl chloride **4** with various nucleophiles, such as phenylhydrazine, *O*-(trimethylsilyl)urea, phenol, thiophenol and 2-aminothiophenol, followed by an intramolecular Michael addition, leads to the various fluorinated heterocycles. Similarly, Schlosser and Michel used the ability of the ketone **5** to react as a Michael acceptor with phenol in the synthesis of the fluorinated analogue of the main flavour component of raspberries (Scheme 2)[6b].

The reaction of fluorocarbenes with imines resulted in the formation of fluoroaziridines[28]. Thus, chloro- and bromofluorocarbenes, generated from $CHFCl_2$ or $CHFBr_2$ by α-dehydrohalogenation, reacted with imines giving bromofluoro-[28a,29] and chlorofluoroaziridines[29b,30] **6** and **7**, and the reaction of imines with monofluorocarbene, generated by reduction of $CHFBr_2$ with active lead, leads to monofluoroaziridines **8** (Scheme 3)[31].

Monofluoroaziridines **8** have a significant potential in the synthesis of fluorine- and nitrogen-containing compounds. They can be isomerized with SbF_3 to α-fluoroimines **9**, capable of undergoing various reactions[31b].



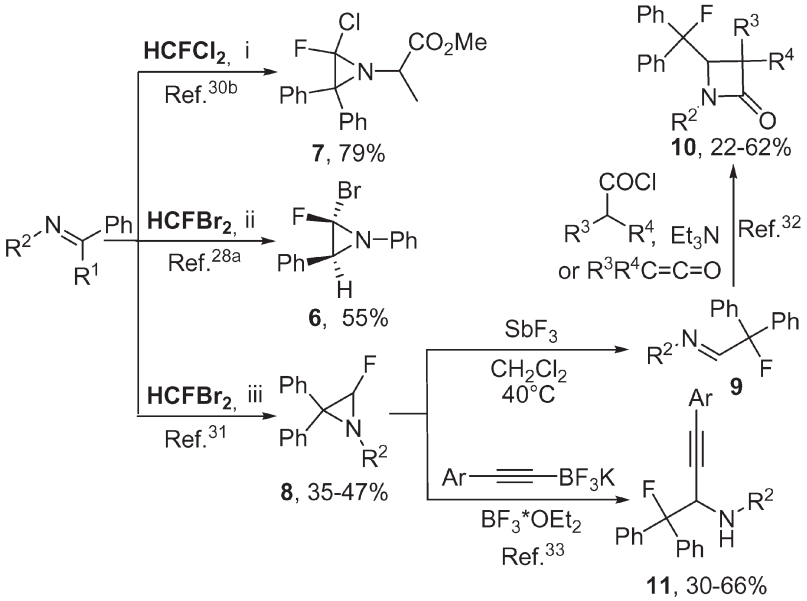
i: 1) BuLi, *o*-aminothiophenol, 2) Me_3Al; ii: 1) NaOH, 2) $SOCl_2$;
iii: 1) PhYH, 2) H^+; iv: 1) $PhNHNH_2$, 2) H_2SO_4;
v: 1) TMSOC(NHLi)=NH, 2) NaOH; vi: PhOH, H^+

SCHEME 2

Thus, the reaction of α-fluoroimines with ketenes generated *in situ* yielded fluorinated β-lactams **10** [32]. Fluorinated propargylamines **11** were synthesized from potassium (arylethynyl)trifluoroborates and α-fluoroimines generated *in situ* from fluoroaziridines in the presence of $BF_3{\cdot}OEt_2$ (Scheme 3)[33].

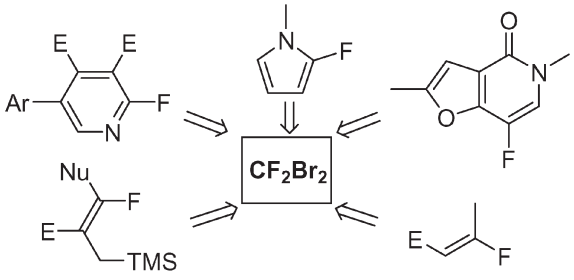
One of the synthetic applications of CF_2Br_2 (Scheme 4) is based on its ability to serve as difluorocarbene precursor. The difluorinated products, formed in the reactions of difluorocarbene, in certain cases prove to be rather unstable, tending to dehydrofluorination and hence leading to monofluorinated compounds.

Thus, the domino reaction of difluorocarbene, imines and electron-deficient alkenes yields 5-fluoro-2,3-dihydropyrroles **12** [34]. The mechanism of the reaction depicted in Scheme 5 involved attack of difluorocarbene onto the nitrogen lone pair of the imine to give azomethine ylide **13** fol-



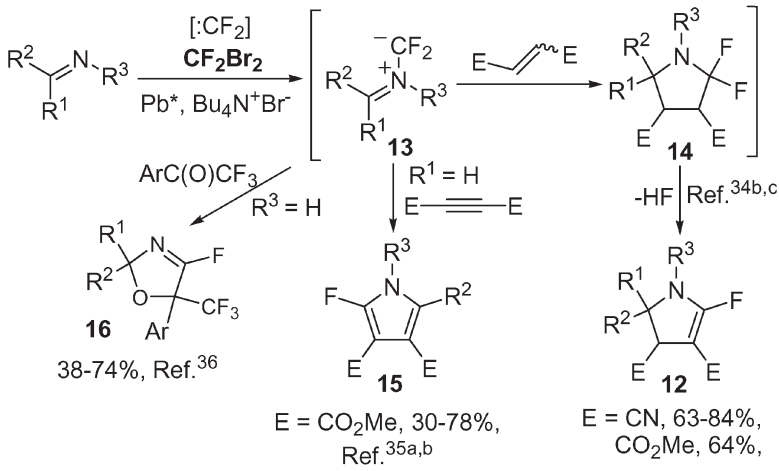
i: R^1 = Ph, R^2=CH(CH_3)CO_2Me; KOH, $BnEt_3N^+Cl^-$, CH_2Cl_2, 8 °C; ii: R^1 = H, R^2 = Ph; KO*t*Bu, hexane; iii: R^1 = Ph, R^2 = alkyl; Pb*, $Bu_4N^+Br^-$, ultrasound

SCHEME 3



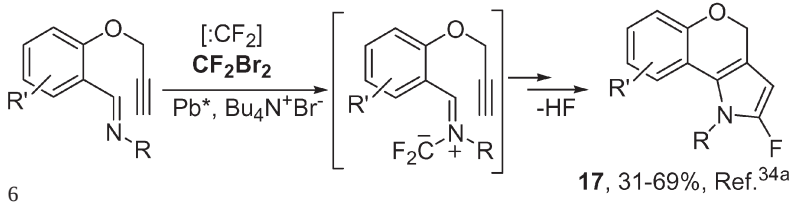
SCHEME 4

lowed by 1,3-dipolar cycloaddition of the latter to the olefin and spontaneous dehydrofluorination of intermediary difluoropyrrolidine **14**. Fluoropyrroles **15** can be obtained by a similar approach[35]. A simple one-step synthesis of a new class of fluorinated heterocycles, 4-fluoro-2,5-dihydrooxazoles **16**, from diarylmethanimines, trifluoroacetophenones and CF_2Br_2 was described[36]. The reaction proceeds via a *gem*-difluorosubstituted NH-azomethine ylide (Scheme 5).



SCHEME 5

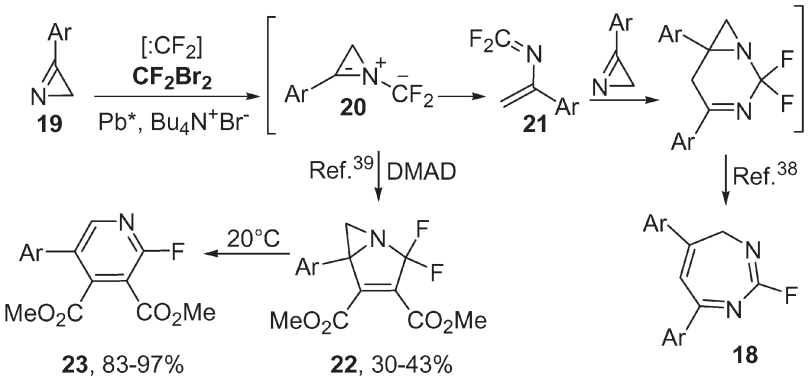
The intramolecular modifications of these reactions led to fluorinated polycondensed heterocyclic systems **17** (Scheme 6)[34a,37].



SCHEME 6

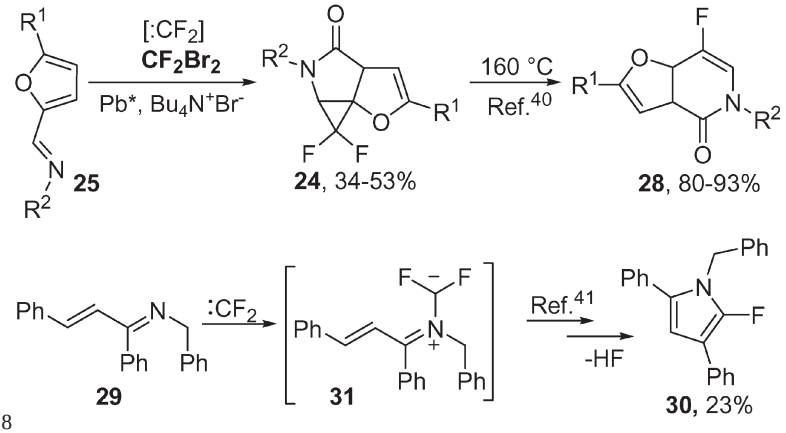
5,7-Diaryl-2-fluoro-4*H*-1,3-diazepines **18** have been synthesized from 3-aryl-substituted 2*H*-azirines **19** and difluorocarbene. The reaction involved isomerization of azirinium ylide **20** into a 2-aza-1,3-diene **21** which underwent [4+2] cycloaddition with the starting azirine followed by ring expansion and dehydrofluorination[38]. The reaction of difluorocarbene,

azirines **19** and DMAD yielded the derivatives of 2,2-difluoro-1-azabicyclo-[3.1.0]hex-3-ene-3,4-dicarboxylic acids **22**, which in mild conditions underwent ring-expansion into 2-fluoropyridine derivatives **23** in high yields (Scheme 7)[39].



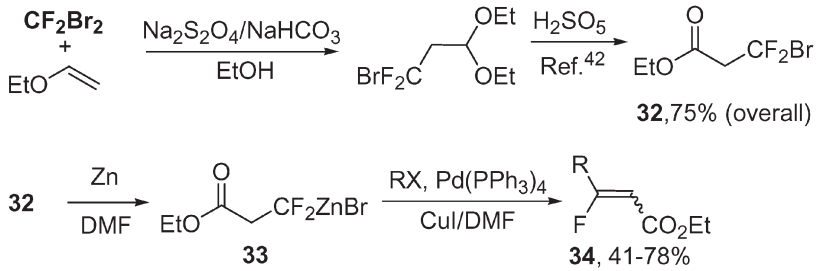
SCHEME 7

Difluorinated polycycles **24**, resulting from 1,5-cyclization of iminium ylides generated from the imines **25** and difluorocarbene, can be transformed into 7-fluorofuro[2,3-c]pyridines **28** simply by heating the reaction mixture to 160 °C [40]. It was found that reaction of azadiene **29** with difluorocarbene gave fluoropyrrole **30**, which arises via intermediate formation of difluoroazomethine ylide **31**, followed by a 1,5-cyclization of the latter into difluoropyrroline, and subsequent HF elimination (Scheme 8)[41].



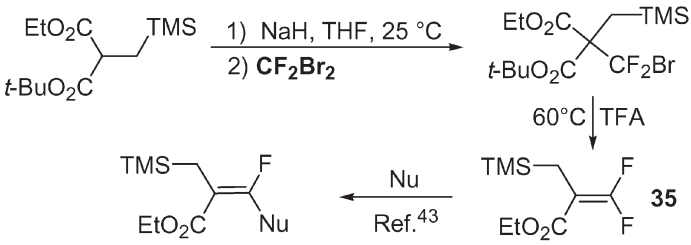
SCHEME 8

Ethyl 3-bromo-3,3-difluoropropanoate (**32**) represents another example of a difluorinated compound obtained from CF_2Br_2 and applied to the synthesis of monofluorinated products. The synthesis of **32** is presented in Scheme 9. The reaction of **32** with Zn in THF yielded organozinc reagent **33**, which underwent a $Pd(PPh_3)_4$/CuI-catalyzed coupling reaction with aryl and vinyl bromides and iodides, forming β-fluoro-α,β-unsaturated esters **34** in 41–78% yield, with the *E*-isomer being the main one. Use of Cu(I) improves the *E*/*Z*-selectivity of the reaction[42].



SCHEME 9

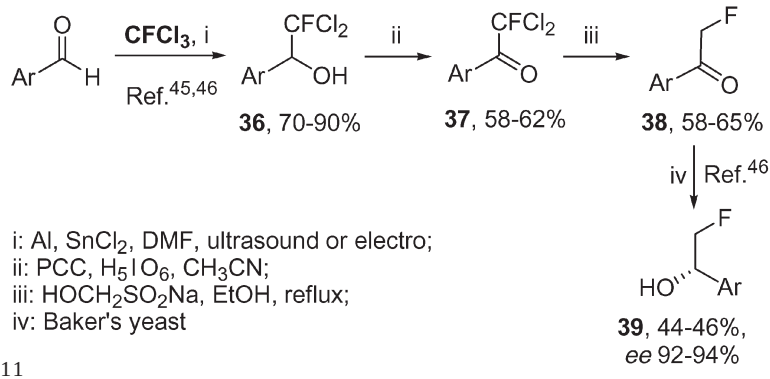
Ethyl 3,3-difluoro-2-[(trimethylsilyl)methyl]propenoate (**35**), which was also synthesized from CF_2Br_2 (Scheme 10), represents a suitable building block for the stereoselective synthesis of fluoroalkenes. Compound **35** underwent a nucleophilic addition/elimination reaction with C-, N- and P-nucleophiles, leading to formation of compounds wherein the main or even the sole isomer has a *cis*-situated fluorine atom and (trimethylsilyl)methyl group. A possible C–F···Si-type coordinative interaction has been proposed to explain the observed stereochemical outcome[43].



SCHEME 10

Application of $CFCl_3$ in the synthesis of monofluoroalkenes by a reaction sequence involving interaction of $CFCl_3$ with Bu_3P yielding bis(tributylphosphonium)fluoromethide, followed by reaction of the latter with aldehydes and hydrolysis of the adducts, has been described in detail in the review by van Steenis and van der Gen[11]. Other examples can be found in ref.[44].

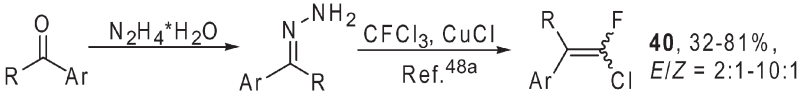
$CFCl_3$ can also serve as the synthetic equivalent of dichlorofluoromethyl anion which could be generated by reduction of the former with active metals[45a] or electrochemically[45b]. Generation of dichlorofluoromethyl anion in the presence of aldehydes yielded alcohols **36**, possessing a dichlorofluoromethyl group[45]. Oxidation of these compounds with PCC/H_5IO_6 gave α,α-dichloro-α-fluoroketones **37**, where one or both chlorine atoms can be replaced with hydrogen. The (chloro)fluoroketones **38** thus obtained represent perspective building blocks. In particular, their enantioselective reduction to yield the corresponding alcohols **39** has been recently described (Scheme 11)[46]. Synthesis of $PhCH_2CCl_2F$ from $PhCH_2OP(NEt_2)_2$ and $CFCl_3$ represents another example, where $CFCl_3$ is considered a synthetic equivalent of Cl_2FC^- (ref.[47]).



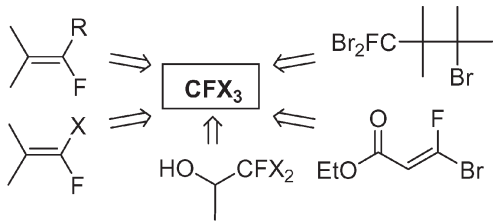
SCHEME 11

Besides, $CFCl_3$ found application in the synthesis of chlorofluorostyrenes **40** by the reaction of hydrazones of aromatic aldehydes and ketones with $CFCl_3$ in the presence of CuCl (Scheme 12). The reaction mechanism includes hydrazone oxidation to diazoalkane with Cu(II), decomposition of the diazoalkane with the formation of copper carbenoide and reaction of the latter with $CFCl_3$, leading to the target chlorofluoroalkene[48].

Synthetic applications of $CFBr_3$ (Scheme 13) are based on its ability to serve as dibromofluoromethyl anion or radical precursor, and on its reactions leading to the formation of phosphorus ylide.

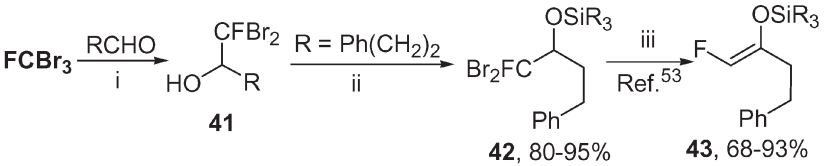


SCHEME 12



SCHEME 13

Dibromofluoromethyl anion is known to be very unstable both from theoretical calculations[49] and experimental data, showing that it decomposes at the temperatures above –116 °C [13a,23g]. It is, therefore, generated from $CFBr_3$ at low temperatures, either by direct metallation with Rieke magnesium at –100 °C followed by rapid addition of carbonyl compound[50], or by metallation with BuLi at –130 °C in the presence of a carbonyl compound, to rapidly intercept the organometallic compound being formed[13a,51]. The use of Et_2Zn instead of BuLi permits the reaction to be performed at a higher temperature (–60 °C, DMF)[52]. The alcohols **41** thus obtained contain reactive dibromofluoromethyl group and can be further modified. Thus, silylation of **41** with trialkylsilyl chloride followed by reduction of the resulting ester **42** with $CrCl_2$/Mn gave silylated α-fluoroenol ethers **43**, which are perspective building blocks in the synthesis of α-fluorocarbonyl compounds. The reaction proceeds stereoselectively with formation of the *Z*-isomer[53]. The authors suggested that the reaction mechanism includes bromine–chromium interchange leading to carbenoid formation. The latter undergoes α-elimination of CrBrX, resulting in alkylfluorocarbene formation. A 1,2-H-shift in the alkylfluorocarbene leads to fluoroalkene (Scheme 14)[53]. β,β-Dibromo-β-fluoroalcohols **41** may also be transformed via esterification followed by base-induced conversion to bromofluoroalkenes[13a]. Protection of alcohols **41** allows performing bromine–lithium interchange by the reaction with BuLi. The resulting organolithium compound can be reacted with various electrophiles[54].

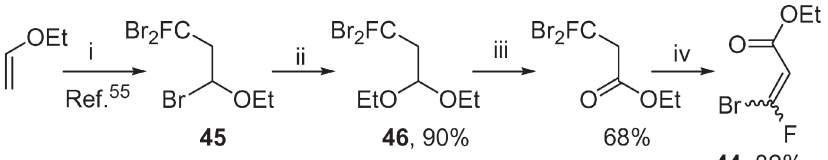


i: BuLi / -130 °C / THF-Et_2O or Mg* /-100 °C / Et_2O
or Et_2Zn /-60 °C / DMF; ii: R_3SiCl, Et_3N, DMAP, THF; iii: $CrCl_2$, Mn, THF

SCHEME 14

The stability of fluorinated carbanions can be increased by the introduction of silicon-containing substituent in the α-position to the anion centre. Application of such silicon-containing compounds, obtained from $CFBr_3$ and alkylchlorosilanes, as well as from their carbanions, has been recently reviewed by Shimizu and Hiyama[13a].

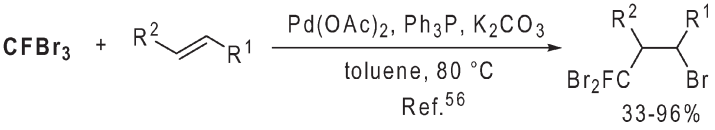
The ability of $CFBr_3$ to serve as dibromofluoromethyl radical precursor was exploited in the synthesis of another building block, ethyl β-bromo-β-fluoroacrylate (**44**) (Scheme 15). Irradiation of $CFBr_3$ in the presence of ethyl vinyl ether induced a radical addition of the dibromofluoromethyl radical formed to the double bond, resulting in the formation of the unstable bromoacetal **45**. The bromine atom in the latter is readily substituted by an ethoxy group in ethanol. Oxidation of the forming acetal **46** with H_2SO_5 followed by dehydrobromination gave compound **44**[55], which is a perspective three-carbon fluorinated building block, possessing, at least, three possibilities of further modifications: AN reactions with carbonyl group, Michael addition and Pd-catalyzed coupling.



i: **$CFBr_3$**, pentane, UV; ii: EtOH; iii: H_2SO_5; iv: Et_3N

SCHEME 15

Formally, the same result as in the radical addition reaction of $CFBr_3$ is observed in the Pd-catalyzed addition of $CFBr_3$ to alkenes. The selectivity of the reaction is determined by steric factors: the dibromofluoromethyl group adds to the least congested carbon atom (Scheme 16)[56].

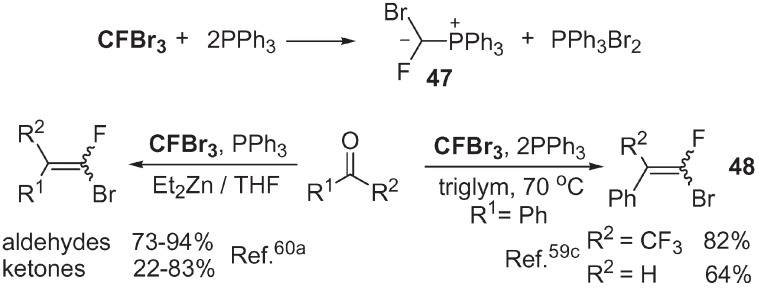


SCHEME 16

1,1,3-Tribromo-1-fluoroalkanes obtained by radical addition of $CFBr_3$ to alkenes represent a convenient source of alkynylfluorocarbenes, which are capable of cyclopropanating alkenes to form alkynylfluorocyclopropanes[57].

Finally, the reaction sequence consisting of generation of dibromofluoromethyl radical, its addition to the double bond of a 1,6-diene followed by intramolecular AR reaction on the second C=C bond was applied in the synthesis of dibromofluoromethyl-substituted cyclopentanes[58].

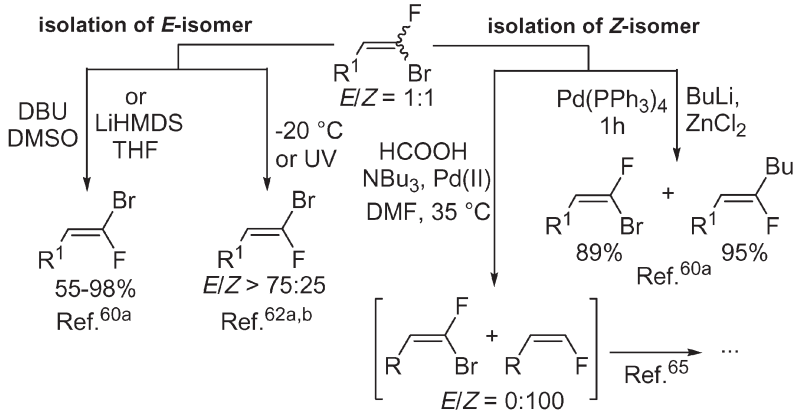
The reaction of $CFBr_3$ with Ph_3P led to ylide **47**. When the reaction was performed in the presence of carbonyl compound the forming ylide underwent a Wittig reaction yielding *gem*-bromofluoroalkenes **48**. The reaction proceeds with activated ketones and aromatic aldehydes yielding an equimolar mixture of (*E*)- and (*Z*)-bromofluoroalkenes[59]. The use of Et_2Zn allows the reaction to be performed even with unactivated aldehydes and ketones (Scheme 17)[60].



SCHEME 17

The bromofluoroalkenes thus obtained possess a significant synthetic potential because they can undergo further palladium-catalyzed bond-forming reactions. They were used in the synthesis of 1-alkenyl-1-fluoroalkenes[61], fluorinated stilbenes[61,62], fluorovinyl phosphonates[63], monofluorinated enynes[64], α-fluoro-α,β-unsaturated esters[65] and other compounds possessing α-fluorovinyl group[51b,60a]. In addition, bromofluoroalkenes can be reduced to fluoroalkenes by Bu_3SnH [55,66].

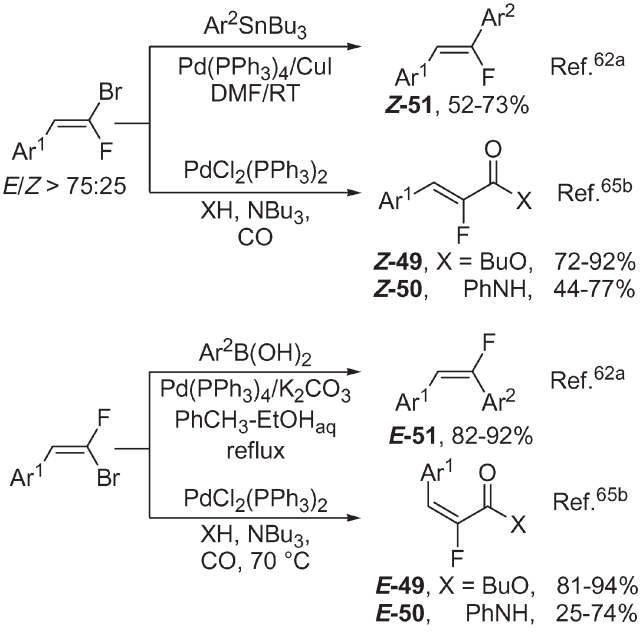
However, there is a significant problem caused by the low selectivity of formation of bromofluoroalkenes. This problem can be solved by one of the following ways. The first one is based on preliminary separation of the mixture of isomers by any means. Physical methods of separation are often difficult to apply to this mixture and chemical methods have therefore been developed. A mixture of *E*/*Z*-isomers can be enriched with *E*-isomer by UV irradiation or by holding the mixture at –20 °C for a week[62a,b,65b]. Besides, addition of a base to the mixture results in selective dehydrobromination of *Z*-isomer, leaving *E*-isomer intact (Scheme 18)[60a]. The methods of isolation of *Z*-isomer are based on the differences in the rates of Pd complexes formation for *E*- and *Z*-isomers. The *E*-isomer reacts much faster, thus allowing its conversion selectively to a compound, which would be easy to separate or which would not interfere in subsequent reactions. Pd-catalyzed reduction with formic acid[65] or coupling with BuLi [60a] (Scheme 18) can be used for this purpose. The unreacted *Z*-isomer can be isolated and introduced into subsequent reactions or can be used without isolation. The drawback of this method is that only one of the two isomers is used.



SCHEME 18

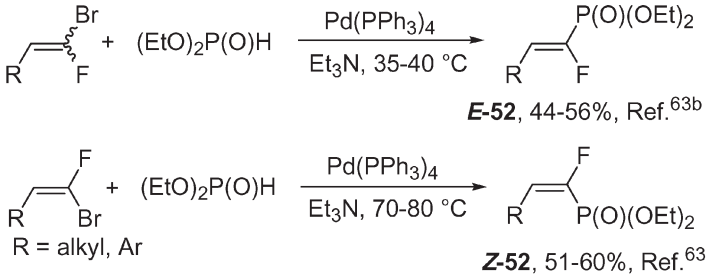
This approach was applied by Burton et al.[65] in the synthesis of (*Z*)-α-fluoro-α,β-unsaturated esters **49** and amides **50** by Pd-catalyzed carbonylation of a mixture of *E*/*Z*-isomeric bromofluoroalkenes, enriched with *E*-isomer by keeping the equimolar mixture at –20 °C. *E*-Isomers of the esters **49** and amides **50** were produced from (*Z*)-bromofluoroalkene, obtained by kinetic separation of an equimolar mixture of isomers by palladium-catalyzed reduction with formic acid. The same method for the

separation of *E*/*Z*-bromofluoroalkenes was used in the synthesis of (*E*)- and (*Z*)-fluorostilbenes **51**. (*Z*)-Fluorostilbenes were synthesized by the Stille reaction of aryltributylstannanes with the mixture of *E*/*Z*-bromofluoroalkenes[62a,b], while (*E*)-fluorostilbenes were prepared by the Suzuki reaction of arylboronic acids with the *Z*-isomer (Scheme 19)[62a,c].



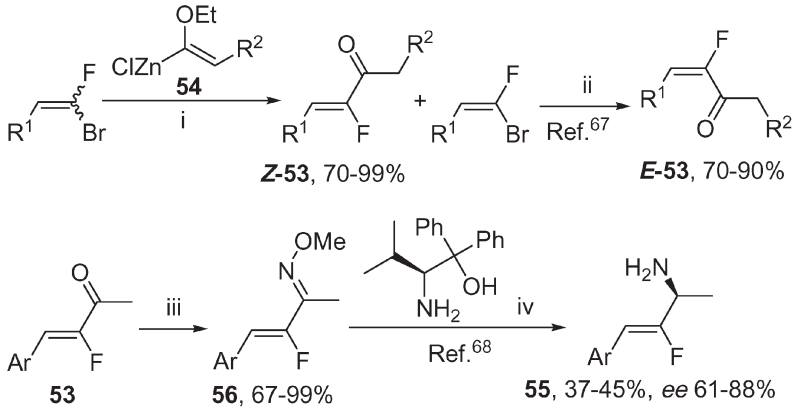
SCHEME 19

Another approach is also based on kinetic separation of a mixture of *E*/*Z*-isomers, though here, the target reaction is used for the separation. The product from the more reactive *E*-isomer is isolated and the residual *Z*-isomer is then allowed to undergo the same reaction, but at a higher temperature or for a longer time. Thus, both isomers are used. This approach has been proposed by Burton and Zhang for stereoselective synthesis of (*E*)- and (*Z*)-fluorovinylphosphonates[63b]. A mixture of *E*/*Z*-bromofluoroalkenes was introduced into Pd-catalyzed coupling reaction with diethyl phosphite. The *E*-isomer reacted almost exclusively at 35 °C. Thus formed (*E*)-phosphonate **52** was isolated by column chromatography, while unreacted *Z*-isomer after isolation was used in the same reaction at 70–80 °C (Scheme 20).



SCHEME 20

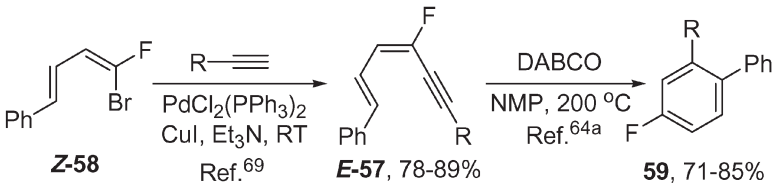
The same approach was used in the synthesis of α-fluoro-α,β-unsaturated ketones **53** by Pd-catalyzed coupling reaction of bromofluoroalkenes with (α-ethoxyvinyl)zinc chloride (**54**) followed by hydrolysis of the intermediate. Only (*E*)-alkene reacted at 10 °C, forming (*Z*)-enone ***Z*-53**. The unreacted (*Z*)-alkene was isolated and re-introduced into the coupling reaction at a higher temperature, yielding (*E*)-enone ***E*-53**. Thus, both isomeric enones were available from the mixture of isomeric alkenes. The reaction gave high yields under mild, non-racemising conditions[67]. The fluoroenones **53** thus obtained were subsequently used in the enantioselective synthesis of β-fluoro-β,γ-unsaturated amines **55**, through conversion of the ketones to oximes **56** followed by their reduction with $NaBH_4$ in the presence of chiral aminoalcohols (Scheme 21)[68].



i: 1) Pd, THF, 10°C, 2) H_3O^+; ii: 1) separation; 2) **54**, Pd, THF, 65 °C, 3) H_3O^+; iii: $MeONH_2 \cdot HCl$/Py, EtOH; iv: $BH_3 \cdot THF$, THF/RT

SCHEME 21

Fluoroenynes **57** were synthesized similarly. When performing the reaction of the mixture of isomeric bromofluoroalkenes **58** with alkynes, in the presence of palladium catalyst and CuI at room temperature for 16–24 h, (*Z*)-monofluoroenyne was formed predominantly. The re-introduction of isolated unreacted (*Z*)-bromofluoroalkene ***Z*-58** into the same reaction conditions for a longer period (48 h) gave (*E*)-monofluoroenyne ***E*-57** [69]. Enynes **57**, obtained from various alkynes and 1-bromo-1-fluoro-4-phenylbuta-1,3-diene, were used in the synthesis of fluorobenzenes **59** (Scheme 22)[64a]. Using a similar scheme, Burton et al.[70] obtained fluorinated derivatives of naphthalene and phenanthrene.



SCHEME 22

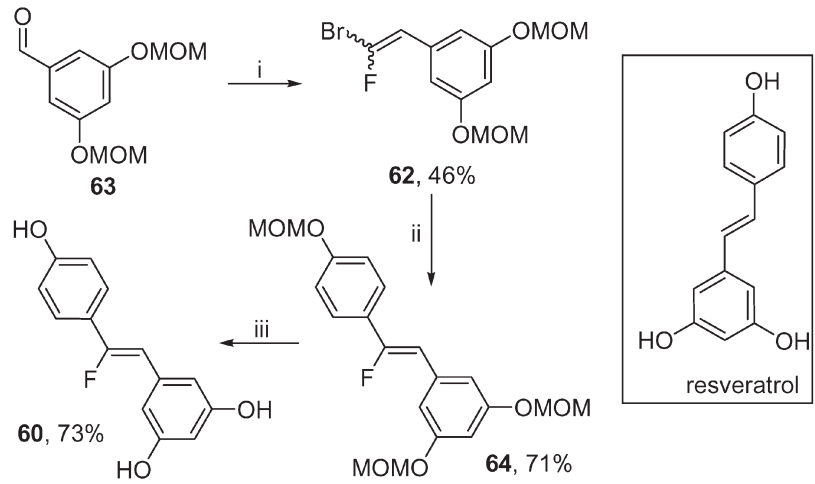
gem-Bromofluoroalkenes can be also used in the synthesis of fluoroallylic alcohols. Introduction of a mixture of (*E*/*Z*)-alkenes into the reaction with aldehydes in the presence of $CrCl_2$ and $NiCl_2$ resulted in the formation of (*Z*)-fluoroallylic alcohols in 60–75% yield (based on the aldehyde). As in the previous cases, the *E*-isomer reacted much faster than the *Z*-isomer, thus accounting for the observed selectivity[71].

The synthesis of the fluorinated analogue of resveratrol **60** (polyhydroxylated stilbene widespread in various plants, particularly in winegrapes[72]) can serve as an example of the application of bromofluoroalkenes in the synthesis of fluorinated analogues of natural bioactive compounds. Arylboronic acid **61** reacted under the Suzuki coupling conditions with (bromofluorovinyl)arene **62** derived from aldehyde **63**, $CFBr_3$ and Ph_3P (Scheme 23). The resulting compound **64** could be transformed into **60** by treatment with acid.

$CFBr_3$ can also be applied to the synthesis of bromofluoroalkenes according to the procedure described above for the synthesis of chlorofluoroalkenes from $CFCl_3$ and hydrazones of aromatic aldehydes and ketones[73]. Substitution of the bromine atom in the bromofluoroalkenes by a cyano group using CuCN leads to fluorinated derivatives of acrylonitrile[74].

In addition, $CFBr_3$ was used as starting material in the synthesis of terminal monofluoroalkenes: (fluoromethyl)triphenylphosphonium tetrafluoro-

borate, prepared from $CFBr_3$ and Ph_3P under strong basic conditions, generated an ylide which reacted with carbonyl compounds yielding monofluoroalkenes[11a,75].

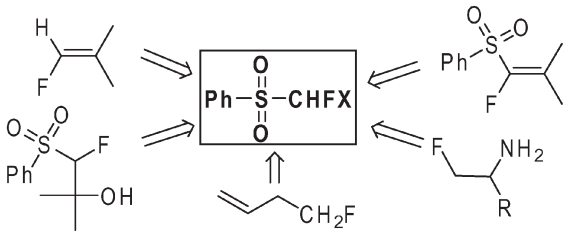


i: $CFBr_3$, PPh_3, Zn(Cu); ii: 4-$MOMOC_6H_4B(OH)_2$ (**61**), $PdCl_2(PPh_3)_2/PPh_3$, $Bu_4N^+HF_2^-$/THF, reflux; iii: HCl/MeOH, reflux

SCHEME 23

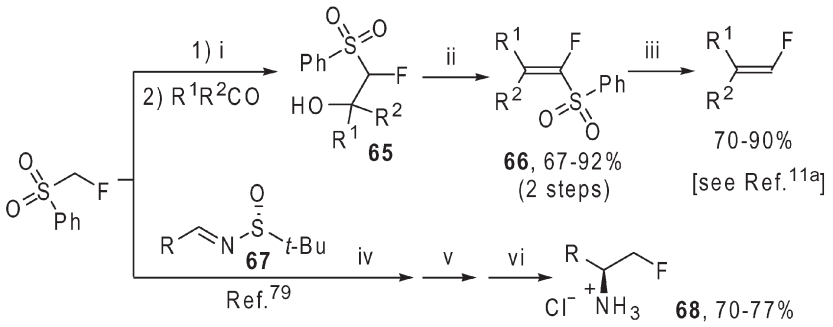
2.2. Fluoromethyl Sulfones and (Fluoromethyl)phosphonates

Another group of fluorinated one-carbon building blocks includes compounds of the general formula $PhSO_2CHFX$, where X = H, SO_2Ph, $P(O)(OEt)_2$, and, for comparison, $Ph_2P(O)CH_2F$. The synthetic applications of these compounds are based on the generation of stabilized carbanions and their reactions with electrophiles, followed by removal or modification of the activating group (Scheme 24).



SCHEME 24

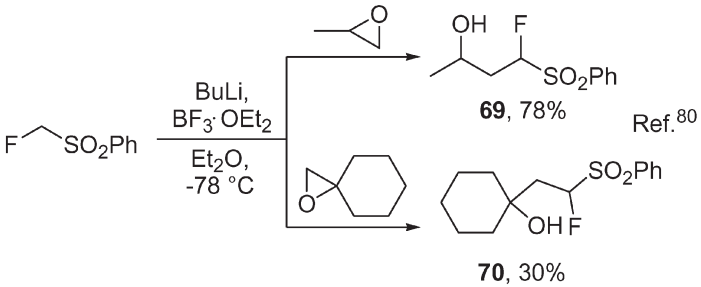
Thus, $PhSO_2CH_2F$ was condensed with carbonyl compounds, yielding α-fluoro-β-hydroxysulfones **65** [4b,11a,76b], which were then dehydrated by acid or through mesylation in the presence of base. The resulting unsaturated sulfones **66** were then reduced with sodium or aluminum amalgam[11a,76,77]. This approach has been used in the synthesis of the fluorinated analogue of vitamin D [78]. Similar condensation of $PhSO_2CH_2F$ with chiral sulfinylimines **67** led to the synthesis of optically active β-fluoroamines **68**, possessing a CH_2F fragment (Scheme 25)[79].



i: BuLi, THF, -78 °C; ii: H_3PO_4/100-165 °C or MsCl, Et_3N, CH_2Cl_2; iii: Al-Hg/THF/H_2O or Na-Hg, Na_2HPO_4, MeOH/THF, -40 - 25 °C; iv: LiHMDS, THF, -78 °C; v: Na-Hg, NaH_2PO_4, MeOH; vi: HCl, dioxane/MeOH

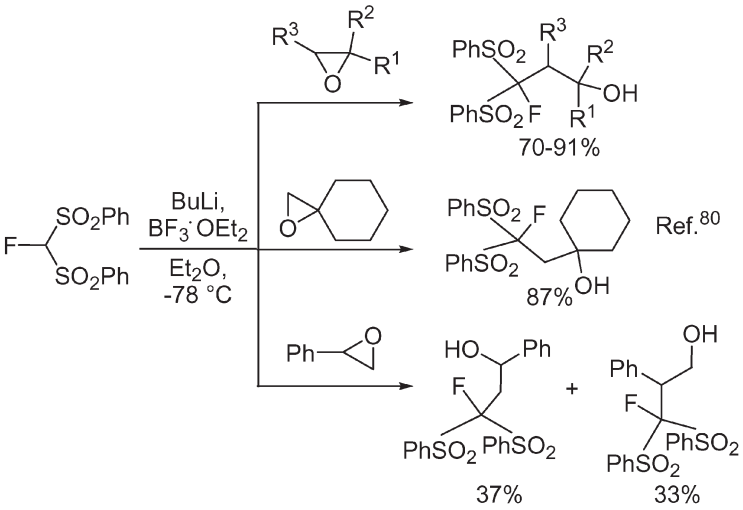
SCHEME 25

Oxirane ring-opening by the carbanion generated from $PhSO_2CH_2F$ led to γ-fluoroalcohols **69** and **70**. The reaction gave γ-fluoroalcohols in good yields with monoalkyl-substituted oxiranes and low yields with aryl- and dialkyl-substituted oxiranes (Scheme 26)[80].



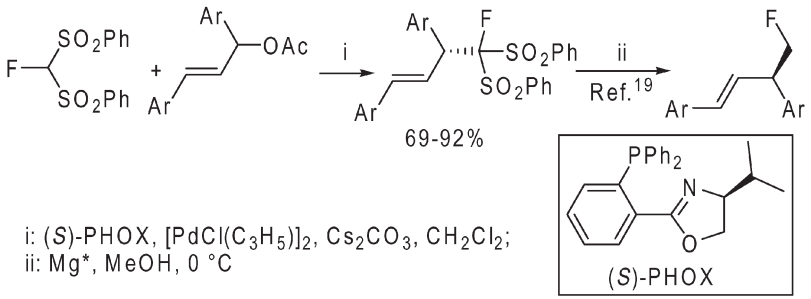
SCHEME 26

Better results were obtained with $(PhSO_2)_2CHF$. In this case, the reaction proceeded regioselectively and with good yields both with mono- and *gem*-dialkyl-substituted epoxides. Aryl epoxides reacted unselectively, yielding two isomers in approximately equal amounts (Scheme 27)[80].



SCHEME 27

$(PhSO_2)_2CHF$ can be also applied in the palladium-catalyzed coupling reactions with allyl acetates followed by reductive removal of phenylsulfonyl groups by active Mg. Chiral ligands in the palladium complex were responsible for producing compounds with a high degree of enantioselectivity (Scheme 28)[19]. It is notable that $(PhSO_2)_2CHF$ gave much higher yields in the coupling reactions than its non-fluorinated counterpart. The authors explained this fact by an increased acidity of hydrogen in $(PhSO_2)_2CHF$.



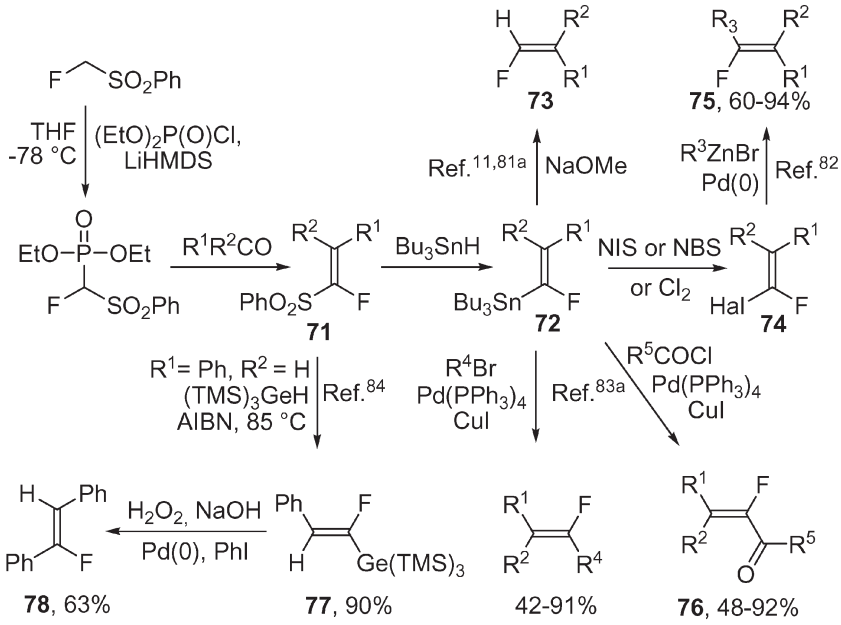
SCHEME 28

The reactions described above justify the consideration of $(PhSO_2)_2CHF$ and $(PhSO_2)CH_2F$ as synthetic equivalents of H_2FC^- anion. Compounds possessing a CH_2F fragment are of significant interest in drug design, based on the principle of isosteric substitution. For example, monofluoroacetic acid is responsible for the "lethal synthesis" and it blocks the Krebs cycle. In addition, monofluoromethylated amino acids, such as D-3-fluoroalanine, represent "suicide substrates" deactivating enzymes[19]. The above described coupling reaction of $(PhSO_2)_2CHF$ with allyl acetates was the key step in the synthesis of the monofluorinated analogue of ibuprofen, a non-steroid anti-inflammatory drug, and monofluorinated β-D-carbaribofuranose, which is of certain interest due to its antiviral properties and enzyme inhibition activity[19].

Similarly to $PhSO_2CH_2F$, also $PhSO_2CHFP(O)(OEt)_2$ can be condensed with carbonyl compounds, giving fluorovinyl sulfones **71**. In this case, no additional dehydration step is required[11a,76a,77,81]. Fluorovinyl sulfones **71** can be converted to fluorovinylstannanes **72** by the action of Bu_3SnH [11a,20a,76a,81]. Treatment of the latter with base led to fluoroalkenes **73**, while halodestannylation by the action of NIS, NBS or Cl_2 gave 1-halo-1-fluoroalkenes **74** [11a,81a]. These halofluoroalkenes coupled with organozinc compounds to give fluorinated polysubstituted alkenes **75** [82]. Fluorovinylstannanes **72** can also couple with aryl- or vinyl iodides giving fluoroalkenes, and with acetyl chlorides yielding α-fluoro-α,β-unsaturated ketones **76** [83]. Fluorovinyl sulfones **71** were used in the synthesis of (fluorovinyl)germanes **77** which then through Pd-catalyzed coupling reaction with aryl halides gave fluorostilbenes **78** (Scheme 29)[84].

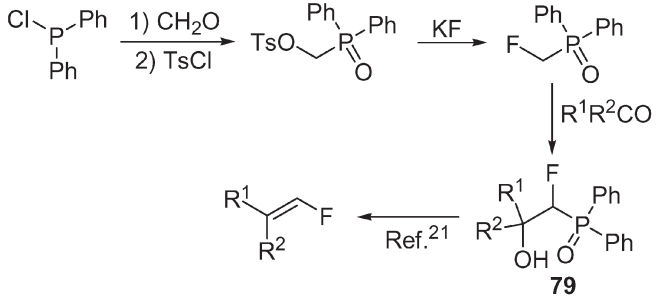
Berkowitz et al.[85] used the approach described above (fluoro-olefination of aldehydes followed by desulfurization with organotin compounds and subsequent reactions) in the synthesis of quaternary amino acids bearing α-fluorovinyl group, which are potential pyridoxal phosphate dependent enzymes inactivators. They report about the exclusive formation of (*E*)-vinyl sulfones and their stereoselective desulfurization with retention of configuration. Usually, formation of a mixture of isomers was observed in such reactions, so the authors explained the unusual selectivity by steric factors. This approach has also been applied in the synthesis of a series of fluorinated trienecarboxylic acids, representing analogues of selective retinoid X receptor modulator[1c]. Other examples of the application of $PhSO_2CHFPO(OEt)_2$ in the synthesis of fluorinated biologically active compounds can be found in the review of van Steenis and van der Gen[11a].

$Ph_2P(O)CH_2F$ found application in the synthesis of fluoroalkenes by the Wittig reaction, playing the role of synthetic equivalent of CHF-fragment.



SCHEME 29

This compound was obtained by condensation of Ph_2PCl with CH_2O, followed by hydroxy group substitution with fluoride through tosylate. Deprotonation of the obtained compound followed by the addition of the generated carbanion to carbonyl compounds led to α-fluoro-β-(hydroxyalkyl)phosphane oxides **79**, which can be converted to fluoroalkenes by the action of base (Scheme 30)[21].



SCHEME 30

$Ph_2P(O)CH_2F$ was also applied in the enantioselective synthesis of 1-fluorovinyl- and fluoromethyl sulfoxides[86].

Another group of fluorinated phosphorus-containing building blocks includes such compounds as $(EtO)_2P(O)CHFX$ (X = I, Br). $(EtO)_2P(O)CHFBr$ was obtained by reduction of $(EtO)_2P(O)CFBr_2$ with Bu_3P in ethanol/THF. The obtained compound was metallated with Zn and the resulting organozinc compound was reacted with various electrophiles, such as allyl halides, ethyl chloroformate and diethyl chlorophosphate. Mixing of the zinc reagent with Cu(I)Br gave a new reagent, which exhibited excellent cross-coupling reactivity with vinyl, alkynyl, and aryl halides[87]. Oxidation of the organozinc compound with I_2 gave $(EtO)_2P(O)CHFI$, which was introduced into Pd(0)- or Cu(0)-catalyzed addition to alkenes. Reduction of the addition product with a $Zn/NiCl_2$ system in wet THF gave (α-fluoroalkyl)phosphonates[88].

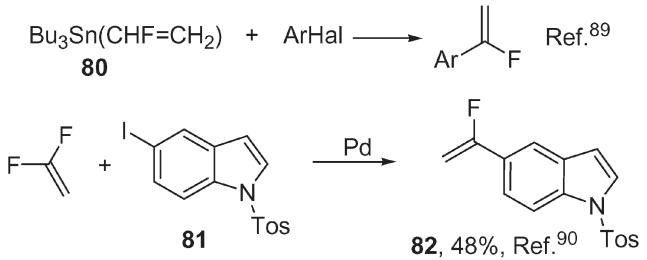
3. SYNTHETIC APPLICATIONS OF TWO-CARBON FLUORINATED BUILDING BLOCKS

Two-carbon fluorinated building blocks are represented by 1,1-difluoroethene, 2-chloro-1,1,2-trifluoroethene, 2-chloro-1,1,2-trifluoroethane, 1,1,1,2-tetrafluoroethane, 2,2,2-trifluoroethan-1-ol, fluoroacetic acid and its derivatives, including halo-substituted ones. Sulfur- and phosphorus-containing compounds were also used. 1,1-Difluoroethene, 1,1,1,2-tetrafluoroethane and 2,2,2-trifluoroethan-1-ol are commercially available.

3.1. 1,1-Difluoroethene

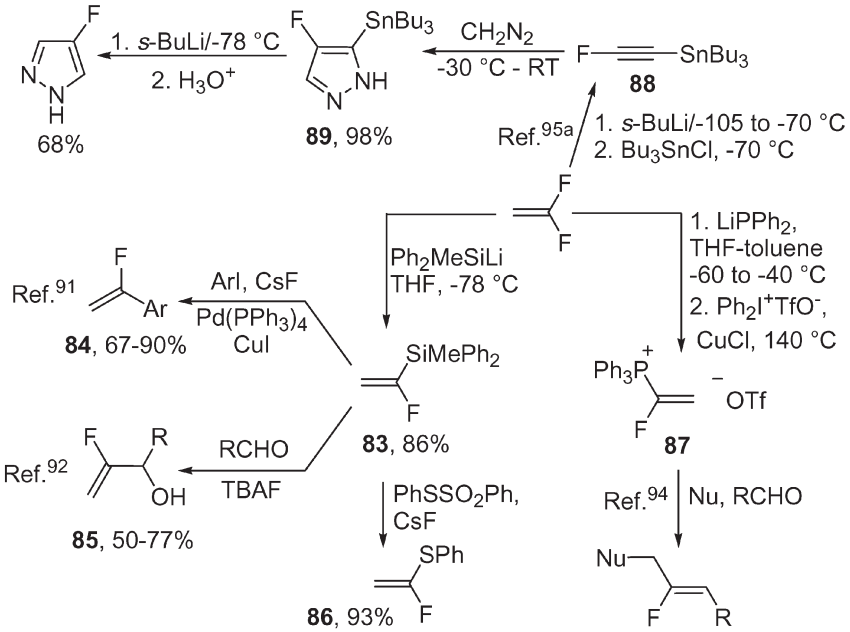
As it has been shown above, synthesis of fluoroalkenes is quite a developed field of synthetic chemistry. However, until recently, no general and convenient method for the introduction of an unsubstituted fluorovinyl group into the molecule has been described. Only two reactions leading to such a product were known. The first one implies a coupling reaction between tributyl(1-fluorovinyl)stannane (**80**) and aryl halides[89]. However, the required organotin compound is rather difficult to synthesize. The second known example of direct monofluorovinylation consisted of a Pd-catalyzed coupling reaction of 1,1-difluoroethene with 5-iodo-1-tosylindole (**81**), leading to 5-(1-fluorovinyl)-1-tosylindole (**82**)[90]. However, this is the only known example of direct involvement of 1,1-difluoroethene in coupling reactions (Scheme 31)[9].

With that end in view, Hanamoto and Kobayashi[91] synthesized from 1,1-difluoroethene a new fluorinated building block, namely (1-fluoro-



SCHEME 31

vinyl)methyldiphenylsilane (**83**). In the presence of F^-, silane **83** entered coupling reactions with aryl iodides, aryl bromides and aryl triflates. The reaction was catalyzed with Pd(0)/Cu(I) and lead to aryl(fluoro)alkenes **84** (Scheme 32). The carbanion, generated from **83** by reaction of F^-, reacted with electrophiles, such as aldehydes and ketones, giving α-fluoroallylic alcohol **85** [92]. The reaction with aldehydes proceeded in 50–77% yield while yields lower than 20% were obtained with ketones. The reaction of monofluorovinyl anion with *S*-phenyl benzenethiosulfonate led to 1-fluorovinyl phenyl sulfide (**86**)[93].



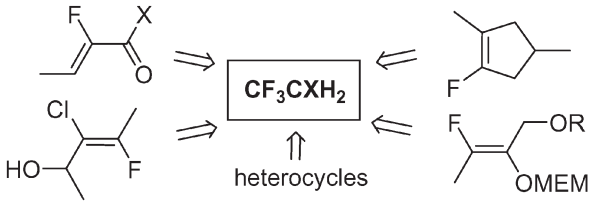
SCHEME 32

(α-Fluorovinyl)triphenylphosphonium triflate **87** is another building block derived from 1,1-difluoroethene. It was obtained by the reaction between 1,1-difluoroethene and Ph_2PLi, followed by quaternization of the resulting phosphane with diphenyliodonium triflate. The reaction of **87** with nucleophiles resulted in the formation of ylides, which were able to undergo Wittig reactions with aldehydes. If both the nucleophile and aldehyde group were fragments of the same molecule, cyclic fluoroalkenes were formed. This approach was applied in the synthesis of fluorinated allyl ethers, allylamines and chromenes[94].

1,1-Difluoroethene is a precursor not only for the CH_2=CF^- synthons, but also for fluoroacetylene **88**, which was used in the synthesis of fluorinated pyrazoles. Treatment of 1,1-difluoroethene with *s*-BuLi followed by the reaction of the resulting 2-fluoroethynyllithium with Bu_3SnCl yields compound **88**, which is introduced without isolation into a 1,3-dipolar cycloaddition reaction with diazomethane, giving 4-fluoro-5-(tributylstannyl)-1*H*-pyrazole (**89**). The Bu_3Sn group can be then substituted with hydrogen, iodine, aryl or an arenecarbonyl substituent, allowing synthesis of various 4-fluoropyrazoles[95].

3.2. Polyhalofluoroethanes

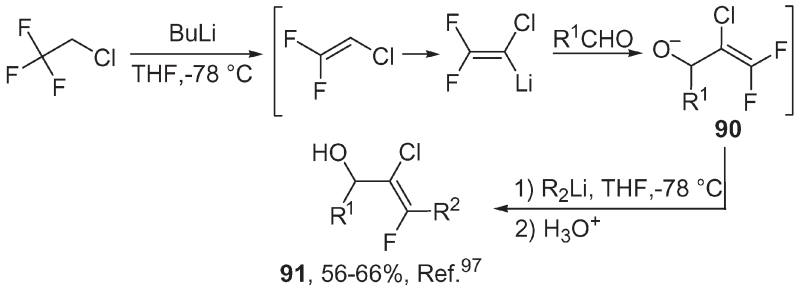
Another set of two-carbon fluorinated building blocks is represented predominantly by fluorinated tri-, tetra- and hexahaloethanes, and derivatives of 2,2,2-trifluoroethan-1-ol. Synthetic applications of these compounds (Scheme 33) are usually based on their dehydrohalogenation followed by the reaction of the resulting ethenes. For example, 2-chloro-1,1,1-trifluoroethane in the presence of KOH in DMSO reacted with heterocyclic amines yielding *N*-(2-chloro-1-fluoroethenyl)-substituted heterocycles[96]. More common are synthetic routes to monofluorinated compounds based on the reaction sequence dehydrohalogenation, metallation with organolithium, leading to 1,1,2-trihalovinyllithium as a key intermediate, which is then in-



SCHEME 33

troduced into reactions with electrophiles. The highly functionalized adducts thus obtained can be further involved in various reactions, allowing the synthesis of a wide spectrum of monofluorinated compounds.

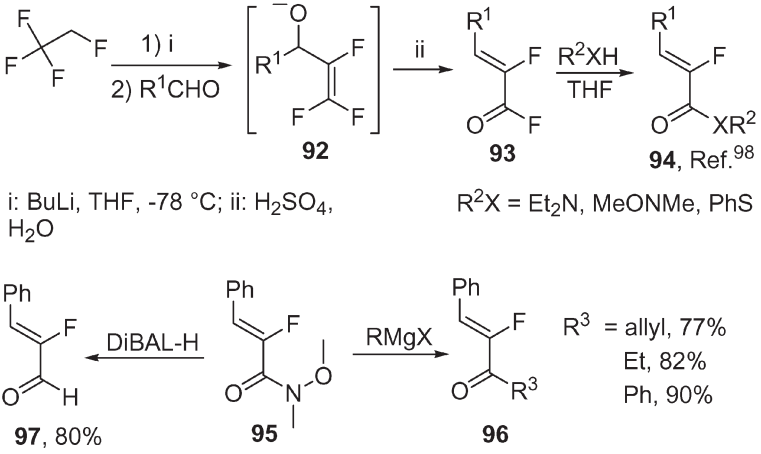
Thus, Percy et al.[97] have developed synthetic approach to fluoroallylic alcohols from 2-chloro-1,1,1-trifluoroethane. 2-Chloro-1,1,1-trifluoroethane was dehydrofluorinated by the action of BuLi. The resulting 2-chloro-1,1-difluoroethene was metallated *in situ*, yielding 1-chloro-2,2-difluorovinyllithium, which reacted with aldehydes. Alkyl- or aryllithium was then added to the resulting adduct **90**, stereoselectively substituting one fluorine atom to give, after hydrolysis, (*E*)-β-chloro-γ-fluoro-β,γ-unsaturated alcohols **91** (Scheme 34). The alcohols thus obtained were used in the synthesis of fluorinated derivatives of succinic acid.



SCHEME 34

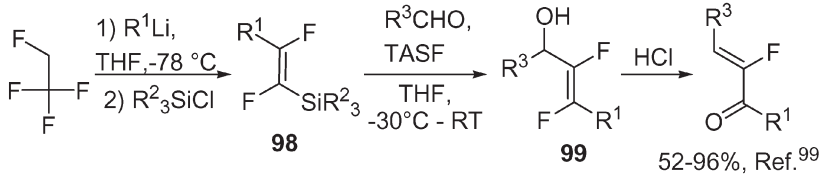
Using the same methodology, Percy and Kanai developed a method to synthesize α-fluoro-α,β-unsaturated carbonyl compounds from 1,1,1,2-tetrafluoroethane[98]. Analogously to the procedure described above for 2-chloro-1,1,1-trifluoroethane, 1,1,1,2-tetrafluoroethane was dehydrofluorinated and metallated with BuLi and the resulting lithium intermediate reacted with aldehyde. Partial hydrolysis of the adduct **92** gave fluorinated acyl fluoride **93**, which was introduced without isolation into reactions with nucleophiles, giving fluoroalkenoic acid derivatives **94** (amides, *N*-methoxyamides and thioesters). Reaction of *N*-methoxyamides **95** with Grignard reagents yielded fluorinated enones **96**, while their reduction with DIBAL-H yielded fluorinated unsaturated aldehydes **97** (Scheme 35).

α-Fluoroenones were also obtained from 1,1,1,2-tetrafluoroethane by another route[99]. 1,1,1,2-Tetrafluoroethane reacted with BuLi and TMSCl to give vicinal difluoride **98** which was introduced into F^--catalyzed addition reaction to aldehydes. The resulting β,γ-difluoroallylic alcohol **99** was hy-



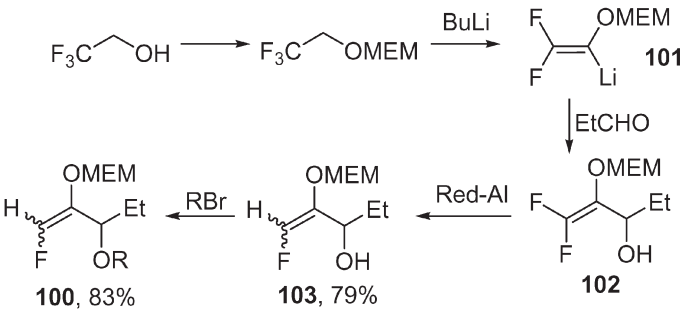
SCHEME 35

drolyzed with aqueous HCl, yielding α-fluoroenone (Scheme 36). Thus, here, the substituent at the carbonyl group was introduced first and then the substituent at β-carbon was introduced[99].

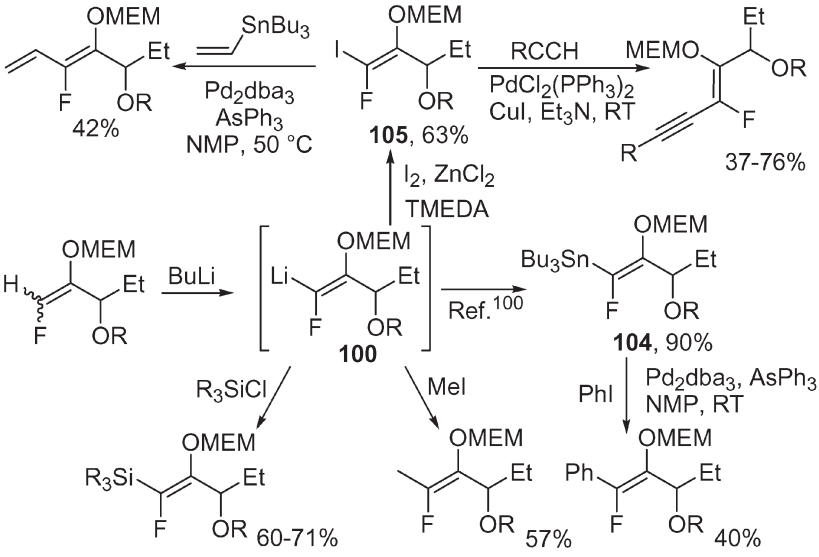


SCHEME 36

The same methodology was applied in the synthesis of compound **100** from 2,2,2-trifluoroethan-1-ol – one more convenient fluorinated building block (Schemes 37, 38). The protected trifluoroethanol underwent dehydrofluorination/metallation by reaction with BuLi and the resulting organolithium compound **101** was added to aldehyde. The difluoroallylic alcohol **102** thus obtained was then reduced with Red-Al into the monofluorinated compound **103**, which, after protection of the hydroxy group, can be metallated with an organolithium compound yielding **100**, which can be then introduced into reactions with various electrophiles. Thus obtained tributylstannanes **104** were introduced into coupling reactions with aryl iodides, whereas vinyl iodides **105** entered coupling reactions with vinyltin compounds and terminal alkynes (Scheme 38)[100].



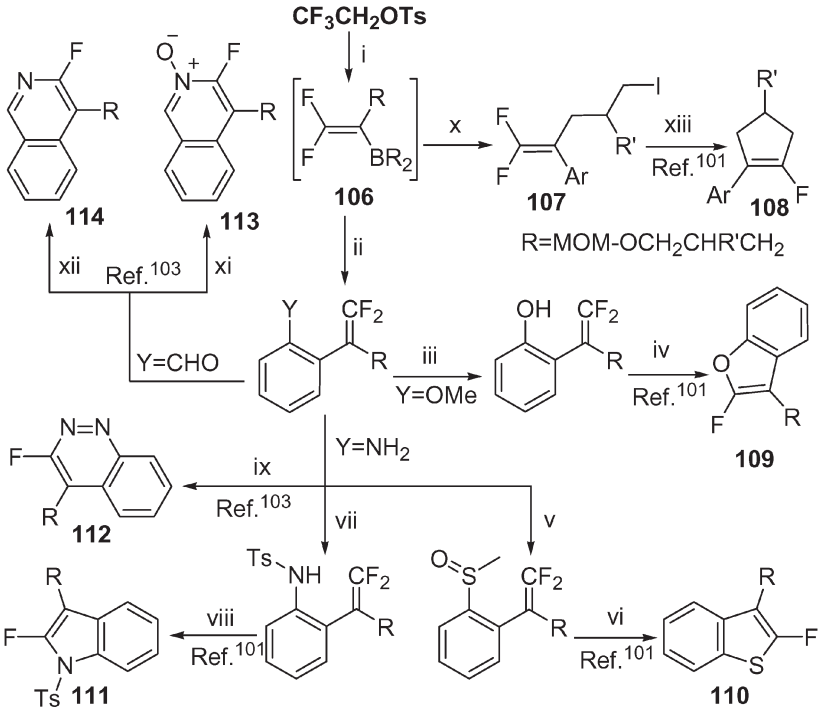
SCHEME 37



SCHEME 38

Generation of difluorovinyl anion and its reaction with electrophiles underlie the synthesis of (difluorovinyl)borane (**106**), possessing a high synthetic potential. On the one hand, application of the appropriate trialkylborane allows construction of 1,1-difluoroalkene **107**, capable of cyclizing into 1-fluorocyclopentene (**108**)[101]. A similar procedure was used in the synthesis of fluorinated dihydrofuran, dihydropyrrole and dihydrothio-

phene derivatives[101,102]. On the other hand, coupling of **106** with *ortho*-substituted aryl iodides (R = OMe, NH_2, CHO) allowed, after appropriate functionalization (Scheme 39), the formation of various monofluorinated heterocycles such as fluorobenzofurans **109** [101], fluorobenzothiophenes **110** [101], fluoroindoles **111**[101], fluorocinnolines **112**[103] and fluoroisoquinolines **113** and **114** [103].

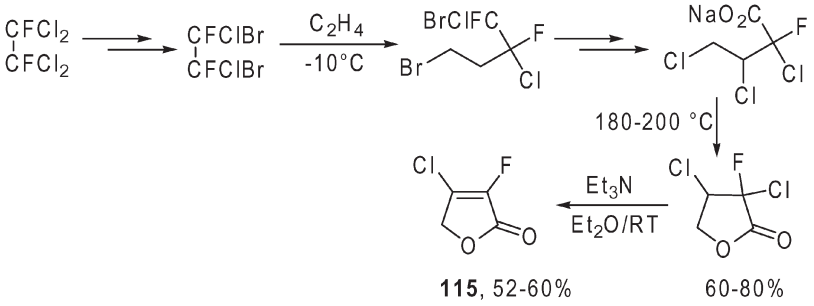


i: 1. BuLi, 2. BR_3; ii: ArI, CuI, Pd, PPh_3; iii: BBr_3; iv: NaH; v: 1. *i*-pentyl-ONO, CF_3CO_2H, 2. NaSMe, 3. $TiCl_3$, H_2O_2; vi: 1. $(CF_3CO)_2O$, Et_3N, 2. K_2CO_3/MeOH; vii: TsCl, Py; viii: NaH; ix: 1. *i*-pentyl-ONO, CF_3CO_2H, 2. PhSH; x: 1. ArI, CuI, Pd, PPh_3, 2. HCl, 3. MsCl/Et_3N, 4. NaI/Me_2CO; xi: NH_2OH·HCl, Et_3N; xii: NH_4OAc; xiii: *t*-BuLi

SCHEME 39

Difluorostyrenes are susceptible to nucleophilic substitution of the vinylic fluorines via an addition-elimination process, in which the fluorine affects the reactivity by both the electrophilic activation of the carbon–carbon double bond by the two fluorine atoms and the stabilization of the intermediary carbanion by the β-anion-stabilizing effect of fluorine[101,103].

Paleta[104] reported the synthesis of 1,2-dibromo-1,2-dichloro-1,2-difluoroethane from the commercially available CFC-112a and described its application in the synthesis of the halogenated analogue of tetronic acid, 4-chloro-3-fluorofuran-2(5*H*)-one **115** (Scheme 40).



SCHEME 40

3.3. Substituted Fluoroacetic Acids

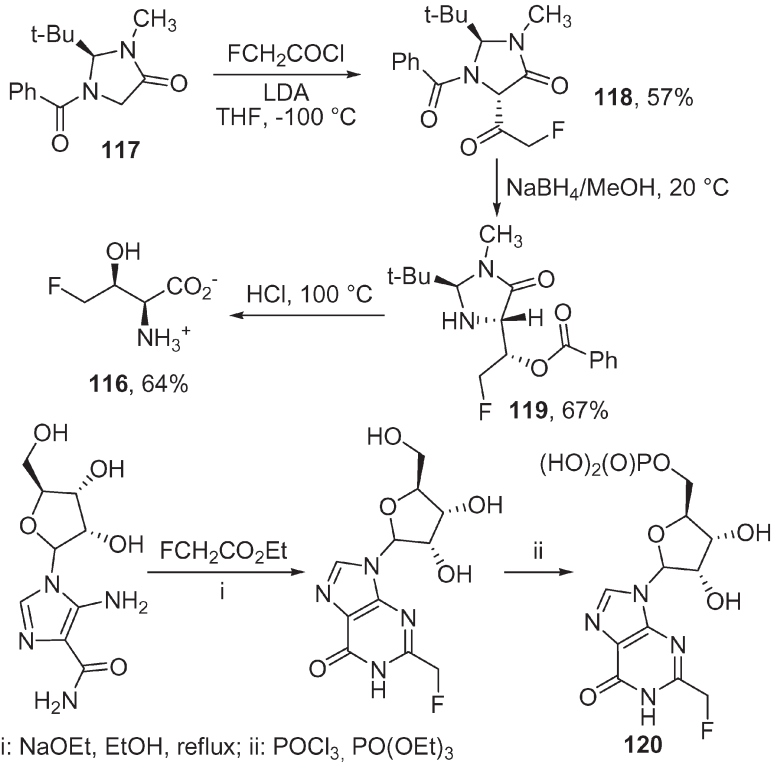
The application of fluoroacetic acid derivatives was described in the review of Percy[9] in 1997. The sections 3.3.1–3.3.4 presented below are recent results.

3.3.1. Fluoroacetic Acid Derivatives

Derivatives of fluoroacetic acid can be used as synthetic equivalents of both CH_2FCO^+ and $YCHF^-$-synthon, where Y = $CONR_2$, CN, etc.

The first case can be illustrated by the application of fluoroacetyl choride in the synthesis of (2*S*,3*S*)-4-fluorothreonine **116** (Scheme 41). Chiral imidazolidinone **117** was acylated with fluoroacetyl choride, the resulting ketone **118** was reduced with $NaBH_4$ to ester **119**, which was then hydrolyzed to **116** [105]. The synthesis of monofluoromethylated inosinic acid analogue **120** from ethyl fluoroacetate can serve as another example. Compound **120** is an irreversible inhibitor of the human-type-II enzyme inosine monophosphate dehydrogenase[106].

Stereoselective synthesis of α-fluorocarboxylic acids **121** by alkylation of pseudoephedrine acetamide **122** followed by removal of the chiral auxiliary can serve as an example of the application of fluoroacetic acid derivatives as synthetic equivalents of $YCHF^-$ anion[107]. Myers, Barbay and Zhong have applied this reaction at the initial stage of the synthesis of monofluorinated



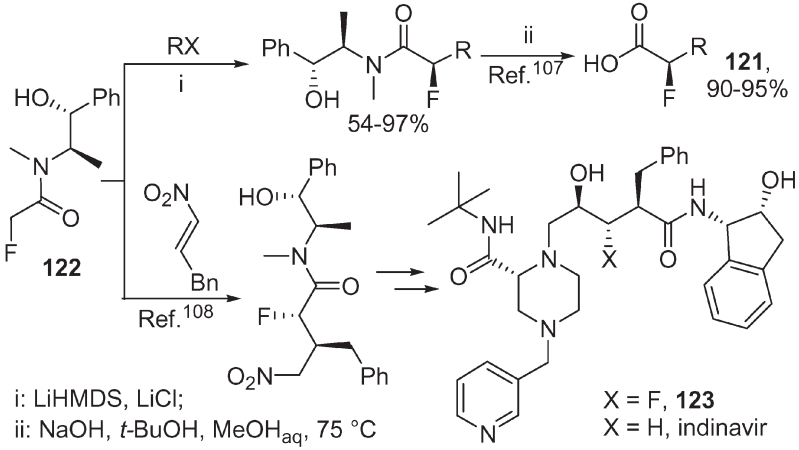
SCHEME 41

analogues of indinavir **123**, which is known to be HIV-protease inhibitor (Scheme 42)[108].

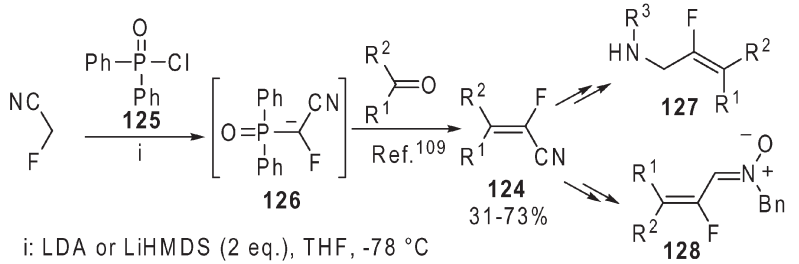
Application of fluoroacetonitrile in the synthesis of fluoroacrylonitriles **124** represents one more example. Reaction of fluoroacetonitrile with diphenylphosphinoyl chloride **125** in the presence of LDA or LiHMDS resulted in the formation of stabilized anion **126**. Its condensation with aldehydes or ketones led to α-fluoroacrylonitriles **124**. The compounds thus obtained were transformed into β-fluoroamines **127** and β-fluoronitrones **128** (Scheme 43)[109].

3.3.2. Monohalofluoroacetic Acids Derivatives

Esters $CHClFCO_2Et$ and $CHBrFCO_2Et$ can serve as synthetic equivalents of $^{-}CHFCO_2R$ anion, $^{\bullet}CHFCO_2R$ radical or $^{+}CHFY$ (Y = CO_2R, CH_2NR_2) cation.

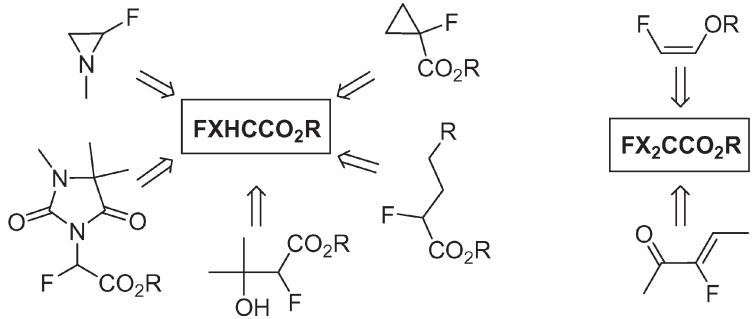


SCHEME 42



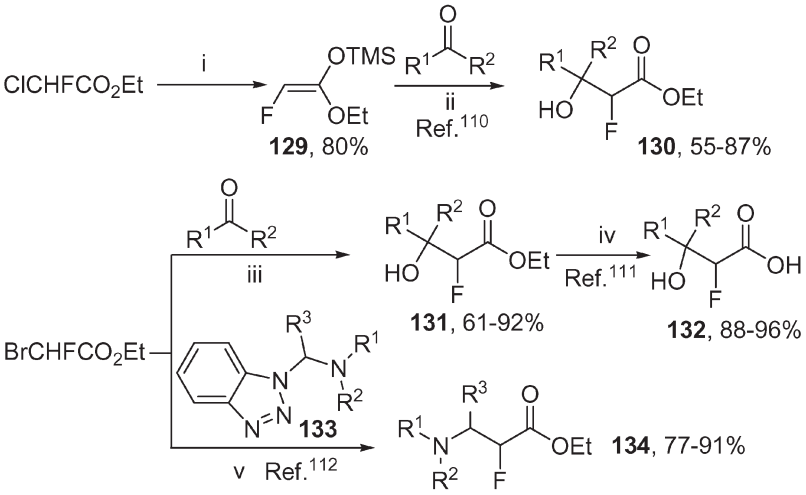
SCHEME 43

The ester $CHFICO_2Et$ is a synthetic equivalent of the $^{\bullet}CHFCO_2R$ radical (Scheme 44).



SCHEME 44

Synthetic equivalence of halofluoroacetic acids to the $^{-}CHFCO_2R$ anion was realized by generation of the corresponding organometallics (see below) or by their conversion to enol ethers. Thus, the ether of silylated enol **129**, obtained from $CHClFCO_2Et$, reacted in the presence of TMSOTf in CH_2Cl_2 at 40 °C with aromatic aldehydes bearing acceptor or weak donor substituents. In the presence of CuCl in HMPA at 50 °C, it also reacted with aromatic aldehydes having electron-donor substituents and ketones, yielding α-fluoro-β-hydroxyesters **130** (Scheme 45)[110].



i: Me_3SiCl, Mg or Zn; ii: TMSOTf/DCM, 40 °C or CuCl/HMPA, 50 °C;
iii: Zn, $CeCl_3$ $7H_2O$/THF; iv: NaOH/EtOH, 0-5 °C; v: Zn, TMSCl/THF, reflux

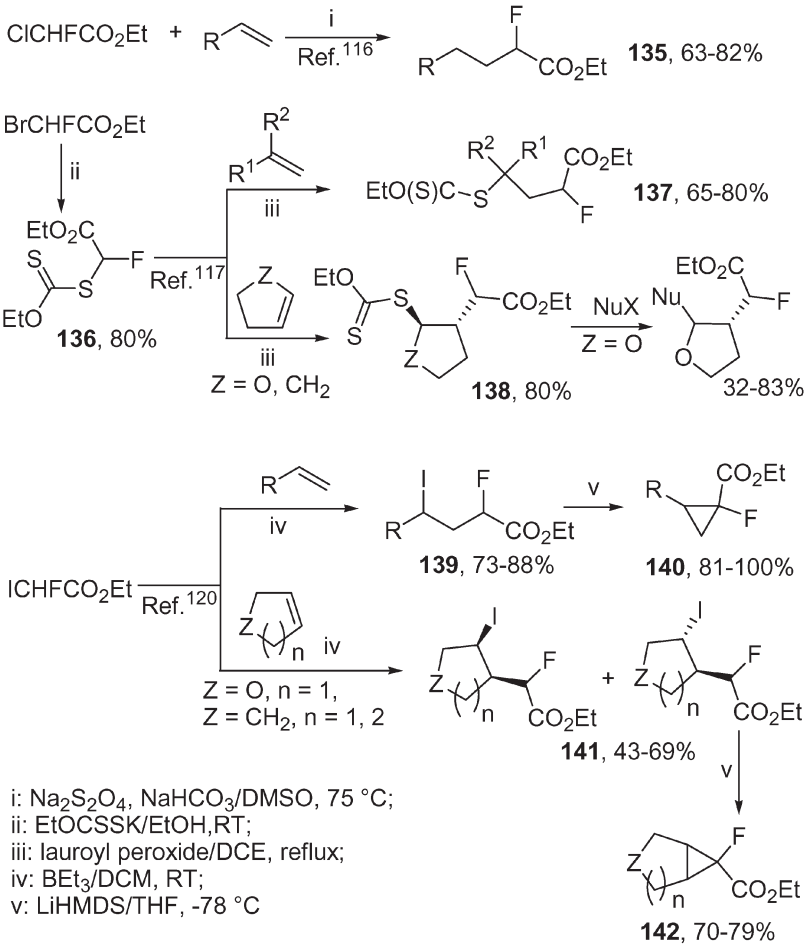
SCHEME 45

Carbanionic intermediate can be generated from $CHBrFCO_2Et$ by the reaction with zinc. Thus, Dolbier et al.[111] obtained α-fluoro-β-hydroxyesters **131** by $CeCl_3$-catalyzed Reformatsky reaction. The esters thus obtained were hydrolyzed to α-fluoro-β-hydroxyacids **132**. Application of the iminium salts, generated *in situ* from *N*-(α-aminoalkyl)benzotriazoles **133**, instead of carbonyl compounds in the Reformatsky reaction with $CHBrFCO_2Et$ allowed synthesis of α-fluoro-β-aminoesters **134** [112].

The Reformatsky reaction with $CHBrFCO_2Et$ was applied in the synthesis of 2-fluoromevalonate[113], fluorinated analogues of enzyme substrates of 3-hydroxyacyl-CoA dehydrogenase[3b] and mevalonate 5-diphosphate decarboxylase[114], which were exploited in the study of the mechanism of enzyme action. This reaction was also applied at the initial stage of the

construction of the fluoropyrrolidone fragment of the substituent at C-7 in the synthesis of DQ-113 – fluoroquinolone derivative, possessing antibacterial activity against Gram-positive bacteria[115].

In the presence of an appropriate initiator, halofluoroacetates were added to multiple carbon–carbon bonds, either directly or after preliminary transformation. So, in the presence of $Na_2S_2O_4$ in DMSO, $CHClFCO_2Et$ added to alkenes and alkynes gave α-fluoroesters **135** (Scheme 46)[116].

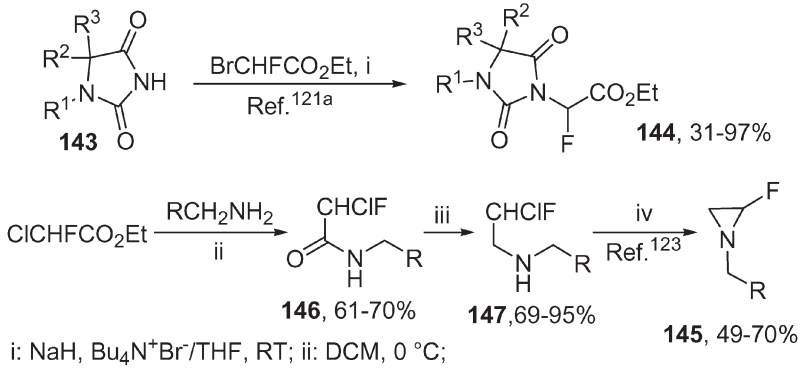


SCHEME 46

Ethyl bromofluoroacetate was converted to xanthate **136**, which can undergo radical addition to cyclic and acyclic alkenes to yield fluoroesters **137** and **138**. In the resulting compounds the ROC(S)S group can be substituted with various O-, C- and N-nucleophiles. This approach was used in the synthesis of the precursor of fluorinated nucleoside[117].

The reaction of iodofluoroacetates with alkenes and zinc in the presence of nickel dichloride hexahydrate and pyridine afforded the corresponding α-fluoroesters in good yields[118]. The iron-powder-initiated radical addition of fluoroiodoacetates proceeded well with electron-rich terminal alkenes yielding α-fluoro-γ-iodoacetates. The reaction with cyclic alkenes gave low yields[119]. Triethylborane-mediated iodine atom-transfer radical addition of fluoroiodoacetate to 1-alkene or cyclic alkene proceeded in a good yield to give the α-fluoro-γ-iodoesters[120]. Treatment of the resulting α-fluoro-γ-iodoesters **139** with base led to fluorocyclopropanes **140**. In the case of cyclic α-fluoro-γ-iodoesters **141**, only the *trans*-isomer gave a cyclopropane with exclusive formation of *endo*-isomer **142**[120].

Like most halogenides, haloacetates can serve as alkylating agents, representing thus synthetic equivalents of $^{+}$CHFY cation. Thus, bromofluoroacetates were used in the synthesis of dipeptides containing the α-fluoroglycine fragment (Scheme 47)[121]. For example, introduction of ethyl bromofluoroacetate in the Gabriel reaction with hydantoins **143** leads to fluorinated carbonyl-bridged peptides **144**. The obtained peptides are quite stable due to the electron-acceptor effect of the imide group and can be further modified[121a]. The stability of dipeptides in this case is quite un-



SCHEME 47

usual, as α-fluoroamino compounds are usually rather unstable and prone to HF elimination and decomposition[121b,122]. For example, alkylation of benzylamine with ethyl bromofluoroacetate resulted in the corresponding α-fluoroglycinate formation in a very low yield of 21%, with the product being unstable on silica gel and in $CDCl_3/D_2O$ [122].

Alkylation with introduction of the CHFX fragment can also be accomplished in an intramolecular process. The synthesis of monofluoroaziridines **145** from $CHClFCO_2Et$ is a good example. Ethyl chlorofluoroacetate was converted to amide **146**, which was reduced to amine **147**. The latter was cyclized to the target fluoroaziridine with LiHMDS [123].

Recently the use of $CHBrFCO_2Et$ in nanocrystalline-MgO-catalyzed Wittig reaction, resulting in α-fluoro-α,β-unsaturated ester formation in excellent yields with high stereoselectivity, has been described[124].

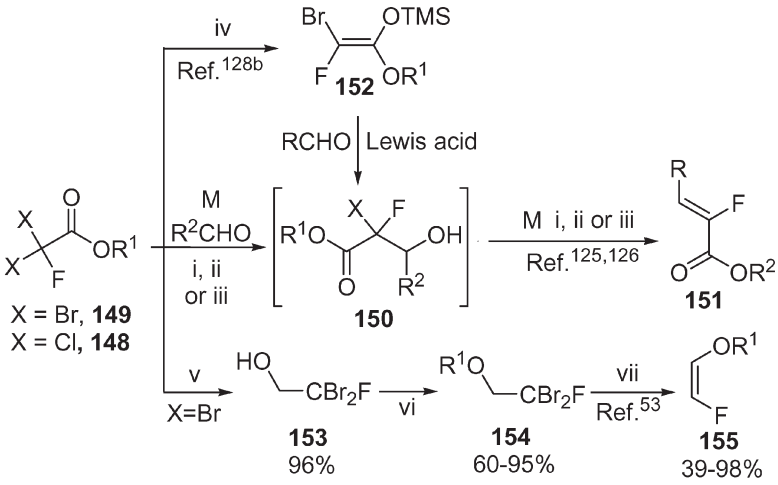
3.3.3. Dihalofluoroacetic Acids Derivatives

Synthetic applications of dihalofluoroacetic acid esters **148**, **149** are based on the reactions of organometallics generated from them. Analogously to bromofluoroacetate, these compounds enter Reformatsky reactions. However, the resulting adduct **150** is prone to subsequent transformations under the used reaction conditions. The conditions were found which permit conversion of **150** to fluoroalkenes. Thus, CFX_2CO_2R (X = Cl, Br) in the presence of Zn(0) [125], Fe(0) [126a] or $CrCl_2$ [126] reacted with aldehydes giving (*Z*)-α-fluoro-α,β-unsaturated esters **151** in high yields. Olefination of aldehydes with methyl dichlorofluoroacetate in the presence of Zn/CuCl was used at the initial stage of the synthesis of fluorinated pyrethroids, representing potential insecticides[127]. β-Fluoro-β-bromoalcohols **150** were obtained from silylated acetal **152** via reaction with aldehydes. Asymmetric modification of this reaction was also realized[128]. β-Bromo-β-fluoroalcohols **150** were reduced to β-fluoroalcohols by the action of tributyltin hydride in the presence of $Et_3B/AlMe_3$ [129].

Analogously to $CFBr_3$, dibromofluoroacetate **149** was introduced into the Wittig reactions with aldehydes or ketones in the presence of diethylzinc and triphenylphosphane, giving α-fluoro-α,β-unsaturated esters with moderate *Z*-stereoselectivity. Application of [3-(diphenylphosphanyl)phenyl]triphenylphosphonium perchlorate instead of Ph_3P eased isolation of the products[130].

CBr_2FCO_2Et found also application in the synthesis of β-fluorovinylic ethers. Dibromofluoroacetate **149** was reduced to alcohol **153**, which was

then converted to ethers **154**. The reaction of resulting ethers with $CrCl_2$ and Mn powder provided 2-fluorovinyl alkyl ethers in high yields and in *Z*-selective manner (Scheme 48)[53].



i: X = Cl, M = Zn, Ac_2O, CuCl, MS 4A/THF, 50 °C; ii: X = Cl, M = Fe, THF, RT - 60°C; iii: X = Br, M = $CrCl_2$, THF, RT; iv: TMSCl, Zn/THF, -20 °C; v: LAH, $B(OMe)_3/Et_2O$; vi: R^1Br, $Bu_4N^+I^-$, NaOH/DCM-H_2O; vii: $CrCl_2$, Mn, $NiCl_2(PPh_3)_2$/THF, RT

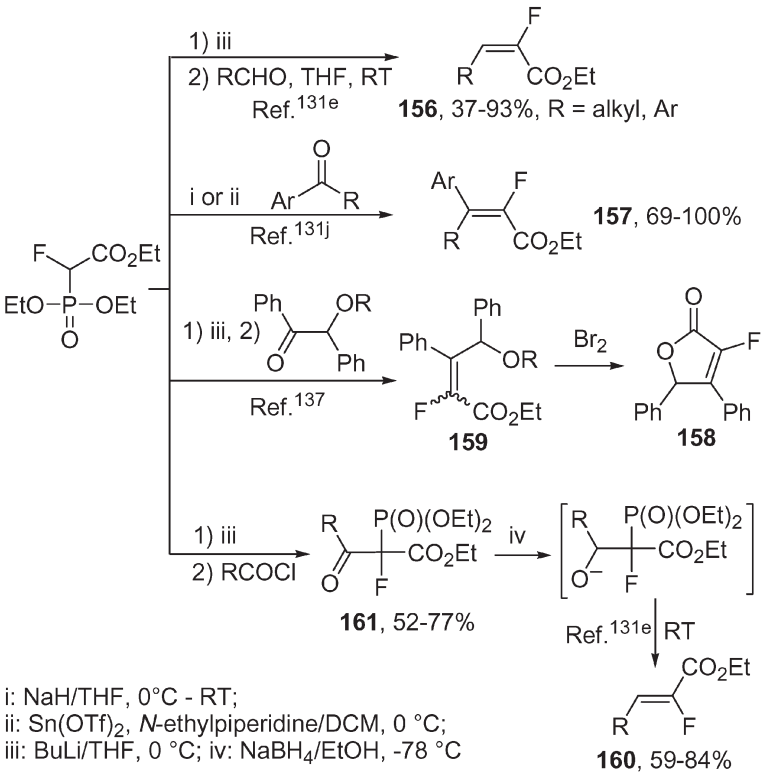
SCHEME 48

3.3.4. Other Derivatives of Fluoroacetic Acid

Commercially available ethyl 2-(diethoxyphosphoryl)-2-fluoroacetate is the synthetic equivalent of $RO_2CCHF(^-)$ anion and it is widely used in the synthesis of both (*E*)- and (*Z*)-α-fluoro-α,β-unsaturated esters[1c,6f,131]. This phosphonate can be also synthesized from ethyl bromofluoroacetate[132], ethyl chlorofluoroacetate[133], $(EtO)_2P(O)CFHBr$ [87], $(EtO)_2P(O)CFBr_2$ [134], chlorotrifluoroethene[135] or obtained by fluorination of $EtO_2CCH_2P(O)(OEt)_2$ with Selectfluor[136].

Condensation of ethyl 2-(diethoxyphosphoryl)-2-fluoroacetate with aldehydes results in predominant formation of (*E*)-α-fluoro-α,β-unsaturated esters **156** [131e]. The Horner–Wadsworth–Emmons (HWE) reaction of $EtO_2CCHFP(O)(OEt)_2$ with aryl alkyl ketones employing $Sn(OTf)_2$ in the presence of *N*-ethylpiperidine proceeded stereoselectively yielding mainly

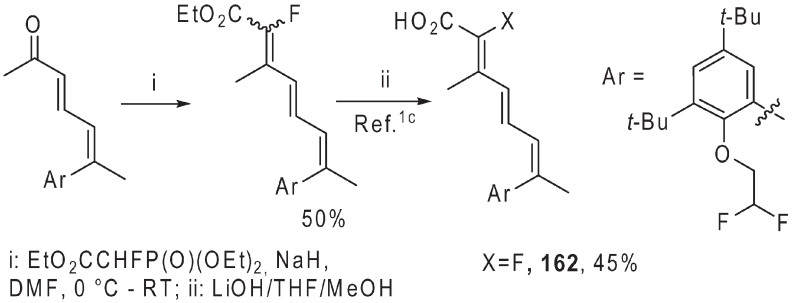
(*E*)-alkenes **157** [131j]. In some cases, (*E*)-α-fluoro-α,β-alkenoates can also be obtained by isomerization of the *Z*-isomer in the mixture of *E*/*Z*-isomers obtained by the HWE reaction of ketone with $EtO_2CCHFP(O)(OEt)_2$ and BuLi as base. Such isomerization with Br_2 in CCl_4 [137] or by UV-irradiation in the appropriate solvent[131k] was used in the synthesis of fluorofuranones **158** (Scheme 49).



SCHEME 49

(*Z*)-α-Fluoro-α,β-unsaturated esters **160** were obtained stereoselectively by acylation of $EtO_2CCHFP(O)(OEt)_2$ with acyl chlorides followed by reduction of the resulting compound **161** with $NaBH_4$ at –78 °C. Heating of the reaction mixture up to room temperature causes the resulting oxyanion to eliminate diethyl phosphonate, giving (*Z*)-fluoroalkene[131e,138]. Recently, the stereoselective synthesis of (*Z*)-α-fluoro-α,β-unsaturated esters by hydrolysis of $EtO_2CCHFP(O)(OEt)_2$ to $HO_2CCHFP(O)(OEt)_2$ followed by *i*-PrMgBr induced addition of anion to aldehyde and esterification of the resulting unsaturated acid was reported[131a].

HWE reaction of 2-(diethoxyphosphoryl)-2-fluoroacetate esters with carbonyl compounds is widely used in the synthesis of fluorinated analogues of biologically active compounds. Using this approach Gernert et al.[1c,139] synthesized fluorinated analogues of retinoid X receptor modulators **162** (X = H) (Scheme 50).



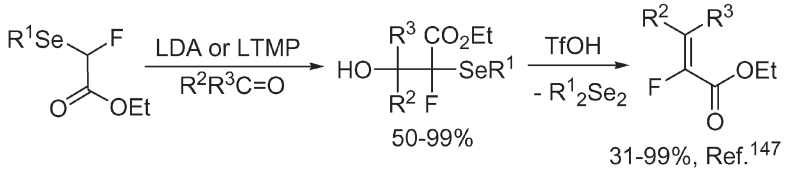
SCHEME 50

HWE reaction of $EtO_2CCHFP(O)(OEt)_2$ were used in the synthesis of fluorocyclopropyl substituted nucleosides[131b,140], fluorinated apio dideoxynucleosides[131d], *N*-substituted glycylpyrrolidides and piperidides[6f], fluorinated conformationally restricted deoxynegamycin analogues[131g], fluorinated retinal analogues[141], fluorinated L-lysine analogues[142], fluorinated urocanic acid[143] and abscissic acid analogues[144].

Analogues of $EtO_2CCHFP(O)(OEt)_2$ with more bulky alkoxy groups, such as isopropoxy, allows performing enantioselective synthesis of α-fluoro-α,β-unsaturated esters. So, the treatment of $EtO_2CCHFP(O)(OiPr)_2$ with $Sn(OTf)_2$/*N*-ethylpiperidine followed by the reaction with prochiral ketones in the presence of an optically active amine led to the corresponding α-fluoro-α,β-unsaturated esters in good yields and high enantioselectivity (ee 60–80%)[145].

The application of $EtO_2CCHFP(O)(OEt)_2$ in the synthesis of α-fluoro-β-ketoesters was reported. Diacylation of $EtO_2CCHFP(O)(OEt)_2$ with aroyl chlorides in the presence of $MgCl_2/Et_3N$ was followed by deacylation of the resulting product with aqueous ethyl acetate in the presence of SiO_2 [146]. α-Fluoro-β-oxoalkylphosphonates were obtained via a similar route[146b].

Selenides $RSeCHFCO_2Et$, prepared by the reaction of ethyl chlorofluoroacetate and $R_2Se_2/NaBH_4$, were applied to the synthesis of α-fluoro-α,β-unsaturated esters according to Scheme 51 [147].



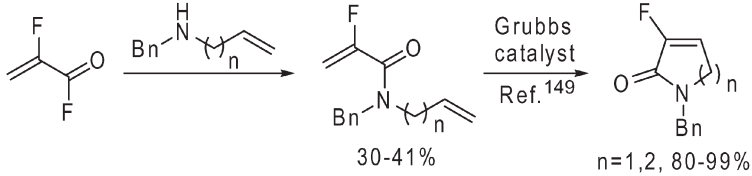
SCHEME 51

4. SYNTHETIC APPLICATIONS OF THREE-CARBON AND LARGER FLUORINATED BUILDING BLOCKS

Three-carbon and larger fluorinated building blocks are either obtained from the appropriate C_1 or C_2 precursors, as described in the corresponding parts of the present review, or by fluorination of fluorine-free precursors, and in this case the building block approach is closely bound to the fluorination approach. The restricted volume of the review prevents us from discussing all building blocks, obtained by fluorination of fluorine-free precursors[5b,c,8,148]. Therefore, described below are only examples of C_3 and larger building blocks that are not derived from C_1 or C_2 blocks and which, for that reason, were not described above. Pericyclic reactions of fluorinated compounds leading to monofluorinated products are also described in this section.

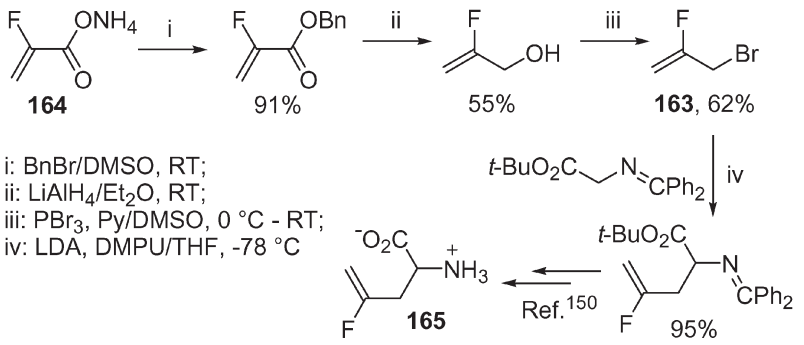
4.1. Three- and Four-Carbon Fluorinated Building Blocks

3-Chloro-2-fluoroprop-1-ene and α-fluoroacryloyl fluoride were used in the synthesis of fluorinated pyrrole and piperidine derivatives via a reaction sequence involving alkylation or acylation of unsaturated amines followed by a metathesis reaction (Scheme 52)[149].



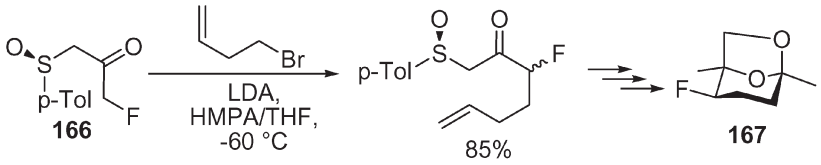
SCHEME 52

3-Bromo-2-fluoroprop-1-ene (**163**) obtained from ammonium α-fluoroacrylate (**164**) was used in the synthesis of monofluorinated aminoacids **165** by alkylation of glycine imines followed by deprotection (Scheme 53)[150].



SCHEME 53

Ketone **166**, derived from ethyl fluoroacetate[151], was used as starting material in the synthesis of fluorinated analogue of frontaline **167**, which is the active component of *Dendroctonus frontalis* pheromone (Scheme 54)[151,152].

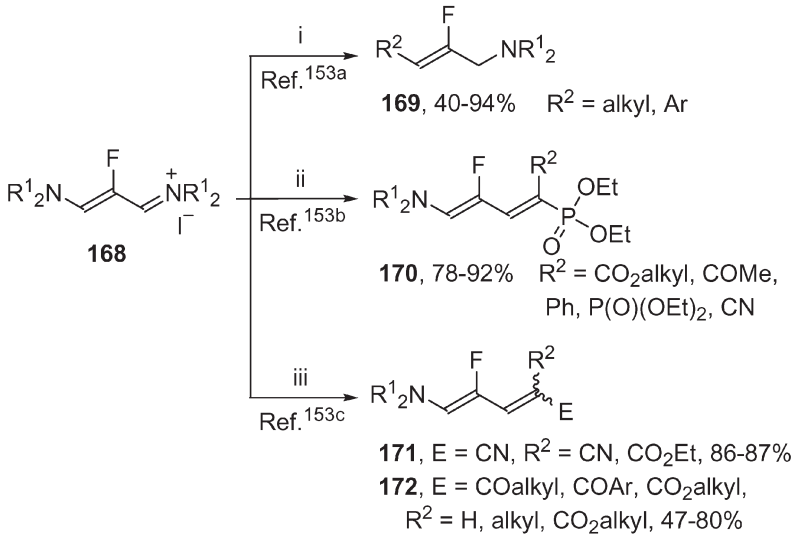


SCHEME 54

An interesting C_3-fluorinated building block – β-fluorovinamidinium salts **168** – was proposed by Yamanaka et al.[153]. The synthetic potential of these compounds is based on their reactions with nucleophiles (Scheme 55). β-Fluorovinamidinium salts were applied for the synthesis of fluorinated allylamines **169** [153a], phosphonates **170** [153b], unsaturated nitriles **171**, and ketones **172** [153c].

Commercially available ethyl 2-fluoroacetoacetate (**173**) was used as synthetic equivalent of the $EtO_2CCH(^-)$ anion in the synthesis of fluorinated derivative of bicyclo[3.1.0]hexane **174**, which is an intermediate in the synthesis of mGluR 2 receptor agonist MGS0028 (Scheme 56)[154].

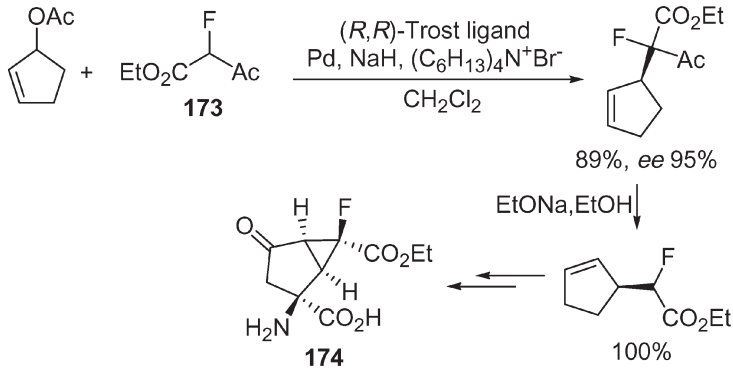
Ethyl 2-fluoroacetoacetate was also used in the enantioselective synthesis of α-fluoro-β-ketoesters **175**. Compound **173** was converted to a chiral enamine **176**. The latter was reacted with various electrophilic alkenes to give adducts **177** which were further hydrolyzed to esters **175**. The reactions proceed in good yields, though ee's of the final products with a fluorine atom at the asymmetric carbon are less than 77% (Scheme 57)[155].



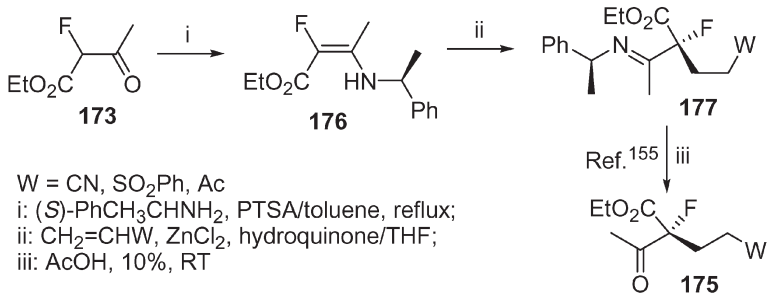
i. R^1 = Et, 1) R^2MgBr/THF, RT; 2) DIBAL or BH_3*THF/THF, RT; 3) H_2O
ii. R^1 = Et, 1) $R^2CH_2P(O)(OEt)_2$, *t*-BuOK/DMF, RT;
2) *t*-BuOK or NaH (or AcOH for R^2 = Ph);

iii. $R^1{}_2N$ =  , R^2CH_2E, LDA or NaH, Et_3N/THF

SCHEME 55

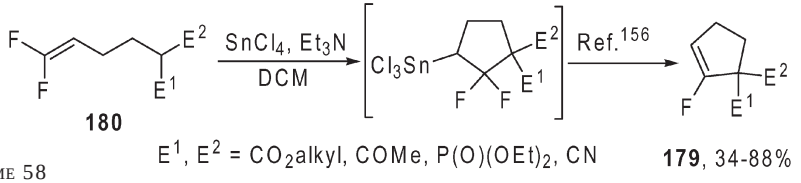


SCHEME 56



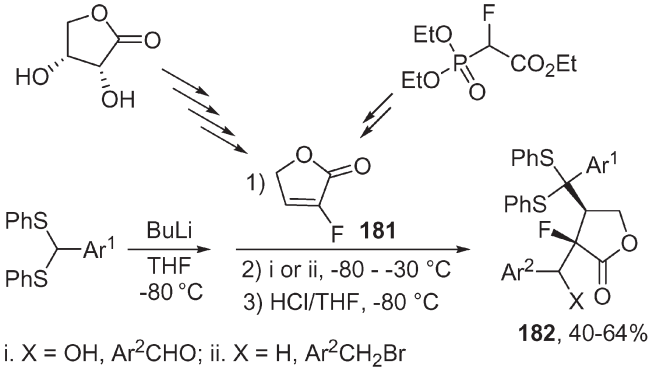
SCHEME 57

An interesting approach to fluorinated cyclopentene derivatives **179**, based on the $SnCl_4$-amine mediated carbocyclization of terminally difluorinated alkenyl active methine compounds **180**, was proposed by Saito et al.[156]. The starting fluorinated compounds can be obtained from 4,4-difluorobut-3-enyl mesylate (Scheme 58).



SCHEME 58

3-Fluorofuran-2(5*H*)-one **181**, which was prepared by transformation of D-erythronolactone or from ethyl 2-(diethoxyphosphoryl)-2-fluoroacetate, enters tandem additions when reacted with soft nucleophiles, such as lithium salts of dithioacetals, and such electrophiles as arenecarboxaldehydes or arylmethyl bromides. The resulting compounds **182** represent synthetic intermediates for the synthesis of fluorinated lignans (Scheme 59)[135,157].



SCHEME 59

4.2. Cycloaddition Reactions of Fluorinated Alkenes and Alkadienes

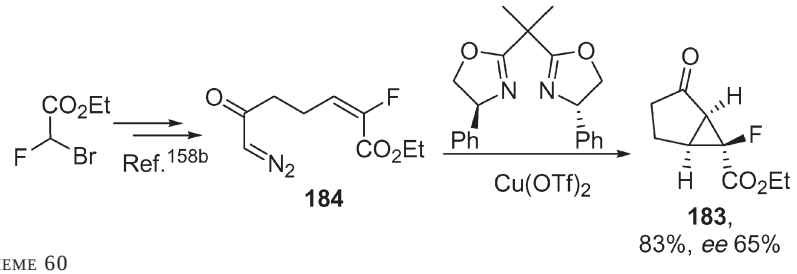
4.2.1. [2+1] Cycloaddition Reactions with Fluorinated Substrates

Synthesis of monofluorinated cyclopropanes and aziridines via [2+1] cycloaddition reactions with fluorinated substrates can be accomplished either by reactions of fluorinated carbenes with non-fluorinated ethenes and imines, or by reactions of non-fluorinated carbenes with fluorinated unsaturated compounds. The first approach was discussed in Section 2.1.

4.2.1.1. Cyclopropanation of Fluoroolefins

Cycloadditions of carbenes to fluoroolefins lead to fluorocyclopropanes[158]. Enantioselective modification of this reaction is also known[158g]. Haufe et al. have developed a technique of enantioselective synthesis of fluorocyclopropanes on the basis of cyclopropanation of 1-fluorostyrene with diazoacetates in the presence of chiral Cu(II)[159] or Rh(II)[158g].

Intramolecular cyclopropanation allows the synthesis of polycyclic compounds possessing fluorocyclopropyl fragment[158b,e]. Intramolecular cyclopropanation of the C=CF fragment was the key step in preparation of the fluorinated bicyclic ketone **183**, key intermediate in the synthesis of biologically active products. The precursor of the ketone, diazocompound **184**, was synthesized in several steps from ethyl bromofluoroacetate[158b]. A catalyst was found which allowed the synthesis of the target compound in good yield and with high enantioselectivity (Scheme 60)[158b]. Cycloadditions of nitrenes to fluoroolefins lead to fluoroaziridines[160].

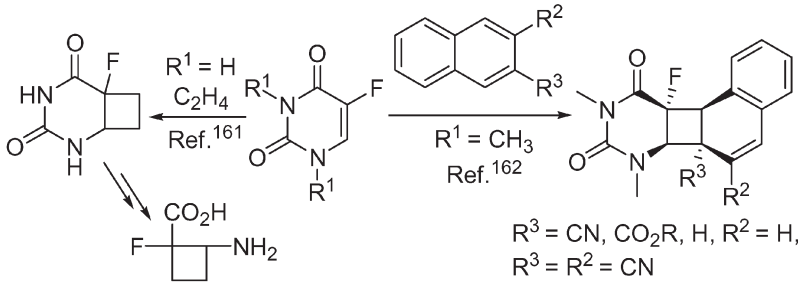


SCHEME 60

4.2.2. [2+2] Cycloaddition Reactions with Fluorinated Substrates

5-Fluorouracil derivatives undergo [2+2] cycloaddition reactions to certain alkenes. Thus, 5-fluorouracil reacted with ethene under UV irradiation.

Degradation of the pyrimidine ring in the adduct led to 2-amino-1-fluorocyclobutanecarboxylic acid[161]. 5-Fluoro-1,3-dimethyluracil reacted with substituted naphthalenes under ultraviolet irradiation in the presence of penta-1,3-diene yielding the corresponding cyclobutane. The reaction proceeded with naphthalenes having both electron-acceptor and electron-donor substituents, but with the opposite regioselectivity (Scheme 61)[162].



SCHEME 61

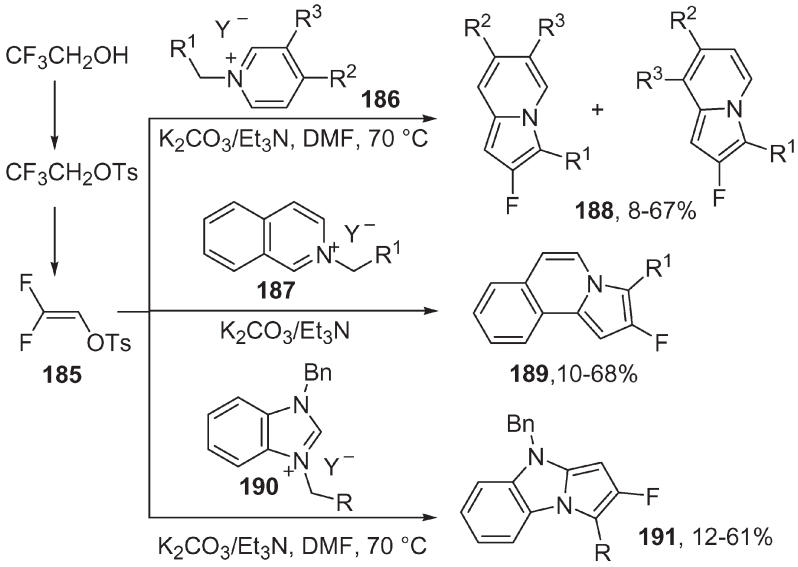
For additional examples, see Section 2.1, Scheme 3.

4.2.3. [3+2] Cycloaddition Reactions with Fluorinated Substrates

Synthesis of monofluorinated compounds via [3+2] cycloaddition reactions with fluorinated substrates can be accomplished either by reacting fluorinated dipoles with non-fluorinated dipolarophiles or vice versa. The former approach was reviewed in Section 2.1 (see Schemes 5–7).

4.2.3.1. Fluorinated Dipolarophiles

2,2-Difluorovinyl tosylate (**185**), obtained from 2,2,2-trifluoroethan-1-ol[101] was used as fluorinated dipolarophile. 1,3-Dipolar cycloaddition of the ylides generated from alkylpyridinium **186** and alkylisoquinolinium salts **187**, upon treatment of **185** with base, gave rise to fluorinated indolizines **188** and **189** after HF and TsOH elimination from the primary adducts. The same reaction with the ylides generated from benzimidazole derivatives **190** gives 4*H*-pyrrolo[1,2-*a*]benzimidazoles **191** (Scheme 62)[163]. Similarly, 1,3-dipolar cycloaddition of pyridinium and isoquinolinium ylides to 1,1-difluoroethene, generated *in situ* from CF_3CH_2X (X = Cl, F) by the action of base at atmospheric pressure in normal glassware, leads to 2-fluoroindolizine derivatives[164].



SCHEME 62

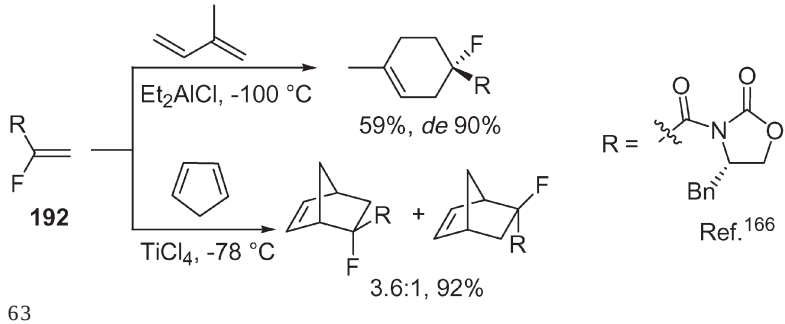
4.2.4. [4+2] Cycloaddition Reactions with Fluorinated Substrates

4.2.4.1. Fluorinated Dienophiles

Derivatives of 2-fluoroacrylic acid were used in the syntheses of fluorinated cyclohexane[165,166] and norbornane derivatives[166,167] via [2+4] cycloaddition reactions. Thus, Taguchi et al.[167a] reported the synthesis of the 2-fluoro analogue of 6-aminonorbornane-2,6-dicarboxylic acid, a conformationally restricted analogue of glutamic acid, in optically pure form starting from benzyl 2-fluoroacrylate. Use of fluoroacrylates having the deca-1,7,9-trienoate system permitted the stereoselective synthesis of fluorinated 3,4,4a,7,8,8a-hexahydro-1*H*-isochromen-1-one derivatives via intramolecular Diels–Alder reaction[168].

Haufe et al.[167c] found that α-fluoro-α,β-unsaturated carbonyl compounds, compared with the corresponding non-fluorinated parent compounds, are less reactive in Diels–Alder reactions with normal 1,3-dienes. Using enantiopure metal complexes of Lewis acids such as titanium TADDOLates, moderate enantioselectivity (enantiomeric excess max. 43%) was found in the cycloaddition of cyclopentadiene with 2-fluorooct-1-en-3-ones. The asymmetric variant of the [2+4] cycloaddition reaction was also realized

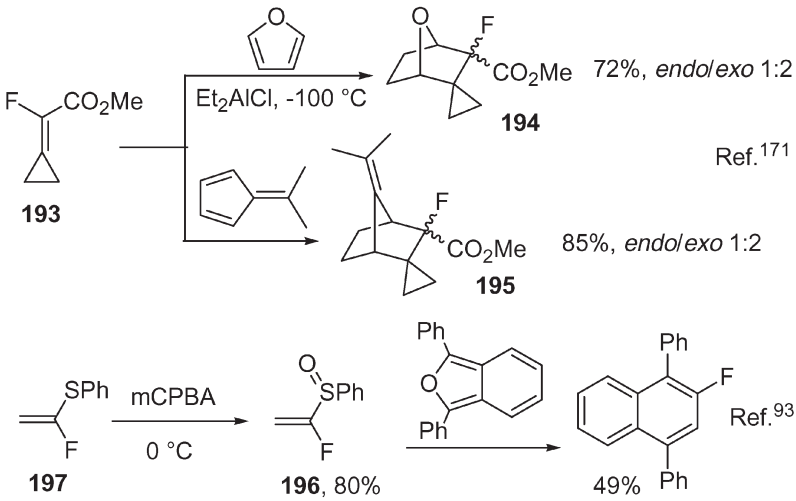
with chiral amides of fluoroacrylic acid[166]. Amide **192** was used in the Diels–Alder reaction with isoprene and cyclopentadiene to give the corresponding cycloadducts, but with high diastereoselectivity only in the first case (Scheme 63).



SCHEME 63

Dimethyl fluorofumarate, synthesized from DMAD and CsF, represents another example of a fluorinated dienophile[169]. Its hydrolysis followed by dehydration of the resulting acid yielded the corresponding anhydride which is able to take part in the Diels–Alder reaction with furan. Hydrogenation of the adduct leads to a fluorinated cantharidin analogue[170].

Diels–Alder reaction of 2-cyclopropylidene-2-fluoroacetate (**193**) with furan and 6,6-dimethylfulvene gave rise to fluorinated polycyclic compounds **194** and **195** (Scheme 64). The reaction of **193** proceeded slower



SCHEME 64

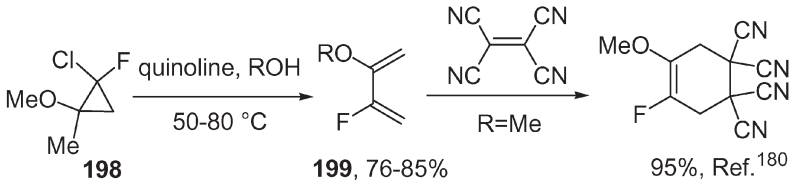
than the reactions of chlorinated, brominated and unsubstituted counterparts. This was explained by the intermediate formation of biradical or zwitterionic intermediates, in which a fluorine atom destabilizes radical or carbanionic centre[171].

Sulfoxide **196**, prepared by oxidation of α-fluorovinyl phenyl sulfide (**197**), reacted with 1,3-diphenylisobenzofuran to give a Diels–Alder reaction adduct in moderate yield, though no reaction was observed with other dienophiles[93].

Other examples of fluorinated dienophiles are (*Z*)-2-fluoro-2-(phenylsulfonyl)vinyl *N*,*N*-diethylcarbamate[172], fluorinated styrenes[173], 2,2-dichoro-1-fluorovinyl phenyl sulfone[174], 5-fluoro-1,3-dimethyluracil[162a,175], fluoroacrylaldehyde[176], diethyl (1-fluoropropa-1,2-dien-1-yl)phosphonate[177], 3-fluorofuran-2(5*H*)-one[178] and fluorinated *p*-benzoquinones[179]. The reaction of the latter with 7-methoxy-4-vinyl-1,2-dihydronaphthalene (Dane's diene) was used in the synthesis of fluorinated D-homosteroids[179].

4.2.4.2. Fluorinated Dienes

Several fluorinated dienes active in [2+4] cycloadditions are known. Heating the alkoxy-substituted chlorofluorocyclopropane **198** (obtained from chlorofluorocarbene and 2-methoxypropene) with quinoline in the corresponding alcohols gave fluorinated alkoxydienes **199**, which readily underwent Diels–Alder reactions (Scheme 65)[180]. The yield of the cycloadducts can be significantly increased by performing the reaction under microwave irradiation[181].

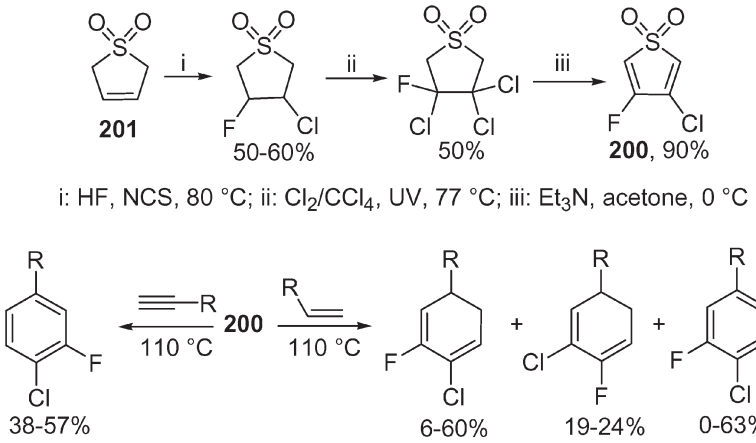


198 **199**, 76-85% 95%, Ref.[180]

SCHEME 65

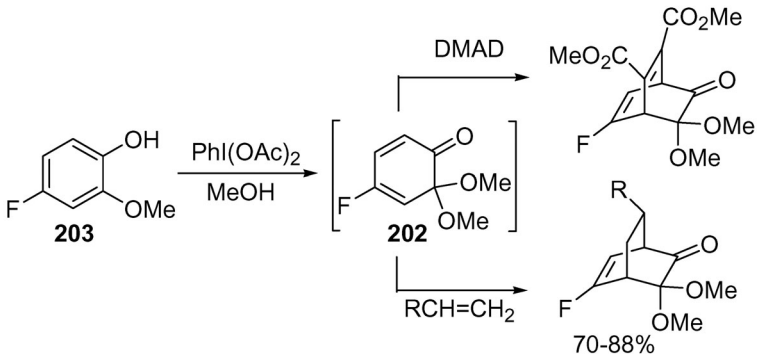
3-Chloro-4-fluorothiophene 1,1-dioxide (**200**), which formed a Diels–Alder adduct with ethenes and acetylenes, was obtained in three steps from sulfolene (**201**) (Scheme 66)[182].

Another example is presented by dienone **202**, which could be generated by oxidation of 4-fluoro-2-methoxyphenol (**203**) with $PhI(OAc)_2$ in methanol. Its reactions with dienophiles led to fluorinated bicyclooctene



SCHEME 66

derivatives (Scheme 67)[183]. *In situ* enzymatic oxidation of *p*-fluorophenol generated 4-fluorocyclohexa-3,5-diene-1,2-dione, which entered into [2+4] cycloaddition reaction to ethyl vinyl ether[184].



SCHEME 67

5. CONCLUDING REMARKS

The design of building blocks for the synthesis of monofluorinated organic compounds is an actively developing field of organic chemistry. Significant success has been achieved in the synthesis of fluorinated unsaturated compounds, such as alkenes, enynes and enones. The synthesis of fluorinated

aromatic compounds is also quite a developed field. At present, however, building blocks for the synthesis of monofluorinated nitrogen-containing compounds are rather rare. Taking into account the significance of such compounds in drug design, the development of synthetic routes to such building blocks is an important and interesting field of research.

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