Recent advances in organofluorine chemistry

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Reviewing the literature published between January 1992 and April 1995

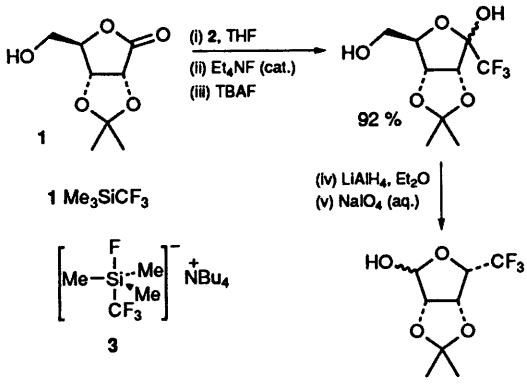
1 Introduction

This Review deals with advances in the chemistry of fluorinated building blocks which are small, readily-available, and manipulable molecules that already contain one or more fluorine atoms. The article concentrates on aliphatic chemistry wherein lies the main intellectual challenge. No effort will be made to cover the burgeoning literature describing functional group transformations with reagents such as DAST, elemental fluorine, or xenon difluoride.[1,2] Recent more specialized reviews have discussed routes to fluorinated amino acids[3] and aspects of the electrochemistry of organofluorine compounds.[4] The material is organized under fairly broad headings reflecting the relative youth of much of the chemistry.

2 Fluorinated carbon nucleophiles

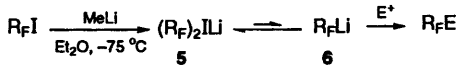
2.1 Perfluoroalkyl organometallic reagents

A multitude of methods exist for the trifluoromethylation of organic substrates, forming the subject of a recent specialized review.[5] One particularly accessible method uses commercially-available (trifluoromethyl) trimethylsilane (Ruppert's reagent) **1** which adds efficiently to carbonyl electrophiles in the presence of fluorine ion sources. The reactive species is presumably the silicon-*ate* complex **3** and recent applications have included syntheses of deoxysugars in both hexose[6] and pentose[7] series. **Scheme 1** shows a typical sequence from protected ribonolactone **2** through to D-lyxose ketal **4**; yields of adducts are high but the reagent usually shows low diastereoselectivity in the addition step. Other perfluoroalkylation reactions



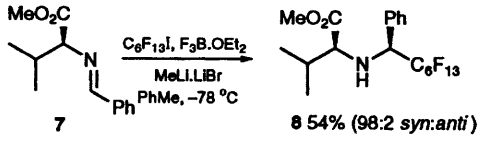
Scheme 1

have been described by Uno and co-workers.[8] Readily-available perfluoroalkyl iodides undergo halogen–metal exchange at low temperature. The first formed perfluoroalkyllithium reagent reacted with the iodide precursor to afford iodinate complex **5** (**Scheme 2**). The *ate*-complex was believed to act as a reservoir for the reactive perfluoroalkyllithium reagents. When the complexes were generated in the presence of electrophiles, good yields of adducts could be obtained via the removal of the reactive but thermally-unstable perfluoroalkyllithium reagent **6** from the equilibrium.



Scheme 2

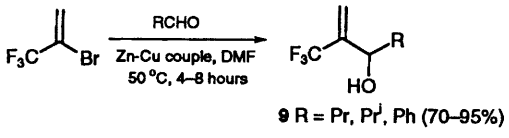
In the presence of boron trifluoride etherate, good yields of adducts with imines were obtained.[9] **Scheme 3** depicts the addition of perfluorohexyl iodide to imine **7** affording **8** in moderate chemical yield but with high diastereoselectivity.



Scheme 3

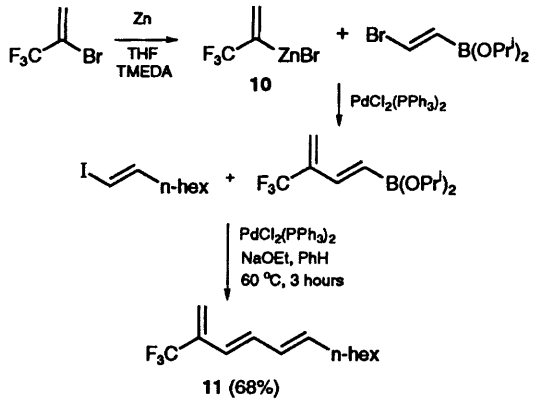
2.2 Fluoroalkenyl organometallic reagents

The pioneering work of Normant, Burton, and others has formed the subject of a recent review.[10] Readily available 2-bromo-1,1,1-trifluoropropene can be used in a range of organometallic reactions. **Scheme 4** shows a Barbier reaction with aldehydes mediated by a zinc-copper couple to afford allylic alcohols **9**.[11]



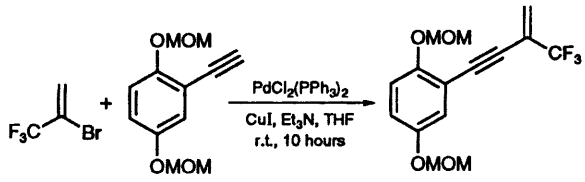
Scheme 4

Interestingly, the vinylzinc reagent **10**, prepared by stoichiometric chemistry in THF or DMF, failed to react with aldehydes. The reactive species in the Barbier reaction was believed to be an unsolvated vinylorganometallic reagent. Hu and co-workers have described coupling reactions of **10** with (bromovinyl)-dialkylboranes (**Scheme 5**), leading to triene **11**.[12] The bromide reacted directly with alkynes under palladium catalysis in the presence of copper(I) iodide to afford trifluoromethyl enynes in good yield.

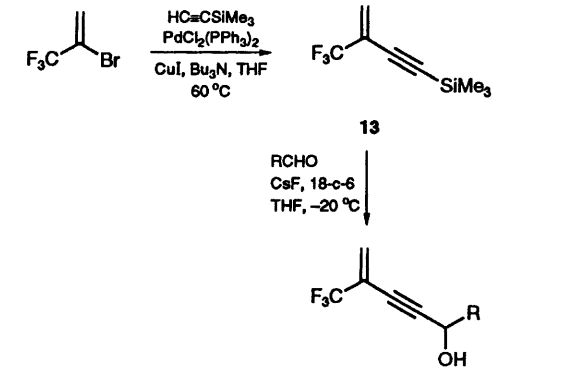


Scheme 5

An analogue **12** of the fungal metabolite siccayne has been prepared in this way (**Scheme 6**).[13] Enynyl silane **13** has been added to aldehydes in the presence of a fluoride source to afford allylic alcohols **14**. Aromatic aldehydes give high (70–80%) yields of adducts but additions to aliphatic aldehydes were less efficient (**Scheme 7**). Treatment of 2-bromo-1,1,1-trifluoropropene with LDA (2 equivalents) afforded lithio trifluoropropyne **15**

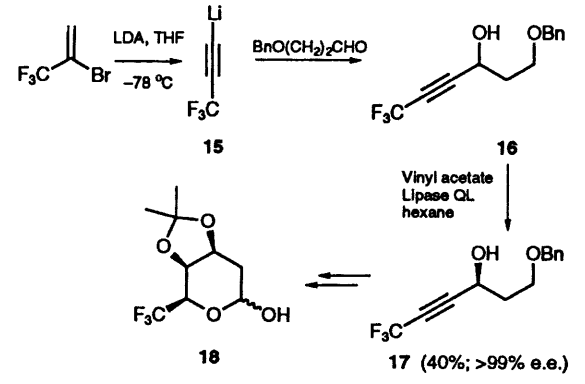


Scheme 6



Scheme 7

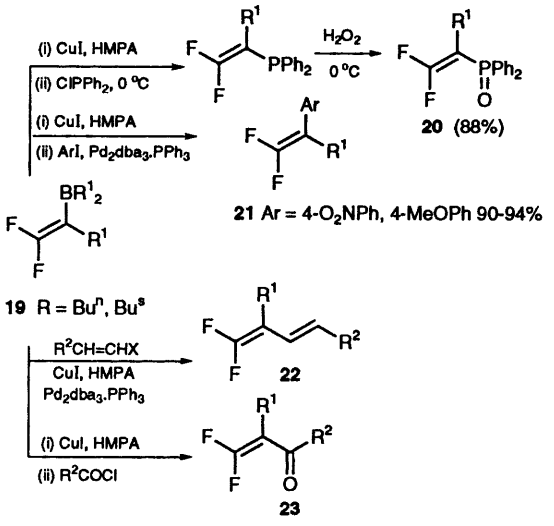
which was trapped *in situ*, with 3-(benzyloxy)propanal at the start of a synthesis of 2,6-dideoxy-6,6,6-trifluorosugars.[14] Lipase-catalysed resolution of **16** allowed the isolation of the enantiomer **17** in high (>99%) e.e. (**Scheme 8**). The protected L-oliose analogue **18** was obtained following standard manipulations.



Scheme 8

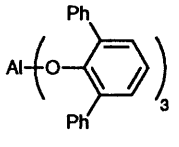
Difluorovinylboranes (see Section 2.3 for their synthesis) are versatile carbon nucleophiles; **Scheme 9** shows some of the products available from borane **19**. Transmetallation with copper(I) salts in HMPA affords a reactive difluorovinylcopper reagent. Phosphine oxide **20** was obtained in good yield following transmetallation of **19**, reaction with the phosphorus electrophile, and oxidation with excess hydrogen peroxide.[15] Vinyl halides[16] and aryl iodides[17] coupled efficiently with **19** under palladium catalysis to afford styrenes **21** (with retention of alkene configuration) and dienes **22**

respectively. The vinylcopper reagent was sufficiently reactive to afford good yields of enones **23** upon treatment wth acid chlorides.[18]

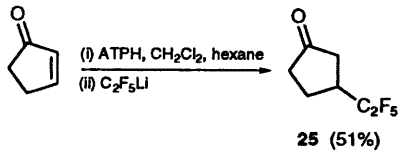


Scheme 9

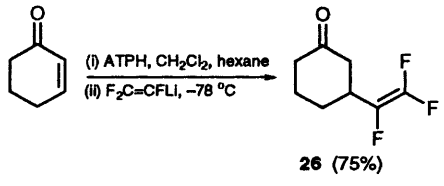
Because of the low reactivity of fluorovinylcopper reagents, conjugate addition of fluoroalkenyl units to enones had not been reported until the publication of a solution by Yamamoto and co-workers.[19] When complexed with a tris(aryloxy)aluminium complex (ATPH **24**), enones underwent 1,4-addition with an excess of fluoroalkenyllithium reagents at low temperature, affording adducts **25** and **26** in good yield (**Schemes 10** and **11**). The procedure therefore avoided transmetallation (and consequent loss of reactivity) of the fluoroalkenyl nucleophile.



24 (ATPH)

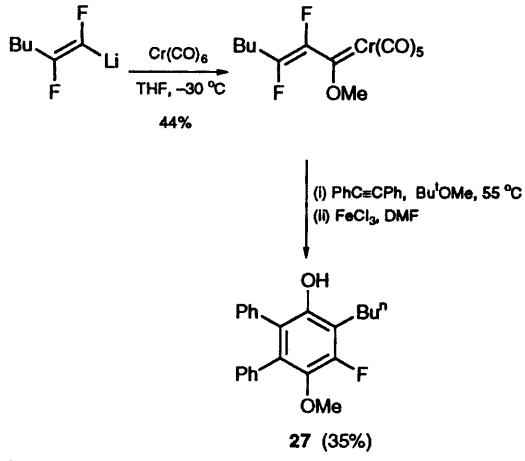


Scheme 10



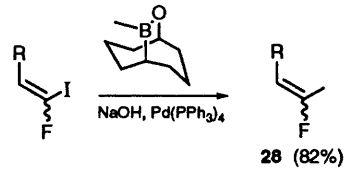
Scheme 11

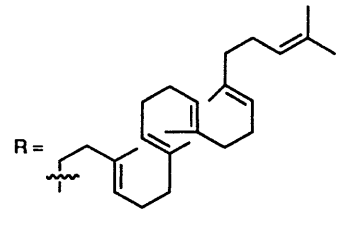
Chromium carbene chemistry has been found to accommodate fluoroalkenyl components. A highly substituted fluorophenol **27** has been formed in a low yielding carbene annulation sequence (**Scheme 12**).[20] Less reactive fluoroalkenyllithium reagents, or alkynes bearing sterically demanding substituents, failed to yield phenolic products.



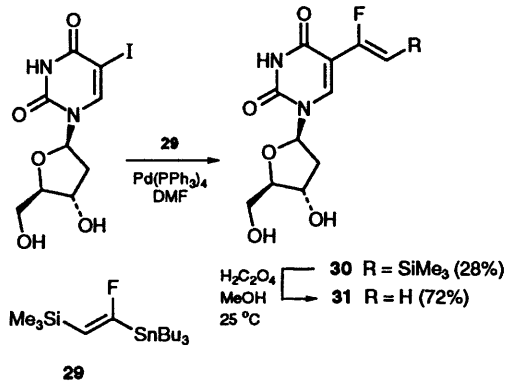
Scheme 12

McCarthy and co-workers have described chemistry that affords synthetic equivalents to α-fluoroalkenyl anions.[21] A squalene epoxidase inhibitor (**28**) has been prepared using a modified Suzuki coupling from an α-fluoroalkenyl iodide (**Scheme 13**).[22] Interestingly, the iodide was prepared from a vinylstannane precursor which presumably failed to undergo Stille coupling. This result suggests that such species are relatively poor coupling partners in palladium-catalysed procedures. Nevertheless, a Stille coupling was used successfully during the synthesis of thymidylate synthetase inhibitor **31** (**Scheme 14**), though DMF was required as the solvent and the reaction occurred slowly.[23] Coupling was also achieved with acid chlorides and aryl iodides. Mild protodesilylation of **30** completed the synthesis of **31**. The synthesis of the α-fluoroalkenyl anion equivalent **29** is discussed in Section 2.5. Vinylphosphonates have also been prepared from the corresponding iodides by a coupling reaction.[24]





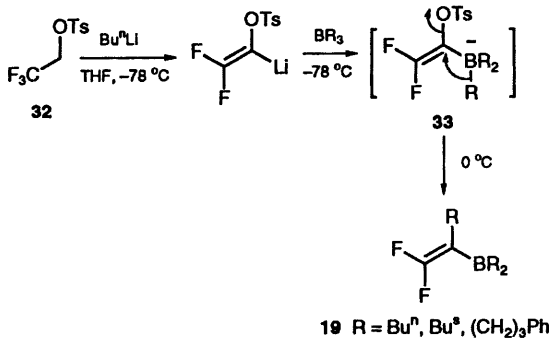
Scheme 13



Scheme 14

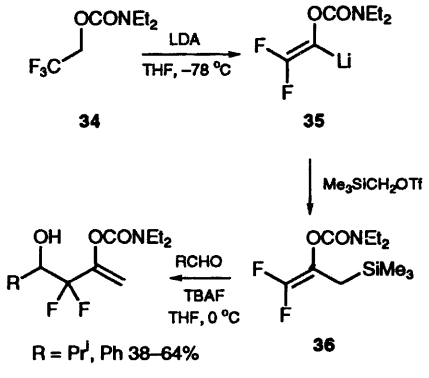
2.3 Metallated fluoroenol derivatives

A dehydrofluorination/metallation sequence from commercial 2,2,2-trifluoroethyl tosylate (**32**) provides the entry point to Ichikawa's versatile borane **19** via 1,2-metal-*ate* rearrangement (**Scheme 15**) of complex **33**.[18] More recently, two groups have



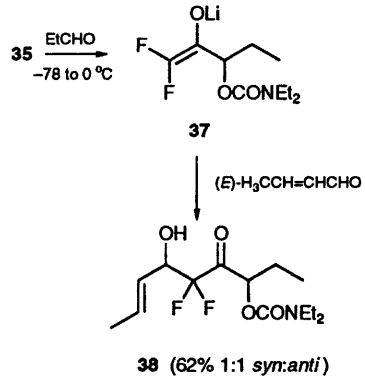
Scheme 15

developed chemistry of the metallated enol carbamate **35**, derived from **34**, in independent studies.[25,26(a)] The intermediate is a versatile carbon nucleophile; the reaction with (trimethylsilyl)methyl triflate affords an allyl silane **36** that adds to aldehydes in the presence of a fluoride ion source (**Scheme 16**).[25]



Scheme 16

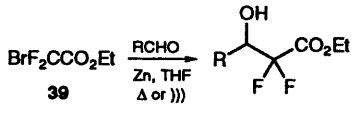
When **35** adds to aldehydes or ketones, the first-formed alkoxide undergoes a rapid transacylation reaction,[26(a)] releasing basic enolate **37** which can be trapped with non-enolizable aldehydes, to afford aldol products **38** in high yield though with low stereoselectivity (**Scheme 17**).[26(b)]



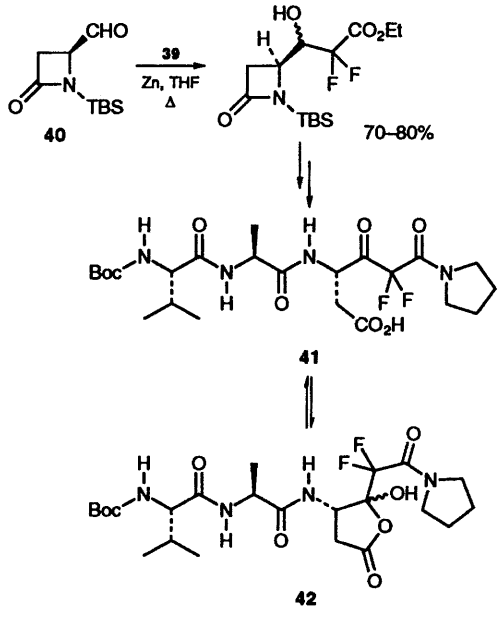
Scheme 17

2.4 Fluoroenolates and enol silyl ethers

The Reformatsky reaction of ethyl bromodifluoroacetate (**39**) with aldehydes (**Scheme 18**) is a ubiquitous process for the synthesis of compounds containing a difluoromethylene group. The zinc-promoted reaction appears to be



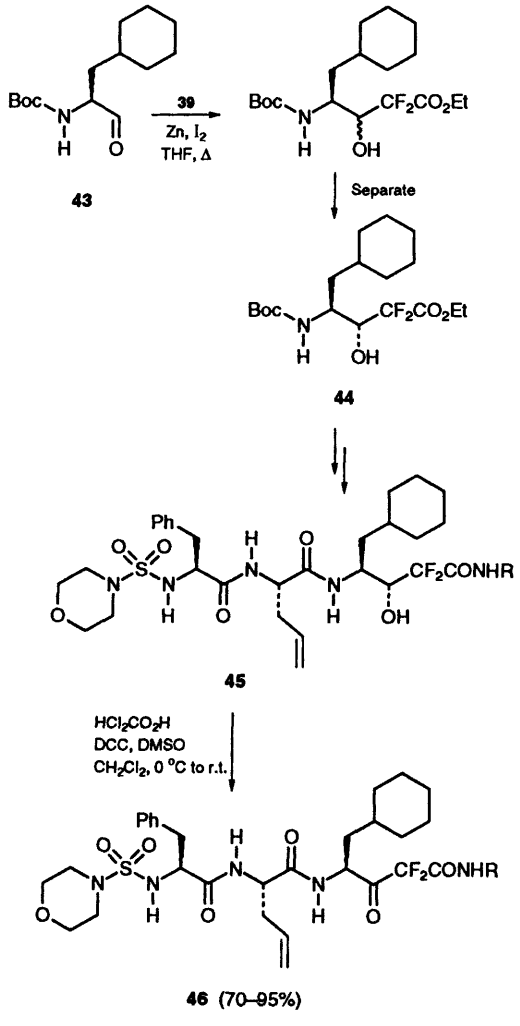
Scheme 18



Scheme 19

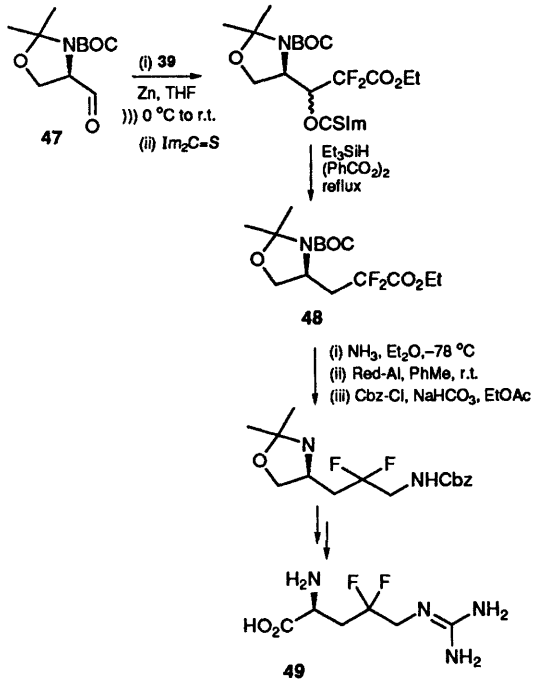
particularly amenable to scale-up; indeed the Eli Lilly plant scale route to the anti-tumour nucleoside gemcitabine is based upon the reaction.[27] The addition reaction displays low diastereoselectivity. On a large-scale, the unwanted diastereoisomer was removed by recrystallization of a benzoate derivative. On smaller-scales, chromatographic separation or recrystallization may be possible. An inhibitor of interleukin-1β converting enzyme has been prepared[28] from **39** and lactam aldehyde **40**. The highly electron-withdrawing nature of the CF_2 group was evinced by the coexistence of **41** with hemiacylal **42** (**Scheme 19**).

Doherty and co-workers have explored the ultrasound promoted Reformatsky reaction to prepare renin inhibitors.[29] On a small-scale, sonication conditions minimized racemization of the sensitive aldehyde **43**, though attempts to use the procedure on a large-scale were unsuccessful. Instead, (*R*)-diastereoisomer **44** was obtained in high purity (>95% d.e. after crystallization) via the thermal reaction, though an excess of **39** was required to obtain reproducible yields (**Scheme 20**).



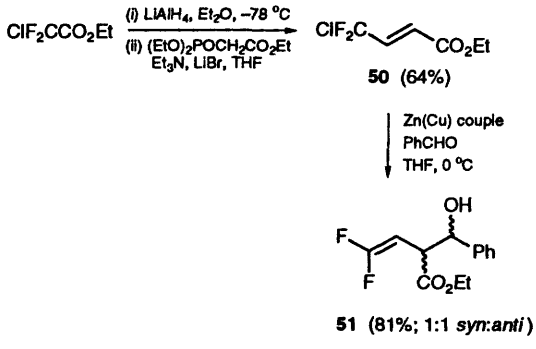
Scheme 20

An interesting, modified Pfitzer–Moffat oxidation procedure has been developed which allows conversion of the secondary alcohol **45** into ketone **46** in good yield (75–90%) with minimal epimerization α- to the ketonic carbonyl group. **Scheme 21** shows the synthesis of a 4,4-difluoro-L-arginine analogue **49**.[30] Reformatsky reaction with Garner's aldehyde (**47**) was followed by treatment with thiocarbonyldiimidazole and free radical deoxygenation to afford **48** in good yield. Amide reduction proceeded smoothly with Red-Al, followed by protection of the primary amino group and manipulation to **49**.



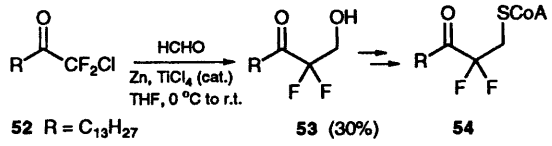
Scheme 21

An extended ester enolate has been generated and trapped in high yield when chlorodifluorocrotonate (**50**) was treated with aldehydes in the presence of a zinc–copper couple (**Scheme 22**).[31] The crotonate was prepared by Wadsworth–Horner–Emmons reaction upon chlorodifluoroacetaldehyde and the extended



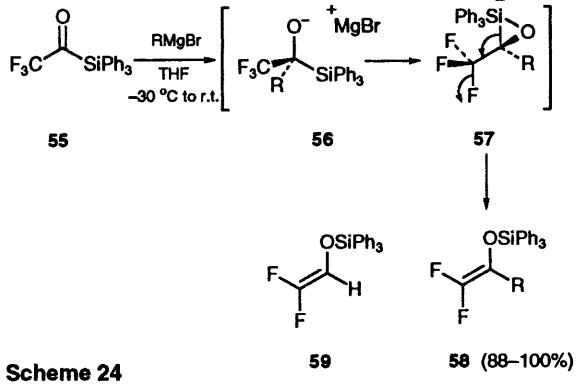
Scheme 22

Reformatsky reaction gave good yields of γ,γ-difluoro homoallyl alcohols **51** with a range of aldehydes. Yields with ketone electrophiles were relatively poor. An aldol reaction between ketone **52** and paraformaldehyde was used recently in the synthesis of a potential myristoyl transferase inhibitor **54** (**Scheme 23**).[32] The reaction was catalytic in titanium tetrachloride and, though direct, occurred in modest yield. Aldol **53** was elaborated by activation to the triflate and displacement by a thiolate nucleophile.



Scheme 23

More efficient Mukaiyama aldol reactions have been performed with difluoroenoxysilanes. Newer methods for their synthesis have exploited the Brook rearrangement. Treatment of acylsilane **55** with a Grignard reagent affords an adduct **56** that collapses to silic-*ate* species, **57** (**Scheme 24**). The carbon–silicon bond is then sufficiently reactive to cause cleavage of an antiperiplanar carbon–fluorine bond, forming the enoxysilane **58**.[33] Using isopropylmagnesium bromide as the nucleophile allowed **59** to be isolated in excellent yield.

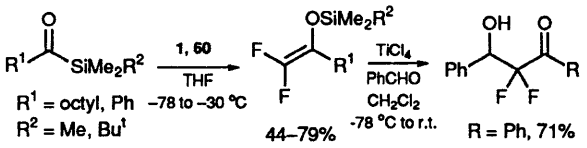


Scheme 24

A similar approach was followed by Portella[34] who introduced a trifluoromethyl nucleophile using Rupperts reagent **1** and the non-hygroscopic fluoride source, **60**, described by Gingras (**Scheme 25**).[35] The difluoroenoxysilanes undergo Mukaiyama aldol reactions when treated with titanium tetrachloride in the presence of aldehydes. A brassinosteroid analogue has been synthesized via this approach.[33] Lithium difluoroenolates have also been deployed in the aldol reaction though only low diastereoselectivities have been reported to date.[26(b)]

$[Ph_3SnF_2]NBu_4$

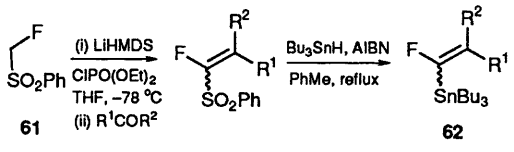
60



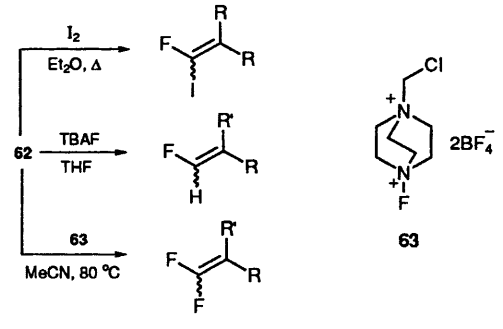
Scheme 25

2.5 Phosphonyl- and sulfonyl-stabilized carbanions

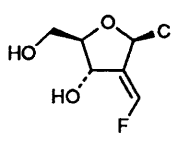
McCarthy[36] has described a range of useful reactions based upon fluoromethylphenylsulfone (**61**). Though the preparation of the compound is non-trivial, it can be used to prepare α-fluorovinylsulfones with interesting properties. Treatment of **61** with an amide base in the presence of diethylphosphochloridate affords a highly stabilized carbanion that is still sufficiently reactive to undergo a Wadsworth–Horner–Emmons reaction with aldehydes and ketones (**Scheme 26**). Mixtures of (E)- and (Z)-vinylsulfones are obtained, which have been separated in some cases.[37] Treatment with tributyltin hydride/AIBN results in stannylative desulfonylation[22] with retention of configuration to afford **62**. The stannyl group can then be used to introduce an iodine, fluorine, or hydrogen atom (**Scheme 27**). Protodestannylation[22] occurred on treatment with sodium methoxide, ammonia in methanol, or TBAF, while reaction with Selectfluor™ **63** in acetonitrile resulted in a high yielding tin/fluorine exchange.[38] The chemistry has been used in the syntheses of an antitumour nucleoside **64**,[39] and analogues of eugenol methyl ether **65**, a sex attractant of the Oriental Fruit Fly.[40]



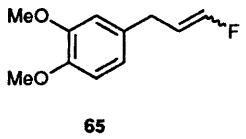
Scheme 26



Scheme 27

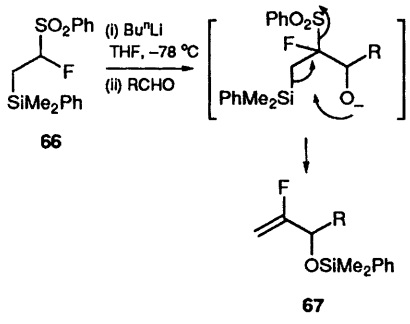


64



65

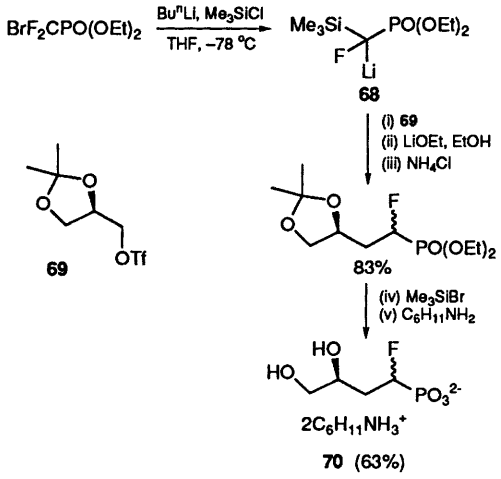
An interesting application of sulfone **61** involves trapping the lithium anion with (chloromethyl)dimethylphenylsilane to afford **66** as a stable crystalline solid in good yield.[41] Retreatment with butyllithium, followed by the addition of an aldehyde triggered a Peterson-type elimination in which carbon–sulfur bond cleavage occurred from the silic-*ate* to afford an allylic silylether **67** (**Scheme 28**). Silane **66** is therefore an extremely useful alternative synthetic equivalent for the α-fluoroethenyl anion.



66 67

Scheme 28

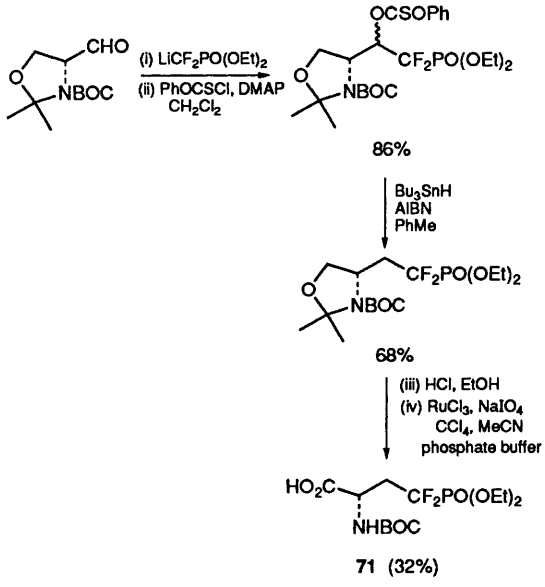
Fluorinated phosphonate carbanions have been used to prepare mimics of biologically important phosphate esters. O'Hagan and Nieschalk[42] have described a synthesis of **70** (**Scheme 29**) involving the alkylation of the fluorophosphonate carbanion **68** with the primary alkyl triflate **69**. Free radical deoxygenation provides an attractive alternative to alkylation chemistry.



68 69 83% 70 (63%)

Scheme 29

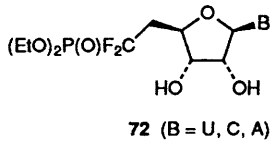
Martin and co-workers[43] have described the basic methodology which was used in a recent syntheses of the phosphoserine analogue[44] **71** (**Scheme 30**) and nucleotide 5′-deoxy-5′-difluoromethylphosphonates[45] **72**. The



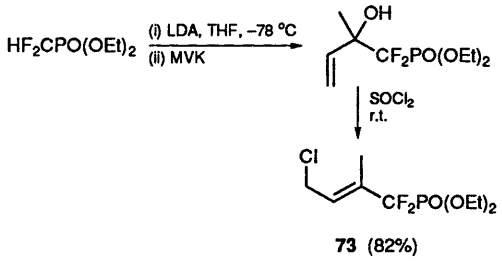
86% 68% 71 (32%)

Scheme 30

attachment of the difluoromethylenephosphonato group to secondary carbon centres remains a problem, though two potentially general solutions have emerged. Addition of a lithiodifluorophosphonate to methyl vinyl ketone, followed by rearrangement of the allylic alcohol product afforded **73** in good yield as a single stereoisomer (**Scheme 31**).[46] **Scheme 32** shows a conjugate addition solution to the problem.[47] In the presence of cerium(III) chloride, the lithiodifluorophosphonate added to nitroalkenes in acceptable yield to produce **74**.

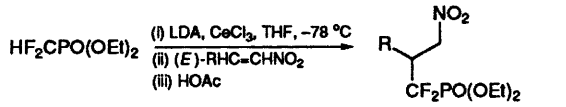


72 (B = U, C, A)



73 (82%)

Scheme 31



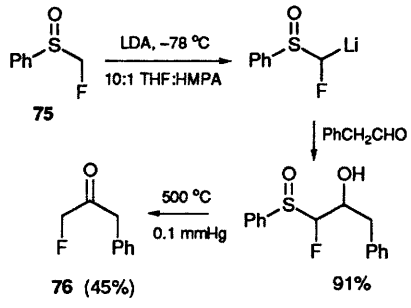
74 R = Et, Pr^{i}, Bu^{t}, Ph 25-62%

Scheme 32

3 Fluorinated carbon electrophiles

3.1 Fluoroalkyl ketones

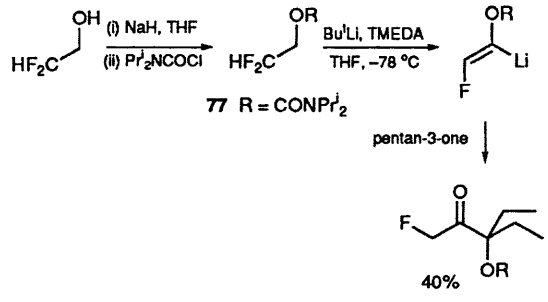
Fluoroalkyl ketones and related carbonyl compounds are reactive carbon electrophiles with diverse synthetic and medicinal chemistry. Fluoroalkyl ketones form the subject of a recent review.[48] Fluoromethyl ketones were prepared by a sequence involving a sulfoxide elimination (**Scheme 33**). The conjugate base of **75** added to aldehydes in excellent yield. Flash vacuum pyrolysis of the adducts has afforded ketones **76** in moderate yield.[49] Simple compounds of this type should be available from the reaction between silyl enol ethers and the Selectfluor™ reagent.[50] Alternatively, the *N,N*-diisopropylcarbamate of difluoroethanol functions as an acyl anion equivalent (**77**) upon treatment with strong base (**Scheme 34**).[51] Difluoromethyl ketones have been prepared from trifluoroethanol by a similar but higher yielding route.[26(a)]



75

76 (45%) 91%

Scheme 33

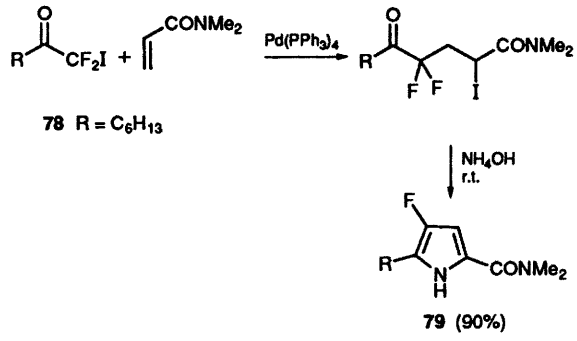


77 R = CONPr^{i}$_2$

40%

Scheme 34

Difluoromethylene ketones are usually prepared by the Reformatsky chemistry described in Section 2.4. An alternative approach was recently described by Burton and Qiu,[52] and deployed in syntheses of β-fluoropyrroles (**Scheme 35**).[53] Palladium-catalysed addition of iododifluoromethyl ketone **78** to *N,N*-dimethylacrylamide afforded the ketoamide in good yield. Treatment with aqueous ammonia converted the reactive difluoromethylene ketone into the corresponding imine. Cyclization followed by dehydrofluorination completed the synthesis of pyrrole **79**.

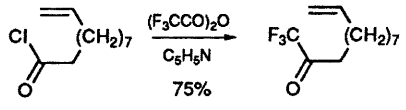


78 R = C_6H_{13}

79 (90%)

Scheme 35

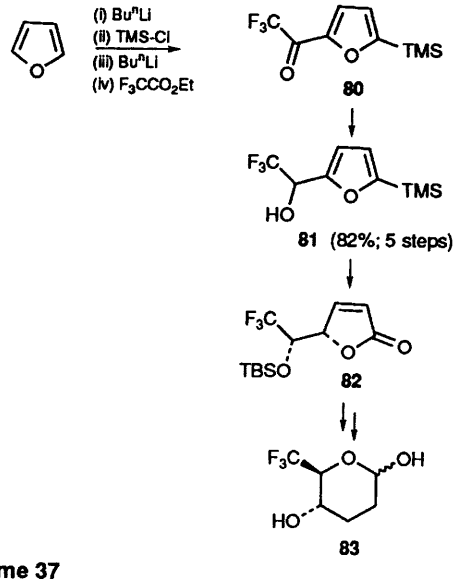
Trifluoromethyl ketones have been prepared in good yield using a new method described by Zard and co-workers.[54] The reaction proceeds via an acyl ketene intermediate but requires the formation of an acid chloride (**Scheme 36**), which limits the range of functionality that can be present. Kitazume and



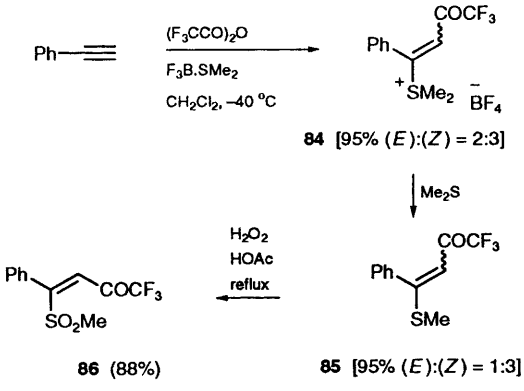
Scheme 36

co-workers have prepared furanyl trifluoromethyl ketones *en route* to a range of 6-deoxy-6,6,6-trifluorosugars.[55] Trifluoroacetylation of lithio-2-trimethylsilylfuran afforded ketone **80**; reduction of the ketone afforded alcohol **81** as a racemic modification in excellent overall yield from furan (**Scheme 37**). Lipase resolution followed by furan oxidation afforded optically pure butenolide **82** which was converted into a range of optically-pure 6-deoxy-6,6,6-trifluorosugars, including **83** (**Scheme 37**).

The direct perfluoroacylation of alkynes has been achieved using an interesting procedure (**Scheme 38**).[56] Presumably, the sequence involves the initial formation of a vinyl cation which is intercepted by the sulfur nucleophilic to afford vinyl sulfonium salt **84**. Demethylation affords **85** in which some isomerization has occurred. Peracetic acid oxidation led to the formation of **86** in excellent chemical yield as the single (Z)-stereoisomer. Analogues of vitamin E have been prepared using Wittig

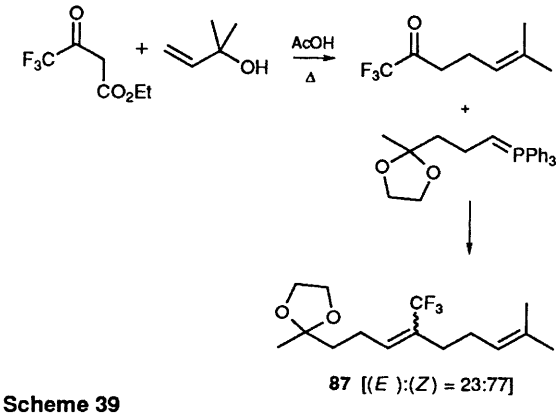


Scheme 37

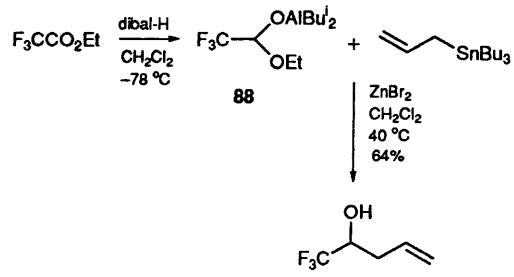


Scheme 38

reactions of trifluoromethylketones, which show high reactivity towards phosphorus ylids.[57] **Scheme 39** shows the preparation of an intermediate **87** from ethyl trifluoroacetoacetate which displays the usual (Z)-selectivity in the reaction of trifluoromethyl ketones with unstablized ylids. A useful aldehyde equivalent has been prepared from ethyl trifluoroacetate. Dibal-H reduction gave **88** *in situ*. Further treatment with an allylstannane and zinc bromide afforded good yields of homoallylic alcohols (**Scheme 40**).[58]



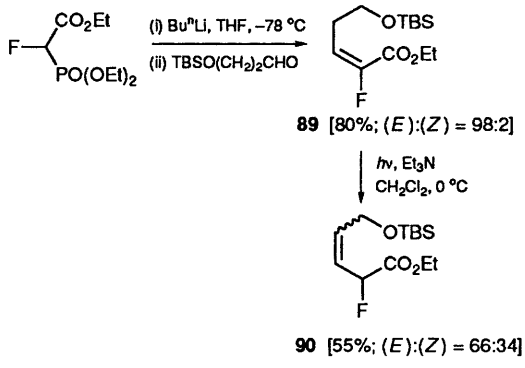
Scheme 39



Scheme 40

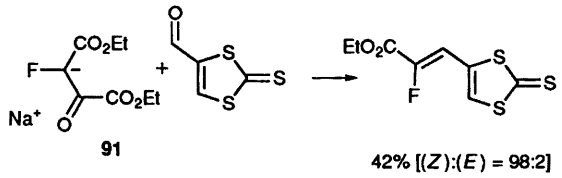
3.2 α-Fluoro-α,β-unsaturated carbonyl compounds

The standard method for the preparation of α-fluoro-enals and -enones involves the fragmentation of chlorofluorocyclopropanes, obtained by halocarbene additions to enol ethers.[59] A full discussion of this methodology lies outside the range of this review and few applications in target synthesis have been reported in the open literature. However, the extensive use made of this methodology by Johnson and co-workers is discussed later in this review. The synthesis of α-fluoroenoate esters by Wadsworth–Horner–Emmons methodology has been described by Burton and Thennapan.[60] A recent application by Piva (**Scheme 41**) displayed the usual selective formation of the (E)-alkene diastereoisomer.[61] Photoisomerization of adduct **89** afforded β,γ-unsaturated ester **90** as a mixture of diastereoisomers in moderate yield. A complementary procedure has been described by



Scheme 41

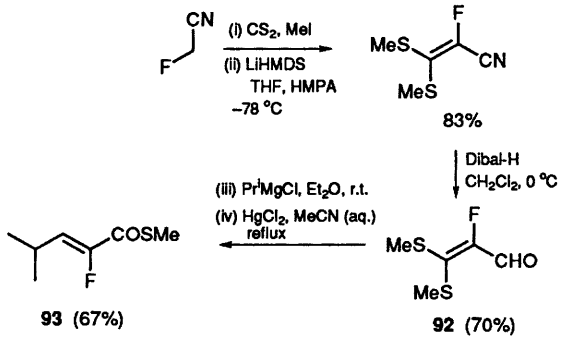
Clemenceau and Cousseau.[62] Sodium salt **91** reacted with aldehydes to afford (Z)-fluoroenoates in moderate chemical yield. High diastereoselectivities resulted when bulky aldehydes were used in the reaction. **Scheme 42** shows the most selective example. (Z)-Fluorothioenoates were prepared using the α-fluoroacrylate-β-cation equivalent **92** prepared from fluoroacetonitrile by a simple procedure (**Scheme 43**). Grignard reagents added at the carbonyl group and treatment with acid initiated dehydration with double bond migration and formation of an allylic thioacetal; thioacetal hydrolysis affords **93**.[63]



91

42% [(*Z*):(*E*) = 98:2]

Scheme 42

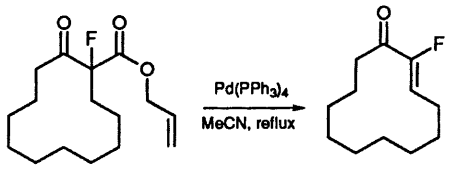


93 (67%)

92 (70%)

Scheme 43

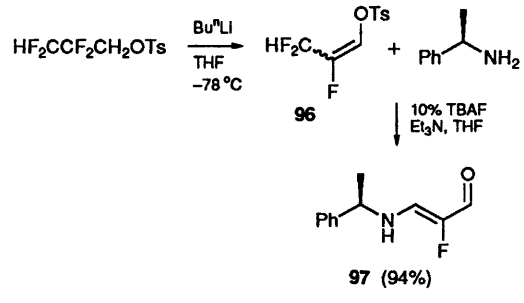
A palladium-catalysed route to α-fluoroenones (**Scheme 44**) was published recently,[64] based upon chemistry developed by Tsuji. In acetonitrile, ketoester **94** underwent decarboxylative elimination to afford enone **95** in good chemical yield. More highly substituted derivatives have been prepared from (2H)tetrafluoropropanol. Conversion into the tosylate and brief exposure to n-butyllithium yielded enol tosylate **96** as a mixture of diastereoisomers. Treatment with a secondary amine in the presence of a fluoride ion source led to the formation of β-aminoenal **97** in excellent yield (**Scheme 45**).[65]



94

95 (74%)

Scheme 44

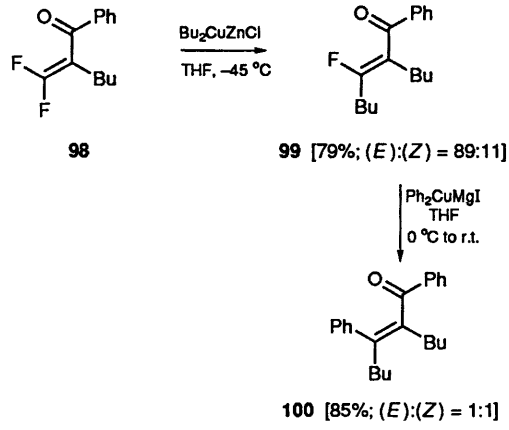


97 (94%)

Scheme 45

3.3 β-Fluoro-α,β-unsaturated carbonyl compounds

Fluorine atoms located on the β-carbon of an α,β-unsaturated carbonyl compound are replaced readily in addition/elimination reactions with nucleophiles. Ichikawa has used difluoroenones to prepare highly substituted enones **100**;[66] **Scheme 46** shows a recent example. There is a significant difference in reactivity between the di- and mono-fluoroenones **98** and **99**, allowing the incremental replacement of the two fluorine atoms with different carbon nucleophiles. Carbon nucleophiles were delivered via cuprate and zincate reagents. A similar sequential displacement with heteroatom nucleophiles has also been described.[67]



98

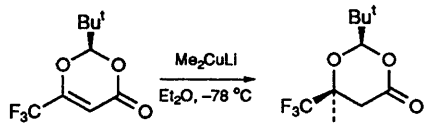
99 [79%; (*E*):(*Z*) = 89:11]

100 [85%; (*E*):(*Z*) = 1:1]

Scheme 46

3.4 γ-Fluoro-α,β-unsaturated carbonyl compounds

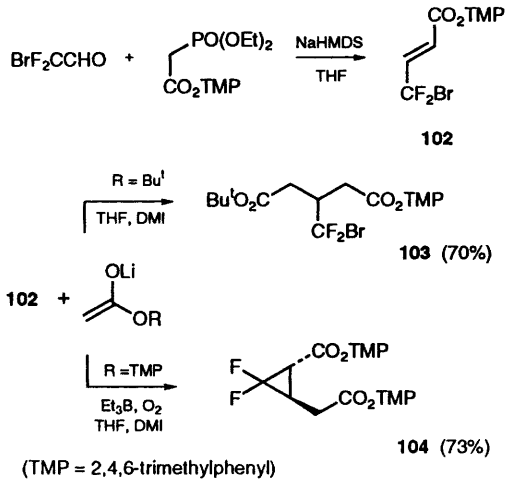
Seebach and co-workers have described a range of useful reactions based upon chiral dioxinone **101** derived from trifluoroacetoacetate.[68] **Scheme 47** shows a diastereoselective conjugate addition of a Gilman reagent. Conjugate additions of alkyllithium reagents to γ,γ,γ-trifluoroenones in the presence of the ATPH complex were described by Yamamoto and co-workers.[69] Taguchi and co-workers have described the preparation and reactions of the interesting bromodifluorocrotonate ester **102**, which underwent Michael additions with lithium enolates to furnish adducts **103** (**Scheme 48**).[70] However, when the intermediate enolate was treated with triethylborane and oxygen, *trans*-cyclopropane **104** was formed in good yield. The reaction is interesting because it presumably involves alkylation of a boron enolate, rather than a free radical reaction. The product cyclopropanes were produced in high e.e. when chiral enolates were used in the Michael addition.[71]



101

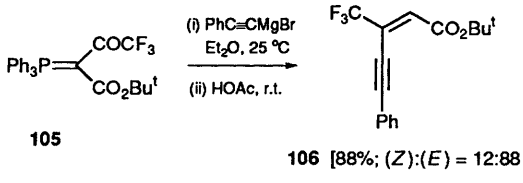
85% 3(*S*):3(*R*) >98:2

Scheme 47



Scheme 48

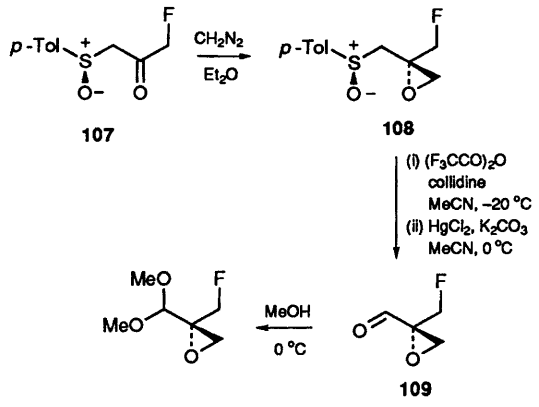
An efficient preparation of γ,γ,γ-trifluorocrotonates has been reported by Shen and Gao.[72] Treatment of **105** with Grignard reagents followed by acidic work-up led to the formation of esters **106** in good yield with high (*E*)-selectivity (**Scheme 49**).



Scheme 49

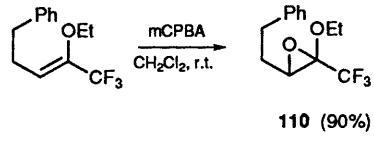
3.5 Fluoroalkyl epoxides

Epoxides are useful building blocks for the synthesis of fluorinated compounds; fluoroalkyl epoxides are more resistant to cleavage under acidic conditions than their non-fluorinated congeners but undergo nucleophilic ring opening. The fluoroalkyl epoxide **108** was formed when the corresponding ketone **107** was treated with diazomethane in ether. Bravo and co-workers have used this approach to prepare a range of optically-enriched building blocks,[73] achieving asymmetric induction with a chiral sulfoxide auxiliary. **Scheme 50** shows elaboration via Pummerer rearrangement and hemithioacetal hydrolysis which afforded reactive epoxyaldehyde **109**. A range of related epoxides containing different fluoroalkyl groups have been prepared.[74] Nucleophiles open the product epoxides in the usual way, via attack at the less-hindered carbon atom. Trifluoromethyl epoxides have been prepared from trifluoromethyl ketones and from trifluoromethyl enol ethers.



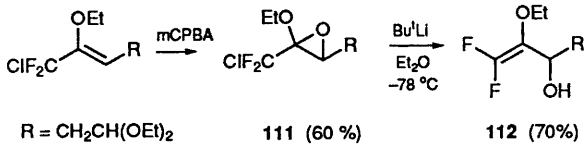
Scheme 50

Bégué and co-workers have reported that trifluoromethylenol ethers underwent oxidation with mCPBA in high yield to afford isolable epoxides **110** (**Scheme 51**).[75] When treated with magnesium bromide etherate, bromotrifluoromethylketones were obtained in good yield. Nucleophilic ring-opening with azide was used in the preparation of human leukocyte elastase inhibitors.[76]



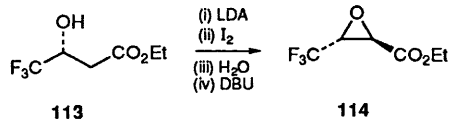
Scheme 51

Ring-opening of chlorodifluoromethyl epoxides **111**, obtained via epoxidation of the corresponding, easily-prepared enol ethers, was achieved upon treatment with t-butyllithium in THF at low temperature, affording difluoroallylic alcohols, including **112**, in good yield (**Scheme 52**).[77] Seebach



Scheme 52

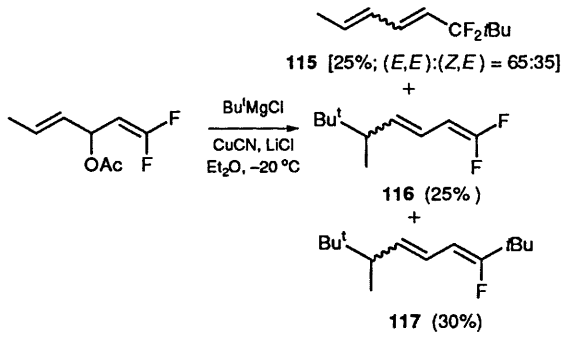
and co-workers have developed a route to the optically-pure epoxyester **114** from 4,4,4-trifluoro-3-oxobutanoate **113** (**Scheme 53**).[78] Phenylcuprate nucleophiles attacked the epoxyester at C-(2), phenylmagnesium bromide attacked competitively at C-(2) and C-(1) while organolithium reagents and alkyl Grignard reagents attacked at the carbonyl carbon leaving the epoxide intact.



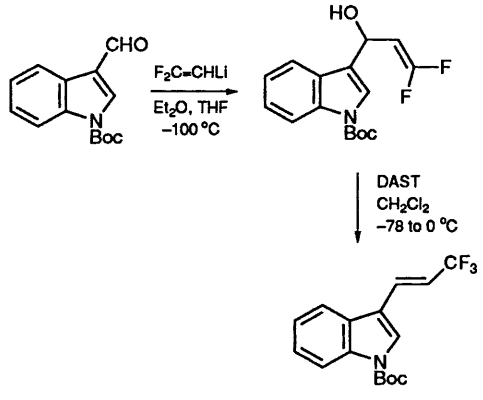
Scheme 53

3.6 Fluoroallylic electrophiles

Though unusual, electrophiles of this type feature in some interesting processes. Difluoroallylic acetates react with Grignard reagents with copper(I) catalysis to afford S_N2' alkylation products in good yield though with variable stereoselectivity. Tellier and Sauvêtre have studied the reaction extensively and a recent publication provides some experimental details.[79] The rates of competing processes may be very similar. **Scheme 54** shows a situation in which nucleophilic attack occurs competitively at fluorinated and non-fluorinated allylic termini. The identical proportions of **115** and **116** illustrate the similar reactivities of the two allylic systems. Diene **117** arises from nucleophilic attack on **115** with loss of fluoride. Exposure of difluoroallylic alcohols to DAST provides a useful synthesis of trifluoromethylalkenes. Yields were not reported but a range of alkenes were prepared. **Scheme 55** depicts a typical procedure.[80]

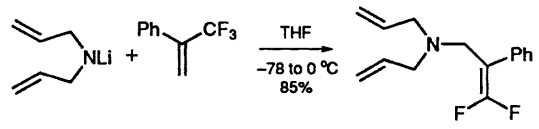


Scheme 54



Scheme 55

The fluoride ion can also function as a leaving group in S_N2' displacements. Lithium amides have been added to α-trifluoromethylstyrene to afford useful yields of difluoroallylic amines.[81] The lithium cation may provide some assistance to the C–F bond cleavage; an attractive six-centre transition state has been written for the reaction (**Scheme 56**). Difluoroallylic amines were of some interest as MAO inhibitors and have been prepared by a less efficient route.

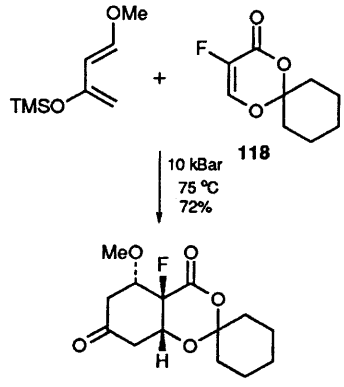


Scheme 56

4. Pericyclic reactions

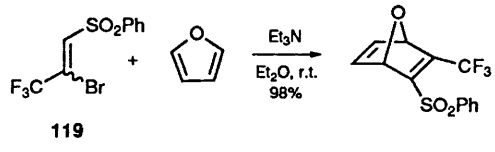
4.1 Diels–Alder and dipolar cycloadditions

Dienophiles bearing fluorine atoms attached directly to the carbon–carbon double bond are rare; the propensity for thermal [2+2] cycloaddition displayed by fluoroalkenes is well known. 5-Fluorodioxinone **118** has been employed as a component in a Diels–Alder reaction; **118** reacted with Danishefsky's diene to afford the expected cycloadduct in moderate yield under high pressure conditions (**Scheme 57**). Dioxinones with an additional substituent at the 6-position failed to react under these conditions. A more efficient reaction was reported with the more electron-deficient trifluoromethyl congener.[82]



Scheme 57

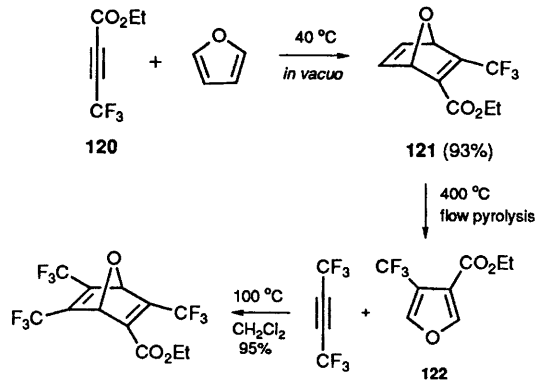
A reactive dienophile, prepared from **119**, has been prepared *in situ* from bromotrifluoropropene via an efficient sequence. High yields of cycloadducts were obtained with electron rich dienes, including furan under mild conditions (**Scheme 58**).[83]



119

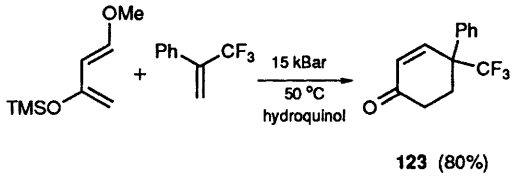
Scheme 58

Tipping and co-workers[84] have reported the smooth cycloaddition reactions of trifluoromethyl propiolate derivative **120** with furan. Pyrolysis of the cycloadduct **121** led to the elimination of ethene, setting the stage for a second cycloaddition reaction between furan **122** and hexafluorobutyne (**Scheme 59**).

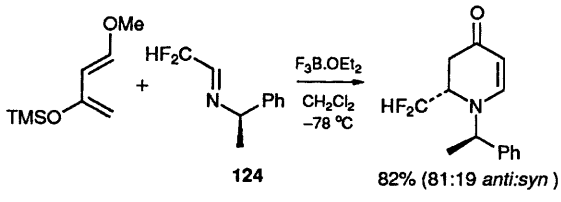


Scheme 59

α-Trifluoromethyl styrene added to Danishefsky's diene under high pressure conditions, leading to cyclohexenone derivative **123** after hydrolysis (**Scheme 60**).[85] The reaction was used to prepare the steroidal A-C ring system with an angular trifluoromethyl group. Fluoroalkyl imines have been explored as building blocks for the synthesis of nitrogen heterocycles with fluoroalkyl substituents. In the presence of boron trifluoride etherate, **124** added efficiently to Danishefsky's diene to afford a separable mixture of dihydropyridinones (**Scheme 61**).[86] The chemical yield and diastereoisomeric purity of each adduct were high.

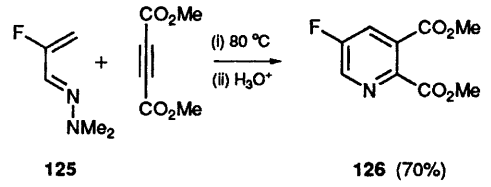


Scheme 60

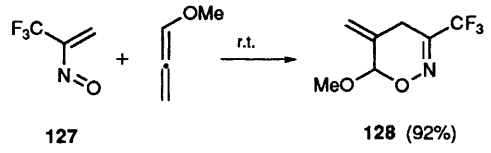


Scheme 61

Homo- and hetero-dienes displaying useful reactivity have been described. Azadiene **125** was prepared from readily-available 2-fluoroacrolein by Schlosser and Ghosh (**Scheme 62**)[87] and added smoothly to DMAD to afford fluoropyridine **126** after hydrolysis. Reissig has described a wide range of cycloaddition reactions of nitrosoalkene **127**.[88] The heterodiene is reactive and easy to prepare; **Scheme 63** depicts a high yielding reaction with 1-methoxyallene to afford cyclo adduct **128** in excellent yield.

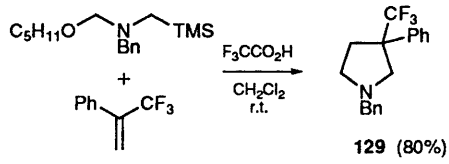


Scheme 62

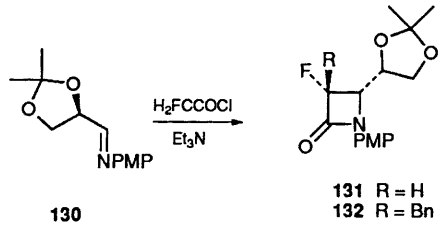


Scheme 63

The LUMO-lowering effects exerted by the trifluoromethyl and carboxylic ester groups are similar.[89] Pyrrolidines have been prepared via the reaction of an azomethine ylid with a range of trifluoromethylalkenes. α-Trifluoromethylstyrene reacted smoothly to afford cycloadduct **129** in good yield (**Scheme 64**). α-Methylstyrene failed to react under the same conditions. The formal [2+2] cycloaddition between fluoroketene and the optically-pure imine **130** was exploited in an efficient asymmetric synthesis of a fluorinated β-lactam (**Scheme 65**).[90] Fluoroketene was generated *in situ* from fluoroacetyl chloride and triethylamine. Lactam **131** was obtained in moderate chemical yield though in high e.e. (≥99%). Lactam **132** was converted into a configurationally fixed alkylmalonamide component of an HIV protease inhibitor.[91]



Scheme 64

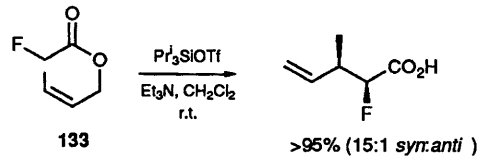


Scheme 65

4.2 Sigmatropic rearrangements and ene reactions

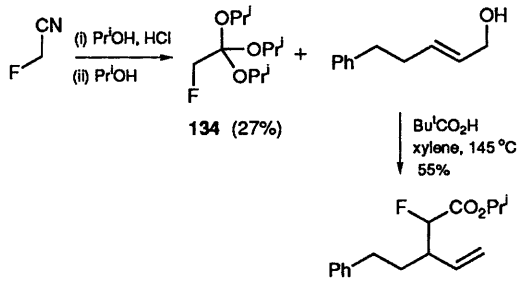
A recent review describes the many applications of [3,3]-rearrangements in organofluorine chemistry.[92] Perhaps the most developed methodology uses the Ireland silyl ketene acetal rearrangement. This has

proved to be a powerful tool in the hands of Welch and co-workers.[93] Allylic fluoroacetate **133** was prepared from highly toxic fluoroacetyl chloride; the (Z)-silyl ketene acetal was formed upon treatment with bulky triisopropyl silyl triflate. **Scheme 66** shows a diastereoselective rearrangement. The rearrangement products have been utilized in syntheses of 2,3-dideoxy-2-fluoro-3-*C*-methyl pentose nucleosides.[94]

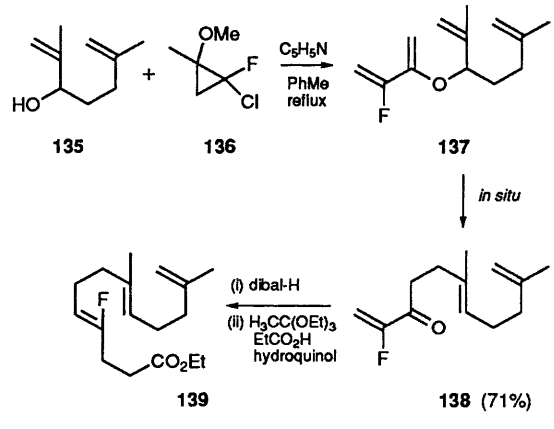


Scheme 66

Orthoester **134** was prepared from fluoroacetonitrile and used in the Johnson–Claisen rearrangement (**Scheme 67**). A range of α-fluoroesters was prepared in this way though the yields were low. The formation of the product ester as a 1:1 mixture of diastereoisomers implied that ketene acetal formation did not occur in a stereoselective manner.[95] Johnson and co-workers[96] have explored a range of rearrangements for the stereoselective construction of highly substituted fluoroalkenes. Fragmentation of cyclcopropane **136** in the presence of alcohol **135** led to the formation of **137** which rearranged to **138** *in situ*. Reduction with Dibal followed by orthoester Claisen rearrangement afforded **139** as a single alkene diastereoisomer (**Scheme 68**).[96]

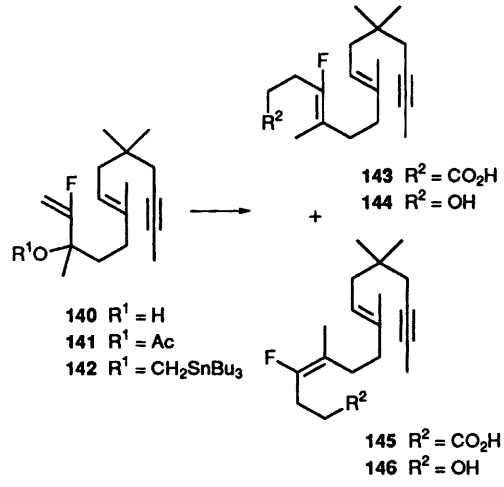


Scheme 67



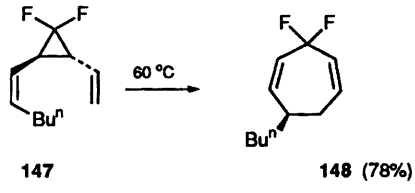
Scheme 68

In a tetrasubstituted series, alcohol **140** was converted into acetate **141** and tributylstannyl methyl ether **142** (**Scheme 69**). Ireland rearrangement of **141** afforded a 4:1 mixture of acids **143** and **145**, whereas Still–Wittig rearrangement of **142** led to the formation of homoallyl alcohols **144** and **146** in a 3:7 ratio.[97]



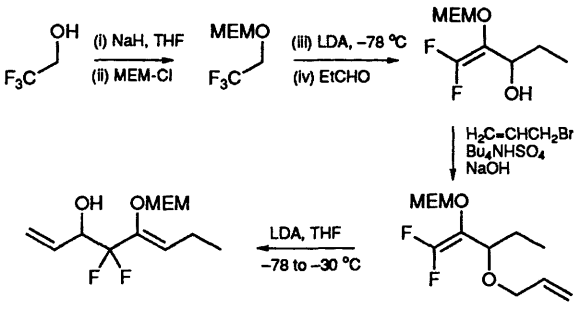
Scheme 69

A number of less common rearrangements have produced interesting results. A Brown Algae pheromone has been prepared by a Cope rearrangement in which strain relief and the weakness of the distal bond within a difluorocyclopropane contributed to an unusually facile conversion[98] of divinylcyclopropane **147** into cycloheptadiene **148** (**Scheme 70**). Difluoroallylic

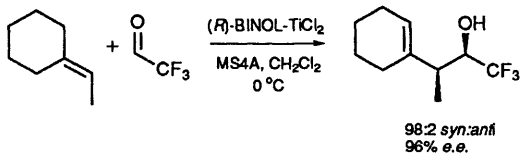


Scheme 70

alcohols have been transposed via the [2,3]-Wittig rearrangement shown in **Scheme 71**. Trifluoroethanol has been converted into a highly functionalized species containing a CF_2 group in this way.[99] Mikami and co-workers[100] have described a catalytic asymmetric ene reaction using trifluoroacetaldehyde (**Scheme 72**). The ene reaction proceeded in high e.e., though the efficiency was lower when 2-methyl-2-butene was used in the reaction.



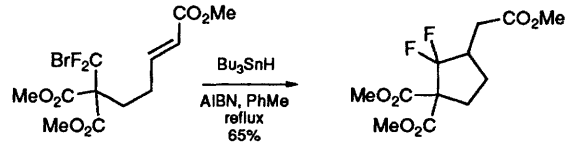
Scheme 71



Scheme 72

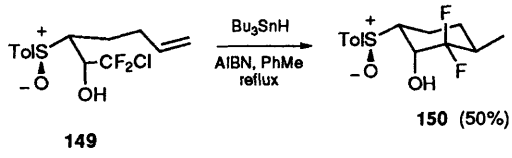
5. Free radical reactions

The high strength of the C–F bond renders it virtually inert under the conditions used to trap and generate free radicals. Fluorine atoms may exert a significant effect on the course of free radical reactions though the magnitude and direction of the effects remain far from clear. Recent physical organic studies have demonstrated the highly electrophilic σ-nature of perfluoroalkyl radicals. The SOMO energy is relatively low because of delocalization of the unpaired spin into the β C–F σ^* orbitals, and the inductive electron withdrawal exerted by the perfluoroalkyl group. Set against this effect is the SOMO raising interaction with the non-bonding electron pairs on the fluorine atoms borne on the radical centre. The trifluoromethyl radical therefore has π-character.[101–103] Buttle and Motherwell have demonstrated that difluoromethyl radicals display some nucleophilic character.[104] Higher yields of cyclization products were obtained when an electrophilic alkene was present to trap the difluoromethyl radical. **Scheme 73** shows a successful cyclization.



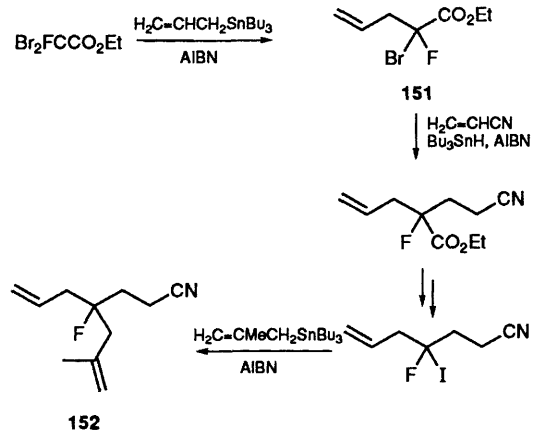
Scheme 73

The precursor was constructed by bromodifluoromethylation of a malonate carbanion in moderate yield. According to Bravo and co-workers, difluoromethyl radicals are electrophilic and highly reactive though their studies do not provide evidence either in support of or against this view.[105] Cyclization of **149** afforded **150** as a single stereoisomer in moderate yield. The preference for the halomethyl group to assume an equatorial orientation is presumably reinforced by the necessity to avoid a 1,3-diaxial repulsion with the axial hydroxyl group (**Scheme 74**). A range of enantiomerically pure difluorocyclohexanes were prepared from **150**. Similar routes to monofluorocyclohexanes[106] and difluorocyclopentanes[107] have been described by these authors.



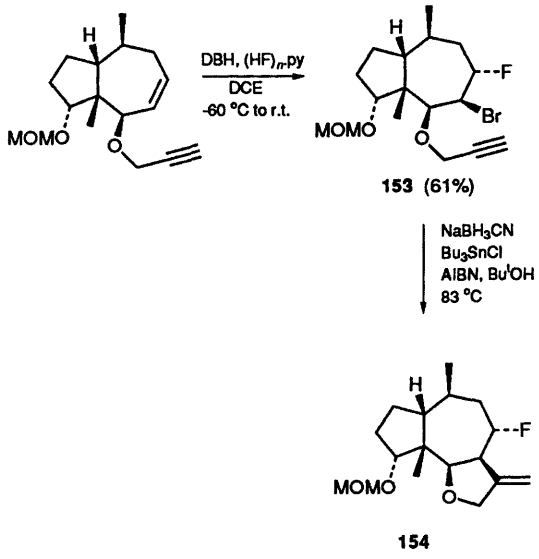
Scheme 74

Takeuchi has described a general free radical route to tertiary alkyl fluorides from esters of dibromofluoroacetic acid.[108] The allylstannane fragmentation method was used to prepare adduct **151** which underwent free radical addition to acrylonitrile (**Scheme 75**), or Reformatsky reaction with aldehydes. A high yielding bromodecarboxylation was achieved using Barton methodology; iodide/bromide exchange set the stage for a second radical allylation affording **152**.



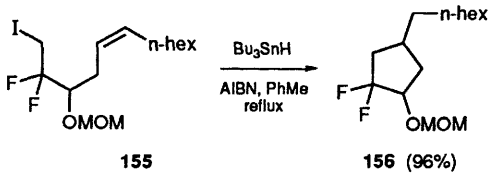
Scheme 75

Radicals generated at the position β to C–F bonds are expected to be more electrophilic than analogous alkyl radicals. Shimizu and co-workers[109] have described a useful bromofluorination/radical cyclization sequence (**Scheme 76**). Bromofluoride **153** and the cyclized product **154** were obtained as single stereoisomers. The catalytic conditions described by Stork proved effective in the cyclization.

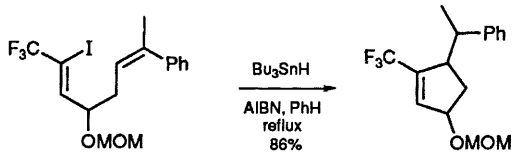


Scheme 76

Taguchi has explored the scope of cyclizations involving primary and secondary β,β-difluoroalkyl radicals.[110] Difluorotetrahydropyrans and cyclohexanes were prepared; **Scheme 77** shows an efficient cyclization. Precursor **155** was prepared via a lengthy sequence involving the elaboration of a Reformatsky adduct of **39**. The cyclic product **156** was obtained as a 1.2:1 mixture of *cis* and *trans* isomers. The presence of the fluorine atoms had no effect on the efficiency of the cyclization reaction. A subsequent study extended the range of cyclizations to include trifluoromethyl alkyl and alkenyl radicals (**Scheme 78**).[111]



Scheme 77



Scheme 78

6 References

1 J.A. Wilkinson, *Chem. Rev.*, 1992, **92**, 505.
2 O.A. Mascaretti, *Aldrichimica Acta*, 1993, **26**, 4758.
3 V.P. Kukhar, *J. Fluorine Chem.*, 1994, **69**, 199.
4 T. Fuchigami, *Top. Curr. Chem.*, 1994, **170**, 1.
5 M.A. McClinton and D.A. McClinton, *Tetrahedron*, 1992, **48**, 6555.
6 R.C. Bansal, B. Dean, S. Hakomori, and T. Toyokuni, *J. Chem. Soc., Chem. Commun.*, 1991, 796.
7 P. Munier, D. Picq, and D. Anker, *Tetrahedron Lett.*, 1993, **34**, 8241.
8 H. Uno and H. Suzuki, *Synlett*, 1993, 91.
9 H. Uno, S. Okada, T. Ono, Y. Shiraishi, and H. Suzuki, *J. Org. Chem.*, 1992, **57**, 1504.
10 D.J. Burton, Y.Z. Yang, and P.A. Morken, *Tetrahedron*, 1994, **50**, 2993.
11 F. Hong, S. Tang and C.-M. Hu, *J. Chem. Soc., Chem. Commun.*, 1994, 289.
12 F. Jin and Y.-Y. Xu, *J. Fluorine Chem.*, 1994, **67**, 1.
13 C.-M. Hu, F. Hong and Y.-Y. Xu, *J. Fluorine Chem.*, 1993, **64**, 1.
14 K. Mizutani, T. Yamazaki, and T. Kitazume, *J. Chem. Soc., Chem. Commun.*, 1995, 51.
15 J. Ichikawa, S. Yonemaru, and T. Minami, *Synlett*, 1992, 833.
16 J. Ichikawa, C. Ikeura, and T. Minami, *Synlett*, 1992, 739.
17 J. Ichikawa, T. Minami, T. Sonoda, and H. Kobayashi, *Tetrahedron Lett.*, 1992, **33**, 3779.
18 J. Ichikawa, S. Hamada, T. Sonoda, and H. Kobayashi, *Tetrahedron Lett.*, 1992, **33**, 337.
19 K.J. Maruoka, I. Shimada, M. Akakura, and H. Yamamoto, *Synlett*, 1994, 847.
20 K.H. Dötz and J. Gläuzer, *J. Chem. Soc., Chem. Commun.*, 1993, 1036.
21 D.P. Matthews, P.P. Waid, J.S. Sabol and J.R. McCarthy, *Tetrahedron Lett.*, 1994, **35**, 5177.
22 W.R. Moore, G.L. Schatzman, E.T. Jarvi, R.S. Gros, and J.R. McCarthy, *J. Am. Chem. Soc.*, 1992, **114**, 360–361.
23 D.P. Matthews, R.S. Gros, and J.R. McCarthy, *Tetrahedron Lett.*, 1994, **35**, 1027.
24 R.S. Gros, S. Mehdi, and J.R. McCarthy, *Tetrahedron Lett.*, 1993, **34**, 7197.
25 J. Lee, M. Tsukazaki, and V. Snieckus, *Tetrahedron Lett.*, 1993, **34**, 415.
26 (a) A.J. Bennett, J.M. Percy, and M.H. Rock, *Synlett*, 1992, 483; (b) J.A. Howarth, W.M. Owton, and J.M. Percy, *J. Chem. Soc., Chem. Commun.*, 1995, 757.
27 T.S. Chou, P.C. Heath, L.E. Paterson, L.M. Poteet, R.E. Lakin, and A.H. Hunt, *Synthesis*, 1992, 565.
28 R.P. Robinson and K.M. Donahue, *J. Org. Chem.*, 1992, **57**, 7309.
29 A.M. Doherty, I. Sircar, B.E. Kornberg, J. Quin, R.T. Winters, J.S. Kaltenbron, M.D. Taylor, B.L. Batley, S.R. Rapundalo, M.T. Ryan, and C.A. Painchaud, *J. Med. Chem.*, 1992, **35**, 2.
30 K.S. Kim and L. Qian, *Tetrahedron Lett.*, 1993, **34**, 7195.
31 T. Tsukamoto and T. Kitazume, *Synlett*, 1992, 977.
32 K.M. Neder, S.A. French, and S.P.F. Miller, *Tetrahedron*, 1994, **50**, 9847.
33 F. Jin, Y. Xu, and W. Huang, *J. Chem. Soc., Perkin Trans. 1*, 1993, 795.
34 T. Briguad, P. Doussot, and C. Portella, *J. Chem. Soc., Chem. Commun.*, 1994, 2117.
35 M. Gingras, *Tetrahedron Lett.*, 1991, **32**, 7381.
36 J.R. McCarthy, D.P. Matthews, and J.P. Paolini, *Org. Synth.*, 1995, **72**, 209.
37 J.R. McCarthy, D.P. Matthews, and J.P. Paolini, *Org. Synth.*, 1995, **72**, 216.
38 D.P. Matthews, S.C. Miller, E.T. Jarvi, J.S. Sabol and J.R. McCarthy, *Tetrahedron Lett.*, 1993, **34**, 3057.
39 D.P. Matthews, R.A. Persichetti, J.S. Sabol, K.T. Stewart, and J.R. McCarthy, *Nucleosides Nucleotides*,

1993, **12**, 115.
40 A.P. Khrinian, A.B. Demilo, R.M. Waters, N.J. Liquido, and J.M. Nicholson, *J. Org. Chem.*, 1994, **59**, 8034.
41 A. Fujii, Y. Usuki, H. Iio, and T. Tokoroyama, *Synlett*, 1994, 725.
42 D. O'Hagan and J. Nieschalk, *J. Chem. Soc., Chem. Commun.*, 1995, 719.
43 S.F. Martin, D.W. Dean, and A.S. Wagman, *Tetrahedron Lett.*, 1992, **33**, 1839.
44 A. Otaka, K. Miyoshi, T.R. Burke, P.P. Roller, H. Kubota, H. Tamamura, and N. Fujii, *Tetrahedron Lett.*, 1995, **36**, 927.
45 J. Matulic-Adamic and N. Usman, *Tetrahedron Lett.*, 1994, **35**, 3227.
46 S. Halazy and V. Gross-Bergès, *J. Chem. Soc., Chem. Commun.*, 1992, 743.
47 T.P. Lequeux and J.M. Percy, *Synlett.*, 1995, 361.
48 J.-P. Bégué and D. Bonnet-Delpon, *Tetrahedron*, 1991, **47**, 3207.
49 V. Retrakul, T. Kruakong, and M. Pohmaktor, *Tetrahedron Lett.*, 1994, **35**, 4851.
50 G.S. Lal, *J. Org. Chem.*, 1993, **58**, 2791.
51 J.A. Howarth, W.M. Owton, and J.M. Percy, *Synlett*, 1994, 503.
52 Z.M. Qiu and D.J. Burton, *Tetrahedron Lett.*, 1993, **34**, 3239.
53 Z.M. Qiu and D.J. Burton, *Tetrahedron Lett.*, 1994, **35**, 4319.
54 J. Boivin, L. El Kaim, and S.R. Zard, *Tetrahedron*, 1995, **51**, 2573.
55 T. Yamazaki, K. Mizutami, and T. Kitazume, *J. Org. Chem.*, 1993, **58**, 4346.
56 V.G. Nenajdenko and E.S. Balenkova, *Tetrahedron*, 1994, **50**, 12407.
57 M. Koyama, M. Tamura, A. Ando, and I. Kumadaki, *Chem. Pharm. Bull.*, 1994, **42**, 2154.
58 T. Ishihara, H. Hayashi, and H. Yamanaka, *Tetrahedron Lett.*, 1993, **34**, 5777.
59 Y. Bessière, D.N-H. Savary, and M. Schlosser, *Helv. Chim. Acta*, 1977 **60**, 1739.
60 A. Thennapan and D.J. Burton, *J. Org. Chem.*, 1990, **55**, 4639.
61 O. Piva, *Synlett*, 1994, 729.
62 D. Clemenceau and J. Cousseau, *Tetrahedron Lett.*, 1993, **34**, 6903.
63 M.C. Pirrung, E.G. Rowley, and C.P. Holmes, *J. Org. Chem.*, 1993, **58**, 5683.
64 I. Shimizu and H. Ishii, *Tetrahedron*, 1994, **50**, 487.
65 K. Funabihi, T. Ohtsuki, T. Ishihara, and H. Yamanaka, *Chem. Lett.*, 1994, 1075.
66 J. Ichikawa, N. Yokota, M. Kobayashi, and T. Minami, *Synlett*, 1993, 186.
67 J. Ichikawa, M. Kobayashi, N. Yokota, Y. Noda, and T. Minami, *Tetrahedron*, 1994, **50**, 11637.
68 M. Gautschi, W.B. Schweizer, and D. Seebach, *Chem. Ber.*, 1994, **127**, 565.
69 K. Maruoka, I. Shimada, H. Imoto, and H. Yamamoto, *Synlett*, 1994, 519.
70 T. Taguchi, H. Sasaki, A. Shibuya, and T. Morikawa, *Tetrahedron Lett.*, 1994, **35**, 913.
71 T. Taguchi, A. Shibuya, H. Sasaki, J. Endo, T. Morikawa, and M. Shiro, *Tetrahedron: Asymmetry*, 1994, **5**, 1423.
72 Y. Shen and S. Gao, *J. Org. Chem.*, 1993, **58**, 4564.
73 A. Arnone, P. Bravo, M. Frigerio, G. Salani, and F. Viani, *Tetrahedron: Asymmetry*, 1994, **5**, 1348.
74 P. Bravo, A. Farina, M. Frigerio, S.V. Mielle, V. Soloshonok, and F. Viani, *Tetrahedron: Asymmetry*, 1994, **5**, 987.
75 F. Benayoud, J.-P. Bégué, D. Bonnet-Delpon, N. Fischer-Durand, and H. Sdassi, *Synthesis*, 1993, 1083.
76 J.-P. Bégué, D. Bonnet-Delpon, N. Fischer-Durand, M. Reboud, and A. Amour, *Tetrahedron: Asymmetry*, 1994, **5**, 1099.
77 J.-P. Bégué, D. Bonnet-Delpon, and M.H. Rock, *Tetrahedron Lett.*, 1994, **35**, 6097.
78 C. Bussche-Hünnefeld and D. Seebach, *Chem. Ber.*, 1992, **125**, 1273.
79 F. Tellier and R.Sauvêtre, *J. Fluorine Chem.*, 1995, **70**, 265.
80 F. Tellier and R. Sauvêtre, *J. Fluorine Chem.*, 1993, **62**, 183.
81 J.-P. Bégué, D. Bonnet-Delpon, and M.H. Rock, *Synlett*, 1995, in press.
82 T. Iwaoka, N. Katagiri, M. Sato, and C. Kaneko, *Chem. Pharm. Bull.*, 1992, **40**, 2319.
83 C-M. Hu, F. Hong, B. Jiang and Y. Xu, *J. Fluorine Chem.*, 1994, **66**, 215.
84 M.G. Barlow, N.N.E. Suliman, and A.E. Tipping, *J. Fluorine Chem.*, 1995, **70**, 59.
85 J.-P. Bégué, D. Bonnet-Delpon, T. Lequeux, J. d'Angelo, and A. Guignant, *Synlett*, 1992, 146.
86 T. Kitazume, K. Murata, A. Okabe, Y. Takahashi, and T. Yamazaki, *Tetrahedron: Asymmetry*, 1994, **5**, 1029.
87 S. Ghosh and M. Schlosser, *J. Fluorine Chem.*, 1994, **67**, 53.
88 R. Zimmer and H-U. Reissig, *J. Org. Chem.*, 1992, **57**, 339.
89 J.-P. Bégué, D. Bonnet-Delpon, and T. Lequeux, *Tetrahedron Lett.*, 1993, **34**, 3279.
90 J.T. Welch, K. Araki, R. Kawecki, and J.A. Wichtowski, *J. Org. Chem.*, 1993, **58**, 2454.
91 A. Abouabdellah and J.T. Welch, *Tetrahedron: Asymmetry*, 1994, **5**, 1005.
92 V.G. Andreev and A.F. Kolomiets, *Uspekhi Khimii*, 1993, **62**, 594.
93 K. Araki and J.T. Welch, *Tetrahedron Lett.*, 1993, **34**, 2251.
94 K. Araki, W.Q. Yun, J. O'Toole, P.J. Toscano, and J.T. Welch, *Carbohydr. Res.*, 1993, **249**, 139.
95 T.R. Elworthy, D.J. Morgans, W.S. Palmer, D.B. Repke, D.B. Smith, and A.M. Waltos, *Tetrahedron Lett.*, 1994, **35**, 4951.
96 W.S. Johnson, B. Chenera, F.S. Tham, and R.K. Kullnig, *J. Am. Chem. Soc.*, 1993, **115**, 493.
97 W.S. Johnson, R.A. Buchanan, W.R. Bartlett, F.S. Tham, and R.K. Kullnig, *J. Am. Chem. Soc.*, 1993, **115**, 504.
98 P. Erbes and W. Boland, *Helv. Chem. Acta*, 1992, **75**, 766.
99 S.T. Patel and J.M. Percy, *J. Chem. Soc., Chem. Commun.*, 1992, 1477.
100. K. Mikami, T. Yajima, M. Terada, E. Kato, and M. Maruta, *Tetrahedron: Asymmetry*, 1994, **5**, 1087.
101 D.V. Avila, K.U. Ingold, J. Lusztyk, W.R. Dolbier, H.-Q. Pan, and M. Muir, *J. Am. Chem. Soc.*, 1994, **116**, 99.
102 X.X. Rong, H.-Q. Pan, W.R. Dolbier, and B.E. Smart, *J. Am. Chem. Soc.*, 1994, **116**, 4521.
103 W.R. Dolbier and X.X. Rong, *Tetrahedron Lett.*, 1994, **35**, 6225.
104 L.A. Buttle and W.B. Motherwell, *Tetrahedron Lett.*, 1994, **35**, 3995.
105 A. Arnone, P. Bravo, M. Frigerio, F. Viani, G. Cavicchio, and M. Crucianelli, *J. Org. Chem.*, 1994, **59**, 3459.
106 A. Arnone, P. Bravo, M. Frigerio, F. Viani, G. Cavicchio, and M. Crucianelli, *Tetrahedron*, 1994, **50**,

12361.
107 A. Arnone, P. Bravo, G. Cavicchio, M. Frigerio, and F. Viani, *Tetrahedron*, 1992, **48**, 8523.
108 Y. Takeuchi, A. Kanada, S. Kawakara, and T. Koizumi, *J. Org. Chem.*, 1993, **58**, 3483.
109 M. Shimizu, O. Morita, S. Itoh, and T. Fujisawa, *Tetrahedron Lett.*, 1992, **33**, 7003.
110 T. Morikawa, Y. Kodama, J. Uchida, M. Takano, Y. Washio, and T. Taguchi, *Tetrahedron*, 1992, **48**, 8915.
111 T. Morikawa, M. Uejima, Y. Kobayashi, and T. Taguchi, *J. Fluorine Chem.*, 1993, **65**, 79.