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Methods for the Synthesis of *gem*-Difluoromethylene Compounds

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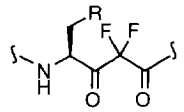
Contents

1 INTRODUCTION

A substantial body of literature relating to the selective introduction of fluorine into organic molecules has accrued during the 1980's and 1990's driven largely by the interest in biologically active compounds and the recognition of the profound effect that selective fluorination can have on biological activity.[1-13] The greater proportion of this work has focused on monofluorination. However, the *gem*-difluoromethylene group, with the CF_2-carbon at both the sp^3 and sp^2 hybridization level, is of singular importance and techniques to meet the particular demands of its deployment have proliferated. *gem*-Difluorination is an oft used modification of biologically active compounds and examples from this area serve to illustrate the properties commonly associated with the CF_2-group.

The high electronegativity of fluorine ensures that the electronic nature of the CF_2-group is a dominant characteristic. α,α-Difluorination of ketones imparts increased electrophilicity to the carbonyl and a consequent propensity for the formation of stable hydrates and hemiketals.[6] Such species have been purported to mimic the tetrahedral transition states involved in the hydrolytic action of proteases and esterases, and enzyme inhibition can occur when the nucleophilic hydroxyl is part of the active site. A crystal structure has been obtained for the covalent complex of porcine pancreatic elastase and peptidyl α,α-difluoro-β-keto amide, containing structural unit **1**, wherein the inhibitor is bound at the active site as a hemiketal by serine residue Ser-195.[14] Peptidyl motif **1** has been the key to potent and selective renin inhibitors.[15] In similar fashion the difluoromethylene group can add stability to neighbouring glycosidic and acetal linkages, which was notably exploited by Fried in the design of chemically stable thromboxane A_2 agonist **2**.[16] It was proposed that acid induced acetal cleavage is disfavoured by strong inductive destabilization of the cation **3**.

The difluoromethylene group has been vaunted as an isoelectronic and isosteric replacement for oxygen in phosphate analogues to the extent that many of the standard *gem*-difluorination techniques have been turned to the synthesis of difluoromethylenephosphonates. The CF_2/O transposition has given rise to several natural products with significant biological activity,[17-19] as exemplified by difluorophosphonates **4a** and **4b**, analogues of 1,3-bis(phosphoglyceric)acid.[18] However, the exact nature of the analogy between O- and CF_2-linkages remains a matter of some discussion.[20-22] The replacement of C-O bond with C-C bonds undoubtedly confers hydrolytic stability and the *gem*-difluoro substituents add polarity lost in simple methylene analogues, although it has recently been suggested that the CHF-group may offer more of an isopolar substitution for oxygen.[22] Nevertheless, the increased acidity of ionizable neighbouring groups is a valuable consequence of *gem*-



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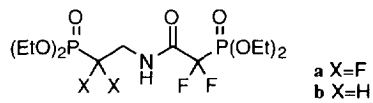

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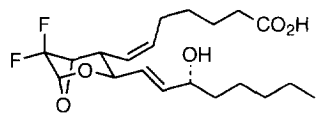
a X=F
b X=H



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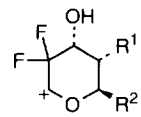

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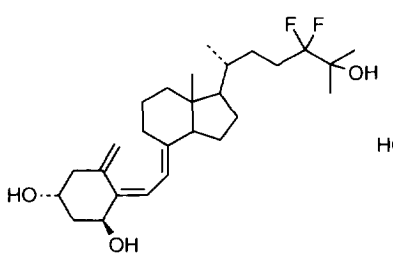
difluorination. The tenet that the CF_2/O transposition is isosteric may also be regarded with caution: Fluorine has a van der Waals radius[23] of 1.47Å (1.35Å is still widely quoted) as compared with 1.20Å for hydrogen and 1.52Å for oxygen, which together with other data indicates that fluorine has a much closer steric relationship with oxygen than hydrogen and it must be borne in mind that modification by F/OH transposition has been widely used in bioactive systems. However, in his intriguing article on the *'Physiological size' of Fluorine Substituents* Schlosser reported the strong similarity in organoleptic properties between some fluorinated compounds and their hydrogen containing parents (F/H transposition) and contrasted this with the more dramatic effect of replacing a hydrogen with a methyl group.[24] The exceptional size of fluorine minimises the steric perturbation of the CF_2-group, but steric interactions need to be considered in conjunction with electronic factors when assessing the implications of *gem*-difluorination. Smart's chapter in *Organofluorine Chemistry: Principles and Commercial Applications* is thoroughly recommended as a clear and concise introduction to the properties of C-F systems that debunks some commonly quoted and misleading generalizations.[25]

The CF_2/CH_2 transposition has been a valuable tool in the blockage of metabolic oxidation. This approach has furnished stable and potent compounds such as vitamin D_3 analogue **5**,[26] in which the C-24 position is blocked to metabolic hydroxylation by difluorination. The *gem*-difluoromethylene replacement of a CHOH-linkage has been used to some effect in cyclitol and carbohydrate systems where the enhancement of neighbouring group stability or acidity may be important: the cytosine analogue gemcitabine **6** is under clinical development for activity against lung, ovarian, renal, pancreatic and head and neck cancers.[27-29] *gem*-Difluoroalkenes have underpinned the success of several mechanism based inhibitors through their enhanced reactivity relative to non-fluorinated systems.[5,30] Allylic amine **7** is an inhibitor of monoamine oxidase and acts by suffering oxidation to a Michael acceptor, which can alkylate nucleophilic residues in the active site.[30]



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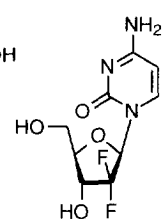

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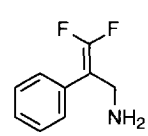

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The preparation of *gem*-difluoromethylene substituted molecules falls broadly into two classes. The first involves direct *gem*-difluorination, and the second draws from the pool of fluorinated reagents to incorporate an intact CF_2-synthon. Direct fluorination is a powerful technique, particularly when used at a late stage in a synthetic scheme on robust intermediates that can withstand the often forcing conditions. A general difficulty associated with the preparation of complex fluorinated molecules is that the change in chemical reactivity brought about by fluorine often leads to unexpected difficulties with reactions commonly used in organic synthesis: for example, reversal of selectivity has been observed in aldol reactions involving Evans's[31,32] or Oppolzer's[33] chiral auxiliaries in the case of α,α-difluoro carbonyl compounds. However, with the increasing accessibility of fluorinated building-blocks, new reactions have emerged for the elaboration of fluorinated intermediates and the CF_2-synthon approach has consequently blossomed.

The purpose of this review is to present modern and practical methods for the selective introduction of the *gem*-difluoromethylene group into organic molecules, using significant examples by way of illustration. The first section will describe the fluorinating reagent approach and the second the CF_2-synthon approach. This report will concentrate on reactions at the fluorinated centre, although some of the important methods for elaborating these products will be mentioned where appropriate.

2 DIRECT *gem*-DIFLUORINATION

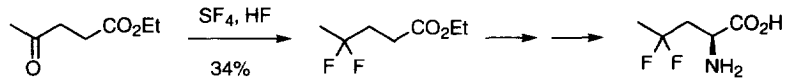
During the last fifteen years the development of strategies for the synthesis and manipulation of small fluorinated molecules has furnished the synthetic chemist with an extensive array of difluoromethylene synthons (*vide infra*). However, the classical means of CF_2-incorporation has been the use of fluorinating reagents, which may be broadly considered as sources of either nucleophilic or electrophilic fluorine.[11]

2.1 Nucleophilic Fluorination

2.1.1 Aldehydes and Ketones

One of the most common and successful strategies for *gem*-difluorination has been the $CO \rightarrow CF_2$ transformation of aldehydes and ketones with several fluorinating reagents, chief amongst which are diethylaminosulfur trifluoride (DAST, Et_2NSF_3) and sulfur tetrafluoride. Selenium tetrafluoride[34] and molybdenum hexafluoride[35,36] have been used on a number of simple systems, but despite their mildness their wider application has been limited by the hazards involved in their synthesis and use, and by the concurrent development of sulfur fluoride chemistry.

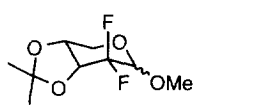
Sulfur tetrafluoride has received much attention as a difluorinating reagent and the scope of its application has been thoroughly reviewed.[37,38] A typical example of its usage and selectivity is provided by a recent synthesis of chiral amino acids with fluorinated side chains (Scheme 2.1.1.1).[39] It has been shown that the presence of excess HF in SF_4 difluorinations can suppress unwanted side reactions.[40] However, SF_4 is a toxic gas, necessitating the use of special apparatus for its frequently forcing and harsh conditions. To a greater degree these drawbacks have been circumvented by the development of dialkylaminosulfur trifluorides. A series of these reagents were shown to have very similar properties to SF_4 in the *gem*-difluorination of



Scheme 2.1.1.1

aldehydes and ketones.[41] The pioneering work of Middleton is responsible for the pre-eminence of the diethyl compound, DAST,[42] a commercially available liquid that frequently permits less forcing conditions than SF_4 and standard laboratory apparatus. Its role in organic chemistry was comprehensively reviewed in 1988[43] and many reviews since have paid testimony to its significance.[11] It has been applied across many classes of natural products and other biologically interesting systems.[9] Several examples drawn mostly from the recent literature will serve to illustrate its scope and potential shortcomings.

In one of the first studies of DAST difluorination in complex systems, Cross[44] noted that, whilst DAST is a convenient reagent, the reaction conditions vary greatly from several days at elevated temperatures to a few hours at 0°C. This is apparent throughout the subsequent literature. Cross commented on the sensitivity to the steric environment and this is particularly apparent with carbohydrates: *gem*-difluoro pentopyranoside **8** was readily accessible from its keto precursor in 78%,[45] whereas carbohydrate ketone **9** was impervious to DAST.[46] DAST has been deployed effectively in related cyclitol systems, particularly difluoro inositol analogues[47] such as *myo*-inositol precursor **10**.[48] The broad compatibility of DAST with the common *O*- and *N*-protecting groups has allowed its application to complex carbohydrate systems such as the analogue **11** of antibacterial agent netilmicin, which was obtained from its keto precursor in 62% yield.[49] The mildness and selectivity is further demonstrated by the sorangicin analogue **12**, derived from its ketone parent in 53% yield.[50]



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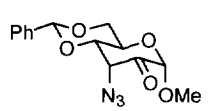

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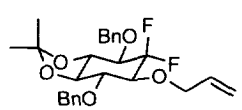

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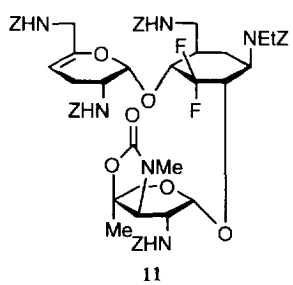

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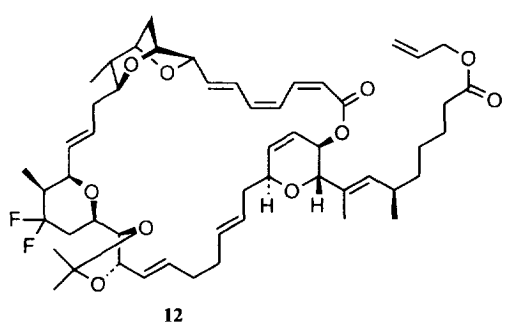

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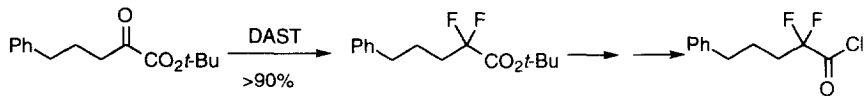
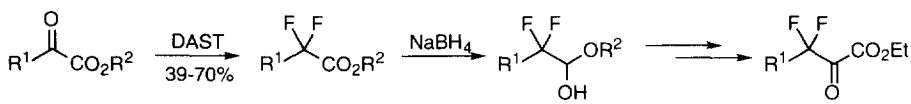
DAST, unlike SF_4, has great utility in the conversion of α-keto esters to α,α-difluoro esters,[51] as demonstrated by the synthesis of 2,2-difluoro-5-phenylpentanoyl chloride (Scheme 2.1.1.2), which, it may be noted, was inaccessible by a CF_2-synthon approach based on the Reformatsky-Claisen rearrangement.[52]



Scheme 2.1.1.2

Among the recent examples of this transformation is Takayama's synthesis of 24,24-difluoro-1α,25-dihydroxyvitamin D_3 **5**,[26] in which the C-24 was blocked to metabolic hydroxylation by difluorination of an advanced intermediate. It has been commented that improved yields can be obtained when DAST is added portion wise over the course of the reaction.[53] The significance of Middleton's original concept can be seen through the frequent use of α,α-difluoro carbonyl systems in serine protease inhibitors, in respect of which Parisi has extended this chemistry to encompass β,β-difluoro-α-keto esters (Scheme 2.1.1.3).[54] A notable feature is the generation of difluoro hemiacetals **13**, which have found some use as CF_2-synthons in their own right[55] and interestingly mimic the key intermediate in the mechanism of serine protease inhibition.



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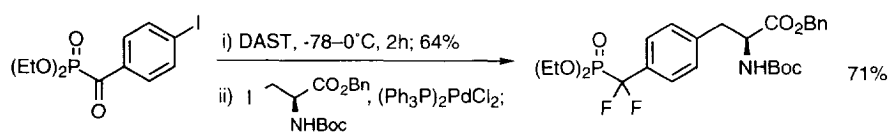
Scheme 2.1.1.3

The isosteric and isoelectronic CF_2/O transposition in phosphonic acids has become a common means to hydrolytically stable phosphate mimetics. The difluorination of α-keto esters has been extended to benzylic α-oxophosphonates in the preparation of α,α-difluorophosphonic acids.[56-59] 4-Phospho(difluoromethyl)-L-phenylalanine **14**, a hydrolytically stable analogue of *O*-phosphotyrosine has been prepared by this route (Scheme 2.1.1.4),[57] and *N*-Fmoc protection has enabled its incorporation into peptides.[60]



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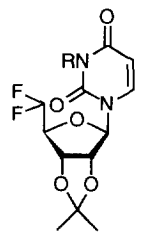
Scheme 2.1.1.4

The choice of protecting groups can be crucial to the success of DAST difluorinations. Scott has recently highlighted the importance of *N*-tosylation or benzylation for 2-acylpyrroles.[61] N-H Protection also determines the success of nucleoside reactions with DAST. 5′,5′-Difluoronucleoside **15** is accessible from the 5′-aldehyde provided that N-3 is blocked with a *p*-methoxybenzyl group,[62] the absence of which results in the formation of *O*2,5′anhydronucleoside **16**. Problems have similarly been reported for the 3′-ketothymidine, although *N*-protection was not explored.[63] Fluoroether formation has also been encountered in the attempted difluorination of β-benzyloxyketone **17**, a *gem*-difluoroprostacyclin precursor.[64] It has been proposed that fluoroether **18** is

the result of intramolecular desilylation of the activated DAST complex **19**. Structurally related ethers have been observed in attempted hydroxyl group fluorinations with DAST.[43] In the case of the α-benzyloxyketone *gem*-difluorination occurs in 74% yield with no desilylation. Presumably the increased steric congestion of the α-face suppresses intramolecular attack in favour of the second fluorination.



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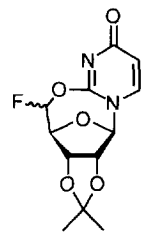

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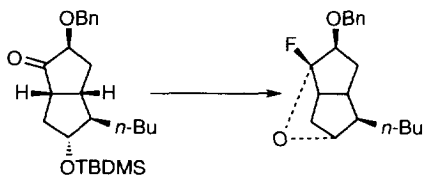
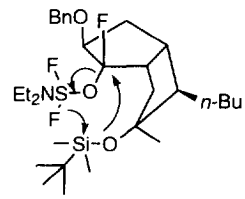


17 **18**



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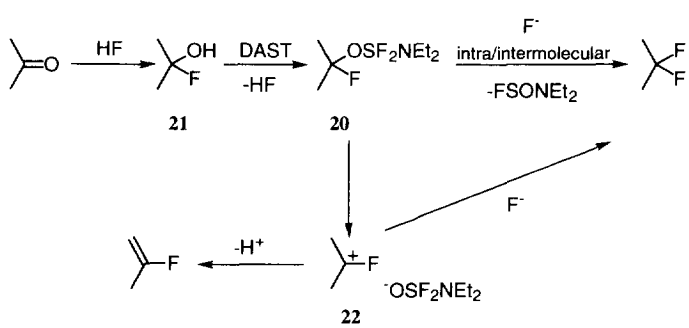
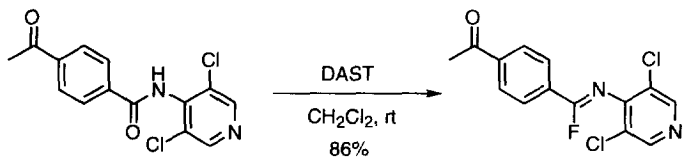
Intermediate **19** (**20**, Scheme 2.1.1.5) may arise from the reaction of DAST with the initially formed α-fluoroalcohol **21**, which itself is the result of trace HF addition across the carbonyl group.[42,43] α-Fluoroalcohols have been observed as the sole products in the attempted *gem*-difluorination 6α-formyl penicillin derivatives even on prolonged exposure to DAST.[65] The *gem*-difluoride can be formed from **20** or fluorocarbocation **22**, which can also be susceptible to α-proton loss leading vinyl fluorides or skeletal rearrangement prior to further proton loss or fluorination. Vinyl fluorides can be significant and recalcitrant side products.[66] The proportion of *gem*-difluoride and vinyl fluoride can be strongly influenced by solvent:[42,43] *gem*-difluorides are usually the major component in non-polar solvents (CH_2Cl_2), but in polar solvents (*N*-methyl pyrrolidone) vinyl fluorides can predominate.[67] Vinyl fluoride formation is not observed in SF_4 difluorinations.[43]



21 **20** **22**

Scheme 2.1.1.5

The selectivity of DAST for the carbonyl group of aldehydes and ketones over esters is implicit in its success as a difluorinating agent. However, the competive difluorination of an ester carbonyl in the presence of a hindered α-keto group has (R^1=^{i}Pr, R^2=Et, Scheme 2.1.1.3) has been reported.[54] There are a few other instances wherein the normal selectivity is usurped by unexpected reactivities, such as reaction at the α-carbon rather than the ketone group of furan-3-ones.[68] A failure of the ketone carbonyl to react was also noted in the case of 4-acetylbenzamide **23**. Rather, fluoroimine **24** was isolated in good yield (Scheme 2.1.1.6).[69] Whilst SF_4[70] and SeF_4[34] are known to convert *N,N*-dialkylbenzamides to α,α-difluorobenzylamines, this is a rare example of a reaction between DAST and an amide.

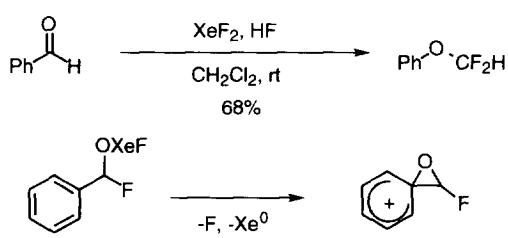


23 **24**

Scheme 2.1.1.6

In spite of the limitations, given with perhaps undue prominence here, DAST is a singularly important reagent for *gem*-difluoride synthesis. The CO→CF_2 transformation for aldehydes and ketones has also been achieved by reaction with dibromodifluoromethane/zinc (section 3.4.1).[71]

A different type of difluorination occurs with xenon difluoride. The reaction of aryl aldehydes with XeF_2 proceeded with aryl group migration to difluoromethyl phenols (Scheme 2.1.1.7).[72] As with DAST the proposed mechanism involves initial nucleophilic fluoride attack at the carbonyl carbon and reaction of the carbonyl oxygen with the electrophilic centre of fluorinating reagent. The resulting species **25** decomposes with rearrangement to phenonium ion **26**.[73] The success of the reaction when applied to aryl ketones is diminished by poor conversions and electrophilic ring fluorination.[74] However, this may be considered as alternative route to difluoromethyl phenols to the more usual alkylation of phenols with difluorohalomethanes (section 3.2.1).



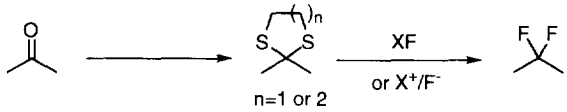
25 **26**

Scheme 2.1.1.7

In the search for ever more mild and selective reagents for the classic CO→CF_2 transformation considerable efforts have been made to move away from the carbonyl group and exploit the various reactivities offered by carbonyl derivatives, notably dithioacetals/ketals and hydrazones.

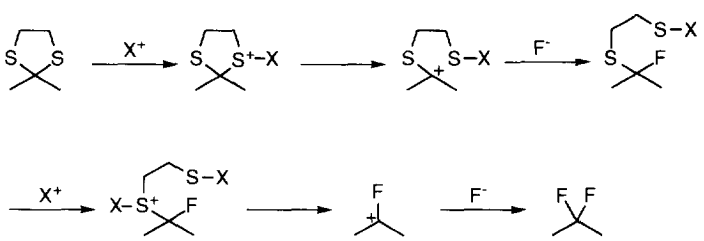
2.1.2 Dithioacetals and Dithioketals

Since Katzenellenbogen's seminal report[75] several closely related techniques have been advanced for the conversion of 1,3-dithiolanes (n=1) and 1,3-dithianes (n=2) to *gem*-difluoro compounds (Scheme 2.1.2.1).



Scheme 2.1.2.1

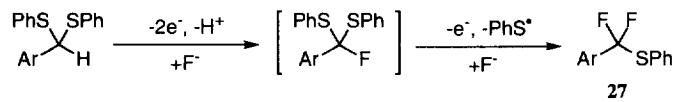
The *in situ* generation of BrF or IF lies at the heart of most of these fluorodesulfurisation reactions. The commonly accepted mechanism depends on the ability of firstly sulfur and then fluorine to stabilise α–carbocations, which are quenched by sources of nucleophilic fluoride (Scheme 2.1.2.2). Katzenellenbogen demonstrated the reaction with 1,3-dithiolane derivatives of aryl and alkyl ketones, using 1,2-dibromo-5,5-dimethylhydantoin (DBH) as the oxidant (X=Br) and pyridinium poly(hydrogen fluoride) (PPHF) as the source of fluoride. *N*-Iodosuccinimide (NIS) (X=I) was used when electrophilic ring bromination presented a problem in the case of electron rich aromatic systems. Katzenellenbogen also observed that the carbocation intermediates can give rise to rearrangements, such that in an independent report a 1,3-dithiolane/dihydro-1,4-dithiin rearrangement prevented difluorination altogether.[76] Whilst 1,3-dithianes were found to react more slowly than 1,3-dithiolanes, it was felt that the wider value of the 1,3-dithiane system lay in its consequent equivalence to a CF_2-dianion.



Scheme 2.1.2.2

Variations on Katzenellenbogen's original theme have helped to explore its scope. Sulfuryl chloride (SO_2Cl_2) (X=Cl) in PPHF, although high yielding, was limited in scope to benzophenone 1,3-dithiolanes by competing chlorination.[77] A milder source of fluoride, tetrabutylammonium dihydrogentrifluoride (TBATF), ensured the survival of an acid sensitive oxirane and an unprotected hydroxyl group but was limited to aromatic carbonyl derivatives.[78] Hexafluoropropene-diethylamine complex ($Et_2NCF_2CHFCF_3$) has been used as an *in situ* source of HF through its reaction with an equivalent of water. The reaction was suitable for 1,3-dithiolanes of ketones and aromatic aldehydes, but not aliphatic aldehydes: α-proton loss from either of the two carbocations (Scheme 2.1.2.2) was implicated in the formation of unexpected products.[79] A combination of nitrosonium tetrafluoroborate($NOBF_4$) and PPHF, in which NO^+ was the activating species, has been applied, in good yields, to the oxidative fluorodesulfurisation of 1,3-dithiolanes of aromatic ketones.[80] The mildness of

this system tolerated electron rich aromatic groups. The hypervalent iodine reagent *p*-iodotoluene difluoride (*p*-$MeC_6H_4IF_2$) (X=the electrophilic iodine centre) acts as both the oxidant and source of fluoride and is most effective with diaryl ketone derivatives.[81] The chemical oxidant may be replaced by an anode:[82] anodic fluorodesulfurisation works well for ketone 1,3-dithiolanes and acyclic dithioketals using triethylamine tris(hydrogen fluoride)[83] as the fluoride source. In contrast aryl dithioacetals under the same conditions gave *gem*-difluorothioethers **27** (Scheme 2.1.2.3) and aliphatic dithioacetals gave monofluorothioethers. This behaviour is attributed to the acidity of the α-proton, which in the case of aryl dithioacetals is such that proton loss and fluorination preceded desulfurisation.



27

Scheme 2.1.2.3

The advent of dilution techniques for elemental fluorine has enabled its use as a selective fluorinating reagent and Chambers has recently described the *gem*-difluorination of diaryl-1,3-dithiolanes with 10%F_2/N_2 and iodine at ambient temperatures in good yields.[84] Whether the fluorinating species is IF, as in other examples of this transformation, is not yet clear.

As an adjunct to the foregoing transformation, Kuroboshi has very recently reported the conversion of β-hydroxy orthothioesters **28**, derived from aldehydes (RCHO), to (1,1-difluoro-1-methylthio)ketones **29** under conditions of oxidative desulfurization, which were sufficient to oxidize the hydroxyl group (Scheme 2.1.2.4).[85]

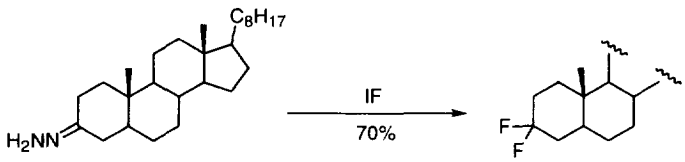
28 **29**

Scheme 2.1.2.4

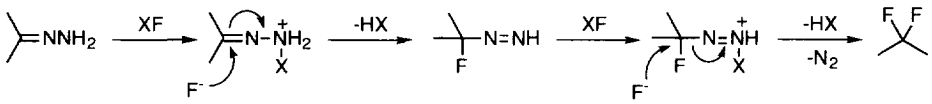
2.1.3 Hydrazones and Oximes

The principle of electrophilic activation and nucleophilic fluorination of carbonyl derivatives was contemporaneously applied to hydrazones and other imine-based derivatives. In Rozen's initial studies[86,87] the preferred reagent was IF itself and the *gem*-difluorination of hydrazones is exemplified by cholestane (Scheme 2.1.3.1). The mechanism is thought to involve electrophilic iodination of the more basic nitrogen followed by HI elimination and nucleophilic fluorination (Scheme 2.1.3.2). Side reactions can occur when α-proton elimination competes with the second fluorination. Unsatisfactory results were obtained when the NIS/PPHF combination was used as an equivalent of IF, although acceptable *gem*-difluorination occurred with *N*-bromosuccinimide (NBS)/PPHF.[88] A severe drawback with unsubstituted hydrazones is their instability and their propensity for forming azines, which are unreactive to IF. This problem was lessened at the expense of lower yields and longer reaction times by using substituted variants such as 2,4-dinitrophenyl and tosyl hydrazones, semicarbazones and oximes. However, azines themselves undergo *gem*-difluorination with

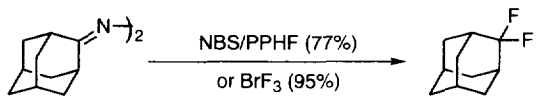
NBS/PPHF (Scheme 2.1.3.3).[88] Rozen has subsequently recommended BrF_3 as a superior reagent to IF because it too reacts with azines.[89]



Scheme 2.1.3.1



Scheme 2.1.3.2

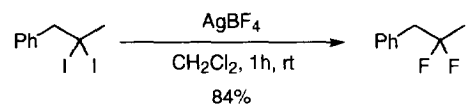


Scheme 2.1.3.3

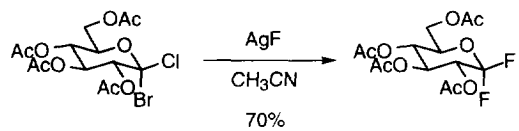
Activating reagents other than electrophilic bromo- or iodo-compounds have been used such as Olah's efficient *gem*-difluorination of *N*-methyl ketoximes with nitrosonium tetrafluoroborate ($NOBF_4$)/PPHF.[90] Aldoximes, on the contrary, underwent oxidation. Hydrazones[91] and diazo compounds[92] have been converted to *gem*-difluorides with elemental fluorine.

2.1.4 gem-*Dihalides and* gem-*Ditriflates*

Whilst halogen-fluoride exchange, $CX_2 \rightarrow CF_2$, is conceptually the simplest route to *gem*-difluorides, it has been used only intermittently and with variable success: side reactions and monofluorination are the most common complications. This is in sharp contrast to the central role that nucleophilic fluoride displacements play in monofluorination strategies.[93] However, Bloodworth has achieved the transformation of *gem*-diiodides and chlorides to *gem*-difluorides with silver tetrafluoroborate (Scheme 2.1.4.1).[94] As the dihalides were derived from carbonyl compounds this is in effect another example of the CF_2/CO transposition. Silver fluoride has been used for halogen-fluoride exchange in the synthesis of a novel glycosyl difluoride (Scheme 2.1.4.2).[95]

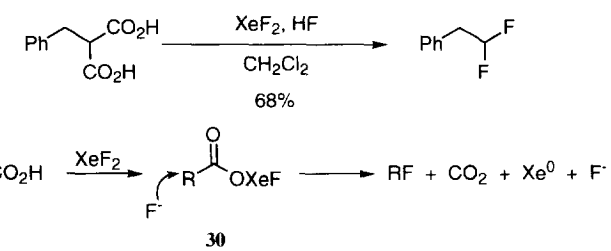


Scheme 2.1.4.1



Scheme 2.1.4.2

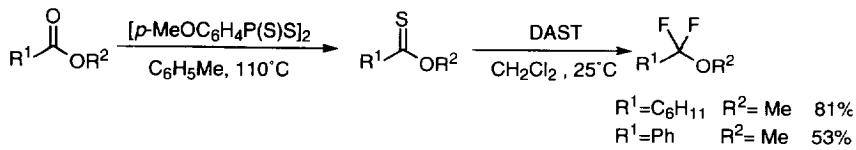
In a similar fashion *gem*-ditriflates, derived from aliphatic aldehydes, undergo *gem*-difluorination with tetrabutylammonium difluorotriphenylstannate ($[n\text{-}Bu_4N]^+[Ph_3SnF_2]^-$), a non-hygroscopic source of fluoride.[96] An interesting equivalent of this transformation is Patrick's fluorodecarboxylation of benzylmalonic acid with xenon difluoride, a Hunsdiecker-type reaction in which the intermediate fluoroxenon ester **30** decomposes either by the depicted ionic route or by radical decarboxylation (Scheme 2.1.4.3).[97]



Scheme 2.1.4.3

2.1.5 The Thiocarbonyl Group

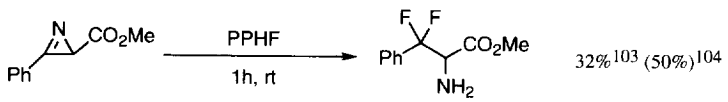
The reduced electrophilicity of ester carbonyls relative to those of aldehydes and ketones is such that esters are unreactive in the presence of DAST. However, thioesters are more electrophilic than their oxygen counterparts and are susceptible to DAST. A series of alkyl and aryl thioesters, easily prepared from esters with Lawesson's reagent, were treated with DAST to give *gem*-difluoroethers in good yields (Scheme 2.1.5.1).[98] To the same end, thioesters undergo fluorodesulfurisation with BrF_3[99] and more significantly TBATF/NBS or NIS.[100] In the latter case thionolactones were also difluorinated, as were cyclic thiocarbonates derived from diols and catechols. Oxidative fluorodesulfurisation of methyl xanthates, ROCSSMe, under very similar conditions affords difluoro(methylthio)methyl ethers, $ROCF_2SMe$.[101] This is to be contrasted with conversion of the same substrates to fluorides RF with $p\text{-}MeC_6H_4IF_2$.[102]



Scheme 2.1.5.1

2.1.6 1-Azirines

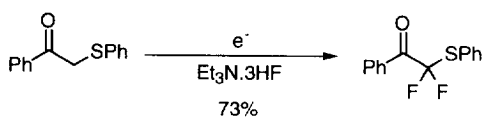
The addition of hydrogen fluoride to 1-azirines is a useful route to β,β-difluoroamines,[103] and has been applied to the synthesis of 3,3-difluorophenylalanine (Scheme 2.1.6.1).[103,104]



Scheme 2.1.6.1

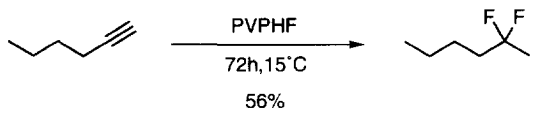
2.1.7 Saturated and Unsaturated Centres

It is more usual to envisage the C-H→C-F transformation in terms of enolates and electrophilic fluorination (section 2.2.1), however, as has been shown already with electrochemical fluorodesulfurisation of aryl dithioacetals, the reverse polarity is also possible. Brigaud and Laurent have difluorinated the α-methylene of sulfides by electrochemical oxidation in the presence of a mild fluoride quench (Scheme 2.1.7.1).[105] *gem*-Difluorination of the benzylic methylene of benzylic esters has been similarly achieved.[106]

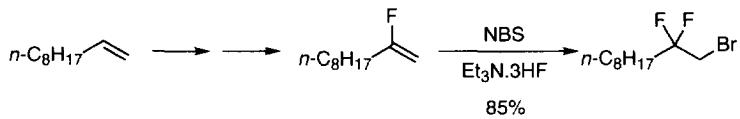


Scheme 2.1.7.1

Activation of alkenes and alkynes with suitable electrophiles can facilitate nucleophilic fluorination. Hydrofluorination of alkynes occurs with Markownikov addition using Olah's solid hydrogen fluoride equivalent reagent, poly 4-vinyl pyridinium poly(hydrogen fluoride) (Scheme 2.1.7.2)[107] and hydrofluorination of but-2-yne with a combination of KHF_2 and SiF_4 has been reported.[108] Halofluorination of alkyl substituted alkynes with IF and BrF creates the $-CF_2CX_2-$ linkage.[108] Phenyl alkynes are more liable to side reactions particularly with IF, the product of which underwent further fluorination at the CI_2 centre.[108] Fluoroalkenes are likely intermediates in these reactions and it has been shown separately that 2-fluoro-1-alkenes undergo regioselective bromofluorination under mild conditions (Scheme 2.1.7.3).[109] The regiocontrol was attributed to the ability of fluorine to stabilise α-carbocations by electron donating resonance.

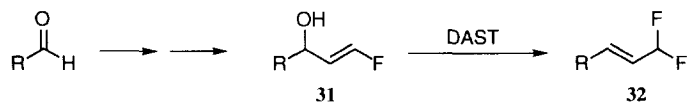


Scheme 2.1.7.2



Scheme 2.1.7.3

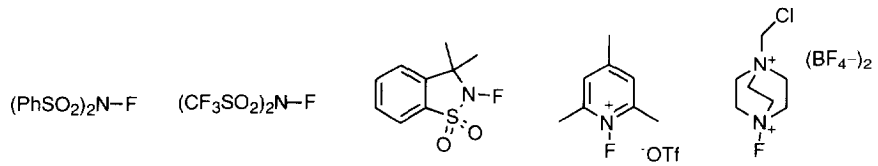
Tellier has very recently described the reaction of 1-fluoro-alkenols **31** with DAST, in which the major products (**32**, Scheme 2.1.7.4) are the result of an S_N2' fluorination.[110] Although this is an example of direct nucleophilic fluorination of a fluoroalkene, it may be more usefully viewed as the alkylidenation of a carbonyl group with $=CHCF_2H$.



Scheme 2.1.7.4

2.2 Electrophilic Fluorination

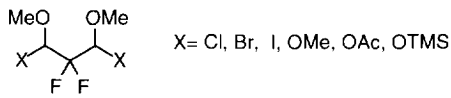
Electrophilic fluorination of various functional groups is a direct means of site specific fluorination.[11,111] Widespread application, however, has been precluded by the fearsome and non-selective nature of some of the traditional reagents. However, during the last 10 years there has been a surge in the development of mild and highly selective electrophilic fluorinating agents, drawing from the discovery that several families of *N*-fluoro compounds offer stable, practicable and mild 'F^+' transfer reagents.[112] The primary concern of most researchers has been the introduction of a single fluorine atom and difluorination has constituted an unwanted reduction of selectivity. However, the specific demands of geminal fluorination are now beginning to be addressed. The key reagents have been *N*-fluoroimides **33**[113] and **34**,[114] *N*-fluorosultam **35**,[115] *N*-fluoropyridinium salt **36**,[116] and Selectfluor **37** (commonly abbreviated to F-TEDA-BF_4, where TEDA is triethylene diamine).[117] It is of great significance that three of these reagents, *N*-fluorobenzenesulfonamide **33**,[118] *N*-fluoro-2,4,6-trimethylpyridinium triflate **36**[118] and 1-chloromethyl-4-fluoro-1,4-diazobicyclo [2.2.2]octane (**37**)[119] are now commercially available.



33 **34** **35** **36** **37** F-TEDA-BF_4

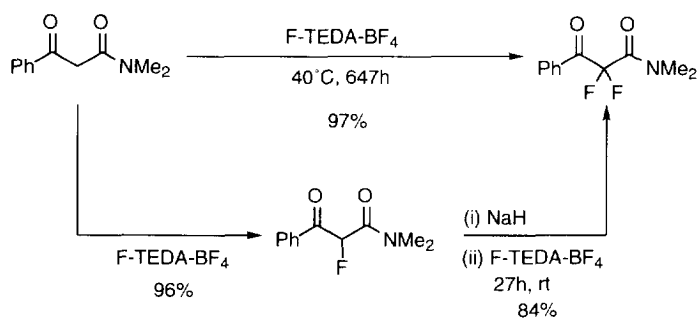
2.2.1 Enolates and Enol Ethers

The potential for *gem*-difluorination of active methylene groups has long been recognised. One of the earliest electrophilic fluorinating reagents, perchloryl fluoride ($FClO_3$), has some proven utility with regard to 1,3-dicarbonyl compounds and it has been ably used in the syntheses of *gem*-difluoro amino acids[9] and prostacyclin analogues.[120] Its use in the synthesis of difluoromalonaldehyde derivatives furnished a host of difluoro substituted synthons **38**.[121]



38

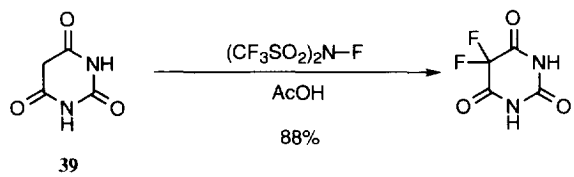
Unwanted difluorinations of 1,3-dicarbonyl compounds have been observed during monofluorinations with the new *N*-fluoro reagents. However, *N*-fluorobis[(trifluoromethyl)sulfonyl]imide **34**, *N*-fluoropyridinium reagent **36** and Selectfluor **37** have been purposefully used for the *gem*-difluorination of active methylene compounds. In a preliminary communication Banks and Lawrence reported that β-keto esters and amides are difluorinated with F-TEDA-BF_4 under neutral conditions in excellent yields.[122] The reaction times can be significantly reduced by carrying out the the two fluorinations sequentially, and importantly, with a sodium enolate of the monofluoro intermediate for the second step (Scheme 2.2.1.1).



Scheme 2.2.1.1

The relative ease of fluorination is believed to depend on the proportion of the enol tautomer and is consequently facilitated by enolate formation. DesMarteau has made similar observations in exploring the chemistry of *N*-fluoroimide **34**:[123] β-diketones and β-keto esters, which contain significant amounts the enol tautomer, undergo efficient difluorinations, whereas malonates, in which the keto/enol equilibrium lies more in

favour of the diester, are unreactive. Sodium enolates were found to promote difluorination, but side reactions proved a limitaton. Enolisation can be promoted by acidic conditions and Umemoto has achieved 2,2-difluorinaton of malonates with the *N*-fluoropyridinium reagent **36** in the presence of a strong Lewis acid catalyst, aluminium trichloride;[116] β-diketones and β-keto esters allowed the use of milder zinc chloride. Furthermore *gem*-difluorination of the otherwise insoluble 2,4,6-trihydroxypyrimidine **39** was performed with *N*-fluoroimide **34** in anhydrous acetic acid (Scheme 2.2.1.2).[124]

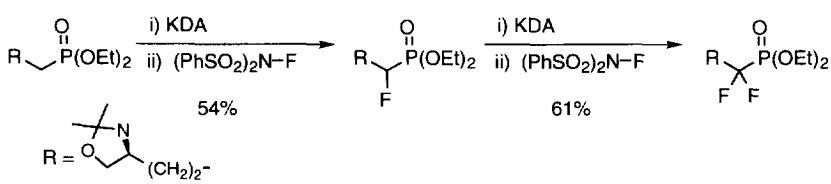


39

Scheme 2.2.1.2

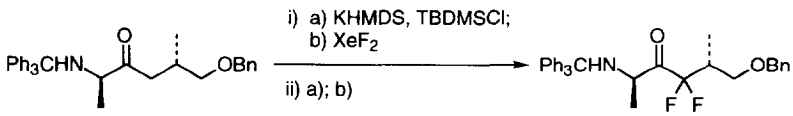
This may be compared with the poor difluorination of **39** on passing $10\%F_2/N_2$ through a solution in formic acid,[125] although this technique is better seen in terms of the monofluorination of non-cyclic 1,3-dicarbonyls.[126] Xenon difluoride has also been used effectively in the selective 2,2-difluorination of acyclic and cyclic 1,3-diketones.[127]

gem-Difluorination in the α-position of less acidic carbonyl compounds requires the use of enolates and enol ethers. With *N*-fluorosultam **35**, Differding observed useful α,α-difluorination of the potassium enolates of some ketones (e.g. PhCOMe), but low yields and poor mono-/di-selectivity dogged the even less acidic examples (e.g. *i*-Pr_2NCOEt).[128] It was proposed that reaction of the excess base with the fluorinating reagent becomes deleteriously competitive with the second deprotonation and fluorination. Differding subsequently adopted a two step procedure for the related α,α-difluorination of phosphonates with *N*-fluoroimide **33** (Scheme 2.2.1.3),[129] a procedure which complements the aforementioned nucleophilic fluorination of α-ketophosphonates (section 2.1.1).



Scheme 2.2.1.3

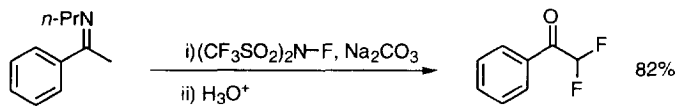
A stepwise approach was also used in the xenon difluoride α,α-difluorination of peptide isostere ketone **40**, although interestingly *t*-butyldimethylsilyl enol ethers were preferred to metal enolates as the reactive species (Scheme 2.2.1.4).[130] The yield of the first fluorination step was 71%, but that of the second was not reported. A mechanistic study of α-carbonyl fluorination with several electrophilic reagents suggested that for practical purposes these reactions may be regarded as ionic processes, although a non-fluorinated product arising from a radical intermediate was observed for XeF_2.[131]



40

Scheme 2.2.1.4

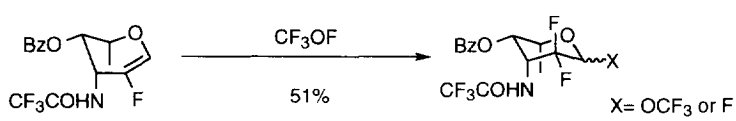
An alternative to the direct fluorination of carbonyl compounds can be found in the reaction of *N*-alkyl imines with *N*-fluoroimide **34** in the presence of a base to generate the imine anion (Scheme 2.2.1.5).[132] α,α-Difluoroketones were obtained in good yields after acidic work up, although the reaction was not selective when two active sites were available for fluorination.



Scheme 2.2.1.5

2.2.2 Alkenes and Alkynes

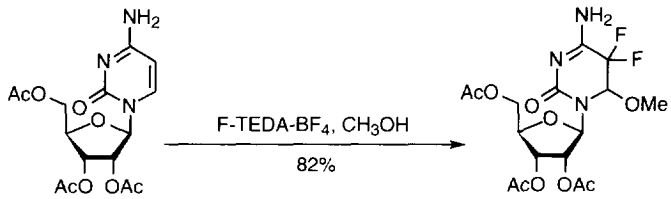
As seen earlier (section 2.1.7), nucleophilic fluorination of alkynes can be induced by the addition of electrophiles and the polarity reversed counterpart of this lies in the electrophilic difluorination of phenylalkynes in the presence of water to 1-phenyl-2,2-difluoroketones. This has been achieved with cesium fluoroxysulfate ($CsSO_4F$)[133] and more recently with F-TEDA-BF_4.[134] The analogous electrophilic fluorination of fluoroalkenes provided an alternative to the failed DAST difluorination of carbohydrate **9**. Thus, the reaction of trifluorofluoroxymethane with 2-fluorogalactal **41** gave a mixture of 2,2-difluorodaunosamine derivatives (Scheme 2.2.2.1).[46]



41

Scheme 2.2.2.1

A measure of the potential for this alkoxyfluorination may lie in the recent discovery that this and related acetoxy- and hydroxyfluorinations can be applied to the synthesis of 5,5-difluoropyrimidines with Selectfluor **37** (Scheme 2.2.2.2).[135]



Scheme 2.2.2.2

In a different type of reaction of fluoroalkenes, *gem*-difluoroalkenes have been prepared by electrophilic fluorination, with F-TEDA-BF_4, of (fluorovinyl)stannanes in moderate to good yields.[136] As the stannanes were obtained from ketones, the value of this direct fluorination must be weighed against the possibility of achieving the overall transformation more succinctly with CF_2-synthon techniques (section 3.5.1).

3 THE FLUORINATED SYNTHON APPROACH

With a view to facilitating a disconnection approach for *gem*-difluoromethylene substituted molecules, this chapter is organised around the formal nucleophilic, electrophilic and radical reactivities of the CF_2-synthons. Approaches will also be described for difluoroalkenes and difluorocyclopropanes. The main focus of attention will be the reactions for incorporating these synthons, but the typical reactivity of the more important intermediates will be discussed.

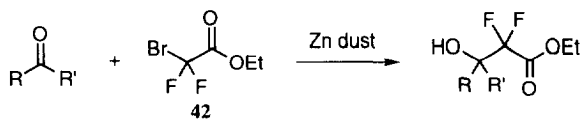
3.1 Nucleophilic Difluoromethylene Synthons

Nucleophilic difluoromethylene synthons usually involve CF_2-carbanions, which are particularly reactive as the destabilising electron pair repulsion overrides the inductive stabilisation.[25] Nucleophilic CF_2-synthons include difluoroenolates, difluoroallyl anions and difluorophosphonyl anions and their reactions with electrophiles will form the basis of this section.

3.1.1 The Reformatsky and Related Reactions

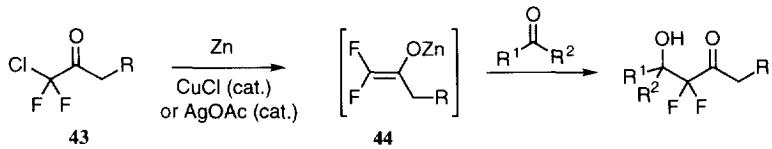
The Reformatsky reaction of halodifluoroacetates and halodifluoroketones is by far the most common of all the CF_2-synthon approaches. Its products are versatile intermediates which have found significant use in the synthesis of peptidase inhibitors designed around α,α-difluoroketones.[13] Since several accounts on the Reformatsky reaction of difluoromethylene compounds have been published,[4,137] this section will concentrate on the key developments and the recent progress.

The low stability and reactivity of lithium difluoroenolates has prompted the search for alternative routes to difluoroenolates.[138,139] In 1984, Fried reported the preparation of 2,2-difluoro-3-hydroxy esters by the Reformatsky reaction of ethyl bromodifluoroacetate **42** with aldehydes and ketones (Scheme 3.1.1.1).[140]



Scheme 3.1.1.1

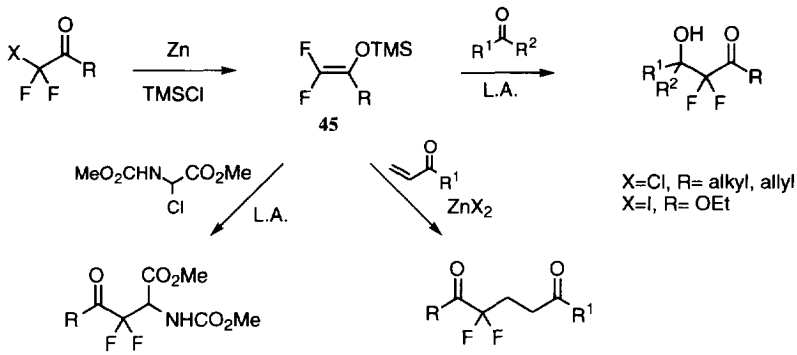
At the same time Ishihara reported the reaction of chlorodifluoromethyl ketones **43** with carbonyl compounds, mediated by zinc and catalytic titanium tetrachloride, to prepare 2,2-difluoro-3-hydroxy ketones in moderate yields (Scheme 3.1.1.2).[141] This procedure was later improved by using copper chloride as a catalyst for the reaction with aldehydes and silver acetate with ketones.[142,143] An intermediate zinc enolate **44** has been observed by ^{19}F NMR.



Scheme 3.1.1.2

Several improvements and variations of the reaction conditions have been reported. Reaction in DMF instead of THF or ether allowed, in certain cases, the replacement of bromodifluoroacetates by readily available but less reactive chlorodifluoroacetates.[144] Addition of a catalytic amount of $CeCl_3$[145] or Et_2AlCl with a catalytic amount of AgOAc[146] facilitated the use of milder conditions. With ultrasonication the organozinc reagent could be prepared from ethyl bromodifluoroacetate prior to the addition of the aldehyde,[147] thus enabling the Reformatsky reaction to be carried out in a two step process as is usually required for aldehydes and ketones bearing a nitro group. An electrochemical nickel catalysed Reformatsky reaction with methyl chlorodifluoroacetate and a sacrificial zinc anode has been described as a low cost, mild and easy to scale up process.[147] A few examples of electroreductive couplings of methyl chlorodifluoroacetate with aldehydes using a lead cathode have also been reported.[148]

The zinc enolates formed under Reformatsky conditions could be trapped as their trimethylsilyl derivative **45** (Scheme 3.1.1.3). The silyl enolethers generated from halodifluoroketones[149] could be isolated but those generated from halodifluoroesters[150] were unstable and are usually reacted *in situ*, with the zinc dihalide acting as a Lewis acid. Under these conditions, both types of enolates condensed with aldehydes and ketones, with the latter also undergoing Michael additions[151] and nucleophilic substitutions[152] as shown by the examples in Scheme 3.1.1.3. One advantage of using the silyl enolether as an intermediate is an improvement in the stereoselectivity of the reaction. In general,[4] these Reformatsky reactions yield preferentially the *syn*-product with α-alkoxyimines and α-aminoaldehydes and the *anti*-product with α-hydroxyaldehydes. The rationale for this difference in selectivity postulates that in the first two cases there is chelation between oxygen, zinc and nitrogen (Figure 3.1.1.1, model B) and in the third case the Felkin-Anh model applies (Figure 3.1.1.1, model A).[153]



Scheme 3.1.1.3.

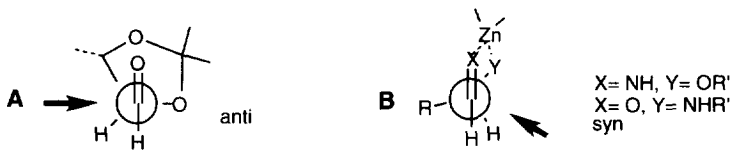
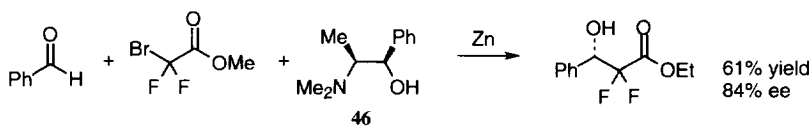


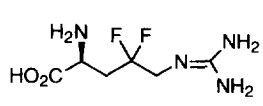
Figure 3.1.1.1

The first enantioselective Reformatsky reaction of a *gem*-difluoromethyl substituted substrate has recently been reported: in the presence of the chiral β-amino alcohol **46**, benzaldehyde reacted with methyl bromodifluoroacetate in 61% yield and 84% enantiomeric excess (Scheme 3.1.1.4).[154]



Scheme 3.1.1.4

The versatility of the Reformatsky reaction is admirably illustrated by the diversity of structural types for which it has been employed. Reformatsky approaches have been used to prepare difluoromethylene analogues of amino acids for incorporation into peptides.[13] Several recent examples include: 4,4-difluoro-L-arginine[155] **47** prepared *via* an ultrasound promoted reaction; potent HIV protease inhibitors[156] incorporating fragment **48**



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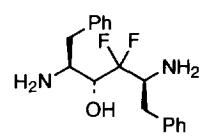
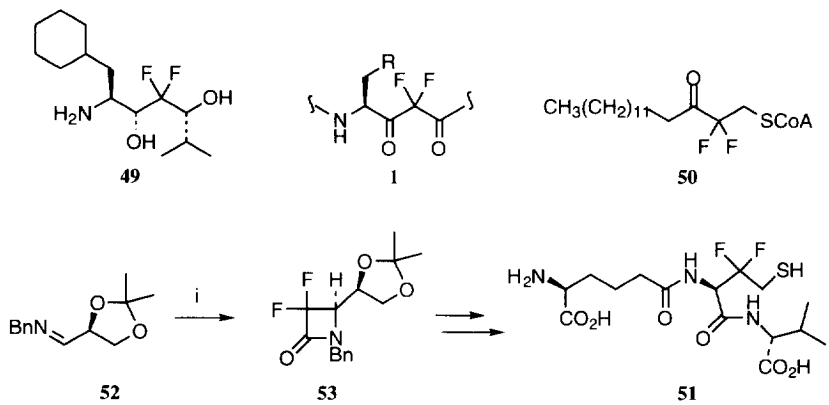


48

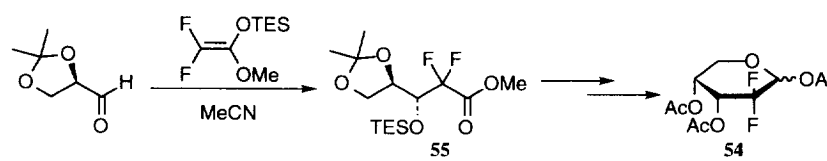
and renin inhibitors[157] containing fragment **49**, both prepared under standard, unactivated conditions. A Reformatsky reaction with paraformaldehyde, mediated by zinc-titanium tetrachloride was used in the synthesis of **50**, an analogue of myristoyl-coenzyme A.[158] Oxidation of the alcohol formed in the Reformatsky reaction has been found to be problematic using Swern, Collins or PDC procedures.[159] The Dess-Martin periodinane has become the method of choice,[160-162] but recently a modified Pfitzner-Moffat reaction has been reported to suppress the epimerisation problems encountered with the Dess-Martin reagent in the preparation of renin inhibitors containing fragment **1**.[159] Peptides containing fragment **1** have also been described as human leukocyte elastase inhibitors.[160] The tripeptide analogue **51**, prepared from benzylimine **52** *via* intermediate **53** (Scheme 3.1.1.5), has been used for mechanistic studies of isopenicillin biosynthesis.[163]



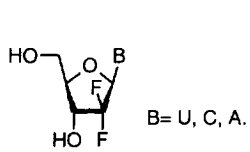
Conditions: i. $BrCF_2COOEt$, Zn.

Scheme 3.1.1.5

Carbohydrate and nucleoside analogues have also been prepared using the Reformatsky reaction.[150,153] An example is the preparation of the ribopyranose analogue **54** by reduction and deprotection of **55**, which was obtained from the silylenol ether version of the Reformatsky reaction (Scheme 3.1.1.6).[150] There is great interest in 2',2'-difluorosubstituted nucleoside analogues with the natural D-configuration[28,29] **56** and their activity as antiviral, antimetabolite and antitumour agents.[27,164] The L-nucleoside analogue **57**,[165] prepared by a classical Reformatsky reaction, has been reported to be a promising anti HIV agent.



Scheme 3.1.1.6



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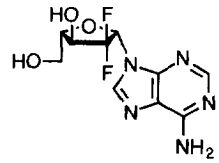
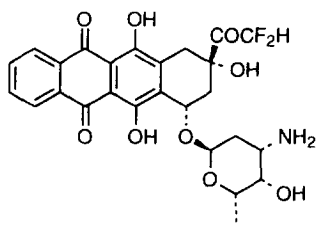


57

Syntheses using the Reformatsky reaction as a key step were also applied to natural product analogues: 14,14 difluoro-4-demethoxydaunomycin **58** was prepared by a classical Reformatsky reaction followed by a decarboxylation.[166,167] Other recent examples include (+)-10,10-difluorothromboxane A2 **2**,[16] difluorinated analogues of vitamin D such as **5**[168] and difluoro-*N*-substituted dibenzoxazepines **59**.[169]



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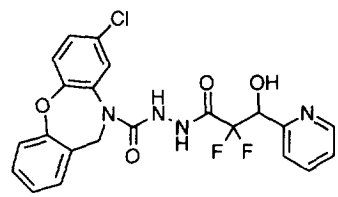
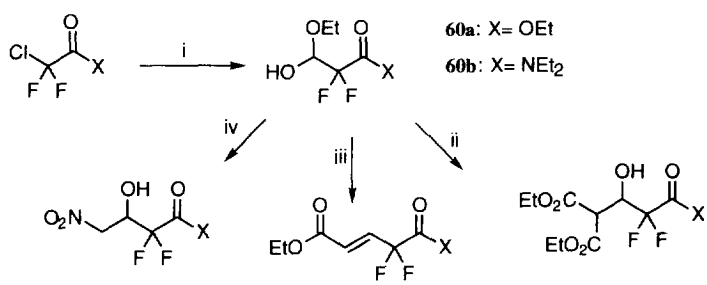


59

Finally, Reformatsky reactions have been used to produce general synthons for further functionalisation. Formylation of the Reformatsky reagent derived from chlorodifluoroacetic acid provided the difluorinated hemiacetals **60a** and **60b**, which were conveniently used as aldehyde equivalents (Scheme 3.1.1.7).[170,171]



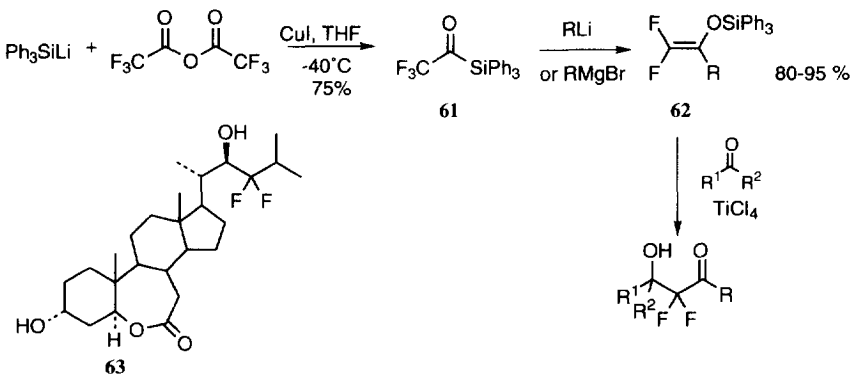
Conditions: i. Zn, DMF, $EtOSO_3Et$; ii. $CH_2(COOEt)_2$, ZnI_2; iii. $(EtO)_2POCH_2CO_2Et$, Et_3N, LiBr; iv. CH_3NO_2, K_2CO_3.

Scheme 3.1.1.7

A vast number of the examples described above have employed the classical Reformatsky reaction with the conditions initially reported by Fried, and most of the variants and improvements have not yet been applied to the synthesis of complex fluorinated products. The Reformatsky reaction is a convenient entry into difluoro aldol products, and the extensive literature attests to the reliability and breadth of application of this route.

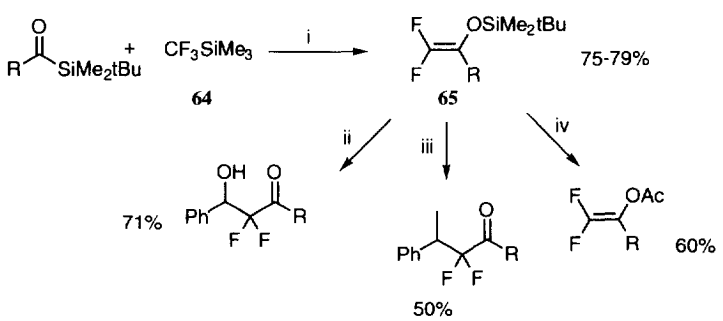
3.1.2 Other Enolates

Recently, novel approaches to the formation of difluoroenolates have appeared in the literature. Xu has reported the preparation of trifluoroacetyltriphenylsilane **61** and its conversion to triphenylsilylenol ethers **62** upon treatment with Grignard or organolithium reagents (Scheme 3.1.2.1).[172,173] The silylenol ethers **62** reacted with aldehydes and ketones with good diastereoselectivity in the presence of a Lewis acid. The difluorinated analogue of a Brassino steroid **63** was synthesised as an example of the versatility of this approach.



Scheme 3.1.2.1.

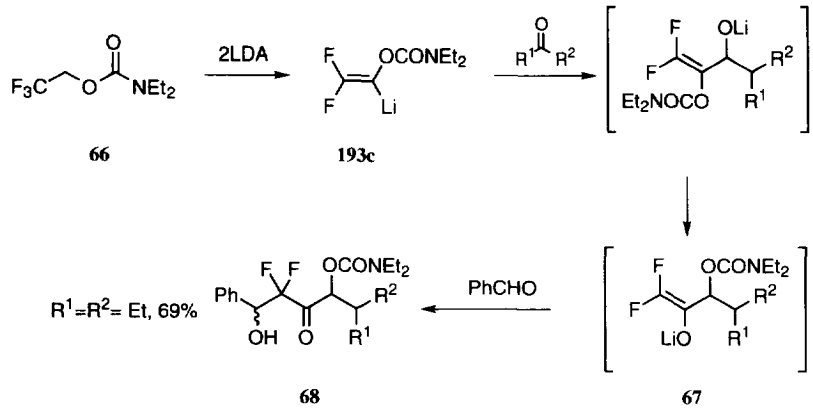
A similar reaction for the preparation of silylenol ethers involved the condensation of trifluoromethyltrimethylsilane **64** with acylsilanes, catalysed by fluoride, to prepare silylenol ethers **65**, which were further reacted with aldehydes, halides and acid chlorides in a one pot sequence (Scheme 3.1.2.2).[174]



Conditions: i. Bu_4N Ph_3SnF_2, THF -78°C to -24°C; ii. PhCHO, $TiCl_4$; iii. $ZnBr_2$, PhCH(Me)Br; iv. $ZnBr_2$, MeCOCl.

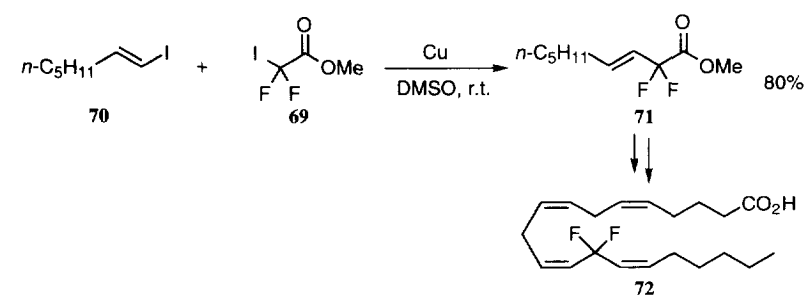
Scheme 3.1.2.2

Percy[175,176] has prepared lithium enolates of difluoroketones from the recently described acyl anion equivalent **193c**,[177] readily available from the *N*,*N*-diethyl carbamate ester of trifluoroethanol **66** (Scheme 3.1.2.3). Reaction of **193c** with an aldehyde or a ketone produced the lithium enolate **67**, which in turn reacted with non-enolisable aldehydes to produce highly functionalised aldol products **68** in one pot and good yields.



Scheme 3.1.2.3

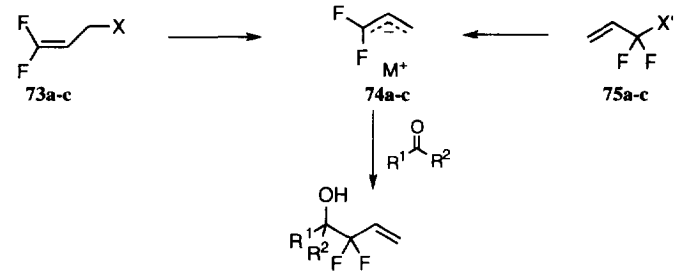
A reaction analogous in outcome is the copper mediated coupling of difluoroiodoacetate **69** with vinyl iodide **70** (Scheme 3.1.2.4).[178,179] The reaction has seldom been used in synthesis, and a rare example is the preparation of the difluoroallyl synthon **71** which was subsequently employed in the synthesis of the arachidonic acid analogue **72**.[180]



Scheme 3.1.2.4

3.1.3 Difluoroallyl Anions

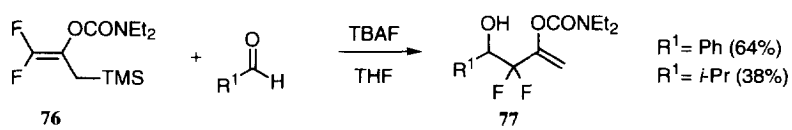
Difluoroallyl anions are emerging as versatile synthons for the synthesis of *gem*-difluorinated molecules, and three different approaches have been described. The synthesis of difluoroallyllithium, by transmetallation of the *gem*-difluoroallyl stannane **73a** with butyllithium, was first reported by Seyferth in 1979,[181] along with its reaction with several electrophiles. The intermediacy of a delocalised allyl anion **74a** was suggested by the observation that reaction of the anion generated from 3-bromo-3,3-difluoropropene **75a** by lithium-halogen exchange afforded the same products, consistently corresponding to substitution at the CF_2-terminus (Scheme 3.1.3.1).[182,183] Difluoroallyllithium reacted with aldehydes and ketones in moderate to good yields, but competing *n*-butyllithium addition became a problem with reactive carbonyl groups.



Entry	Substrates	M^+	Conditions
a	X= $SnMe_3$, X'= Br	Li	*n*-BuLi, -95°C
b	X= X'= $SiMe_2Ph$	$(Me_2N)_3S$	$(Me_2N)_3S$-Me_2SiF_2 (cat), DMPU, r.t.
c	X= Br, X'= I	ZnBr/ ZnI	Zn, THF, 0°C-r.t.

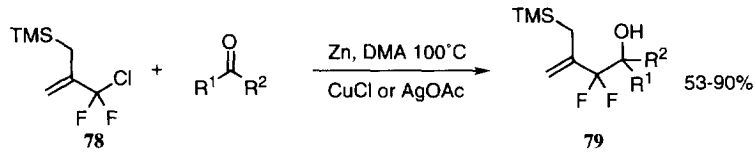
Scheme 3.1.3.1

A different approach to a similar reactive intermediate **74b** involved the preparation of the difluoroallyl silane **73b** and its fluoride catalysed addition to carbonyl compounds (Scheme 3.1.3.1).[184-186] Once again generation of the difluoroallyl anion from both isomers afforded a common intermediate anion **74b**, which reacted exclusively at the CF_2-terminus. Reactions with aldehydes and ketones proceeded in moderate to good yields and this strategy has recently been used in the condensation of the difluoro carbamoyloxy allylsilane **76** with aldehydes to the produce functionalised synthons **77** (Scheme 3.1.3.2).[187]



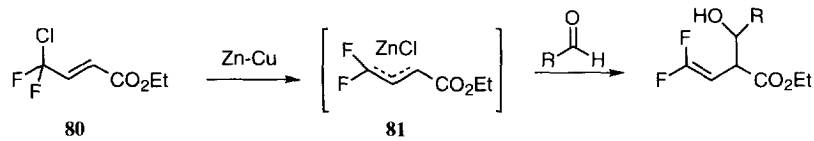
Scheme 3.1.3.2

The most practical method described so far for the generation of a difluoroallyl anion was inspired by the Reformatsky reaction and involves the preparation and reaction of a *gem*-difluoroallylzinc intermediate.[188,189] The reaction of easily available 3-bromo-3,3-difluoropropene **75c** or 1,1-difluoro-3-iodopropene **73c** with zinc generated a common intermediate **74c**, which reacted with aldehydes and ketones to afford the corresponding homoallylic alcohols in good yields (Scheme 3.1.3.1). An example of this is the zinc/copper chloride or silver acetate promoted coupling of 2-trimethylsilyl-methyl-3-chloro-3,3-difluoro propene **78** with carbonyl compounds to prepare the synthon **79** for further functionalisation (Scheme 3.1.3.3).[190]



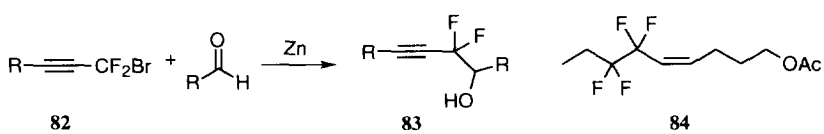
Scheme 3.1.3.3

The selective reaction at the difluoro-carbon of difluoroallyl anions, with both hard and soft electrophiles, is in agreement with an *ab initio* theoretical study of the structure and stability of the 1,1-difluoroallyl anion and its lithiated counterpart.[191] In the free and lithiated anion, the charge distribution lies towards the CF_2-terminus, which accounts for the reaction with hard electrophiles, and the largest coefficient of the highest occupied molecular orbital (HOMO) is also on the CF_2-terminus, explaining the outcome of the reaction with soft electrophiles. An opposite reactivity has been observed in the reaction of halodifluoromethylene α,β-unsaturated esters **80** under Reformatsky conditions (Scheme 3.1.3.4).[192] The zinc chloride allylic anion **81** reacted with aldehydes to afford exclusively α-substituted products, in moderate to good yields.



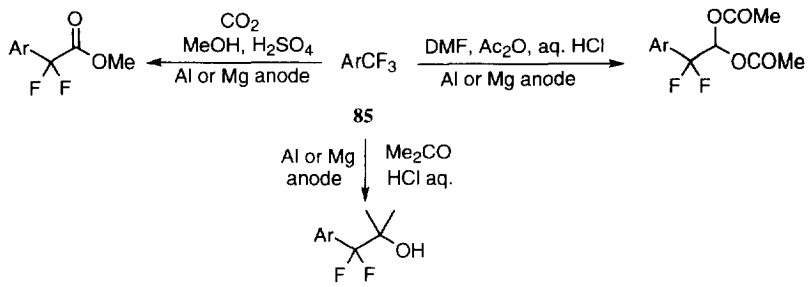
Scheme 3.1.3.4

An approach related to the difluoroallylzinc reaction is the reaction of zinc intermediates, generated from bromodifluoromethyl acetylene derivatives **82**, with carbonyl compounds to prepare difluorinated propargyl alcohols **83**.[193] This reaction was used as a key step to introduce the two allylic fluorines in the synthesis of the fluorinated analogue of (*Z*)-5-decenyl acetate **84** (Scheme 3.1.3.5).[194]



Scheme 3.1.3.5

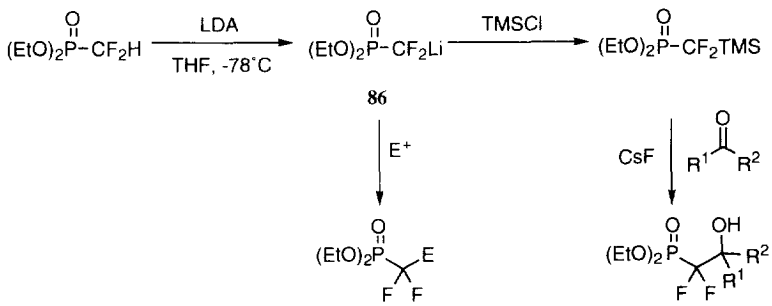
A close relative of the difluoroallyl anion is the difluorobenzylic anion, an equivalent of which was generated by the electroreduction of trifluoromethylarene **85**. When performed in the presence of electrophiles such as carbon dioxide, acetone or *N,N*-dimethylformamide, using a sacrificial magnesium or aluminium anode, $ArCF_2$ branched molecules were obtained in good yields (Scheme 3.1.3.6).[195]



Scheme 3.1.3.6

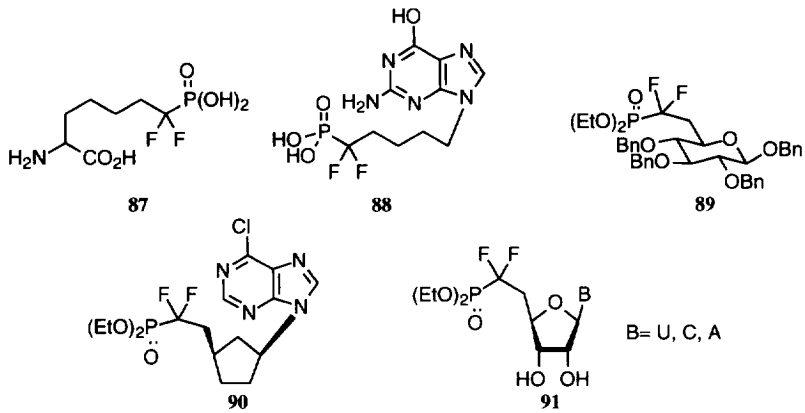
3.1.4 Difluoromethylenephosphonates

There is a wide interest in difluoromethylenephosphonates as hydrolytically stable analogues of phosphate esters. The preparation of these compounds commonly involves the reaction of lithium difluoromethylenephosphonates or similar cadmium or zinc reagents with electrophiles.[4] Obayashi and Kondo originally reported the preparation of lithium diethyl difluoromethylphosphonate **86** by the treatment of diethyl difluoromethylphosphonate[196] with LDA at -78°C, and its reaction *in situ* with organic halides and aldehydes (Scheme 3.1.4.1).[197] For base sensitive electrophiles, **86** can be silylated with TMSCl and subsequently reacted with aldehydes or ketones using the caesium fluoride protocol.[198]

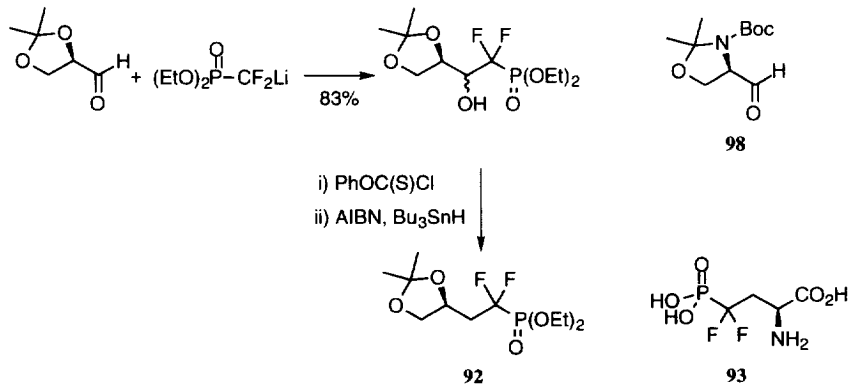


Scheme 3.1.4.1

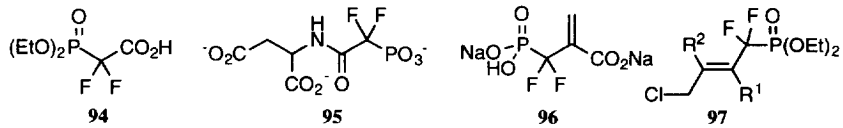
Whilst the nucleophilic substitution of primary bromides and iodides with lithium diethyl difluoromethylphosphonate **86** has been used in the preparation of compounds such as the amino acid analogue **87**[199] and the purine nucleoside phosphorylase inhibitor **88**,[200] it is not without its problems.[201] The displacement of triflates seems to be a reliable alternative and has been used in carbohydrate and nucleoside chemistry: examples include analogues of naturally occurring monosaccharide phosphates such as **89**[201] and nucleosides analogues such as **90**[202] and **91**.[203,204] The often harshly acidic or hydrolytic conditions required for the deprotection of the alkyl esters commonly used for these syntheses may be overcome by the use of lithium diallyl difluoromethylphosphonate.[205]



Another alternative to the nucleophilic substitution of primary halides with difluoromethylene-phosphonate **86** is the condensation of this reagent with aldehydes and Barton-McCombie deoxygenation of the resultant alcohol (Scheme 3.1.4.2).[206] This approach has been used for the preparation of enantiopure **92** from glyceraldehyde[206,207] and the amino acid analogue **93** from Garner's aldehyde **98** (Scheme 3.1.4.2).[208] In general, lithium diethyl difluoromethylphosphonate **86** reacted in good yields with aldehydes, ketones, acid chlorides, and phosphinyl chlorides,[209] and with esters in presence of cerium trichloride.[210] Blackburn has reported its reaction with carbon dioxide to produce the fluorinated phosphonoacetic acid **94**,[211] which in turn has been used for the synthesis of the aspartame transcarbamoylase (ATC) inhibitor **95**.[212] The reaction of **86** with di-*tert*-butyl oxalate was the first step in the preparation of the phosphoenolpyruvate analogue **96**,[213] and its 1,2-addition to α,β-unsaturated aldehydes and ketones, with conversion of the unstable allylic alcohol to the allylic chloride, provided a route to **97**, a versatile intermediate for the preparation of allylic difluorophosphonates.[214] Cerium mediated conjugate addition of **86** to nitroalkenes has also recently been reported.[215]

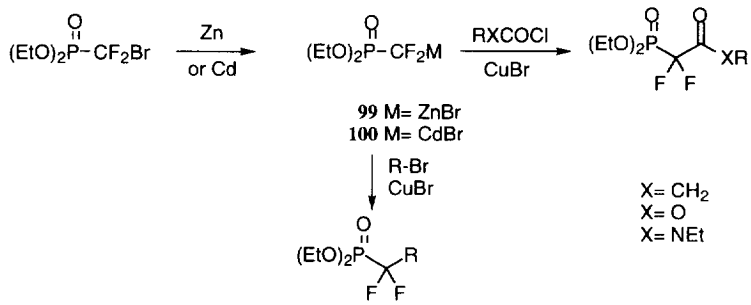


Scheme 3.1.4.2

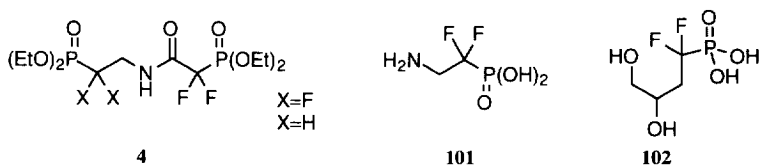


94 **95** **96** **97**

By analogy with the Reformatsky reaction, a convenient zinc reagent **99**[216] prepared from bromodifluoromethyl phosphonate has been reported by Burton.[217] It was reacted with acid chlorides and chloroformates[218,219] and with allylic and primary bromides[220] in presence of catalytic copper(I) bromide (Scheme 3.1.4.3). Examples include the preparation of 1,3-bis(phosphoglyceric) acid analogues such as **4**[18] and the preparation of 2-amino-1,1-difluoroethylphosphonic acid **101**.[221] A similar cadmium reagent **100**[222] has been used for reactions with allylic bromides: reaction of **100** with 3-bromopropene and subsequent dihydroxylation afforded the difluoromethylene analogue of glycerol-3-phosphate **102**.[17,223]

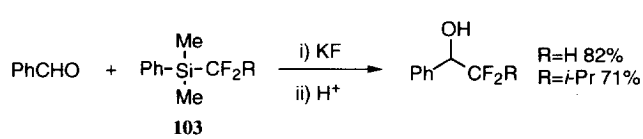


Scheme 3.1.4.3



4 **101** **102**

3.1.5 (1,1-Difluoroalkyl)silanes



103

Scheme 3.1.5.1

Trifluoromethylsilane has become an important reagent for the trifluoromethylation of carbonyl compounds,[6] and in a very recent communication Fuchikami has reported reagents for its difluoromethyl and difluoroalkyl counterparts (Scheme 3.1.5.1).[224] (Difluoromethyl)dimethylphenylsilane (**103** R=H), in the

presence of a catalytic source of fluoride, was reacted efficiently with aryl and alkyl aldehydes to produce difluoromethyl carbinols. Difluoromethylation of ketones was lower yielding and initial results with (difluoroalkyl)silanes (**103** R=alkyl) and the optimum aldehyde, benzaldehyde, were variable.

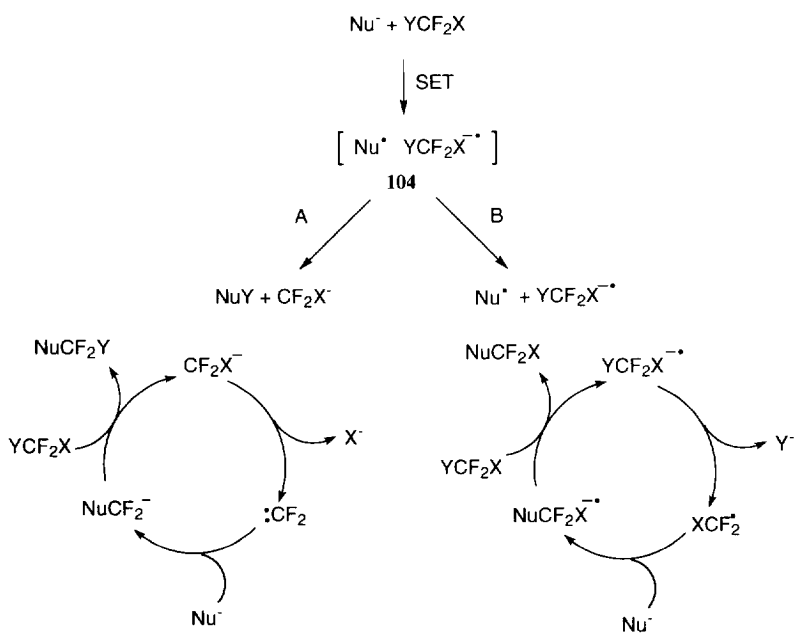
The foregoing methods represent a large proportion of the literature on *gem*-difluorinated synthons and this dominant view of the difluoromethylene unit as a nucleophile should be borne in mind when disconnecting *gem*-difluorinated target molecules. Reformatsky reagents and difluoromethylphosphonate anions are well established techniques and the manipulation of their reaction products is well documented. Difluoroallylic anions have appeared more recently, but it is not unreasonable to suspect that they will also become popular reagents.

3.2 Electrophilic Difluoromethylene Synthons

There are two main types of reactions of difluoromethylene units with nucleophiles: the apparent "nucleophilic substitution" of halodifluoromethanes, which usually involves a radical or carbene mechanism, and nucleophilic addition to halodifluoroalkenes and Michael acceptors.

3.2.1 Reactions of Halodifluoromethane Derivatives

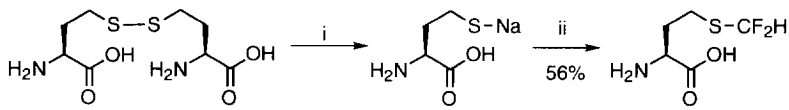
Halodifluoromethanes react with nucleophiles such as phenoxides, thiophenoxides, carbanions or enamines in an apparent nucleophilic displacement reaction, which involves two possible mechanisms (Scheme 3.2.1.1).[225] The reaction is initiated by single electron transfer and, depending on the nature of the nucleophile



Scheme 3.2.1.1

and the solvent, follows either the carbene path A or the radical path B from a common radical/radical anion pair intermediate **104**. Path B predominates when the radical Nu• is stabilised or the solvent favours dissociation of the radical/radical anion intermediate **104**.

Reactions of thiophenoxides[226,227] and phenoxides[227-232] with halodifluoromethanes proceed *via* the carbene mechanism (A) to produce difluoromethylated sulfides or alkoxides. Wakselman has shown that, in the case of thiophenoxides, changing the solvent from benzene to DMF switches the mechanism from the carbene to concurrent carbene and radical mechanisms.[225] From a synthetic point of view, these reactions have been used to prepare di- and trifluoromethyl alkoxides and sulphides in moderate to good yields. An example is the preparation of the difluorinated cysteine analogue **107** from **105** by the reaction of the sodium salt of homocysteine **106** with chlorodifluoromethane (Scheme 3.2.1.2).[233]

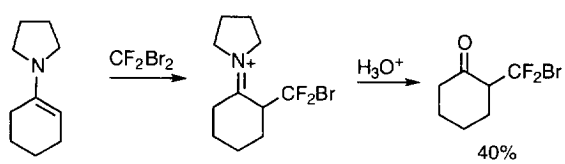


105 **106** **107**

Conditions: i. Na-NH_3; ii. CHF_2Cl, KO*t*-Bu, MeOH.

Scheme 3.2.1.2

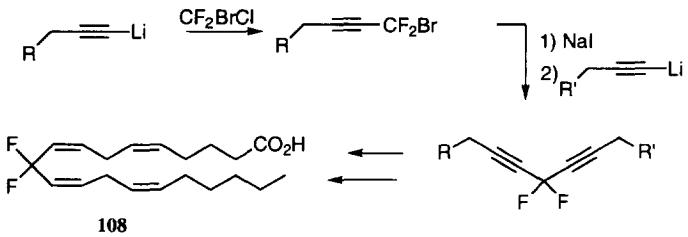
Enamine and ynamines condense with dibromodifluoro- and bromochlorodifluoromethane in a radical chain mechanism (Scheme 3.2.1.3).[234] The reaction proceeds in moderate to good yields but has received surprisingly little attention elsewhere in the literature.



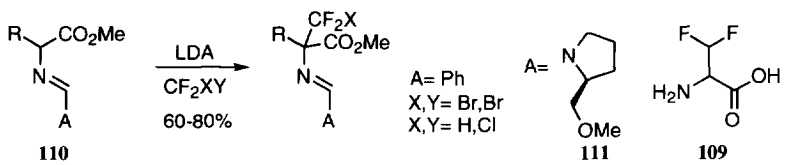
Scheme 3.2.1.3

In contrast, the reaction of halodifluoromethanes with carbanions has been widely employed in synthetic schemes. The reaction of acetylenic carbanions and enolates with halodifluoromethanes *via* the carbene mechanism, is capricious and yields are variable.[235] Fried has used the reaction of acetylenic carbanions and bromochlorodifluoromethane in a synthesis of the fluorinated analogue of arachidonic acid **108** (Scheme 3.2.1.4).[236] Amino acid analogues, such as difluoroalanine **109**[237] have been prepared by difluorocarbene insertion into enolates, and a general high yielding method involving imines **110** has been developed for their synthesis (Scheme 3.2.1.5).[238,239] An asymmetric version involving the chiral auxiliary **111** met with limited success.[240] Recently Kobayashi and Iseki have described the diastereoselective bromodifluoromethylation of the chiral imide enolate **112** (Scheme 3.2.1.6),[241] a difluorocarbene insertion which occurred with consistent and acceptable yields when the concentration of the enolate was carefully controlled. One example of the reaction of an amide anion with chlorodifluoromethane has been reported in the preparation of fluorinated

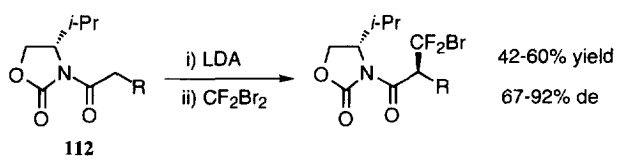
lactams.[242] The amide anion generated from **113** underwent "carbene insertion" followed by nucleophilic displacement of the iodide to produce the fluorinated lactam **114** in low yields (Scheme 3.2.1.7).



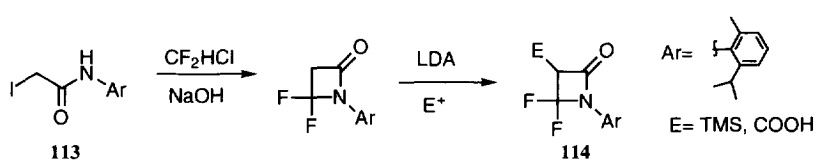
Scheme 3.2.1.4



Scheme 3.2.1.5



Scheme 3.2.1.6

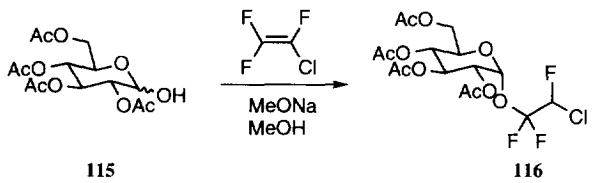


Scheme 3.2.1.7

3.2.2 Nucleophilic Additions to Difluoroalkenes and Miscellaneous Approaches

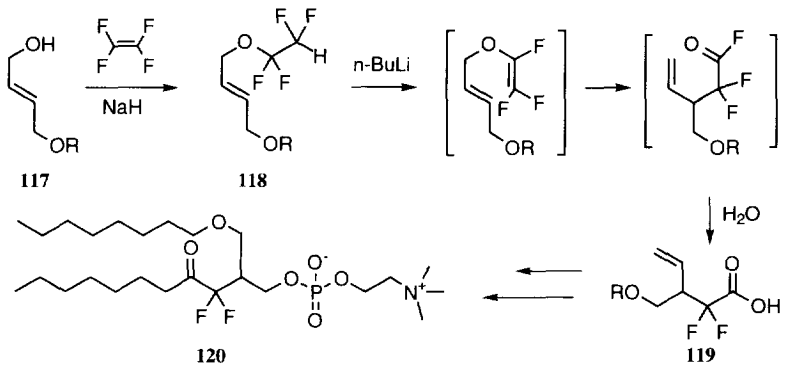
Most examples of nucleophilic addition to fluorinated alkenes involve tri- or tetrafluorinated ethylenes,[230,231,243] an example of which is the reaction of the protected glucopyranose **115** with chlorotrifluoroethylene to produce the glucosidase inhibitor **116** (Scheme 3.2.2.1).[244] Difluoromethylene compounds have, nevertheless, been prepared from these higher fluorinated intermediates: when tetrafluoroethylene was reacted with the allylic alcohol **117**, elimination and Claisen rearrangement of the

tetrafluorinated intermediate **118** allowed the preparation of the difluoromethylene carboxylic acid **119** as a key intermediate in the synthesis of the cobra venom phospholipase inhibitor **120** (Scheme 3.2.2.2).[245]



115 116

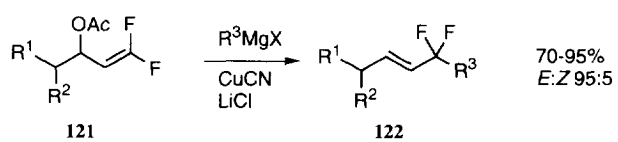
Scheme 3.2.2.1



117 118 119 120

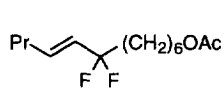
Scheme 3.2.2.2

The nucleophilic addition of Grignard reagents to functionalised *gem*-difluoroalkenes has been described as a general and convenient route to molecules bearing a difluoromethylene unit in the allylic position. The nucleophilic addition-elimination sequence with *gem*-difluoro-3-oxyacetate **121** afforded fluorinated alkenes **122** in good yields (Scheme 3.2.2.3).[246,247] This reaction has been applied to the preparation of oriental fruit moth sex pheromone analogue **123**.[247] Reaction with thionyl chloride instead of Grignard reagents afforded the chlorinated synthon **124**,[248] which was subsequently used in radical reactions and to generate a difluoroallyl anion (see section 3.1.3).

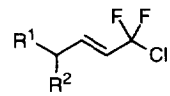


121 122

Scheme 3.2.2.3

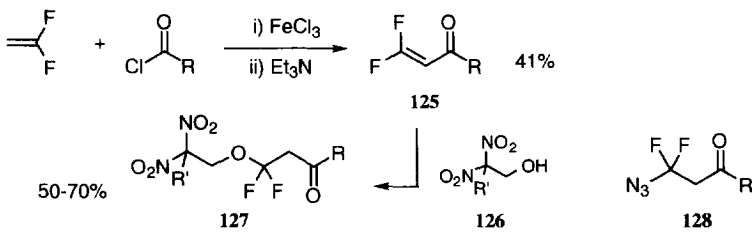


123



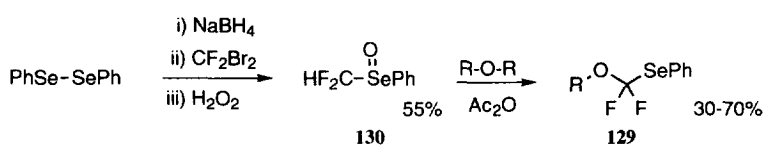
124

There are few examples of Michael-type additions to β,β-difluoro-α,β-unsaturated carbonyl compounds. The reason for this paucity is presumably the high reactivity and consequent instability of these compounds,[249] although a profitable manifestation of this is their tendency to undergo addition-elimination reactions and thereby act as intermediates in the synthesis of monofluorinated products.[250,251] Nevertheless, methods have recently been developed for the preparation of β,β-difluoro-α,β-unsaturated carbonyl compounds (see section 3.5.1),[252] which have been utilised in the preparation of difluoronitroethers:[253] β,β-difluoro-α,β-unsaturated ketones and esters **125** were prepared by nucleophilic acylation of 1,1-difluoroethylene with subsequent dehydrochlorination and condensed with geminal β-dinitroalcohols **126**, which are unreactive with non-fluorinated Michael acceptors (Scheme 3.2.3.1). Difluoronitroethers **127** were thus produced in good yields and a similar reaction with sodium azide afforded azido difluoro derivatives **128**.



Scheme 3.2.3.1

In addition to the methods mentioned thus far, it is worth noting an interesting approach to a difluorocation equivalent *via* a Pummerer-type reaction of difluoromethyl phenyl selenoxide **130**.[254,255] This compound was prepared by the reaction of diphenyldiselenide and dibromodifluoromethane under reductive conditions followed by oxidation, and it reacted with cyclic or acyclic ethers in presence of acetic anhydride to afford the corresponding difluoromethyl ethers **129** (Scheme 3.2.3.2).



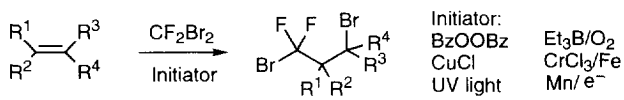
Scheme 3.2.3.2

3.3 Difluoromethylene Radicals

Difluoroalkyl radicals are very promising intermediates for the preparation of complex fluorinated molecules under mild conditions. They are usually more reactive than the corresponding non-fluorinated radicals in carbon-carbon bond forming reactions, because of the σ-nature of the radical and the increased strength of the bond formed.[256,257] Difluoromethylene radicals are generally considered as strongly electrophilic,[25] although in some additions to alkenes better results have been obtained with electron deficient rather than electron rich alkenes.[258]

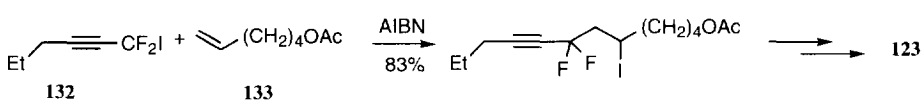
3.3.1 Addition of Halodifluoroalkyl Radicals to Alkenes

The addition of dibromodifluoromethane across alkenes initiated by dibenzoyl peroxide,[259] copper(I) chloride,[260] or UV light[261] in the case of electron rich alkenes, has been known for some time (Scheme 3.3.1.1).[260] Modern initiators for this reaction have also been reported: triethylborane/oxygen at room temperature;[262] a chromium trichloride/iron bimetal redox system;[263] and a manganese mediated electrochemical initiation.[264] Reduction of the 1,3-dibromo-1,1-difluoroalkane **131** with sodium borohydride has been shown in some cases to remove selectively one bromine atom, leaving the bromodifluoromethyl group intact for further functionalisation.[265] Difluorodiiodomethane has recently been reported as a good source of difluoroiodomethyl radicals,[266] and its reaction with alkenes initiated by dibenzoyl peroxide afforded 1,3-diiodo-1,1-difluoroalkanes in good yields.[267]

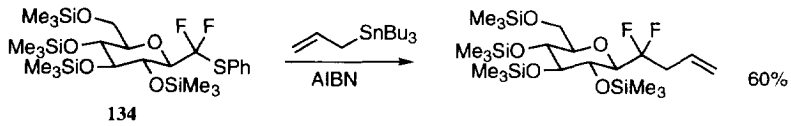


Scheme 3.3.1.1

The majority of recent synthetic examples of radical reactions of halodifluoroalkanes with alkenes involve intramolecular cyclisations, which are described in section 3.3.3. Fried has reacted the iodide **132** (prepared from the corresponding bromide: see Scheme 3.2.1.4) with the alkene **133** in the first synthesis of the fluorinated analogue of the oriental fruit moth sex pheromone **123** (Scheme 3.3.1.2).[268] Carbohydrate *gem*-difluoromethyl radicals have been generated from the corresponding phenylsulfide **134** and reacted with allystannanes, in a general route to CF_2-glycosides (Scheme 3.3.1.3).[269]

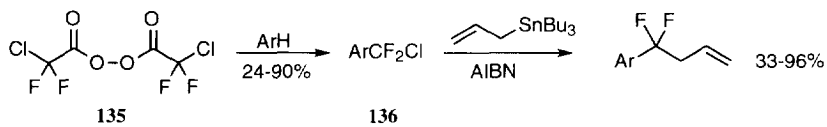


Scheme 3.3.1.2



Scheme 3.3.1.3

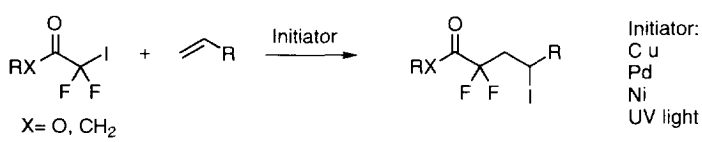
Recently, a novel entry into difluoromethylarene substituted compounds by radical reactions has been reported.[270,271] Reaction of bis(chlorodifluoroacetyl) peroxide **135** with aromatic compounds afforded chlorodifluoromethylarenes **136,** which could be functionalised further by radical reactions with allylstannanes (Scheme 3.3.1.4).



Scheme 3.3.1.4

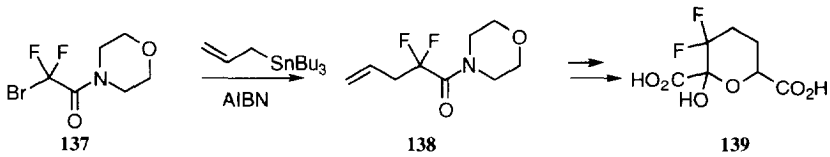
3.3.2 Difluoroacetyl Radicals

Radical additions of difluoroiodo esters and ketones across alkenes has emerged as a mild and convenient alternative to the Reformatsky reaction for the preparation of α,α-difluorinated esters and ketones (Scheme 3.3.2.1). Kobayashi[272] and Burton[273] simultaneously reported the atom transfer reaction of difluoroiodoacetyl derivatives with electron rich alkenes initiated by a copper catalyst. Later, a one pot atom transfer reaction of difluoroiodoesters and reduction of the resulting iodide was described, using zinc metal and catalytic nickel chloride.[274,275] Difluoroiodoketones have been shown to react in good yields with electron rich olefins in atom transfer reactions initiated by palladium,[276,277] and UV light initiation allowed the reaction to proceed with electron deficient alkenes.[278] Evidence for the radical nature of these reactions was provided by radical trapping experiments and inhibition by radical scavengers.



Scheme 3.3.2.1

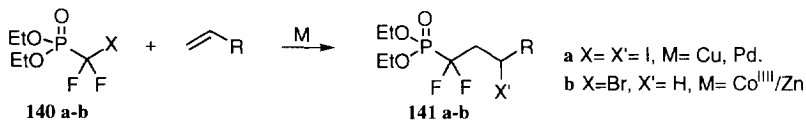
Electrochemical[279] and AIBN/organostannane systems[280] have also been used to produce difluoroacetyl radicals. Reaction of the α-bromoamide **137** with tributylallyltin initiated by AIBN afforded the intermediate **138** in the preparation of **139**, an analogue of the hydrated form of tetrahydrodipicolinic acid (Scheme 3.3.2.2).



137 138 139

Scheme 3.3.2.2

Radical reactions have also offered a mild route to difluoromethylphosphonates. Atom transfer reaction of ethyl iododifluoromethylphosphonate **140a** with alkenes initiated by copper or palladium has been reported.[281,282] The similar reaction of ethyl bromodifluoromethylphosphonate **140b** with electron deficient alkenes in the presence of a bromo(pyridine)cobaloxime(III)/zinc bimetal redox system led to the reduced adduct **141b** (Scheme 3.3.2.3).[283]

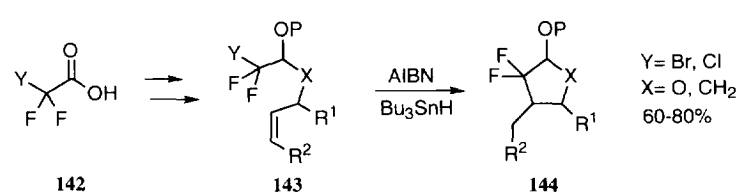


140 a-b **141 a-b**

Scheme 3.3.2.3

3.3.3 Intramolecular Cyclisations

Intramolecular radical cyclisations have been used as a convenient route to difluoromethylene substituted three, five and six membered rings. Investigation of the radical cyclisations of bromo- or chlorodifluoromethyl esters[284] and ketones,[285] prepared from the corresponding acid **142**, to form five membered rings revealed that the tin mediated cyclisation would only proceed if the ketone carbonyl was reduced and the resulant alcohol protected.[284,286] Thus, cyclisation of **143** proceeded smoothly to afford difluorinated cyclopentanes and lactols **144** in good yields (Scheme 3.3.3.1). A comparative study of alkenes and alkynes in 5-*exo* radical cyclisations reported that reactions mediated by organosilanes, samarium diiodide and organocobalt complexes were more efficient than those with organotin hydrides and in the case of organocobalt complexes allowed further functionalisation.[258]

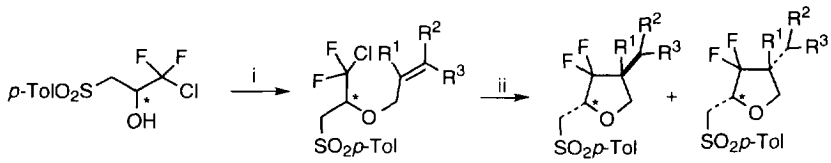


142 **143** **144**

Scheme 3.3.3.1

Cavicchio and Bravo have investigated a stereocontrolled route to functionalised furans, cyclopentanes and cyclohexanes involving sulfur substituted chiral intermediates. The chiral difluorinated synthons **145a-b**,

prepared by microbial reduction of the corresponding ketones, reacted with allylic bromides and the resulting chloroalkenes underwent 5-*exo-trig* cyclisation as a route to functionalised furans **146** (Scheme 3.3.3.2).[287,288] A moderate to fair diastereoselectivity was observed in these reactions, always in favour of the *trans*-isomer.

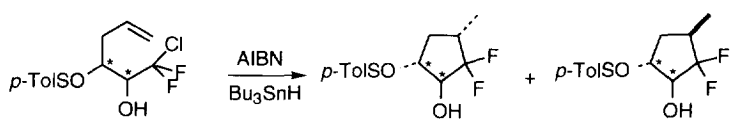


145a (*R*), **145b** (*S*) **146** *trans* **146** *cis*

Conditions: i. $BrCH_2$-CR^1=CR^2R^3; ii. AIBN, Bu_3SnH.

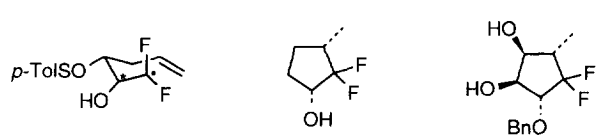
Scheme 3.3.3.2

In similar fashion the stereochemical outcome of 5-*exo-trig* and 6-*exo-trig* cyclisations of all four diastereomers of **147** and **148** has been investigated. In the cyclopentane series,[289] a moderate diastereoselectivity was found in favour of the isomer having the methyl and the sulfinyl group in a 1,3-*cis*-relationship (Scheme 3.3.3.3). It was proposed that the molecule in an early transition state **149** preferentially adopted a conformation in which the larger sulfinyl substituent was in a pseudo-equatorial position. Five membered ring intermediates **150** could then be converted into functionalised cyclopentanes such as **151** and **152**.



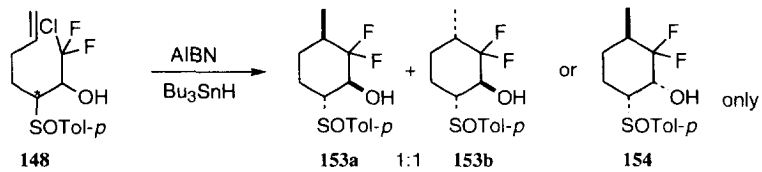
147 **150**

Scheme 3.3.3.3

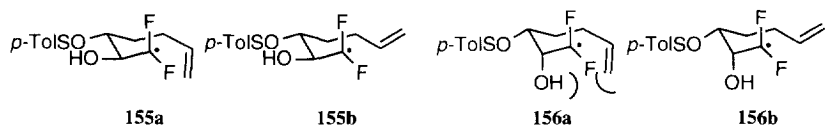


149 **151** **152**

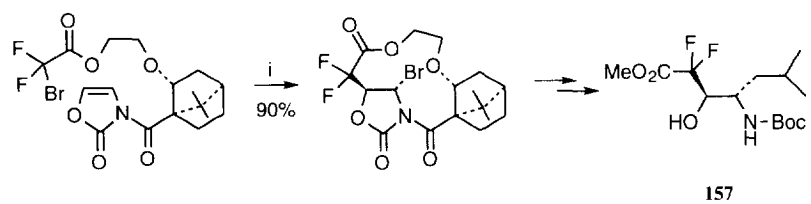
In the cyclohexane series,[290] when the arylsulfinyl and hydroxy substituents had a relative *threo*-configuration, an equimolar mixture of the two diastereomers **153a** and **153b** was produced, whereas with an *erythro*-arrangement, a single cyclisation product **154** was observed (Scheme 3.3.3.4). The rationale for this difference in selectivity proposed that in the first case both transition states **155a** and **155b** were similarly populated, whereas in the second case a 1,3-diaxial relationship between the alkene and the hydroxy groups in **156a** favoured transition state **156b**.



Scheme 3.3.3.4



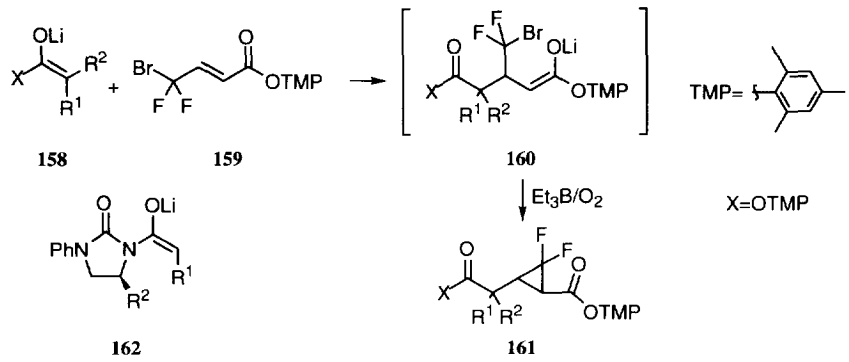
Removable tethers have been used to induce stereoselectivity in intramolecular radical cyclisations. A key step in the preparation of 2,2-difluorostatine **157** was the efficient ruthenium catalysed intramolecular addition of a difluoroacetyl radical to a 2-oxazolone derivative, permitting introduction of the difluoromethylene group with high diastereoselectivity (Scheme 3.3.3.5).[291]



Conditions: i. $RuCl_2(PPh_3)_3$, benzene, reflux.

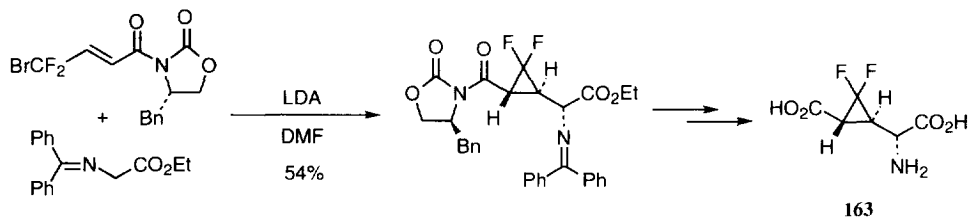
Scheme 3.3.3.5

Finally, difluorocyclopropanes have been prepared by the cyclisation of a lithium enolate,[292] although the radical nature of this reaction is open to discussion. Michael addition of lithium enolates **158** to the ester **159**, followed by triethylborane-oxygen induced cyclopropanation of intermediates **160** afforded the cyclopropanes **161** in good yields (Scheme 3.3.3.6). An asymmetric version using the lithium enolate of *N*-acylimidazolidinone **162** has also been reported.[293] The converse strategy, with the chiral auxiliary attached to the Michael acceptor, has been used in a highly diastereoselective synthesis of *trans*-3,4-(difluoromethano)glutamic acid **163** (Scheme 3.3.3.7).[294] It was also found that additives were not essential to the cyclisation step, casting further doubt on the involvement of a radical mechanism.



158 159 160 162 161

Scheme 3.3.3.6



163

Scheme 3.3.3.7

Radical methodologies are being developed as mild alternatives to reactions involving fluorine substituted carbanions and there is little doubt that they hold an increasingly important position among the synthetic strategies for *gem*-difluoro compounds.

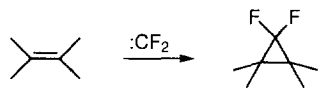
3.4 Difluorocarbene and Cyclopropanes

gem-Difluorocyclopropanes were considered fifteen years ago as versatile intermediates for the preparation of difluoromethylene substituted compounds,[295] but since then have not been extensively used in synthesis. They are almost invariably prepared by the addition of difluorocarbene to double bonds, and are involved in several ring opening reactions. Taguchi's non-carbene synthesis of highly functionalised difluorocyclopropanes was described in section 3.3.3. *gem*-Difluorocarbene is very electrophilic and exists as a ground state singlet.[296,297] As such, its addition to alkenes is stereospecific and it does not insert into C-H bonds in competition with C=C addition.[298,299]

3.4.1 Generation of Difluorocarbenes

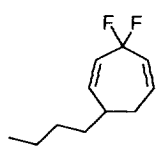
A variety of methods exists for the generation of difluorocarbene (Scheme 3.4.1.1). Tin[300] and mercury[301-303] trifluoromethyl complexes are toxic but efficient difluorocarbene sources in the presence of sodium iodide. The mercury complex has been used recently in the preparation of the algal pheromone

dictyotene analogue **164** (*vide infra*).[304] Thermolysis of sodium chlorodifluoroacetate[305] has long been the method of choice for the generation of difluorocarbene, but Burton's phosphonium salt/potassium fluoride system[306] is now being recognised as the most convenient means of generation. Recently, a dramatic increase in yield was noticed when a catalytic amount of 18-crown-6 was added to the reaction mixture,[307] and the reagent has been used in the preparation of fluorinated insecticides of the type **165**[308] and of *gem*-difluorocyclopropenes **166**.[309] Halofluorosulfonyldifluoroacetic acids have been reported as an easy to handle source of difluorocarbene under mild conditions,[310,311] and were used in a new preparation of iododifluoromethane.[312]

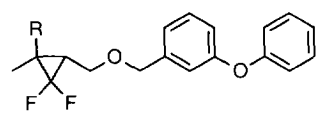


Me_3SnCF_3[300]
$PhHgCF_3$[301-303]
ClF_2CCO_2Na[305]
ClF_2CCO_2Me/LiCl/HMPA[313,314]
$[(Me_2N)_3PCF_2Br]^+Br^-$/KF[306,307]
$[Ph_3PCF_2Br]^+Br^-$/KF[306,307]
CF_2Br_2/$TiCl_4$/$LiAlH_4$[315]
CF_2Br_2/Zn/I_2 (cat.)[316]
CF_2Br_2/$CHBr_3$/KOH/TBAHS[317,318]
$FO_2SCF_2CO_2H$/Nu[310]

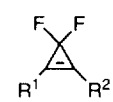
Scheme 3.4.1.1



164

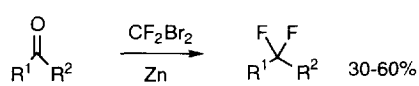


165

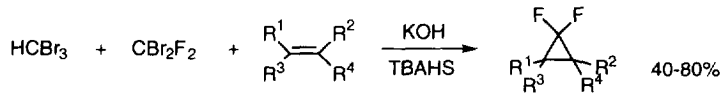


166

New methods for the generation of difluorocarbene have recently been reported: reaction of dibromodifluoromethane with alkenes in presence of titanium tetrachloride and lithium aluminium hydride afforded cyclopropanes in low yields.[315] Dibromodifluoromethane, zinc and a catalytic amount of iodine constitutes a convenient preparation of difluorocarbene, which reacted with alkenes in yields comparable to Burton's phosphonium salt method.[316] Interestingly, carbenes generated from CF_2Br_2/ Zn act as fluorinating agents with aldehydes and ketones to form the corresponding *gem*-difluoro compounds (Scheme 3.4.1.2).[71] A remarkably economical and simple procedure for the synthesis of *gem*-difluorocyclopropanes, using a phase transfer catalysed system, has been reported:[317,318] stirring a mixture of bromoform, dibromodifluoromethane and nucleophilic alkenes with 60% aqueous potassium hydroxide and tetrabutylammonium hydrogensulfate (TBAHS) afforded the corresponding difluorocyclopropanes in moderate to good yields (Scheme 3.4.1.3).



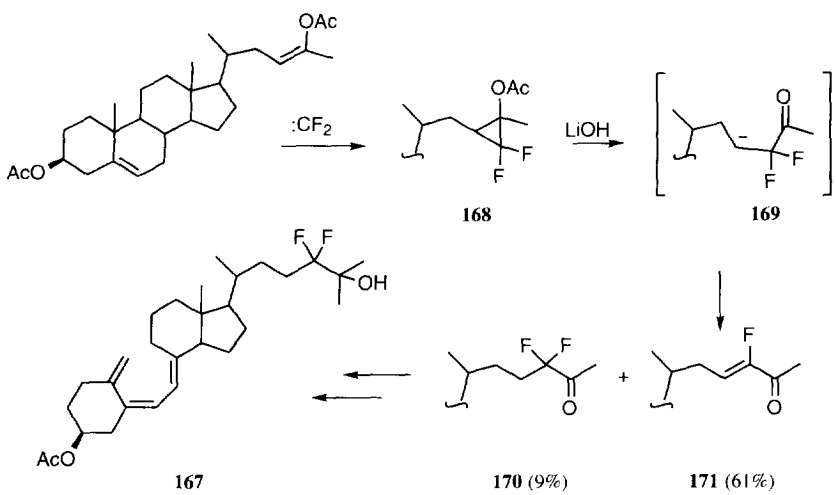
Scheme 3.4.1.2



Scheme 3.4.1.3

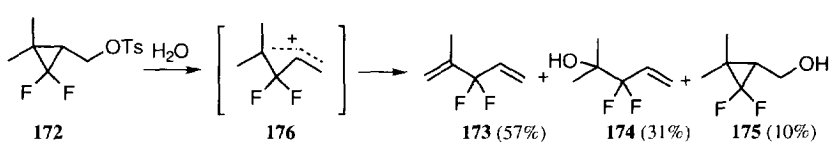
3.4.2 Reactions of gem*-Difluorocyclopropanes*

Several ring opening reactions of *gem*-difluorocyclopropanes involving anionic, cationic or radical intermediates are known. A problem generally associated with the anionic ring opening is that the β,β-difluoro anion produced has a tendency to eliminate, leading to monofluoroalkenes.[318] An interesting example of this phenomenon can be found in the synthesis of 24,24-difluoro-25-hydroxy-vitamin-D_3 **167** where ring opening of the intermediate **168**, *via* the β,β-difluoro anion **169**, afforded only 9% of the protonated product **170** and 61% of the elimination product **171** (Scheme 3.4.2.1).[319]



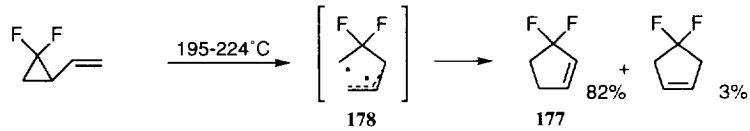
Scheme 3.4.2.1

There is one report of a cationic ring opening of a difluorocyclopropane: solvolysis of the tosylate **172** in refluxing aqueous dioxane afforded the homoconjugated diene **173** along with the tertiary alcohol **174** and the primary alcohol **175**.[320] A non-classical cation **176** was proposed as a common intermediate for the three products (Scheme 3.4.2.2).

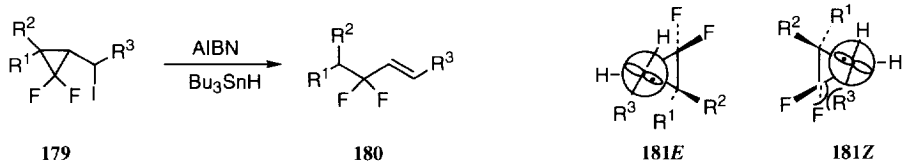


Scheme 3.4.2.2

In contrast to their non-fluorinated counterparts, homolytic ring opening of *gem*-difluorocyclopropanes can be synthetically useful reactions, because the bond opposite to the difluoromethylene unit is weaker than the other two and hence good regioselectivity is usually obtained.[321] Thus difluorovinylcyclopropane undergoes a thermally induced ring opening reaction to produce cyclopentene **177** as the major product,[322] presumably *via* a diradical intermediate **178** (Scheme 3.4.2.3).[323] Radical induced ring opening of difluorocyclopropanes not only occurs with good regioselectivity,[324] but also with good stereoselectivity. Reaction of radicals generated from iodides **179** afforded mainly the *E*-alkenes **180** (Scheme 3.4.2.4).[325] A rationale proposed for this selectivity is that steric repulsion between R^3 and the cyclopropane ring disfavours the transition state **181*Z*** compared to the transition state **181*E***.

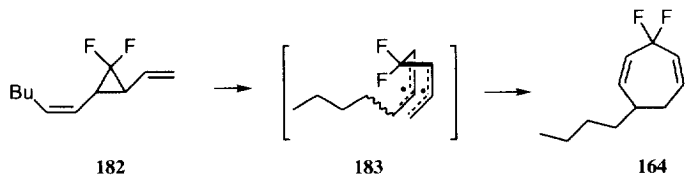


Scheme 3.4.2.3



Scheme 3.4.2.4

Sigmatropic rearrangements involving difluorocyclopropanes are also more facile and selective than their non-fluorinated counterparts. A recent example is the preparation of **164**, a fluorinated analogue of marine brown algae pheromone, by a [3,3]-sigmatropic rearrangement of the divinylcyclopropane **182**, which proceeded at room temperature, presumably *via* a diradical intermediate **183** (Scheme 3.4.2.5).[304]



Scheme 3.4.2.5

Considering the number of methods available to prepare *gem*-difluorocyclopropanes and their facile regio- and stereoselective ring opening under mild conditions, it is surprising that this approach has not been more frequently employed in the synthesis of difluoromethylene substituted compounds.

3.5 Difluoroalkenes

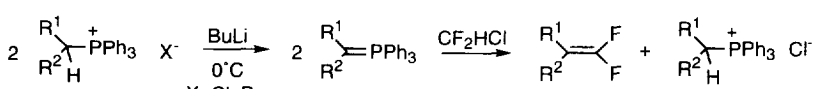
gem-Difluoroalkenes have become versatile intermediates in the synthesis of fluorinated molecules. Great effort has been put into the search for efficient and general methods for their preparation and a review has been published on the subject.[5] Much of the current work is aimed towards the development of new reactions for the elaboration of *gem*-difluoroalkenes.

3.5.1 Preparation of gem-*Difluoroalkenes*

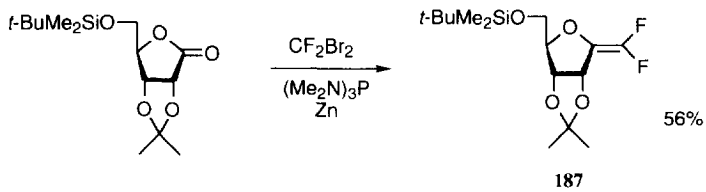
A variety of methods have been reported for the preparation of fluorinated *gem*-difluoroalkenes, based on Wittig, organometallic or elimination approaches. Wittig approaches (Scheme 3.5.1.1) have been used for the conversion of aldehydes, ketones and even lactones to the corresponding difluoroalkenes. The ylid is usually generated through the reaction of difluorocarbene with a phosphine[326] or reduction of a phosphonium salt by phosphines[327,328] or zinc metal.[329] Triphenylphosphine, dibromodifluoromethane and zinc are the reagents of choice, and tris(dimethylamino)phosphine has been used for less reactive carbonyl compounds.[329] Replacement of zinc by a second equivalent of phosphine produces an olefinating solution with long lasting reactivity, but in this case the reaction is very sensitive to water.[328-330] Wadsworth-Emmons[331] and Horner[332] approaches, using either commercially available ethyl difluoromethylenephosphonate or diphenyldifluoromethylphosphine oxide, have also been reported. The opposite approach,[333,334] where a non-fluorinated ylid is reacted with a fluorinated synthon has been developed as an economical and easy to scale up process: one equivalent of the ylid **184**, generated from the phosphonium salt **185** at 0°C, deprotonated chlorodifluoromethane to generate a difluorocarbene, which reacted with the second equivalent of the ylid **184** to afford the difluoroalkene **186** in good yield along with one equivalent of the starting phosphonium salt (Scheme 3.5.1.2). Recent applications of the Wittig methodology include the preparation of carbohydrate exocyclic *gem*-difluoroenolethers **187** from the corresponding lactones (Scheme 3.5.1.3).[335,336]

$ClCF_2CO_2Na/Ph_3P/160°C$[326]
CF_2Br_2/Ph_3P (2eq)[327]
$CF_2Br_2/(Me_2N)_3P$ (2eq)[328]
CF_2Br_2/Ph_3P (1eq)/ Zn[329]
$CF_2Br_2/(Me_2N)_3P$ (1eq)/ Zn[329]
$HCF_2PO(OEt)_2$/base[331]
$HCF_2PO(Ph)_2$/base[332]

Scheme 3.5.1.1

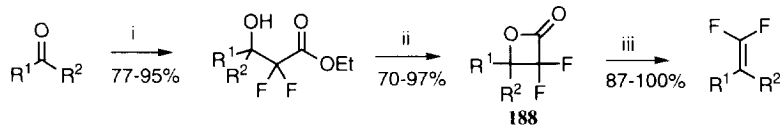


Scheme 3.5.1.2



Scheme 3.5.1.3

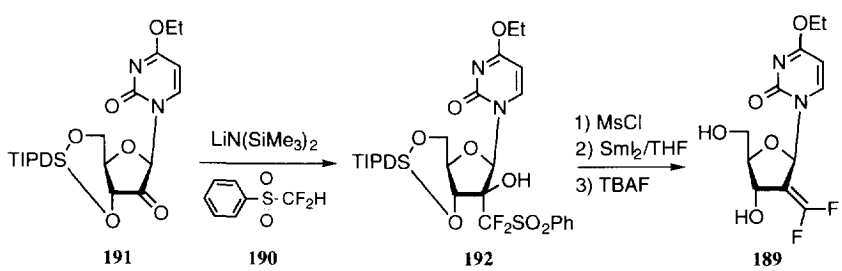
A formal difluoromethylenation of carbonyl substrates *via* α,α-difluoro-β-lactones has been described: the combination of a Reformatsky reaction followed by hydrolysis of the ester and cyclisation afforded β-lactones **188** which underwent thermal decarboxylation to produce the difluoroalkenes in high yields (Scheme 3.5.1.4).[337]



Conditions: i. BrF_2CCO_2Et, Zn; ii. 1) NaOH; 2) $PhSO_2Cl$, pyridine; iii. 100-150 °C.

Scheme 3.5.1.4

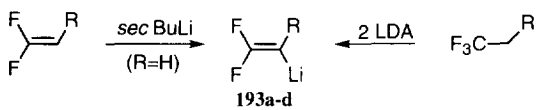
A modified Julia approach to 1,1-difluoroalkenes has recently been reported for the preparation of 2'-deoxy-2'-difluoromethylene cytidine **189** in response to the failure of difluoromethyldiphenylphosphine or Wittig olefination with $CF_2Br_2/(Me_2N)_3P$ (Scheme 3.5.1.5).[338] Addition of lithium hexamethyldisilazide to a mixture of the sulfone **190** and the ketone **191** afforded the alcohol **192**, which was then converted to the corresponding mesylate. Reductive elimination with samarium diiodide/THF followed by deprotection produced the citidine analogue **189**, a mechanism based inhibitor of ribonucleoside diphosphate reductase.



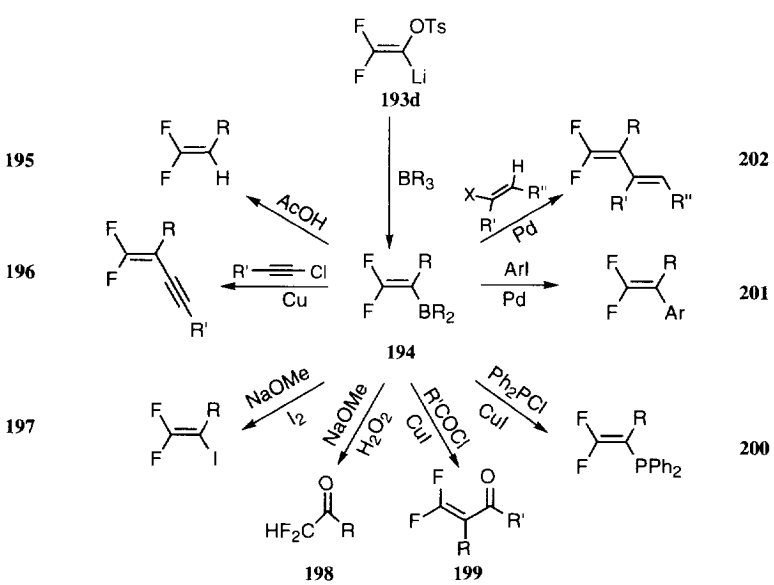
Scheme 3.5.1.5

A second, prefabricated approach to *gem*-difluoroalkenes may be found in the reactions of difluorovinyl organometallic reagents, the preparation and reactivity of which has been the subject of a review.[339] From a synthetic point of view, difluorovinyllithium reagents have received a lot of attention and have proved to be versatile intermediates (Scheme 3.5.1.6). Normant reported the first preparation of difluorovinyllithium **193a**

(R=H) from difluoroethylene and its reaction with aldehydes and ketones.[340] Percy[341,342] prepared the stabilised difluorovinyl anion **193b** (R=OMEM) and the acyl anion equivalent **193c** (R= $OCONEt_2$, see section 3.1.2 for reactions of **193c**) from derivatives of trifluoroethanol, and described their reactions with electrophiles.[175-177,187] By converting the difluorovinyllithium tosylate **193d** (R=OTs) to 2,2-alkenylborane **194**, Ichikawa has developed a synthon for a wide range of difluoroalkenes (Scheme 3.5.1.7).[343] Thus, protonation with acetic acid afforded monosubstituted difluoroalkenes **195**;[343] copper mediated coupling with acetylenes provided a general route to enynes **196**;[344] reaction with iodine and sodium methoxide furnished the vinyl iodide **197** for coupling reactions;[345] oxidation with alkaline hydrogen peroxide produced difluoromethylketones **198**;[346] coupling with acid chlorides opened a general access to Michael acceptors **199**;[347] coupling with phosphine chloride yielded difluorovinylphosphines **200**;[348] and palladium coupling with arenes and alkenes afforded styrenes[349] **201** and dienes[350] **202** (Scheme 3.5.1.7).



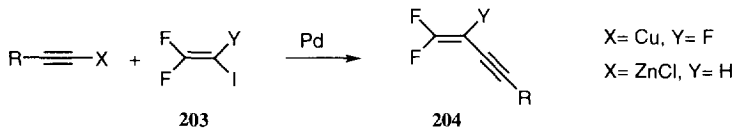
Scheme 3.5.1.6



Scheme 3.5.1.7

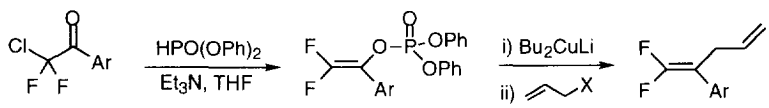
Other difluorovinyl organometallic reagents have been reported. Palladium catalysed coupling of difluorovinyl iodides **203** with alkenes has been used in the preparation of fluorinated enynes **204** (Scheme 3.5.1.8).[351,352] Organocuprates, prepared from difluoroenolphosphate **205**, reacted with allyl halides to produce homoconjugated dienes **206** (Scheme 3.5.1.9).[353] Finally, the reaction of dichlorotrifluoroethane

(HCFC-123) with aldehydes and zinc produced allylic alcohol **207**, reportedly *via* the organometallic intermediate **208** (Scheme 3.5.1.10).[354-356]



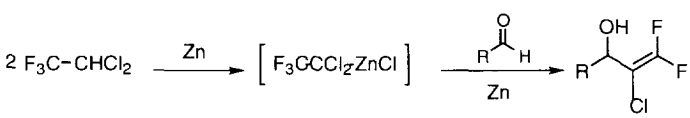
203 **204**

Scheme 3.5.1.8



205 **206**

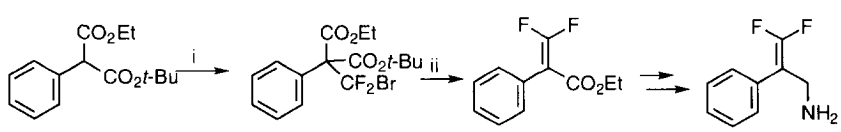
Scheme 3.5.1.9



208 **207**

Scheme 3.5.1.10

A third general approach to the preparation of *gem*-difluoroalkenes is *via* β-elimination or addition-elimination. Reaction of dibromodifluoromethane with enolates (carbene insertion) or alkenes (radical addition), followed by β-elimination or decarboxylative elimination is a convenient route to difluoroalkenes.[249,357] An example is the synthesis of the mononamine oxidase inhibitor **7** by decarboxylative elimination of the bromide **209** (Scheme 3.5.1.11).[358]



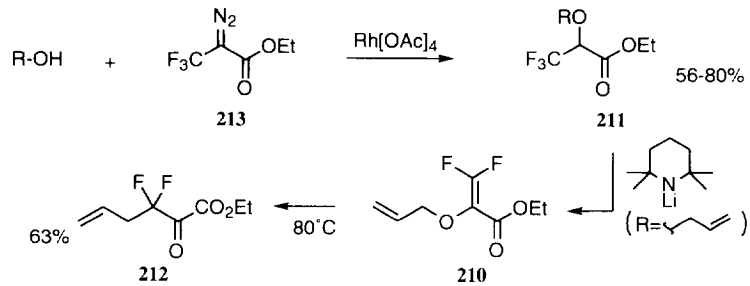
209 **7**

Conditions: i. LDA, CF_2Br_2, 83%; ii. 1) CF_3COOH, 2) NaOH, 96%.

Scheme 3.5.1.11

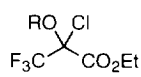
Elimination of hydrogen fluoride to form a difluoroalkene from a trifluoromethyl containing compound is another possibility. This is illustrated by the preparation of the substrate **210** by β-elimination of the trifluoromethyl substituted ester **211**, which subsequently underwent a Claisen rearrangement (*vide infra*) to produce the β,β-difluoro-α-keto ester **212** (Scheme 3.5.1.12).[359] It is interesting to note that hemiketal **211** was prepared by a rhodium mediated insertion into an allylic alcohol of the carbene generated from the

trifluorodiazo synthon **213**.[360] The overall sequence constitutes a new entry into difluoromethylene substituted compounds,[359] as demonstrated by the reductive amination of the keto-group of α-keto ester **212**, which furnished versatile β,β-difluoro-α-amino acid precursors.[361]



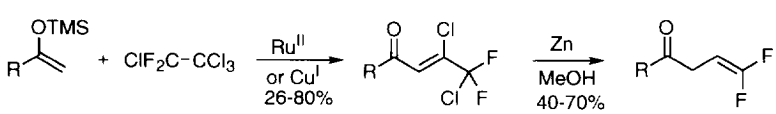
Scheme 3.5.1.12

Reductive dehalogenation has also been used in the preparation of *gem*-difluoroalkenes by zinc metal reduction or lithium halogen exchange and it is to be noted that Shi has subsequently published a more efficient route to **210**, involving zinc mediated dechlorofluorination of hemiacetal **214**.[361] The side reactions that blighted the initial approach were thereby avoided.



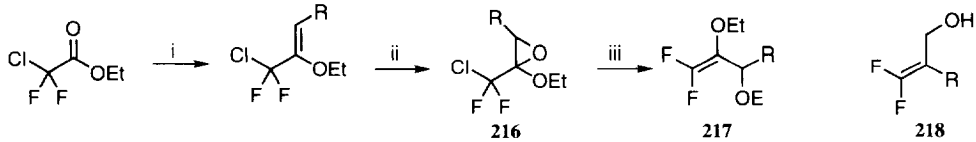
214

Another recent example is the reductive hydrodechlorination of the adduct **215**, which was obtained by radical addition of difluorotetrachloroethane to a trimethylsilyl enolether, followed by spontaneous elimination (Scheme 3.5.1.13).[362] Lithium halogen exchange,[363] followed by ring opening of an epoxide has been reported as part of a general route to (3,3-difluoro-2-ethoxy)allylic alcohols from ethyl chlorodifluoroacetate (Scheme 3.5.1.14): Wittig olefination of ethyl chlorodifluoroacetate, followed by epoxidation and treatment of the epoxide **216** with *t*-BuLi and an electrophile, produced the *gem*-difluoroenolether **217**. A similar approach involved the reaction of diazomethane with chlorofluoromethyl ketones to afford epoxides which underwent ring opening upon treatment with butyllithium to afford *gem*-difluoroallylic alcohols **218** as suitable substrates for Claisen rearrangement (*vide infra*).[364]



215

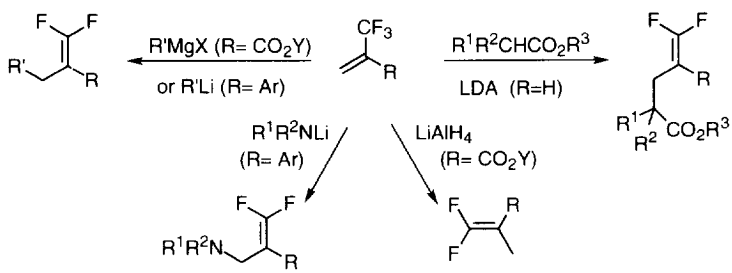
Scheme 3.5.1.13



Conditions: i. Ph_3P=CHR; ii. *m*-CPBA; iii. *t*-BuLi, E^+ (TMSCl, NH_4Cl).

Scheme 3.5.1.14.

Finally, nucleophilic addition-elimination with trifluoromethylvinyl compounds has become a general preparation of difluorinated alkenes. Reaction of organolithiums,[365] Grignard reagents,[250,365,366], *N*-lithiated amines,[367] lithium aluminium hydride[250] or ester enolates[368] with trifluoromethyl substituted alkenes afforded the corresponding *gem*-difluoroalkenes (Scheme 3.5.1.15).



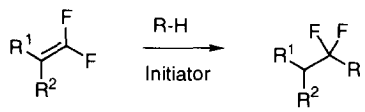
Scheme 3.5.1.15

3.5.2 Reactions of gem-*Difluoroalkenes*

Several types of reactions involving *gem*-difluoroalkenes have gained synthetic utility and they can be divided in three main categories: radical and nucleophilic additions, cycloadditions and rearrangements. Nucleophilic additions have already been covered in section 3.2.2.

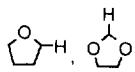
The kinetics and orientation of free radical additions to fluorinated alkenes are governed by a complex combination of steric and polar factors, but in most examples involving substituted 1,1-difluoroalkenes, addition occurred at the CF_2-terminus.[369-373] Computerised coefficients[374] have predicted that *gem*-difluoroalkenes have a slightly lower energy LUMO and a much lower HOMO than their non-fluorinated counterparts and the dominance of the interaction between the LUMO and the radical SOMO is consistent with the electrophilic behaviour observed.[370,372] Radical additions to *gem*-difluoroalkenes have been utilised in synthesis since 1981, when Suda[375] reported the addition of thiols and aldehydes across CF_2-alkenes initiated by dibenzoyl peroxide (Scheme 3.5.2.1A). Several radical methodologies have since then been reported: addition of tetrahydrofuran, hexanal and benzaldehyde to β,β-difluoroacrylate initiated by benzoyl peroxides or AIBN produced the corresponding β,β-difluoroesters in moderate to good yields (Scheme 3.5.2.1B).[376] A general route to α,α-difluorocarboxylic acids **219** has been described, involving the addition of radicals

generated from Barton esters **220** to difluorodichloroethylene, followed by hydrolysis with aqueous silver nitrate (Scheme 3.5.2.2).[377,378]

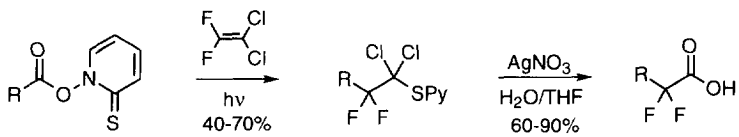


A: R^1= $C_{10}H_{21}$, Ar
R^2= H
R-H= PhS-H, RS-H, RCOH

B: R^1= CO_2Et
R^2= Me
R-H= RCOH,



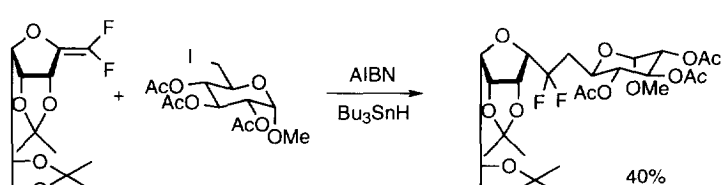
Scheme 3.5.2.1



220 **219**

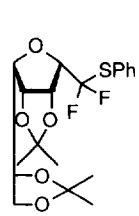
Scheme 3.5.2.2

Motherwell has described the addition of both carbon- and heteroatom-centred radicals to carbohydrate derived *gem*-difluoroalkenes. The synthesis of CF_2-glycosides, such as disaccharide **222**, has been reported through the tin-mediated addition of alkyl radicals to carbohydrate exocyclic *gem*-difluoroenol ethers (Scheme 3.5.2.3).[269,379] The stereochemistry was governed by the final delivery of a hydrogen atom from the least encumbered convex face of the [3.3.0] bicyclic system.[269,137] This is also the case for the addition of thiols, such that CF_2-glycoside **223** was obtained in 83% yield from its *gem*-difluoroenol ether precursor **221**. In contrast, the addition under reductive conditions of a phosphonyl radical, derived from diethyl (phenylselenyl)phosphonate ($(EtO)_2P(O)SePh$), gave difluoromethylenephosphonate **224** .[380]

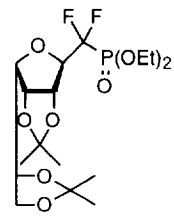


221 **222**

Scheme 3.5.2.3

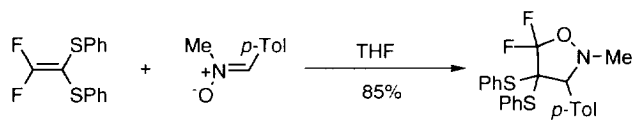


223



224

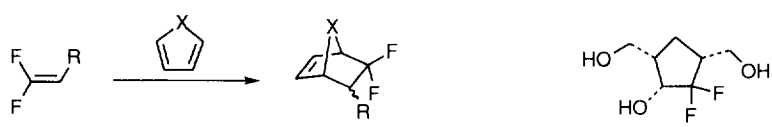
Cycloadditions involving difluoroalkenes have been long thought to be limited to [2+2] additions.[299] Fluoroalkenes usually undergo [2+2] reactions much faster than [4+2] reactions[381] and theoretical studies have suggested that this is because fluorine stabilises diradical intermediates.[382] Nevertheless, [3+2] and [4+2] cycloaddition reactions have recently been reported using difluorinated alkenes and dienes. Purrington has reported an example of [3+2] cycloaddition of the nitrone **225** with difluorodiphenylthioethylene **226** as a preparation of the fluorinated isoxazolidine **227** (Scheme 3.5.2.4).[383,384]



226 **225** **227**

Scheme 3.5.2.4

Two examples of [4+2] cycloaddition of a difluoroalkene with a non-fluorinated diene have been reported. The Michael acceptor **228a** was shown to react with furan to produce the adduct **229a**,[249] and the oxygen substituted difluoroalkene **228b** with cyclopentadiene to afford **229b**, which was then converted to the functionalised cyclopentane **230** (Scheme 3.5.2.5).[385]



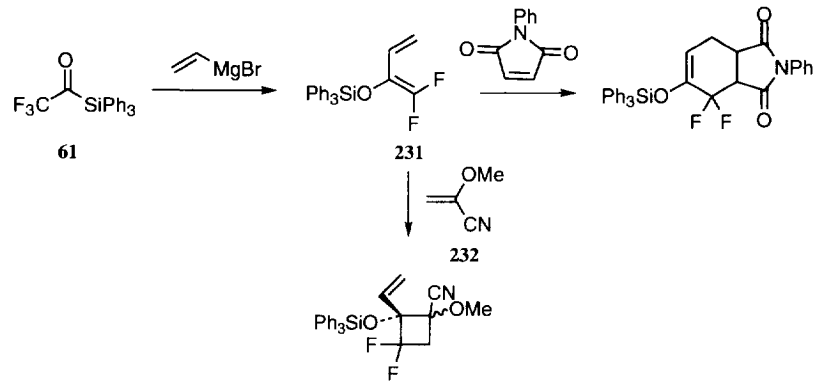
228a R= CO_2Et
228b R= $OCONEt_2$

229a R= CO_2Et, X= O
229b R= $OCONEt_2$, X= CH_2

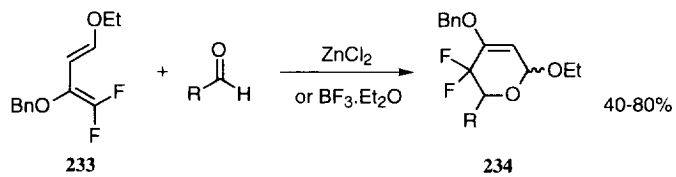
230

Scheme 3.5.2.5

Difluorodienes have also been used in Diels-Alder reactions: 1,1-difluoro-2-triphenylsiloxybuta-1,3-diene **231**, prepared by reaction of vinylmagnesium bromide with trifluoroacetyltriphenylsilane **61**, underwent [4+2] cycloadditions with typical dienophiles such as *N*-phenylmaleimide and [2+2] reactions with alkenes bearing captodative substituents (e.g. **232**, Scheme 3.5.2.6).[386] The Lewis acid promoted hetero Diels-Alder reaction of diene **233** with aldehydes provided a novel route to difluoropyranosides **234** (Scheme 3.5.2.7).[387]

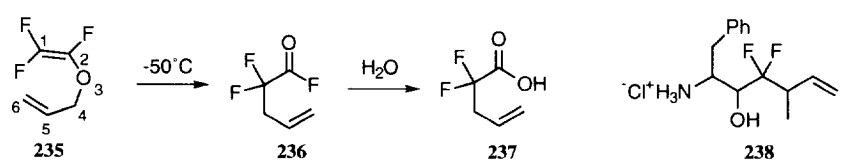


Scheme 3.5.2.6



Scheme 3.5.2.7

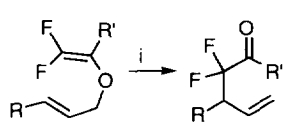
[3,3]-Sigmatropic rearrangements have been reviewed recently,[388] and they form a third class of reactions of *gem*-difluoroalkenes. The effects of fluorine substitution on the Cope[389] and Claisen rearrangements have been studied. Electron acceptor substituents on the 2,4,5-carbons are known to accelerate the Claisen rearrangement[390,391] and the reaction of the trifluorinated compound **235** proceeded easily at -50°C to produce the acid fluoride **236** which was hydrolysed *in situ* to the acid **237** (Scheme 3.5.2.8).[392] A preparative flow technique for this reaction has been reported in the large scale preparation of the acid **237**,[393] which has been used in the synthesis of the fluorinated intermediate **238** for incorporation into peptides analogues.[394-397] Another example of this reaction is the preparation of the cobra venom phospholipase inhibitor **120** (section 3.2.2).



Scheme 3.5.2.8

The Claisen rearrangement of functionalised difluoroalkenes as a route to α,α- and β,β-difluorocarbonyl compounds has also been reported. The rearrangement of dienes **239**, generally prepared by elimination of the

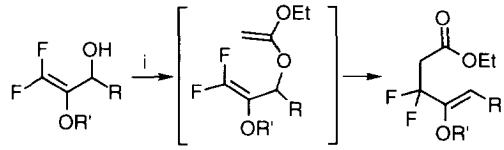
corresponding trifluoromethyl substrate (see section 3.5.1), proceeded smoothly to afford ketones and aldehydes **240** (Scheme 3.5.2.9).[398] A slightly different approach involved the reaction of difluoroallylic alcohols **241** with triethyl orthoacetate, followed by an orthoacetate Claisen rearrangement to prepare β,β-difluoroesters **242** in good yields (Scheme 3.5.2.10).[398,399] An investigation of the reaction of substrates **241** with dimethylacetamide dimethyl acetal and ethylvinyl ether has recently been reported.[400]



239 **240**

Conditions: i. CCl_4, 80°C.

Scheme 3.5.2.9

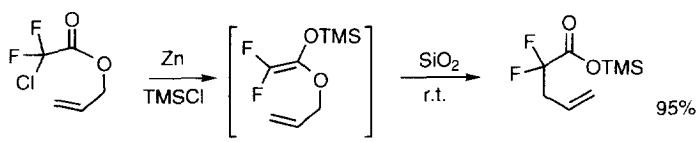


241 **242**

Conditions: i. $HC(OEt)_3$, $CH_3CH_2CO_2H$, 120°C.

Scheme 3.5.2.10

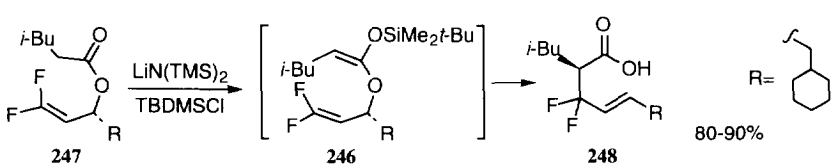
Two approaches utilising the Ireland-Claisen rearrangement with different positions of fluorination have been described: in the first a Reformatsky-Claisen rearrangement of the chlorodifluoroester **243**, through the silylenol ether **244**, was used to prepare the α,α-difluoroester **245** in high yield (Scheme 3.5.2.11).[401] The second approach involves the generation of the silylenol ether **246** from the ester **247**, followed by a [3,3]-sigmatropic rearrangement to prepare the β,β-difluoroacid **248** with very good stereoselectivity, and high yield (Scheme 3.5.2.12).[402] The stereochemical outcome was consistent with formation of the *E*-enol ether and cyclisation *via* the expected chair transition state. The β,β-difluoroacid **248** was subsequently converted to the dipeptide analogue **249**.[403]



243 **244** **245**

95%

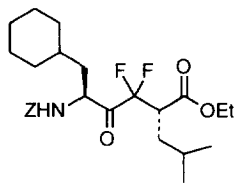
Scheme 3.5.2.11



247 **246** **248**

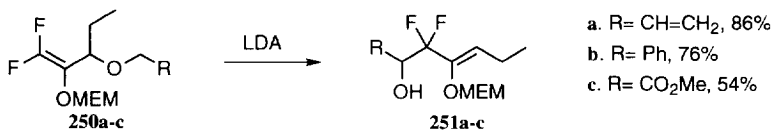
80-90%

Scheme 3.5.2.12



249

Finally, the [2,3]-Wittig rearrangement has been recently applied to fluorinated substrates: compounds **250a-c**, upon treatment with LDA, underwent rearrangement to afford alcohols **251a-c** in good yields (Scheme 3.5.2.13).[404]



250a-c **251a-c**

a. R= $CH{=}CH_2$, 86%
b. R= Ph, 76%
c. R= CO_2Me, 54%

Scheme 3.5.2.13

The wealth of practical methods for their preparation and the versatility for their further conversion has made 1,1-difluoroalkenes particularly attractive intermediates in the synthesis of difluoromethylene substituted compounds.

4 CONCLUSION

gem-Difluoromethylene substituted molecules constitute a distinct class of fluorinated compounds and a special chemistry continues to be developed for their preparation. Direct fluorination has been dominated by the reaction of DAST with aldehydes and ketones and it remains extremely popular in spite of the chemical limitations and practical drawbacks frequently cited by proponents of alternative techniques. Whilst new and mild sources of hydrogen fluoride and fluoride have been instrumental to the development of such alternatives, the advent of new electrophilic fluorinating reagents, notably Selectfluor, seems to offer the greatest potential for growth in the area of direct *gem*-difluorination. However, it is the proliferation of difluorinated synthon approaches that has given the synthesis of *gem*-difluoromethylene compounds its current depth and variety. The Reformatsky reaction has been widely applied in many series of compounds and is a thoroughly established strategy for CF_2-incorporation. Other difluoroenolate based methods have been subsequently developed and the related reactions of difluoromethylenephosphonate reagents are of significant value. Reformatsky precursors, halodifluorocarbonyl compounds, have also been used in the increasingly successful area of sigmatropic rearrangements. *gem*-Difluoroalkenes are accessible by a considerable number of routes and are useful intermediates in a range of transformations. It is hoped that this review provides a thorough, if not exhaustive, guide for chemists wishing to incorporate and manipulate the *gem*-difluoromethylene unit.

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