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REVIEW

Fluorinated Enol Ethers: Synthesis and Reactivity

M. Decostanzi, J.-M. Campagne and E. Leclerc*

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Thanks to the beneficial effect of fluorine substitution on the pharmacokinetic properties of molecules, an ever growing number of marketed drugs incorporate a fluorine atom in their structure. As a consequence, the synthesis of fluorinated molecules has become a very active research field. Among the numerous approaches, fluorinated enol ethers are valuable building blocks that allow the introduction of a fluoro- or difluoromethyl group through a wide variety of reactions. The present review inventories the different methods for their preparation and scans their numerous synthetic applications.

I. Introduction

It took several decades, after the discovery of elemental fluorine by Moissan, to organic chemists to get involved in the chemistry of fluorinated compounds. Indeed, this element and its derivatives have long been studied almost exclusively by mineral and material chemists, with, at key, impressive industrial applications (UF6, Teflon ®,…). The weak number of fluorinated natural organic molecules certainly explains this late interest that was eventually triggered by the discovery of fluorouracil and of fluorinated corticosteroids.[1,2] Since then, the number of fluorinated bioactive molecules has exponentially increased and, among the drugs or agrochemicals released on the market every year since 2000, up to 30% of them feature a fluorinated group in their structure.[Erreur ! Signet non défini.] This success finds its origin in the modification of the biological properties of bioactive molecules that is induced by the judicious introduction of fluorine atoms or fluorinated groups on key positions.[3] These modifications range from increased lipophilicity to metabolic stabilisation and crucial reactivity modulations (transition state analogues). In consequence, the demand for new synthetic methodologies for the efficient and selective introduction of fluorine atoms or fluorinated groups has grown. If direct fluorination, difluoromethylation and trifluoromethylation reactions constitute a privileged research field, such methods require sometimes highly sophisticated reagents and might suffer from a limited scope, thereby limiting their use.[4] In such cases, the fluorinated building-block strategy is often a nice alternative. Indeed, performing synthetic transformations on an appropriately functionalized fluorinated synthon might offer a higher flexibility and give access to a greater molecular diversity. Among these molecular bricks, fluorinated enol ethers are interesting partners due to their versatile reactivity and to their well-documented preparation. Depending on which type of reactivity is involved, a fluoromethyl or difluoromethyl group, an alkoxy or carbonyl moiety and/or other functional groups can be introduced in a single reaction. To the best of our knowledge, no review summing up the literature relative to fluorinated enol ethers has ever been reported. The present review will thus focus, in a first section, on the synthesis (preparative methods as well as *in situ* generations) and, in a second section, on the reactivity of species depicted in figure 1. Only the enol ethers featuring at least one fluorine atom attached to the double bond and in which the oxygen atom is convalently bonded to a carbon, silicon, sulfur or phosphorus atom are therefore considered. Publications refering only to highly reactive enolate species, such as metal enolates, for which any isolation is almost forbidden, are willingly ignored. Such intermediates are considered only if they are involved in the preparation or in the synthetic applications of species depicted in figure 1.

II. Synthesis

II.1 Enolization/trapping of carbonyl derivatives

A classical synthesis of non-fluorinated enol ethers consists in the deprotonation and the trapping with the appropriate electrophile of carbonyl derivatives. In contrast, this approach is not the favoured one for the preparation of fluorinated enol ethers, due to the lower availability of the required starting materials. As a consequence, the deprotonation of α-fluoro- or α,α-difluoroketones or esters with lithium amides, which is a very common strategy in the non-fluorinated series, has been reported only in few instances.

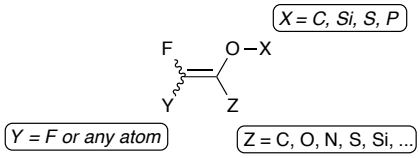
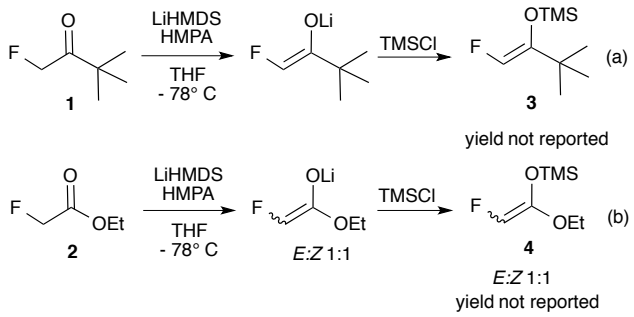
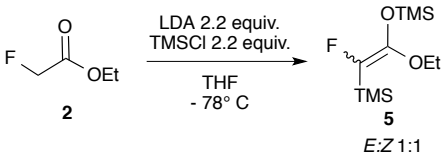


Figure 1

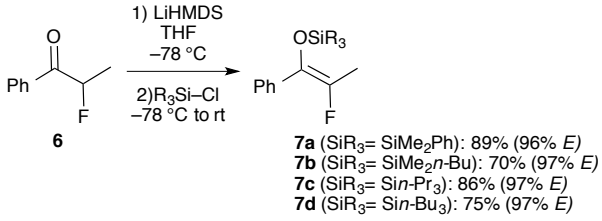
Institut Charles Gerhardt UMR 5253 CNRS-UM2-UM1-ENSCM 8, rue de l'Ecole Normale, 34296 Montpellier Cedex 5, France. E-mail: eric.leclerc@enscm.fr



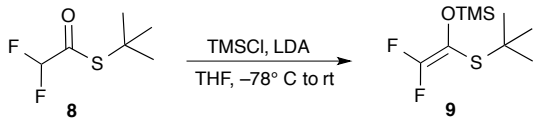
Scheme 1



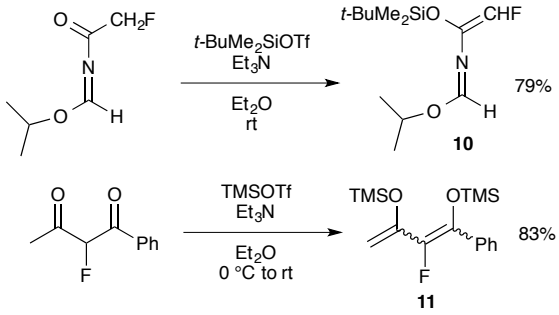
Scheme 2



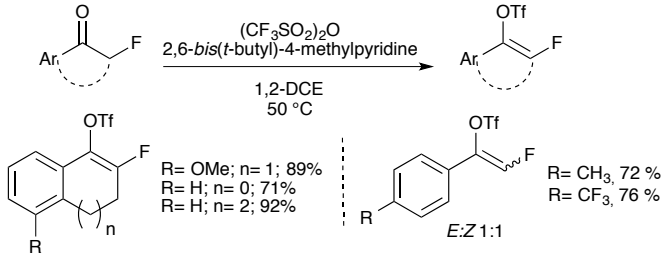
Scheme 3



Scheme 4



Scheme 5



Scheme 6

LiHMDS in the presence of HMPA was used by Welch to deprotonate α-fluoroketone **1** and fluoroacetate **2**.[5] The resulting lithium enolate was trapped with TMSCl to afford silyl enol ethers **3** and **4** in yields that were not reported, presumably because no purification was possible (Scheme 1). Ethyl fluoroacetate **2** could also be C- and O-silylated using 2.2 equivalents of LDA and 2.2 equivalents of TMSCl (Scheme 2).[6] A similar approach provided tetrasubstituted silyl fluoroenol ethers that were isolated in good yields and with a high *E* selectivity (Scheme 3).[7] The increased stability of enoxysilanes **7** could be due either to the bulkier silicon groups that were used or to the higher degree of substitution compared to the previous examples.

In contrast to ethyl fluoroacetate, ethyl difluoroacetate was reported to be a poor substrate for such deprotonation/trapping reactions. Indeed, according to Weigel, its treatment with LiHMDS/TMSCl only led to self-condensation or C-silylation products.[8] A solution was to move to the corresponding *tert*-butyl thioester **8**. The latter underwent a clean conversion to the TMS-enol ether **9** that was directly subjected to Mukaiyama aldol reactions (Scheme 4).[8] Indeed, **9** could not be isolated due to its weak stability, a problem which is commonly encountered for trimethylsilyl fluoroenol ethers.

Alternatively, weak bases such as tertiary amines can also be used to prepare fluorinated enol derivatives. Such conditions require, of course, stronger electrophiles to promote O-functionalization. Regarding silyl enol ethers, heterodiene **10** and diene **11** were prepared using the corresponding trialkylsilyl triflate using triethylamine as a base (Scheme 5).[9,10] In contrast to standard trimethylsilyl enol ethers, **11**, as well as **10**, could be isolated and stored at –20°C for several weeks. The use of triflic anhydride as the electrophile, in the presence of 2,6-di-*tert*-butyl-4-methylpyridine, allowed the conversion of cyclic and acyclic α-fluoroketones to the corresponding fluorinated enol triflates.[11] All the compounds were isolated in good yields but acyclic derivatives were obtained in an equimolar E:Z mixture (Scheme 6). These enol triflates were thereafter subjected to cross-coupling reactions (see section III.3).

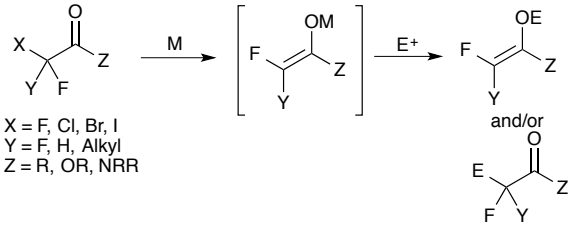
II.2 Reduction/trapping of α-halocarbonyl derivatives

The reduction of α-dihalo- or α-trihalocarbonyl derivatives followed by trapping with the appropriate electrophile is a popular and efficient method to prepare fluorinated enol ethers (Scheme 7). The wide availability of the required precursors (trifluoroacetates, bromo- or chlorodifluoroacetates and bromo- or chlorofluoroacetates) certainly explains the greater success of this method compared to the classical deprotonation/trapping described above. A

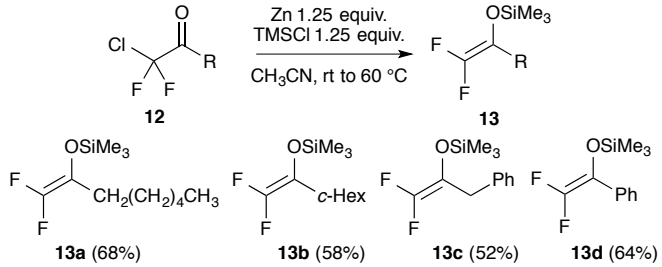
wide range of fluorinated enol ethers can be prepared through this method, as illustrated in general scheme 7.

The conversion of chlorodifluoromethylketones **12** to difluoroenoxysilanes **13** under Reformatsky conditions was the first example of this type.[12] The compounds were purified by distillation and isolated in fair yields (Scheme 8). **13a** and **13b** were stable at room temperature for several months, whereas phenyl substituted enoxysilanes **13c** and **13d** could be stored at 4°C only for a few days.

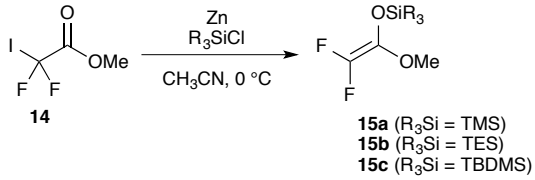
Difluoroketene silyl acetals can also be prepared using a similar process, as illustrated by the preparation of **15** from methyl iododifluoroacetate **14** (Scheme 9).[13] As for ketones, MeCN proved to be the best solvent for this transformation. Difluoroketene trimethylsilyl acetal **15a** was highly unstable and was preferentially prepared *in situ* for further reactions. TES and TBDMS derivatives **15b** and **15c** were more stable and more easily handled. The preparation of monofluorinated ketene silyl acetal from ethyl chlorofluoroacetate has more recently been reported by Chen.[14] Two sets of conditions were devised for this transformation, both leading to fluoroketene trimethylsilyl acetal **4** in good isolated yield and, more intriguingly, as a single *E* isomer (Scheme 10). This high stereoselectivity is surprising, especially in light of the result obtained for bromofluoroketene trimethylsilyl acetal **16**, previously prepared in a similar fashion by Iseki and obtained as a *E*/*Z* mixture (Scheme 11).[15] Despite its isolation as a pure material after distillation, no yield is given by the authors for this transformation. It should be mentioned that α-sulfuryl or α-sulfonylcarbonyl compounds have also been used as precursors through triethylgermanate- or magnesium-mediated reduction processes.[16,17]



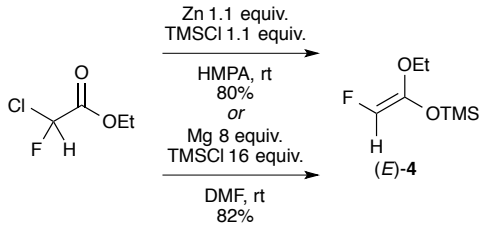
Scheme 7



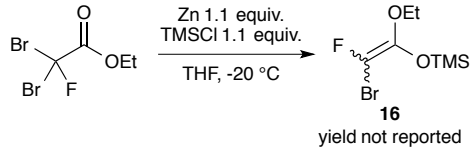
Scheme 8



Scheme 9

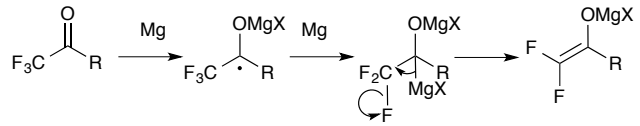


Scheme 10

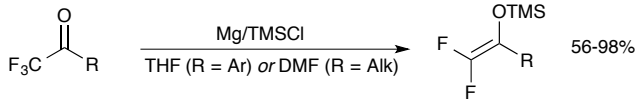


Scheme 11

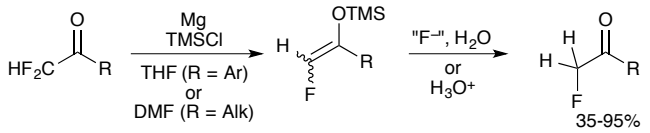
The magnesium-mediated reduction of trifluoromethylketones is the second method of choice to produce difluoroenol ethers through a reduction/trapping process.[18] As opposed to Reformatsky-like reactions, the C–F bond can not be directly reduced by Mg(0) to produce an enolate. Instead, the carbonyl group of the trifluoromethylketone is reduced through two single electron transfers to the corresponding *bis*-magnesium compound that spontaneously undergoes a fluoride elimination to deliver the difluoroenolate (Scheme 12). This mechanism has been proposed by Uneyama in his first report on the preparation of difluoroenoxysilanes from trifluoromethylketones.[19] Difluoroenoxysilanes were obtained in good NMR yields after a simple filtration from the reaction mixture (Scheme 13). The reaction was conducted in THF with the exception of aliphatic ketones that required the use of DMF as the solvent. Uneyama had previously reported the same transformation under electroreductive conditions but in slightly lower yields.[20]



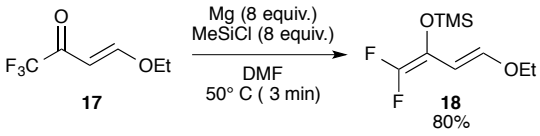
Scheme 12



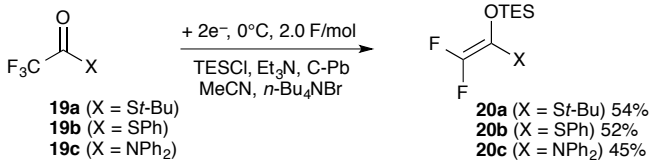
Scheme 13



Scheme 14



Scheme 15



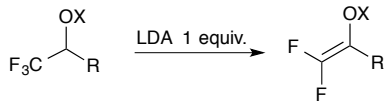
Scheme 16

An iterative process can allow the formation of monofluorinated enoxysilanes as illustrated by the work of Prakash.[21] Hydrolysis of the previous difluoroenoxysilane led to the corresponding difluoromethylketone that could undergo a second Mg-mediated reduction in the presence of TMSCl to provide a fluoroenoxysilane (Scheme 14). In this report, the latter was directly hydrolyzed to the corresponding fluoromethylketone. Welch and Uneyama have also reported other examples of difluoromethyl- or pentafluoroethylketones that are converted into their corresponding fluoroenoxysilane.[22] This method has also been applied to the preparation of difluorinated Danishefsky's diene **18** from enone **17** (Scheme 15).[23] This magnesium mediated-reduction applied to trifluoroacetates or trifluoroacetamides as substrates provided only C-silylation products.[24] However, the electroreductive method first published by Uneyama allowed the conversion of thioesters and amides **19** to the corresponding difluoroketene silyl hemithioacetal or hemiaminal **20** in moderate isolated yields (Scheme 16).[25] Interestingly, the same reaction with alkyl trifluoroacetates provided predominantly C-silylation products that can be obtained exclusively by increasing the reaction temperature to 50°C.[26]

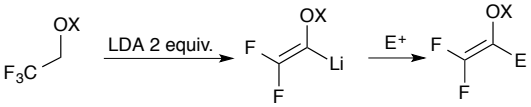
II.3 Elimination reactions

II.3.1 Base-mediated eliminations.

First investigated by Nakai and Ishikawa, the base-mediated elimination reaction of trifluoroethyl ethers is a widespread method for the preparation of difluoroenol ethers and follows the general trend illustrated in scheme 17.[27] This reaction was afterwards extensively applied to various trifluoroethanol (TFE) derivatives, substituted or not, featuring a wide range of X groups, from standard alkyl or aryl groups to carbamate or tosylate functions. However, it should be mentioned that reactions with unsubstituted TFE ethers (R=H) required the use of an excess of base. Indeed, the vinylic proton is more acidic than the methylene protons and this results in the *in situ* formation of lithiated difluoroenol ethers. The latter could be trapped with a wide range of electrophiles to provide tetrasubstituted difluoroenol ethers (Scheme 18). Nakai and Metcalf have for example reported the addition of lithiated alkyl and tosyl enolate onto aldehydes and ketones.[27b,27c,28] Percy has afterwards extensively developed the reaction of lithiated MEM difluoroenol ethers and difluoroenol carbamates with carbonyl compounds.[29,30] Other electrophiles such as alkyl triflates,[31] chlorotrialkylsilanes,[28,29a,32] tributyltin chloride,[29b,33] trialkylborates,[34] or iodine[35] were also used to trap the lithiated enol ether. The elimination/addition reaction of various trifluoroethanol ethers or carbamates onto carbonyl compounds is more precisely described on scheme 19. This transformation was fairly efficient with MEM ether **21a** while enol carbamates **21b** and **21c** led to slightly lower yields.[29,30] The elimination/metallation sequence from **21a** followed by trapping with TMSCl or Bu_3SnCl afforded **22** and **23** in good yields (scheme 20). As mentioned above, the reaction of lithiated fluoroenolates with trialkyl borates allows the formation of alkenylboron compounds that can act as substrates in cross coupling reaction (see section II.5.2). The reaction with diisopropyl iodomethylboronate was a particular case in which the intermediate *ate*-complex directly led to allylboronate **24** through a Matteson 1,2-rearrangement.[36] **24** subsequently reacted with benzaldehyde to afford compound **25** in good overall yield from **21d** (scheme 21).

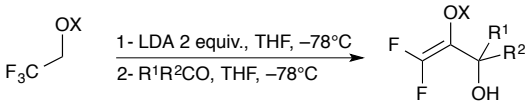


Scheme 17



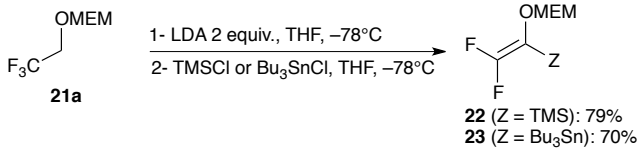
X = Ar, Bn, Allyl,Alyl, MEM, $CONEt_2$, CON(*i*-Pr)($CH_2CH_2OTBDPS$), SiR_3
$E^+ = R^1R^2CO$, ROTf, R_3SiCl, Bu_3SnCl, $B(OR)_3$, I_2

Scheme 18

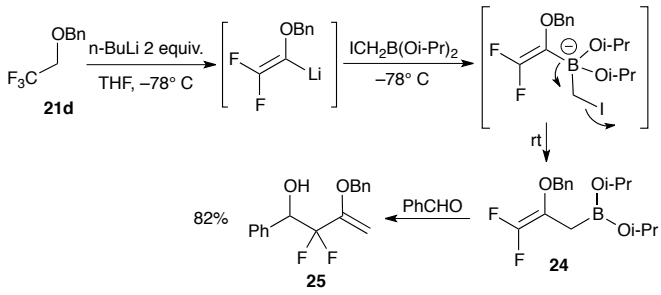


21a (X = MEM)
21b (X = $CONEt_2$)
21c [X = CON(*i*-Pr)($CH_2CH_2OTBDPS$)]

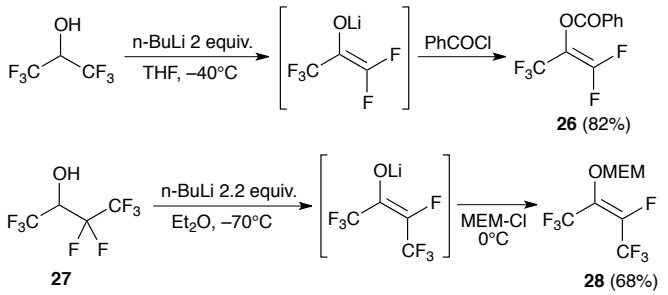
Scheme 19



Scheme 20

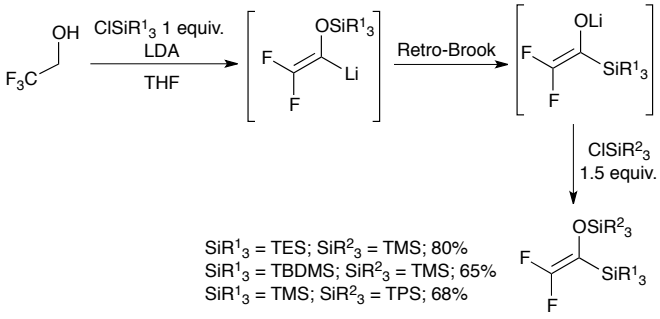


Scheme 21

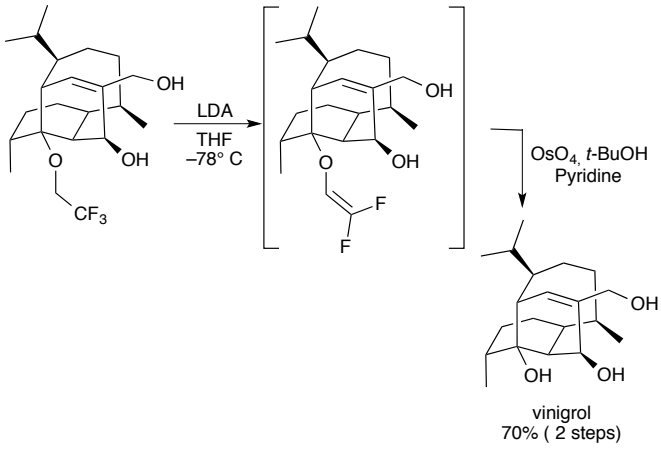


Scheme 24

The silylation of lithiated fluoroenol ethers is also possible and Welch has reported an interesting preparation of α-silylated difluoroenoxysilanes directly from trifluoroethanol.[32] The reaction of TFE with a first chlorotrialkylsilane and an excess of LDA allowed O-silylation, elimination and metallation to occur (scheme 22). A retro-Brook rearrangement followed to provide the corresponding enolate that can be trapped with a second chlorotrialkylsilane. Of interest is the exploitation of the base-mediated elimination reaction of a TFE-ether in a total synthesis of Vinigrol in which the trifluoroethyl moiety was used as a protecting group for an alcohol function.[37] The final deprotection was performed by conversion of the TFE ether to the corresponding difluoroenol ether in the presence of LDA and oxidative degradation of the latter (Scheme 23).



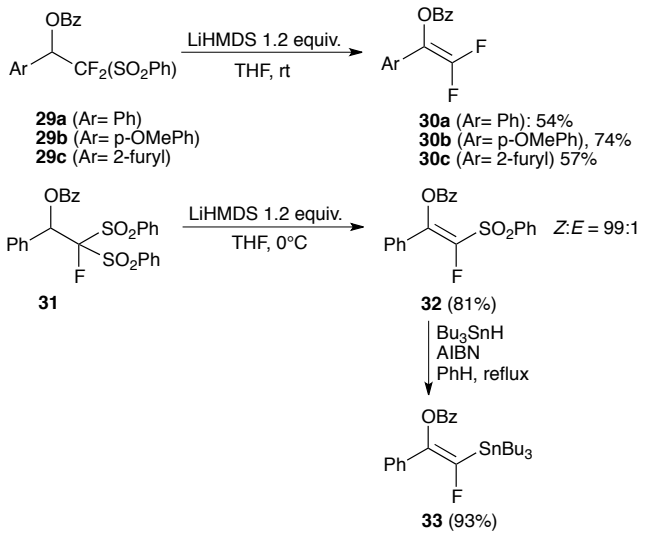
Scheme 22



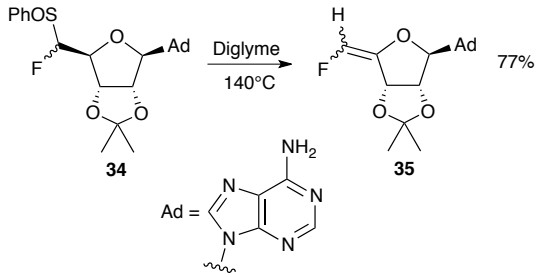
Scheme 23

The work of Nakai on the elimination reaction and O-protection sequence of hexafluoro-*iso*-propanol (HFIP) and other highly fluorinated alcohols should also be mentioned.[27c-e] Perfluorinated enol ethers **26** and **28** were easily prepared according to this method and, in the case of alcohol **27**, only the "internal" enolate was formed (scheme 24). **28** was obtained as a single *Z* isomer when the reaction was performed in Et_2O. Other polyfluorinated enol tosylates have been prepared by Funabiki by *n*-BuLi-mediated elimination of the corresponding tosylates.[38] The preparation of difluoroketene acetals or hemiaminals using a fluoride elimination reaction has been reported in only two cases.[39,40] Each time, these reactive species were directly engaged in a Mukaiyama aldol reaction or in a [3,3]-sigmatropic rearrangement (see section III.1.1.1 and III.2.1.1).

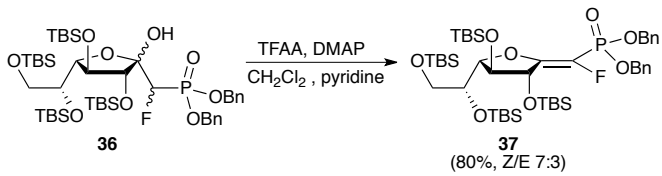
The availability of TFE, HFIP, trifluoroacetates and derivatives has made such a process very popular. The preparation of fluorinated enol ether through an elimination reaction is however not limited to the use of fluoride as the leaving group. The elimination of the phenylsulfonyl group from substrates **29** and **31** has for example been reported by Hu.[41] Both compounds were easily obtained by the addition of, respectively, difluoromethylphenylsulfone and fluoro-*bis*-(phenylsulfonyl)methane (FBSM) to aldehydes followed by benzoylation. Difluoroenol ethers **30** were obtained in fair yield while monofluorinated enol ether **32** was isolated in 81% and with high *Z* selectivity (Scheme 25). The latter can also be converted to stannyl derivative **42** through a radical process involving the β-elimination of a sulfonyl radical. The sulfinyl group has also served as a leaving group, as demonstrated by McCarthy and later on by Wnuk in a synthesis of unsaturated 5'-fluoroadenosine nucleosides.[42] The thermolysis of α-fluorosulfoxide **34** indeed allowed the formation of monofluorinated enol ether **35** in good yield (Scheme 26). Finally, another example of preparation of a fluorinated *exo*-glycal has been reported, this time by elimination of a trifluoroacetate.[43] Precursor **36**, obtained by fluorohydroxylation of the corresponding unsaturated compound, is directly converted to **37** in the presence of trifluoroacetic anhydride (TFAA) and DMAP (Scheme 27).



Scheme 25



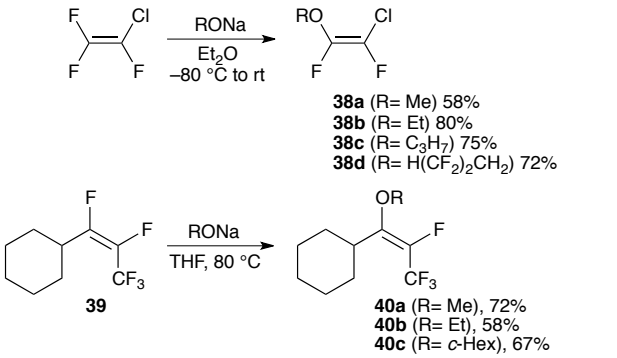
Scheme 26



Scheme 27

II.3.2 Addition of alkoxides to fluoroolefins.

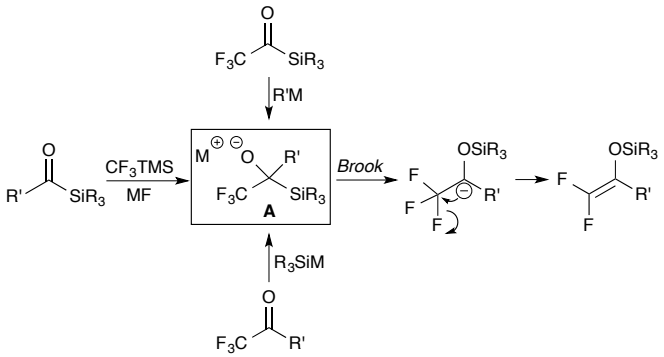
The addition/elimination sequence resulting from the reaction between fluoroolefins and alkoxides is a long known access to fluorinated enol ethers.[44] The reaction often leads to α-fluorovinylethers that have found numerous applications in material and polymer chemistry but are less useful for the synthetic organic chemist. Two representative examples are described in scheme 28. The addition of various sodium alkoxide to chlorotrifluoroethylene allowed the formation enolethers **38** in good yields,[45] while the same reaction with tetrafluoroethylene is much less efficient.[46] A similar reaction using fluorolefins such as **39** provides compounds **40** in fair yields.[47]



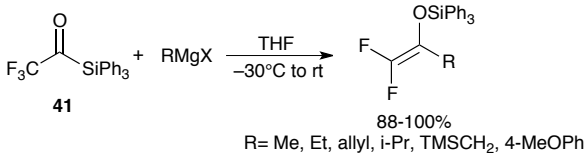
Scheme 28

II.3.3 Brook rearrangement/elimination sequence.

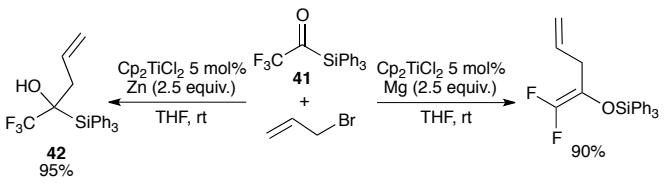
A popular approach to fluorinated enol ethers consists in the Brook rearrangement/fluoride elimination sequence that can occur from α-silylated alkoxides **A** (Scheme 29). Such intermediates can be generated *in situ* either by addition of organometallic reagents to trifluoroacetylsilanes, by addition of the Ruppert-Prakash reagent to acylsilanes or by the addition of silylmetal reagents to trifluoromethylketones. In their pioneering work, Xu and Huang reported the preparation of silyl difluoroenol ethers by addition of organolithium or Grignard reagents to trifluoroacetyltriphenylsilane **41**.[48] The reaction was very efficient and provided the corresponding triphenylsilyl difluoroenol ethers in excellent isolated yield (Scheme 30). Much later, Wu demonstrated that the reaction outcome is dependant on the nature of the alkoxide intermediate.[49] If magnesium alkoxides underwent the Brook/elimination sequence, the corresponding zinc alkoxide did not rearrange under the reaction conditions. Addition product **42** was indeed obtained in excellent yield (Scheme 31).



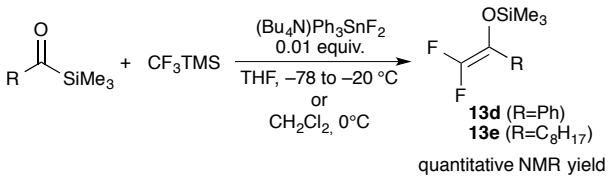
Scheme 29



Scheme 30



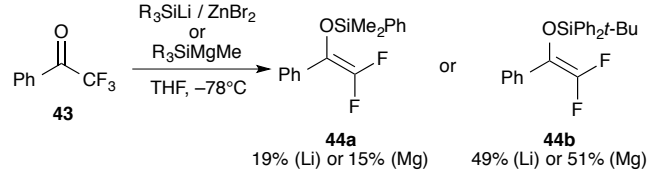
Scheme 31



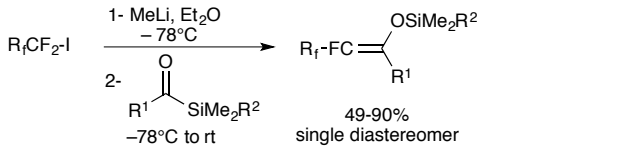
Scheme 32

A complementary approach based on the addition of Ruppert-Prakash reagent to acyltrimethylsilanes was reported by Portella shortly after Xu's first report.[50] The intermediate alkoxide can indeed undergo a Brook/elimination sequence (scheme 29) to afford trimethylsilyl difluoroenol ethers **13d-e** (Scheme 32). The addition of CF_3TMS to acyltrimethylsilanes required the use of an uncommon fluoride source, tetrabutylammunium difluorotriphenylstannate (DFTPS), since more reactive and more traditional reagents such as TBAF led to a self-condensation product. Difluoroenoxysilanes such as **13d-e** have been used *in situ* as nucleophiles in numerous reactions (*vide infra*), without isolation of this sensitive and reactive material. TBDMS derivatives were also prepared through this method from the corresponding acyl-*tert*-butyldimethylsilanes, and could be purified and isolated as pure materials.

Later on, the last variant of this strategy has been reported by Fleming.[51] The addition of dimethylphenylsilylmetal or *tert*-butyldiphenylsilylmetal reagents to trifluoroacetylbenzene **43** afforded the corresponding difluoroenoxysilanes **44** in low to moderate yields (Scheme 33). The use of the silyllithium reagents in the presence of $ZnBr_2$ or of the corresponding methylmagnesium reagents led to similar results.

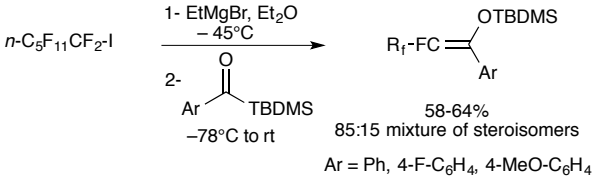


Scheme 33



R¹ = *n*-C_3H_7, *n*-C_5H_{11}, CH_3CH=CH, *n*-C_3H_7CH=CH, PhCH=CH
R² = Me, *t*-Bu
R_f = CF_3, *n*-C_5F_{11}, *n*-C_7F_{15}

Scheme 34

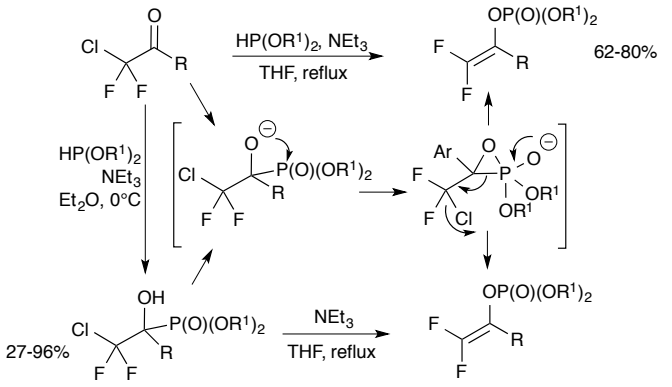


Scheme 35

The addition of perfluoroalkylmetal reagents to acylsilanes leading, in a similar process, to the preparation of highly fluorinated enoxysilanes, was reported by Portella in 1993.[52] The addition of perfluoroalkyllithium reagents to aliphatic acylsilanes was fairly efficient and provided the corresponding enoxysilanes in moderate to high yields (Scheme 34). All compounds were obtained as a single stereoisomer of unknown configuration. In contrast, aromatic acylsilanes required the use of perfluoroalkylmagnesium reagents to avoid a side reaction leading to fluorinated enones. The corresponding enoxysilanes were obtained as a mixture of two stereoisomers in a ≈85:15 ratio (Scheme 35). In all cases, the TBDMS derivatives were obtained in higher yields and were easier to handle than their TMS counterparts.

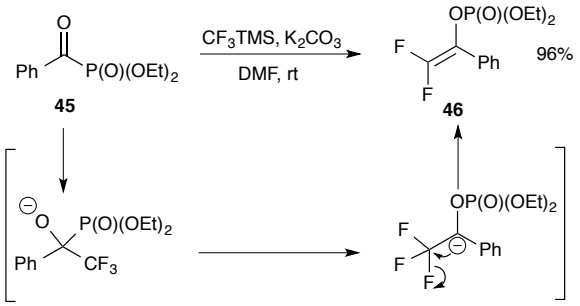
II.3.4 Phosphate migration/elimination sequence.

Processes similar to the Brook/elimination sequence detailed above have also been reported for the preparation of fluorinated enol phosphates. A phosphonyl group can indeed easily migrate to an adjacent alkoxide group and thus trigger a migration/elimination sequence to produce fluoroenol phosphates. The first example of this type was reported by Ishihara with the addition of dialkyl or diarylphosphites to chlorodifluoromethylketones.[53] Difluoroenolphosphates were either obtained directly when the reaction was performed in refluxing THF, while addition products were first isolated under milder conditions and then converted to enol phosphates (Scheme 36). A mechanism involving a stepwise migration of the phosphate group from carbon to oxygen and a concerted chloride elimination was drawn out from these results. The same authors have reported variants of this reaction based on the addition of trialkylphosphites to perfluorinated acyl chlorides.[54]



R = Me, C_6H_{13}, c-Hex, $PhCH_2$, Ph
R¹ = Ph or Et

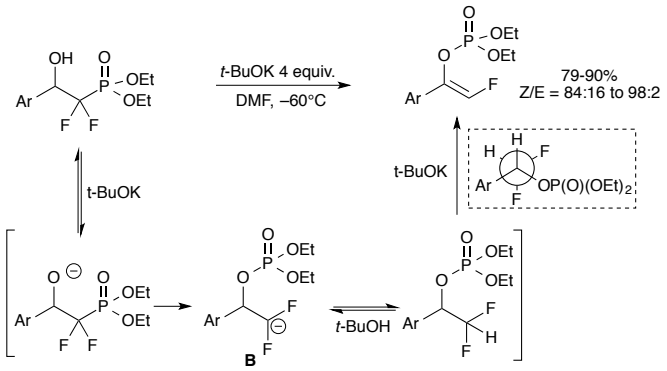
Scheme 36



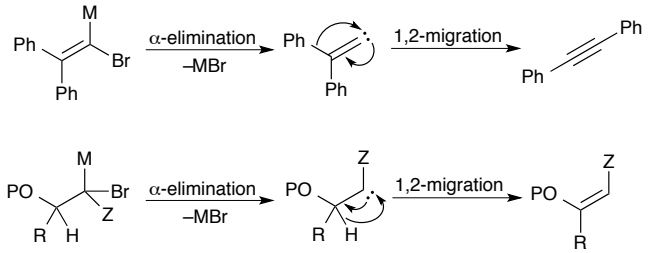
Scheme 37

More recently, and in a process very close to Portella's methodology, the addition of (trifluoromethyl)trimethylsilane to aromatic acylphosphonates such as **45** led to the corresponding difluoroenol phosphate **46** in high yields.[55] A 1,2-migration of the phosphonyl group from carbon to oxygen triggered the same fluoride elimination as for the acylsilane reaction. Enol phosphates were indeed obtained in high yield while the reaction with aliphatic acylphosphonates stopped at the addition level (Scheme 37).

A 1,3-migration process has been used in the conversion of β-hydroxy-α,α-difluorophosphonates to monofluoroenol phosphates.[56] Under basic conditions, the corresponding alkoxide could be generated and underwent a 1,3-migration of the phosphate group to oxygen. According to the authors, the resulting carbanion **B** was then reprotonated with *tert*-butanol and a fluoride elimination reaction occured (Scheme 38). The reaction was strongly *Z* selective and fluoroenol phosphates were obtained in good yields. The authors suggested that the observed *Z*-selectivity arose from the corresponding reactive conformation that would be favored by two gauche interactions between the fluorine atoms and the phosphate oxygen. Alternatively to this interpretation and to the mechanism described above, it might be postulated that the fluorinated carbanion **B** was not reprotonated by *tert*-butanol and directly underwent a carbenoidic rearrangement of known *Z* selectivity, similar to the ones described in the following section.



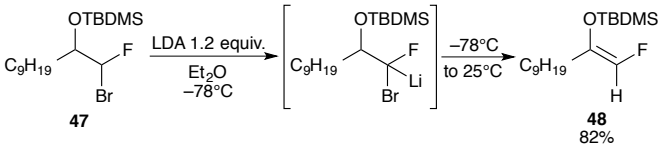
Scheme 38



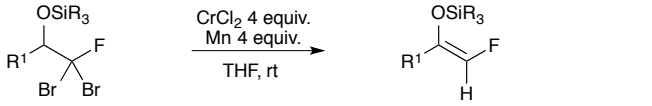
Scheme 39

II.3.5 Carbenoidic rearrangement (α-elimination).

The Fritsch-Buttenberg-Wiechell rearrangement of sp^2 carbenoids is a well known reaction for the synthesis of alkynes from bromoalkenes (Scheme 39). The rearrangement of sp^3 carbenoids leading to alkenes is less common but is particularly efficient from polyhalogenated alcohols. Indeed, the hydrogen which sits next to the oxygen atom easily undergoes a 1,2-migration after α-elimination of the carbenoid to the carbene (Scheme 39). The first efficient rearrangement of this type leading to a fluoroenol ether was reported by Utimoto.[57] The reaction of halogenated alcohol **47** with LDA led directly to fluoroenoxysilane **48** upon warming of the reaction mixture, presumably *via* a lithium carbenoid intermediate (Scheme 40).

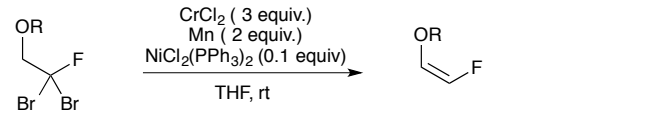


Scheme 40



R^1 = H, R_3Si = TBDPS, 68%
R^1 = CH_2CH_2Ph, R_3Si = TMS, 93%
R^1 = CH_2CH_2Ph, R_3Si = TES, 91%
R^1 = CH_2CH_2Ph, R_3Si = TBDMS, 68%
R^1 = $(CH_2)_3OBn$, R_3Si = TMS, 70%

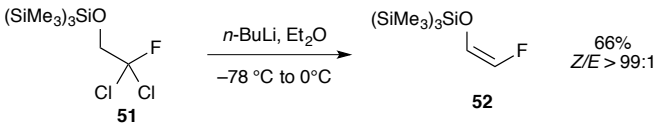
Scheme 41



49a (R = Bn)
49b (R = PMB)
49c [R = $(CH_2)_4Ph$]

50a (R = Bn), 76%
50b (R = PMB), 98%
50c [R = $(CH_2)_4Ph$], 66%

Scheme 42



Scheme 43

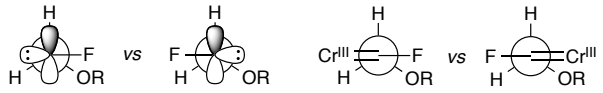


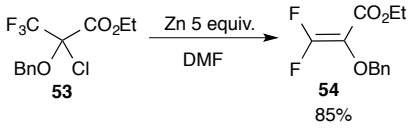
Figure 2

A similar methodology was later on extended to a range of fluorinated substrates by Taguchi.[58] The intermediate carbenoid is, this time, not generated by deprotonation but by reduction of 2,2-dibromo-2-fluoroethyl silyl ethers with chromium(II) chloride in the presence of manganese. The resulting chromium carbenoids rearrange efficiently to provide the corresponding fluoroenoxysilanes in good yields and as a single *Z* isomer (Scheme 41). The same reaction with unsubstituted 2,2-dibromo-2-fluoroethyl alkyl ethers **49** required the use of a Ni(II) co-catalyst to ensure a complete conversion and a fast reaction. Interestingly, this co-catalysis was deleterious in the previous silyl ether case (Scheme 42). Finally, the lithium carbenoid approach has recently been revisited by Yamamoto. Monofluorinated enol ether **52** protected with a "supersilyl" group was prepared from 2,2-dichloro-2-fluoroethyl ether **51** (Scheme 43).[59]

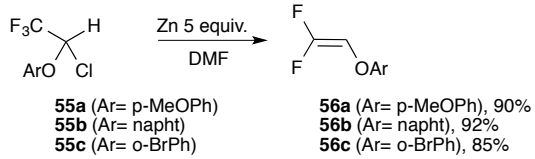
The strong *Z*-selectivity observed in these rearrangements has been rationalized for non fluorinated substrates. In the case of lithium carbenoïds, Pirrung suggested that the conformation leading to the *E* enoxysilane was destabilized by a strong electronic repulsion between the lone pair of the carbene and the silyloxy group (Figure 2).[60] In contrast, the conformation leading to the *Z* enoxysilane might be stabilized by hyperconjugation between the carbene lone pair and the σ* orbital of the C–O bond. In the case of chromium carbenes, Mioskowski suggested that, in addition to these stereoelectronic considerations, a steric interaction between the coordinated chromium and the silyloxy group could destabilize the conformation leading to the *E* enoxysilane (Figure 2).[61]

II.3.6 Reduction/elimination reactions.

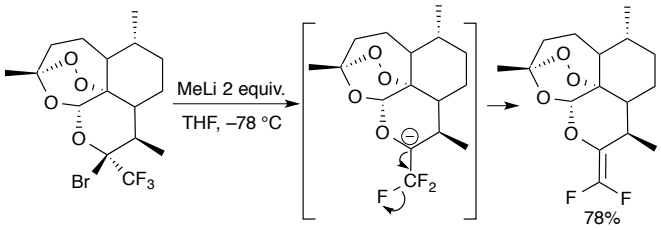
The zinc-mediated reduction of 1-halo-2,2,2-trifluoroethyl ethers can trigger a fluoride-elimination reaction to afford a difluoroenol ether. This approach was first reported by Shi using substrate **53**, obtained by chlorination of trifluoropyruvate benzyl hemiketal.[62] The reduction of **53** using zinc powder in DMF afforded difluoroacrylate **54** in 85% yield (Scheme 44). More recently, Chen demonstrated that unactivated ethers such as **55** could undergo the same transformation to afford aryl difluoroenol ethers **56** in high yields (Scheme 45).[63] Aryl ethers **55** were obtained by a copper mediated cross-coupling reaction between the corresponding phenol and 2,2-dichloro-1,1,1-trifluoroethane (HCFC-123). An halogen/lithium exchange reaction can be performed instead of a zinc-mediated reduction, as demonstrated by Bégué and Bonnet-Delpon in the synthesis of fluoro-artemisinins (Scheme 46).[64]



Scheme 44



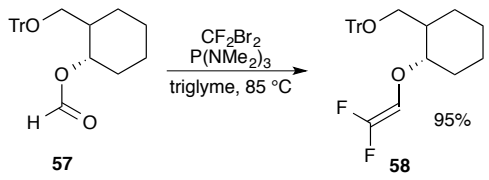
Scheme 45



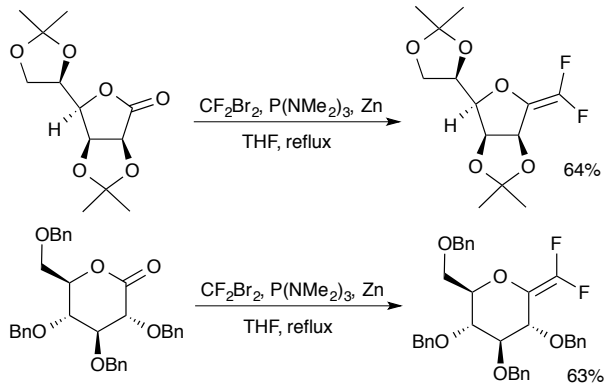
Scheme 46

II.4 Olefination reactions

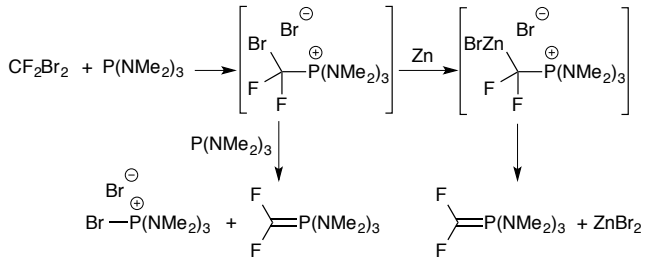
Similarly to the nonfluorinated series, fluoroolefination reactions of esters and lactones to produce fluorinated enol ethers are less documented than the reaction with more reactive aldehydes or ketones.[65] Regarding difluoromethylenation reactions, all existing methods derive from the pioneering work of Burton based on the use of dibromodifluoromethane in the presence of triphenylphosphine or *tris*(dimethylamino)phosphine (HMPT), presumably to generate *in situ* a phosphorus ylide.[66] The first application of this difluoromethylenation method to an ester was reported by Fried.[67] Difluoroenol ether **58** was obtained in very high yield from formate **57** (Scheme 47). Afterwards, this reaction was mainly applied to the preparation of difluorinated *exo*-glycals, as in Motherwell's studies concerning the synthesis of difluorinated *C*-glycosides (Scheme 48).[68] This group introduced a modified procedure using zinc as an additional reagent to reduce the amount of HMPT. Indeed, according to the authors, zinc acts as a reducing agent to debrominate the intermediate phosphonium salt and generate the ylide, a step which is usually effected by a second equivalent of HMPT (Scheme 49). The original reaction was also successfully used by Sinaÿ and Sollogoub on sugar lactones (Scheme 50).[69,70]



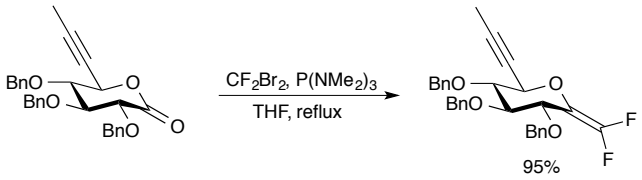
Scheme 47



Scheme 48



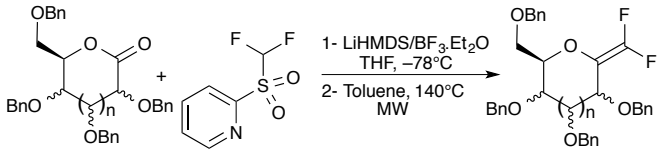
Scheme 49



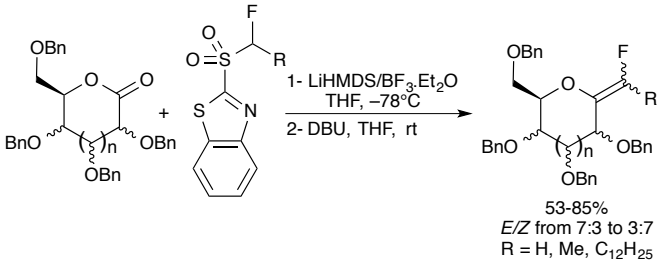
Scheme 50

A Julia-Kociensky difluoromethylenation reaction was recently devised by Gueyrard.[71] Difluoromethyl-2-pyridyl sulfone was prepared in three steps and 29% overall yield and was added to glyconolactones in the presence of LiHMDS and $BF_3.Et_2O$. The subsequent Smiles rearrangement was not effective under standard basic conditions and had to be performed under acid or neutral conditions, preferentially under microwave irradiation (Scheme 51). The Julia-Kociensky reaction was also effective for the preparation of monofluorinated *exo*-glycals.[72] 2-Benzothiazolyl fluoroalkyl sulfones were condensed to a wide range of glyconolactones to afford the corresponding *exo*-glycals in good yields but with a moderate, and hardly predictable, *E*/*Z* selectivity (Scheme 52).

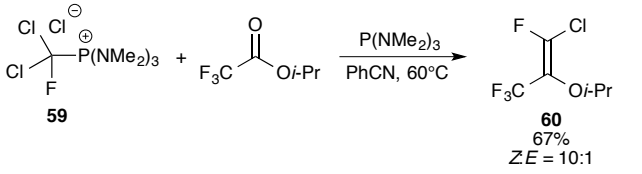
The chlorofluoromethylenation of carbonyl compounds was also studied by Burton.[73] The reaction of *iso*-propyl trifluoroacetate with phosphonium salt **59** afforded chlorofluoroenol ether **60** in 67% yield and with a surprising 10:1 selectivity in favor of the *Z* isomer (Scheme 53). Burton also developed an ethoxycarbonylfluoromethylene phosphonium ylide that can react with activated esters (such as ethyl formate or perfluorinated esters) to afford the corresponding 3-ethoxy-2-fluoroacrylates in fair yields and substantial *E* selectivity.[74]



Scheme 51



Scheme 52

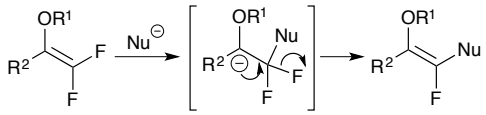


Scheme 53

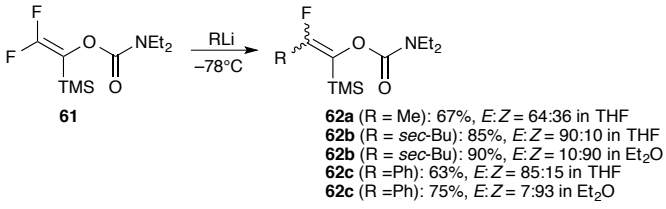
II.5 Synthesis from other fluorinated enol ethers

II.5.1 Monofluorinated enol ethers from difluorinated ones

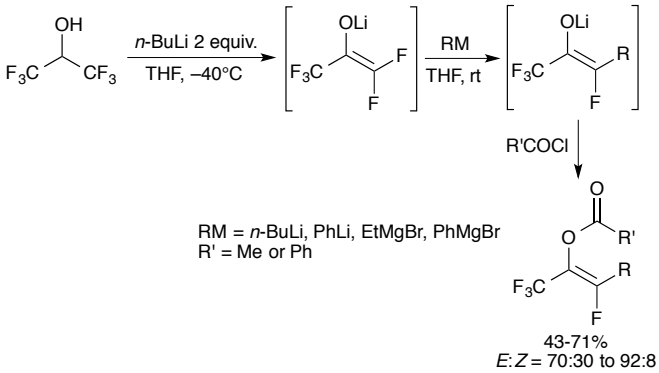
Difluorinated enol ethers have an ambident reactivity: they can of course act as nucleophiles but the high electron-withdrawing ability of the two fluorine atoms makes them suitable electrophiles. The addition of nucleophiles at the difluorinated carbon generally results in the subsequent fluoride elimination that provides the corresponding functionalized monofluoroenol ether (Scheme 54). The addition of organolithium compounds to difluoroenol carbamate **61** was for example reported by Snieckus.[31] If the addition of MeLi was weakly selective, *sec*-BuLi and PhLi led to the *E* isomer when the reaction was performed in THF while the *Z* isomer was obtained in Et_2O (Scheme 55).



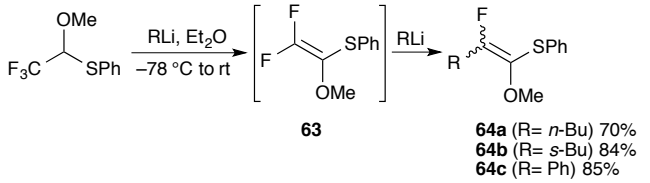
Scheme 54



Scheme 55



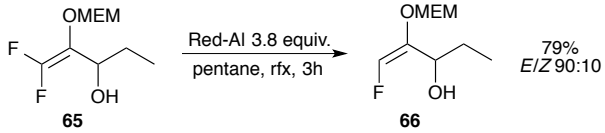
Scheme 56



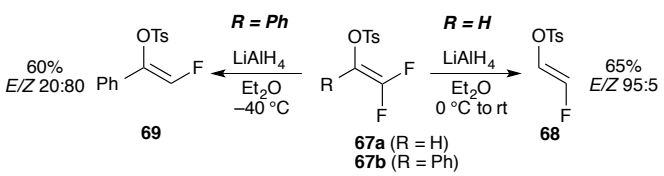
Scheme 57

The addition of organolithium compounds had previously been performed on difluoroenol intermediates generated *in situ* and not isolated. The reaction of the lithium perfluoroenolate derived from HFIP with *n*-BuLi, PhLi or Grignard reagents is noteworthy (Scheme 56).[27d] Similarly, difluoroenol ether **63**, prepared in situ from the corresponding trifluoroethyl ether, led to monofluorinated compounds **64** in good yields but of unknown configuration (Scheme 57).[75]

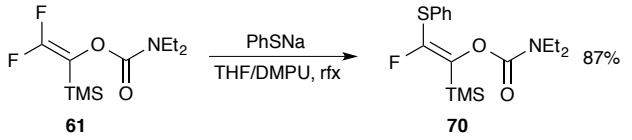
The addition of aluminium hydride reagents can lead to a clean defluorination reaction as demonstrated by Percy and more recently by Hong.[76,77] The reaction reported by Percy afforded the corresponding monofluoroenol ether **66** as a 90:10 *E*:*Z* mixture from **65** (Scheme 58). The case of enol tosylates **67** is more complicated : **68** was obtained from unsubstituted subtrate **67a** almost exclusively as its *E* isomer while **69** was obtained predominantly as its *Z* isomer when the reaction was performed on phenyl-substituted substrate **67b** (Scheme 59).



Scheme 58



Scheme 59



Scheme 60

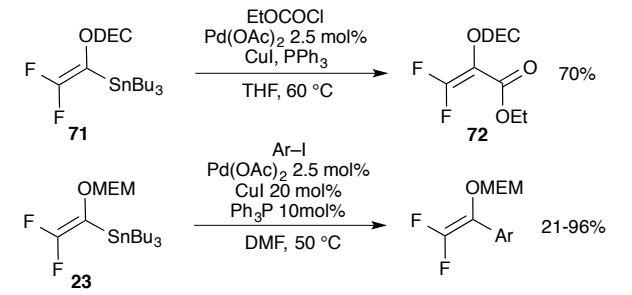
The addition of soft nucleophiles was also reported. Cuprate reagents were, for example, added to 1-alkoxy-2,2-difluoroacrylates.[62,78] The addition of thiophenolate to difluoroenol carbamate **61** was also described by Percy, affording compound **70** in 87% yield and as a single *E* isomer (Scheme 60).[79] The addition of sodium phenoxide to aryl perfluoroenol ethers was recently published.[44l]

II.5.2 Cross-coupling reactions of functionalized fluoroenol ethers

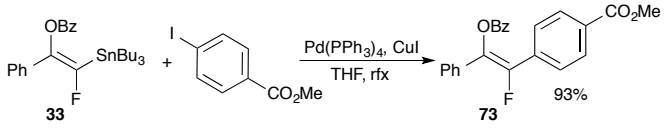
As seen in section II.3.1, lithiated difluoroenol ethers, generated from trifluoroethyl ethers using an excess of base, can be trapped with various electrophiles such as trialkyltin halides, trialkylborates or iodine. The resulting difluoroenol ethers can act as substrates for cross-coupling reactions to allow further functionalization.

Percy often used tin derivatives in palladium-catalyzed reactions.[33,80,81] Ethoxycarbonylation reactions or Stille cross-couplings with aryl or vinyl iodide were for example reported with substrates **23** and **71** (Scheme 61).[80,81] Although prepared in a different way (see section II.3.1), tin derivative **33** could also be coupled with an aryl iodide under similar conditions to afford monofluoroenol ether **73** in high yield (Scheme 62).[41b]

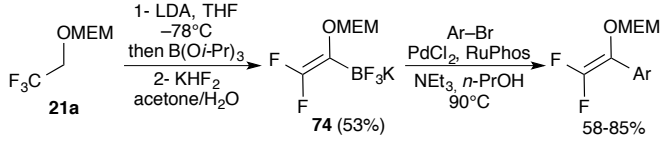
The preparation of tetrafluoroborate salt **74** in two steps from MEM trifluoroethyl ether **21a** was described by Katz and this intermediate was efficiently coupled with various aromatic bromides (Scheme 63).[34]



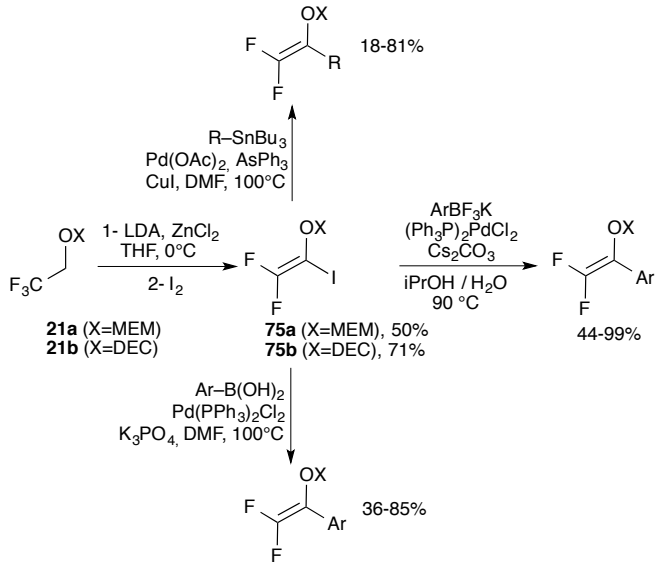
Scheme 61



Scheme 62



Scheme 63



Scheme 64

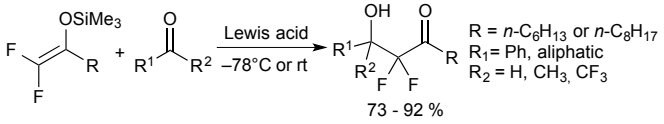
Percy also demonstrated that iodo derivatives **75** could be engaged in various cross coupling reactions with a wide range of tin derivatives, boronic acids and potassium trifluoroborate salts (Scheme 64).[35,81a] Compounds **75** were obtained from the corresponding trifluoromethyl ether **21** by elimination, metallation, transmetallation to zinc and iodolysis. It should be mentioned that the difluorovinylzinc intermediate was also directly engaged in Negishi-type reactions.[82]

III. Reactivity

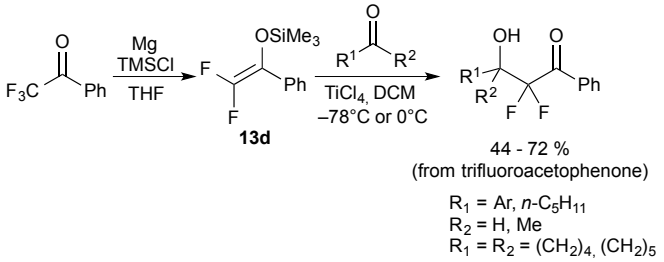
III.1 Fluorinated enol ethers as nucleophiles

III.1.1 Aldol, Mannich, Michael reactions and related transformations

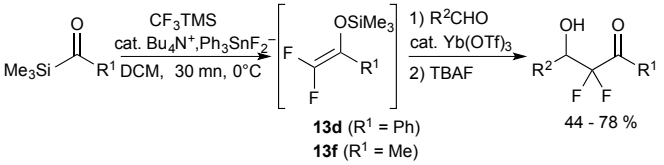
Mukaiyama aldol reactions. The first example of a Mukaiyama aldol reaction with a fluorinated enol ether was reported by Ishihara in 1983.[12] The difluoroenoxysilanes were generated from the corresponding chlorodifluoromethylketone and added to several aldehydes and ketones. Unfortunately, if some yields were given, the nature of the Lewis acid was not indicated and no precise reaction conditions were described (Scheme 65). This reaction was, later on, more accurately described by Uneyama and Welch.[22a] Compound **13d**, obtained by Mg-mediated reduction of trifluoroacetophenone, was added to aldehydes and ketones in the presence of $TiCl_4$, affording the corresponding aldols in moderate to good yields (Scheme 66). It should be mentioned that the corresponding dimethylphenysilyl and *tert*-butydiphenylsilyl enol ethers led to decreased yields under the same conditions.[51] In their seminal paper reporting the preparation of a difluoroenoxysilane from an acylsilane and Ruppert-Prakash reagent, Portella et al. described a similar $TiCl_4$-mediated aldol reaction.[50] In a following report, they demonstrated that stoichiometric amounts of $TiCl_4$ and $BF_3.Et_2O$ could efficiently be replaced by a catalytic amount of $Yb(OTf)_3$ (Scheme 67).[83]



Scheme 65



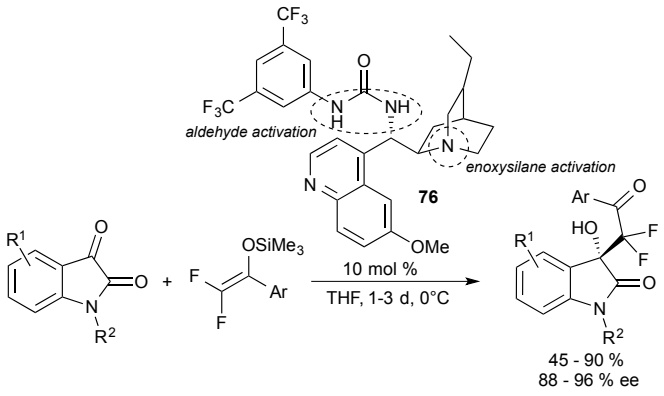
Scheme 66



Scheme 67

The BF_3•Et_2O-promoted addition of a difluoroenoxysilane (generated according to Uneyama's methodology) to an artemisin-related aldehyde was also used in a synthesis of fluoroartemisinin reported by Bégué and Bonnet-Delpon.[84] Methyl difluoroenol ethers were used in one instance in the Lewis acid-promoted addition to aldehydes.[85]

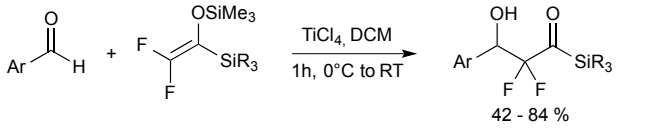
Zhou et al. recently reported a catalytic asymmetric addition reaction of difluoroenoxysilanes to isatins. Cinchonin-derived urea **76** efficiently catalyzed this reaction, affording the corresponding adducts in good yields and high ee's (Scheme 68).[86] **76** presumably acts as a dual catalyst, activating isatins through H-bonding from the urea moiety and triggering the addition of the enoxysilane thanks to a Lewis base-type interaction. A fluoride activation of a difluoroenoxysilane to promote its addition onto aldehydes was also reported.[49]



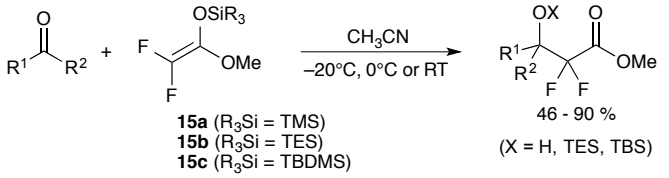
Scheme 68

Beside ketone-derived difluoroenoxysilanes, other difluorinated enol ethers were used as nucleophiles. β-Hydroxy-α,α-difluoroacylsilanes were as well prepared through a $TiCl_4$-mediated addition of the corresponding enoxysilane to aldehydes (Scheme 69).[87]

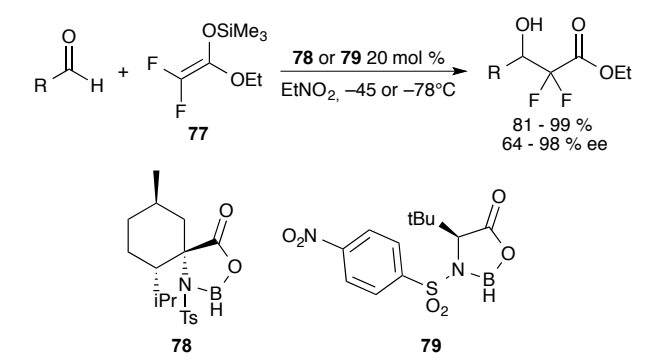
Many examples of aldol reaction starting from difluoroketene silyl acetals were also reported, starting with the work of Kobayashi.[13] The nucleophiles were prepared *in situ* from the corresponding iodofluoroacetate under Reformatsky conditions and reacted with aldehydes or ketones to afford the corresponding aldols in fair to good yields (scheme 70). The zinc salts generated during the preparation of the difluoroketene silyl acetal were suspected to promote the Mukaiyama aldol reaction. The removal of these zinc salts by successive precipitations with pentane followed by distillation of the enoxysilane enabled the development of a catalytic asymmetric version. Indeed, Masamune's catalyst **78** efficiently promoted the addition of salt-free difluoroketene trimethylsilyl ethyl acetal **77** to a wide range of aromatic and aliphatic aldehydes in high yields and ee's (Scheme 71).[88] Warming up the reaction at –45°C resulted in a reversal of the enantioselectivity, a switch that was also observed with the bromofluoroketene silyl acetal addition (see below). An open transition state for the –78°C reaction and a cyclic chair-like transition state for the –45°C reaction were also postulated to explain this feature.



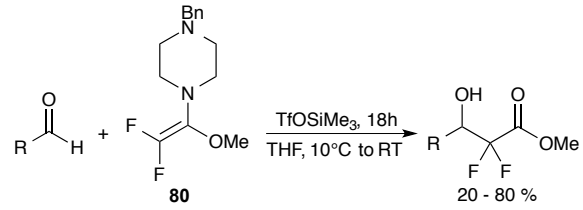
Scheme 69



Scheme 70



Scheme 71

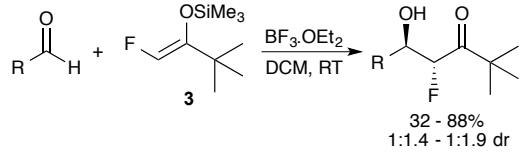


Scheme 72

Difluoroketene hemiaminal **80** derived from a trifluoroacetamide was also added, under $TfOSiMe_3$, catalysis to a small range of aromatic and aliphatic aldehydes (Scheme 72).[40]

Monofluorinated enol ethers were also used as nucleophiles in Mukaiyama aldol reactions. Welch reported the addition of silyl enol ether **3** derived from 3,3-dimethyl-1-fluorobutan-2-one to benzaldehyde and various aliphatic aldehydes.[5a] In contrast with non-fluorinated enoxysilanes that were able to react at low temperature, the BF_3•Et_2O-mediated reaction occured only at room temperature. The yields were good but the diasteroselectivity of the reaction was reversed and reduced compared to the direct addition of the parent lithium enolate (Scheme 73). This unusual diastereoselectivity (Mukaiyama aldol reaction usually proceeds though an open transition state and lead to the *syn* aldol) deserves some comments. The lithium enolate was assigned as purely *Z* and its trapping with TMSCl afforded only one isomer. This was confirmed by the isolation of *syn* aldols with high selectivities from the lithium enolate reaction. The low *anti* selectivity observed in the Lewis acid-mediated reaction was, according to the authors, due to a secondary interaction between the *t*-Bu substituent and R which prevailed on the classical *gauche* interaction between R and F (Figure 3).

Much later, Yamamoto improved the diastereomeric ratios thanks to the "supersilyl" group strategy. Indeed, (*Z*)-enoxysilane **52**, obtained stereoselectively by a carbenoid rearrangement, was added to wide range of aromatic and aliphatic aldehydes.[59] The aldol reaction was catalyzed by $C_6F_5CHTf_2$ and provided the corresponding β-hydroxy-α-fluoroaldehydes in good yields and with high *anti* selectivities (Scheme 74).



Scheme 73

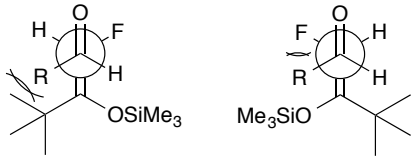
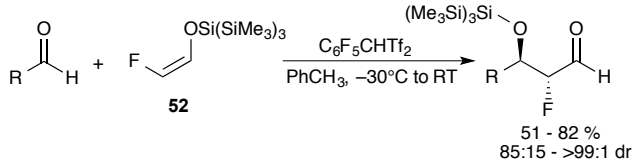
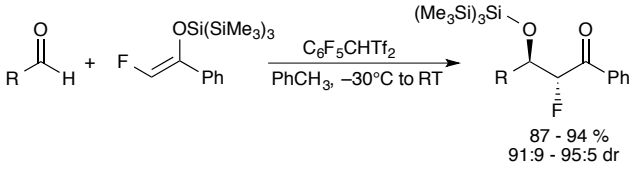


Figure 3



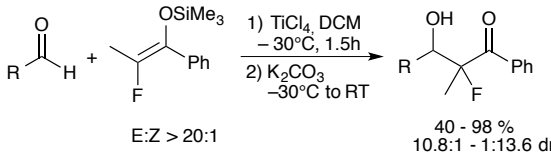
Scheme 74



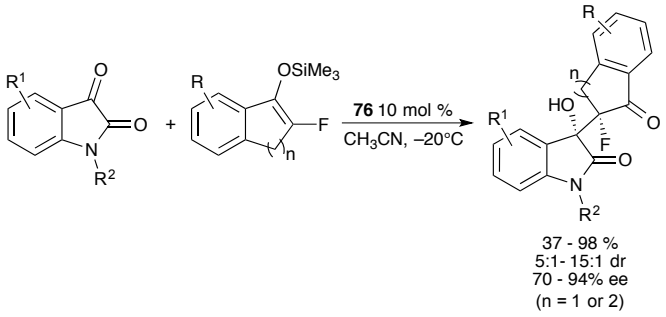
Scheme 75

The origin of this *anti* selectivity is not thoroughly elucidated, despite DFT calculations provided by the authors. This stereochemical outcome might even seem unexpected in light of the transition state postulated by Welch (Figure 3). β-Hydroxy-α-fluoroketones were also prepared with the same efficiency (Scheme 75).[89]

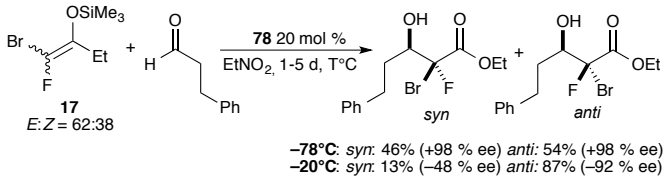
Other examples of monofluorinated aldols featuring a fluorinated quaternary stereogenic centre were also reported. Guo reported the $TiCl_4$-mediated addition of tetrasubstituted fluoroenoxysilane to aldehydes, which yielded the corresponding aldols in fair to good yields.[90] The diastereoselectivity outcome was, in contrast, unpredictable, with large variations and reversals caused by subtle structural changes (Scheme 76). A catalytic asymmetric addition of cyclic fluoroenoxysilanes to isatins was recently reported by Zhou, using a strategy similar to their work on difluoroenoxysilanes (scheme 68).[91] High enantio- and diastereoselectivities were reached and it should be mentioned that such catalysts are much less efficient with non-fluorinated silyl enol ethers (Scheme 77).



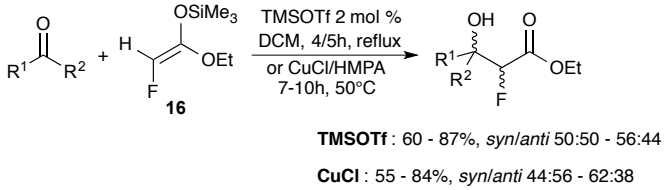
Scheme 76



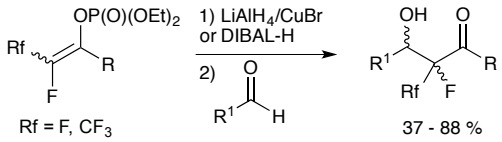
Scheme 77



Scheme 78



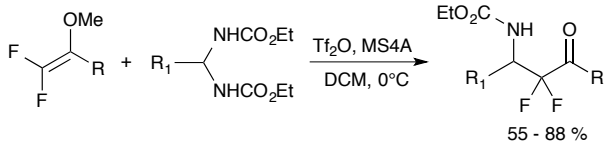
Scheme 79



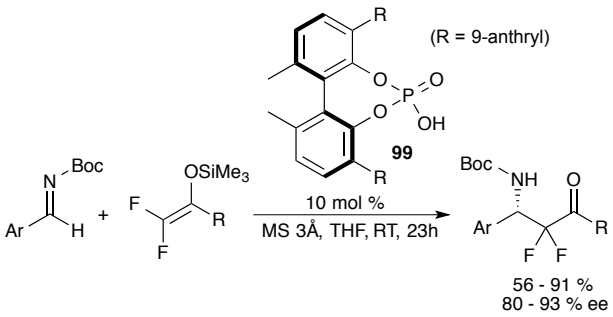
Scheme 80

An example of acyclic control to generate a fluorinated quaternary stereogenic centre was formerly reported by Iseki through the catalytic asymmetric Mukaiyama aldol reaction of bromofluoroketene silyl ethyl acetal **17**.[92] The initial reaction proceeded at –78°C with good level of enantioselectivity, using Masamune's catalyst **78**, but with little *syn*/*anti* selectivity.[15] Surprisingly, performing the reaction at –20°C not only led to an improvement of the diastereoselectivity but also to a reversal of the enantioselectivity. The authors suggested that a conversion of the silylenol ether to the boron enolate occured at –45°C, thus involving a closed Zimmerman-Traxler transition state as opposed to the open transition state hypothesized for the reaction at –78°C (Scheme 78).[92] Chen later on reported the Mukaiyama aldol reaction of monofluoroketene ethyl trimethylsilyl acetal **16**.[14] The reaction was catalyzed by TMSOTf and afforded the corresponding monofluorinated aldols in good yields but with no *syn*/*anti* selectivity (Scheme 79). Conversion of **16** to the copper enolate using CuCl in HMPA did not improve this selectivity. Ishihara had previously described the aldol reaction of fluorinated enolphosphates by generating *in situ* the corresponding copper or aluminium enolate (Scheme 80).[93]

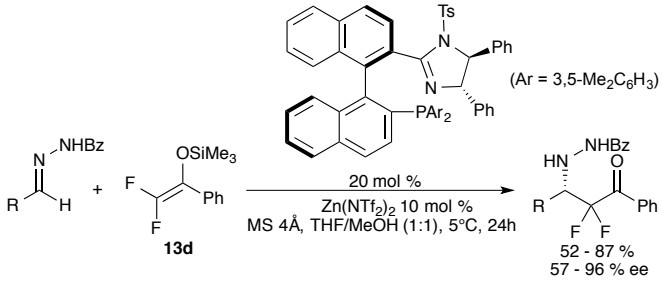
Mannich reactions. The addition of ketone-derived enoxysilane to iminium ions was first reported by Whitten.[94] The $AlCl_3$-mediated addition of a single enoxysilane to an α-chloroglycinate afforded the Mannich adduct in moderate yield. This iminium approach was later on used by Taguchi to perform the addition of a methyl difluoroenol ether. The triflic anhydride-mediated addition to aliphatic aminals afforded Mannich products in good yields (Scheme 81).[95]



Scheme 81



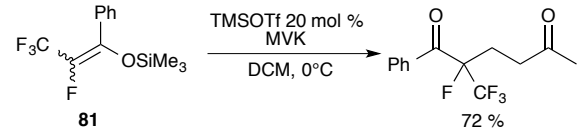
Scheme 82



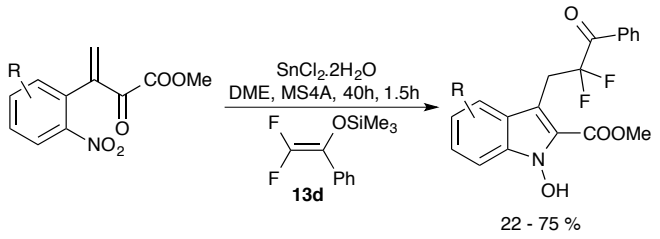
Scheme 83

Efforts have rapidly focused on the development of asymmetric Mannich reactions of ketone-derived difluoroenoxysilanes. Portella reported the addition of such nucleophiles to chiral imines or oxazolines in good yields and moderate diastereoselectivities.[96] A first attempt of catalytic enantioselective Mannich reaction was published by Shi in 2010, using a chiral Lewis acid as the catalyst but leading to low enantioselectivities.[97] Chiral phosphoric acid **99** was better suited to this purpose as demonstrated by Akiyama one year later.[98] The addition of ketone-derived difluoroenoxysilanes to a wide range of aromatic N-Boc aldimines afforded the corresponding β-amino-α,α-difluoroketones in good yields and high ee's (Scheme 82). The reaction was however totally unefficient with aliphatic aldimines. This drawback was partially addressed by Li using hydrazones as starting materials and a chiral zinc complex as the catalyst.[99] Aliphatic hydrazones were indeed suitable partners, although a decrease in yields and ee's was observed (Scheme 83).

Michael and S_N2' reactions. The Michael addition of fluorinated enoxysilanes was first investigated by Taguchi using difluoroketene silyl acetal **15a** and **15b** and various acceptors.[100] If a clean 1,4-addition was observed with cyclohexenone and, of course, with an enamide and a nitroolefin, mixtures of 1,2- and 1,4-adducts were observed for acyclic enones and enals.



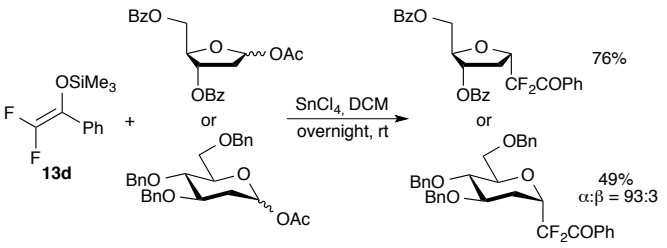
Scheme 84



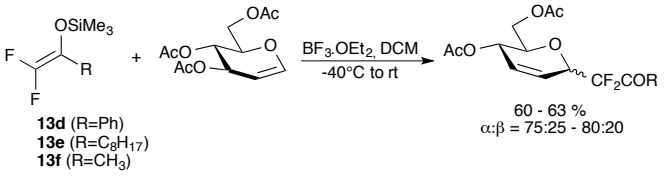
Scheme 85

Later on, Portella et al reported the clean addition of enoxysilane **81** to methylvinylketone (MVK, scheme 84).[101] Nicolaou also reported the Michael addition of various enoxysilanes, including fluorinated ones such as **13d**, to an *in situ* generated nitrone (Scheme 85).[102]

Miscellaneous addition reactions. Acylsilanes were also used as electrophiles for the Lewis acid-mediated addition of fluorinated enol ethers.[103] The use of acyl chlorides was also reported, first by Iseki using difluoroketene ethyl trimethylsilyl acetal **77** and then by Langlois using his piperazine-derived difluoroketene hemi-aminal **80**.[40,104] The addition to acetals was more widely investigated. Portella first reported the $SnCl_4$-promoted addition of difluoroenoxysilane **13d** to various glycosyl donors.[105] The results were however disappointing since the addition did not occur at C-1 as desired. The expected regioselectivity was observed only for 2-deoxyglycosyl donors or for glycals (Scheme 86 and 87). Artemisinin-derived acetals were also successfully used for such glycosylation-type reactions.[106]

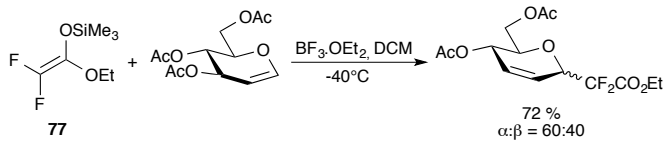


Scheme 86

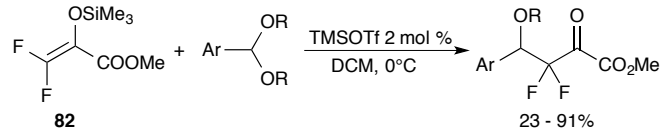


13d (R=Ph)
13e (R=C_8H_{17})
13f (R=CH_3)

Scheme 87

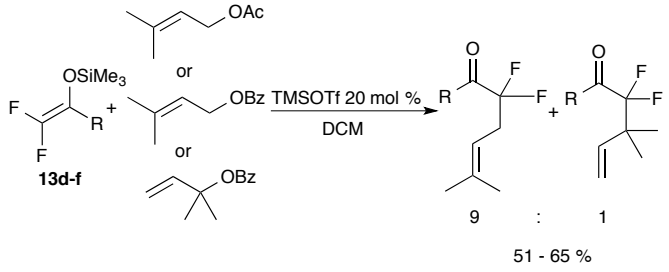


Scheme 88

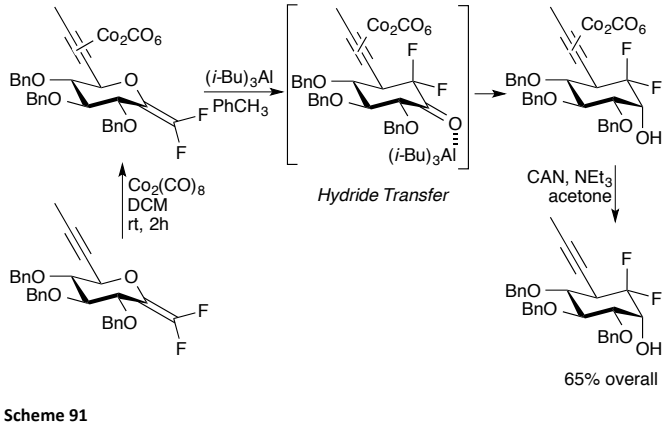


Scheme 89

A similar procedure was used by Leclerc for the addition of difluoroketene ethyl trimethylsilyl acetals to tri-*O*-acetylglucal (Scheme 88).[107] The addition of 2,2-difluoro-1-trimethylsilyloxyacrylate **82** to aldehyde-derived methyl acetals was also reported by Shi and Uneyama (Scheme 89).[108] Nucleophilic substitution reactions were also investigated, mostly using "activated" electrophiles. Portella reported the addition of difluoroenoxysilanes **13d-f** to a benzylic bromide or to prenyl donors. In the latter case, it is worth mentioning that, whatever the prenyl donor, the expected compound was always accompanied by the same amount of its regioisomer (Scheme 90).[109] Fluorinated carbasugars were prepared by Sollogoub et al using a sugar-to-carbocycle rearrangement, based on an intramolecular Nicholas reaction (Scheme 91).[69]



Scheme 90

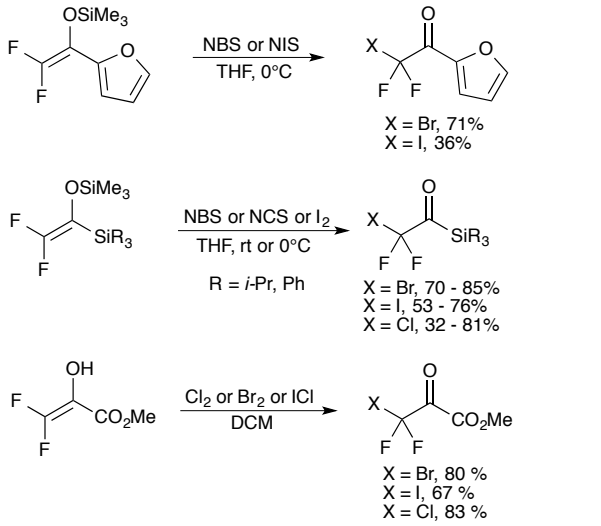


Scheme 91

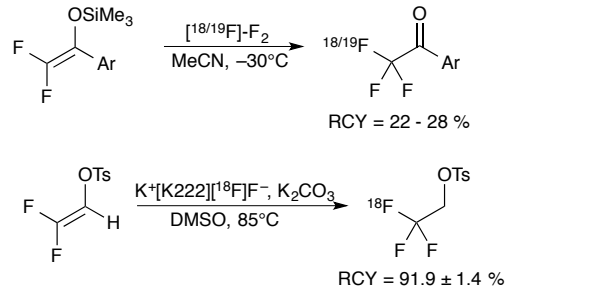
III.1.2 Halogenation reactions

Halogenation reactions of fluorinated enol ethers might appear as a degenerative process since the substrates are often obtained from trihalogenated compounds. However, the bromination or iodination reactions of difluoroenol ethers obtained from trifluoromethyl derivatives allowed, in some cases, the formation of reactive and less accessible bromo- or iododifluoroacetyl derivatives from stable and readily available trifluoroethanol or trifluoroacetates (Scheme 92).[110]

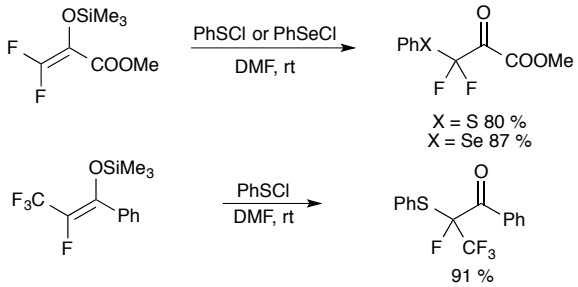
Fluorination reactions of fluorinated enol ethers demonstrated their utility in the radiosynthesis of [^{18}F]-labelled compounds (Scheme 93).[111] Addition of electrophilic sources of chalcogens were also reported, affording the corresponding α-thio or α-seleno difluorinated carbonyl compounds (Scheme 94).[22b,112]



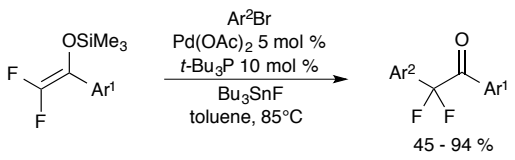
Scheme 92



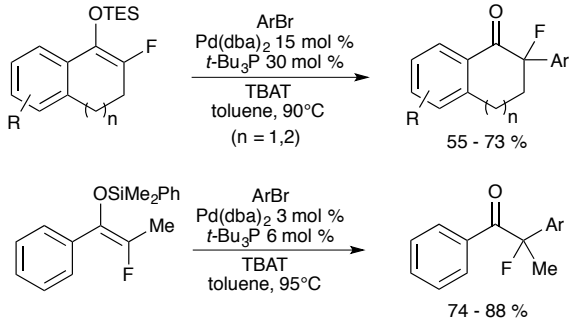
Scheme 93



Scheme 94



Scheme 95



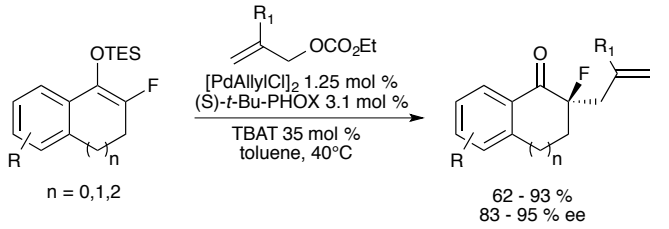
Scheme 96

III.1.3 Pd-catalyzed arylation and allylation reactions

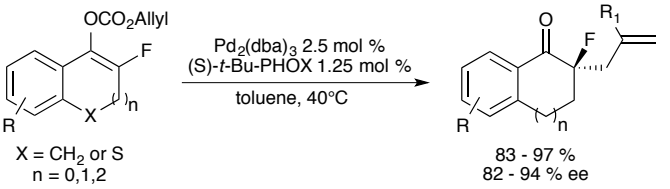
Cross-coupling reactions of substituted silyl enol ethers are a method of choice for the preparation of α-arylated carbonyl compounds.[113] This reaction was first applied to fluorinated enoxysilanes by Shreeve in 2007 and ketone-derived difluoroenoxysilanes underwent a clean cross-coupling reaction with aryl bromides. The yields of the resulting α-aryl-α,α-difluoroketones were high, with the exception of α-bromostyrene (Scheme 95).[114]

The same authors extended the methodology to monofluorinated enol ethers, first with cyclic substrates and then with acyclic ones. In the first case, TES-enol ethers and high catalyst loadings were mandatory for a successful reaction but acyclic enol ethers failed to react even under these conditions. The reaction with acyclic enoxysilanes was eventually successful, provided a bulkier silicon group is used in order to slow down the hydrolysis of the substrate (Scheme 96).[115] Cross-coupling reactions affording α-aryl-α,α-difluoroamides, but starting from the corresponding C-silylated α-trimethylsilyl-α,α-difluoroacetamide, were recently reported by Amii and Hartwig.[116]

Finally, Paquin reported an asymmetric Pd-catalyzed allylation reaction of cyclic monofluorinated enol ethers which provided α-allyl-α,α-difluoroketones in high yield and enantioselectivities (Scheme 97).[117] A similar catalytic system allowed the intramolecular allylation reaction of allyl fluoroenol carbonates to proceed with high enantioselectivities (Scheme 98).[118] It is worth mentioning that the latter reaction required a ligand/metal ratio smaller than 1 to achieve high ee's, while the previous intermolecular version did not depend on this parameter. Acyclic substrates could undergo both reactions but with only poor enantioselectivities. A reaction with acyclic substrates, but starting directly from α-fluoroketones, was recently reported by Chen and Guo.[119]



Scheme 97

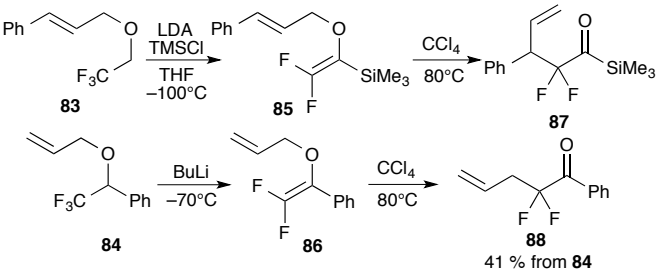


Scheme 98

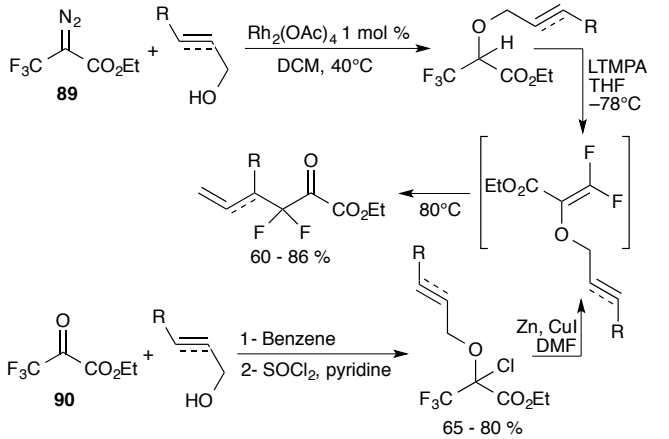
III.2 Pericyclic reactions

III.2.1 [3,3]-Sigmatropic rearrangements

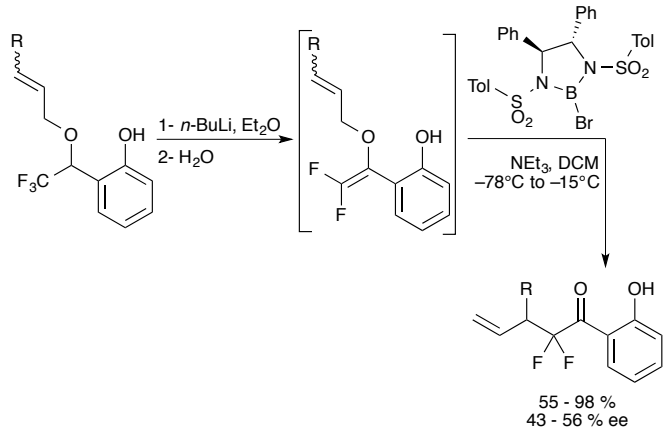
Difluorovinyl allyl ethers. The first [3,3]-rearrangement of a fluorovinyl allyl ether was reported by Metcalf in 1985.[28] Trifluoroethyl allyl ethers **83** and **84** were converted to intermediates **85** and **86** which, upon heating at 80°C, underwent a Claisen rearrangement to afford **87** and **88** (Scheme 99). A similar strategy, using a trifluorovinyl allyl ether and leading to a final acylfluoride, was used by Gelb in a synthesis of phospholipid analogues.[120]



Scheme 99



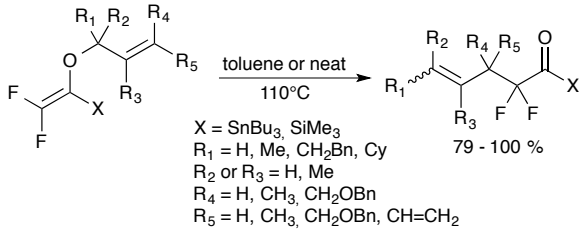
Scheme 100



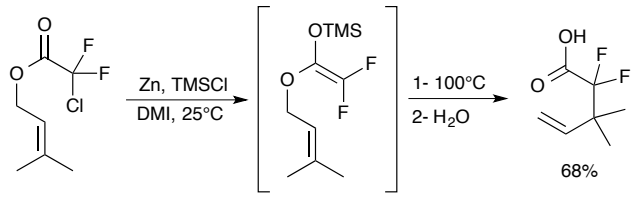
Scheme 101

Shi and co-workers developped an efficient [3,3]-rearrangement of 2,2-difluoro-1-allyloxyacrylates, that were first prepared from trifluoromethyldiazoacetate **89** then from ethyl trifluoropyruvate **90**.[121] The addition of the corresponding alylic alcohols to either reagent indeed afforded a trifluorolactyl ether which, upon elimination and heating, led to Claisen rearrangement products in good yields (Scheme 100). It should be mentioned that these [3,3]-rearrangements occured at a lower temperature than what is required for their non-fluorinated counterparts. A greater stability of the sp^3-hybridized CF_2 group compared to the sp^2-hybridized CF_2 group was invoked to support this experimental feature.[122] An enantioselective Claisen rearrangement catalyzed by a chiral boron Lewis acid was reported by Taguchi.[123] The reaction afforded the corresponding α,α-difluoroketones in good yields and moderate enantioselectivities, which depended on the *Z* or *E* configuration of the double bond (Scheme 101). The catalyzed rearrangement occurs at temperatures below 0°C.

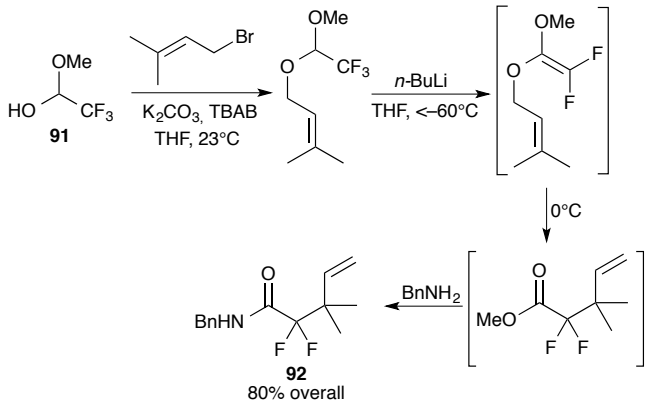
Percy reported the Claisen rearrangement of 2,2-difluoro-1-trimethylsilyl or 2,2-difluoro-1-tri(*n*-butyl)stannylvinyl allyl ethers, affording the corresponding acylsilanes and acylstannanes (Scheme 102).[124] The latter were afterwards converted to ketones using standard chemistry.



Scheme 102



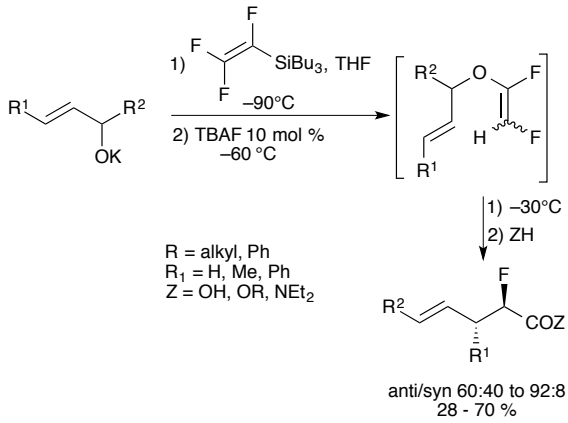
Scheme 103



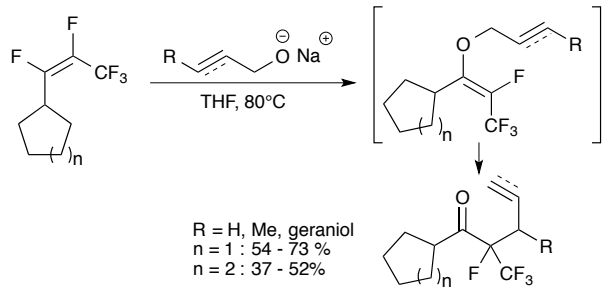
Scheme 104

Difluoroketene allyltrimethylsilyl acetals were also used in such rearrangements as illustrated by Chen in his synthesis of a difluoroproline (Scheme 103).[39] The sequence was improved with conditions more compatible with large-scale production. Trifluoroacetaldehyde methyl hemiacetal **91** was allylated and directly subjected to *n*-BuLi-mediated elimination, Claisen rearrangement by warming to 0°C and amidation. Amide **92** was obtained in a remarkable 80% overall yield (Scheme 104).[39]

In contrast, the [3,3]-rearrangement reactions of monofluorinated species were much less studied. A seminal but fragmentary study by Villieras was published in 1974.[125] Much later, Tellier reported the Claisen rearrangement of transient allyl 1,2-difluorovinyl ethers, affording the corresponding homoallylic fluorides in fair yields and good diastereoselectivities (Scheme 105).[126] A similar strategy was used by Sandford for fluorotrifluoromethylvinyl allyl ethers.[127] The latter were prepared by the regioselective and stereoselective addition of alkoxides to the corresponding perfluoroalkenes and spontaneously rearranged under the reaction conditions to provide the corresponding α-fluoro-α-trifluoromethylketones in moderate to good yields (Scheme 106).

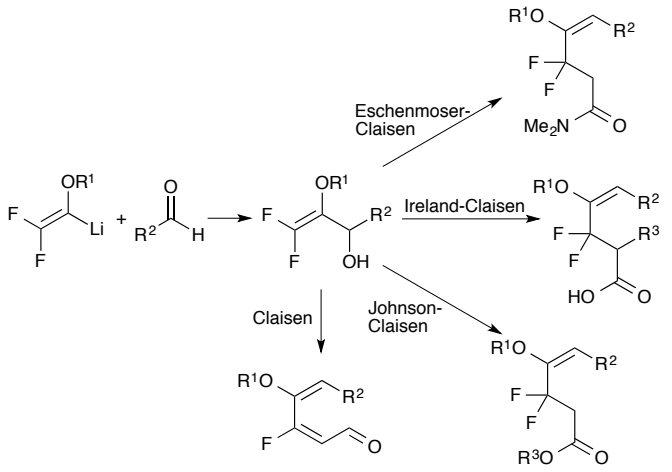


Scheme 105

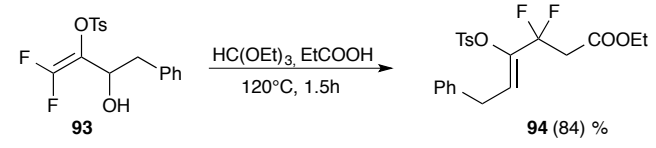


Scheme 106

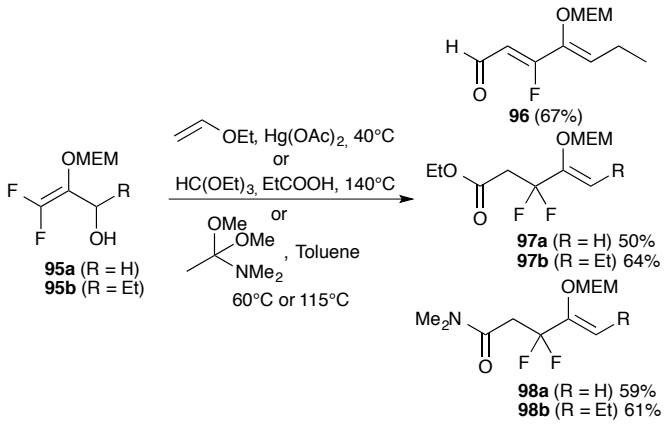
Difluoroallyl vinyl ethers. The addition of lithiated difluoroenol ethers to aldehydes provides 2-alkoxy-3,3-difluoroallylic alcohols that were used as precursors for Claisen, Johnson-Claisen, Eschenmoser-Claisen and Ireland-Claisen rearrangements (Scheme 107). Metcalf explored this approach using 2-alkoxy-3,3-difluoroallylic alcohol **93** that was subjected to a high yielding orthoacetate Claisen rearrangement (Scheme 108).[28] Percy extensively studied and performed all types of [3,3]-rearrangements to afford β,β-difluoroaldehydes, esters and amides from allylic alcohols **95**.[128] If Johnson and Eschenmoser modifications were efficient and provided compounds **97** and **98** in good yields, the standard Claisen conditions failed to afford the expected products. The reaction from unsubstituted derivative **95a** (R = H) stopped to the corresponding difluoroallyl vinyl ether while **95b** (R = Et) led to **96** after fluoride elimination from the Claisen rearrangement product (Scheme 109).



Scheme 107



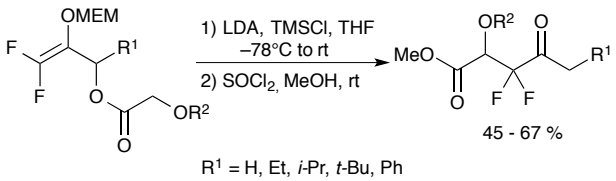
Scheme 108



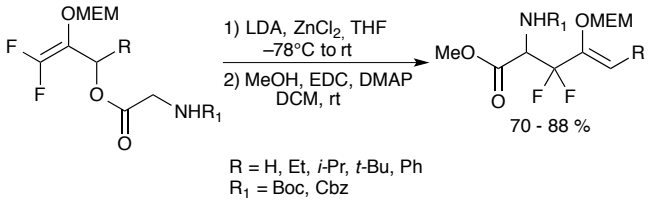
Scheme 109

The Ireland modification received more attention and α-alkoxy- and α-amino-β,β-difluoroesters were efficiently prepared through this method. If simple aliphatic esters failed to produce any rearrangement products due to the fragmentation of the corresponding enolate, α-alkoxy- and α-aminoesters underwent an efficient Ireland-Claisen rearrangement (Scheme 110 and 111). Methoxy or benzyloxyacetates were converted to the corresponding ketene silyl acetal which rearranged upon warming to room temperature (Scheme 110).[129] *N*-Boc and *N*-Cbz aminoacetates underwent the [3,3]-rearrangement using the Kazmaier modification of the reaction conditions (Scheme 111).[130] Another difference was that deprotected esters were directly isolated from α-alkoxyesters after esterification while the enol ether functionality could be retained when α-aminoesters were used as the substrates.

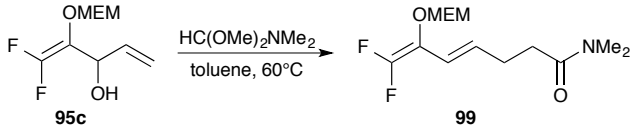
Percy et al demonstrated that, in contrast with 2,2-difluorovinyl allyl ethers, fluorine substitution of the allylic moiety (C-6) decreases the rate of the rearrangement. Indeed, substrate **95c** leads exclusively to product **99** which results from a Claisen rearrangement occuring only from the non-fluorinated terminus (Scheme 112).[129b]



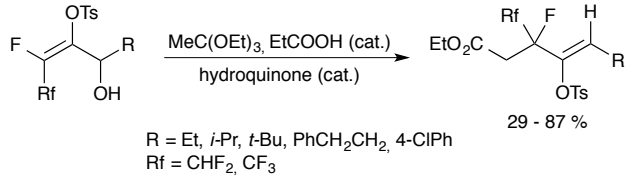
Scheme 110



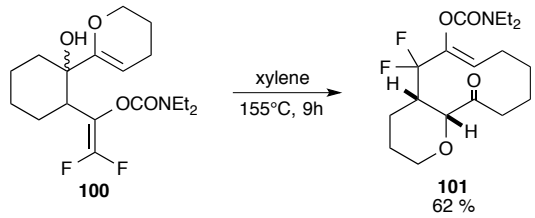
Scheme 111



Scheme 112



Scheme 113

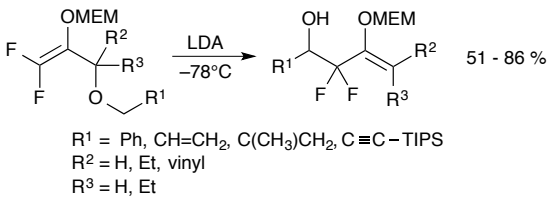


Scheme 114

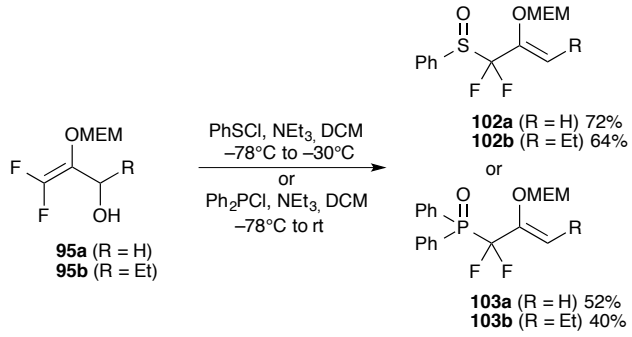
The Johnson-Claisen rearrangement of other highly fluorinated allylic alcohols was also reported by Funabiki (Scheme 113).[131] Finally, in a study of the oxy-Cope rearrangement of difluorinated dienes, Percy reported one example in which the difluroovinyl moiety is substituted by an oxygen atom.[132] This substrate **100** undergoes a clean rearrangement to produce cyclic ketone **101** in 84% yield (Scheme 114).

III.2.2 [2,3]-Sigmatropic rearrangements

Percy extended his work on Claisen-type rearrangements of 2-alkoxy-3,3-difluoroallylic alcohols to various [2,3]-sigmatropic rearrangements, from the classical Wittig rearrangement to sulfenate/sulfoxide and phosphinite/phosphine oxide transpositions. Allyl, benzyl or propargyl 3,3-difluoroallyl ethers underwent efficient [2,3]-Wittig rearrangement reactions under standard conditions to afford the corresponding difluorinated homoallylic alcohols (Scheme 115).[133] [2,3]-Rearrangement reactions of allylic sulfenates and phosphinites were also reported.[134] Starting from alcohols **95**, the formation of the corresponding sulfenate or phosphinite by reaction with phenyl sulfenyl chloride or chlorodiphenylphosphine led directly to the rearranged products **102** and **103** (Scheme 116).



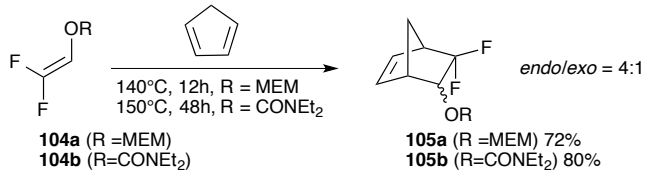
Scheme 115



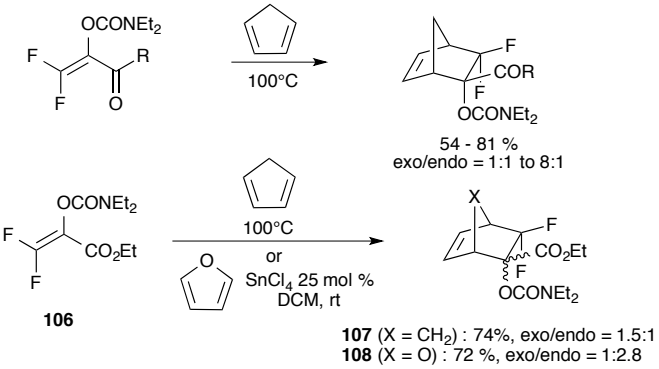
Scheme 116

III.2.3 [4+2]-Cycloaddition reactions

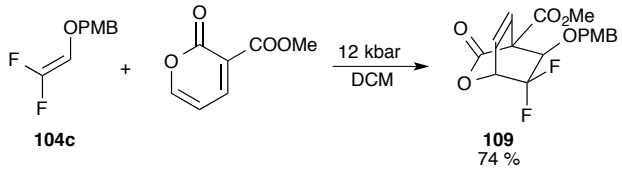
Fluorinated dienophiles. Fluorinated alkenes were long considered as unsuitable dienophiles for the Diels-Alder reaction. They usually undergo preferentially [2+2]-cycloadditions due to the ability of fluorine atoms to stabilize diradical intermediates.[135] Percy demonstrated that the introduction of an oxygen atom could restore the ability of difluoroolefins **104** to undergo a [4+2]-cycloaddition.[136] Cycloadducts **105** were obtained by reaction with cyclopentadiene in good yields (Scheme 117). The introduction of an electron-withdrawing group in 1-position is also possible, as illustrated by the successful Diels-Alder reaction between β,β-difluoro-α,β-unsaturated ketones or esters with various cyclic dienes (Scheme 118).[80,137] The last reaction was applied to the synthesis of difluorinated analogues of (hydroxymethyl)conduritol.[82a,138] DFT calculations allowed to rationalize the high reactivity of difluoroenoate **106** in the tin-catalyzed reaction with furan in comparaison to its non-fluorinated analogue.[139] As for [3,3]-rearrangement reactions, the higher stability of the sp^3-hybridized CF_2 group compared to the sp^2-hybridized CF_2 group is beneficial and, in that case, prevents the cycloreversion.



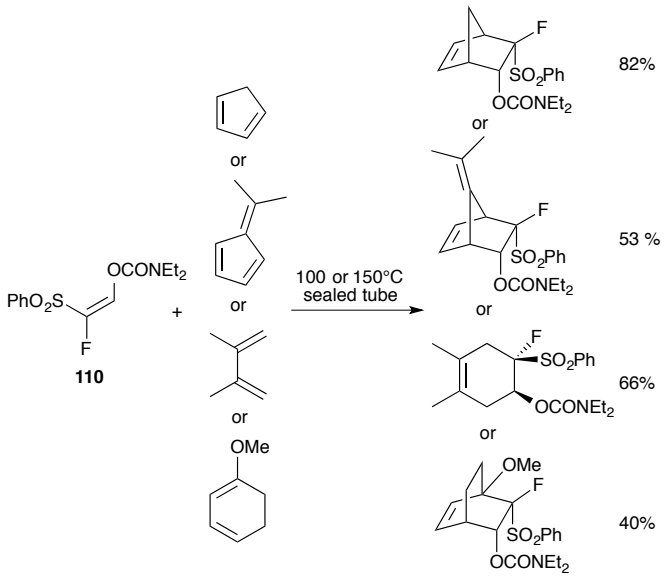
Scheme 117



Scheme 118



Scheme 119

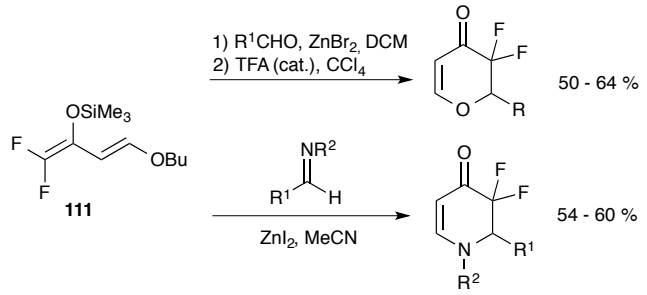


Scheme 120

Possner also reported the Diels-Alder reaction of **104c** with 3-methoxycarbonyl-2-pyrone under high pressure conditions (Scheme 119).[140]

Monofluorinated derivatives were also used as dienophiles as illustrated by the reaction of **110** with various dienes under thermal conditions.[79] Cycloadducts were obtained as mixtures of *endo*/*exo* isomers (Scheme 120).

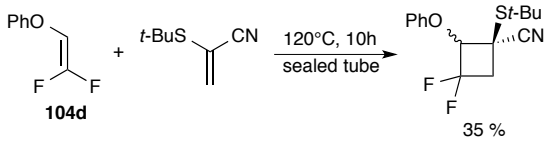
Fluorinated dienes. The reaction of difluorinated dienes with standard dienophiles and with aldehydes (hetero Diels-Alder reaction) was also investigated. Huang showed that the [2+2]-cycloaddition pathway was usually preferred with standard electron-poor dienophiles. The Diels-Alder cycloadduct was indeed isolated only on rare occasions.[141] In contrast, the reaction with heterodienophiles was fairly efficient, as first illustrated by the work of Taguchi with aldehydes.[142] Later on, Uneyama reported a similar [4+2]-cycloaddition between difluorinated **111** diene and aldehydes or imines (Scheme 121).[23] The reaction of some monofluorinated dienes with standard dienophiles was also reported,[143] as well a study by Ghosez on the [4+2]-cycloaddition of monofluorinated azadienes with aldehydes.[144]



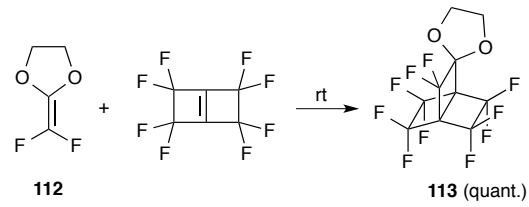
Scheme 121

III.2.4 [2+2]-Cycloaddition reactions

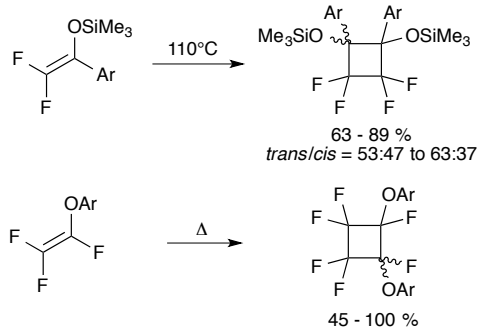
The [2+2]-cycloaddition reaction of fluoroolefins was investigated by Viehe.[145] Among the various "captodative olefins" that were studied and proved to be excellent partners for this reaction, difluoroenol ether **104d** was used in one instance (Scheme 122). A synthesis of a highly fluorinated [2.2.2]-propellane was based on a [2+2]-cycloaddition between difluoroketene acetal **112** and a strained perfluoroalkene.[146] The transformation was particularly easy since **113** was obtained in quantitative yield at room temperature. Even more surprising is the remarkable stability of this [2.2.2]-propellane which, according to the authors, was due to "the stabilizion of cyclobutane rings by fluorine substitution" (Scheme 123).[147] The cyclodimerization of difluoroenol ethers was also studied, first by Uneyama and later on by Smith (Scheme 124).[148,149]



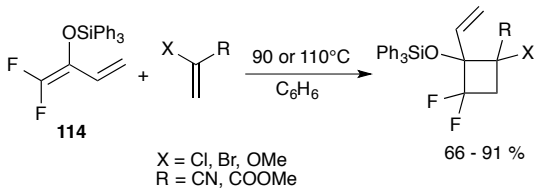
Scheme 122



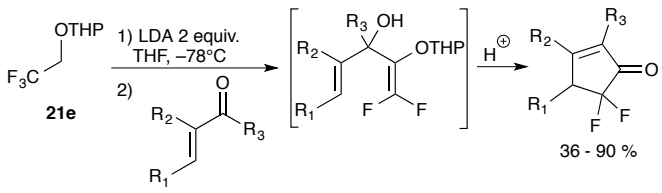
Scheme 123



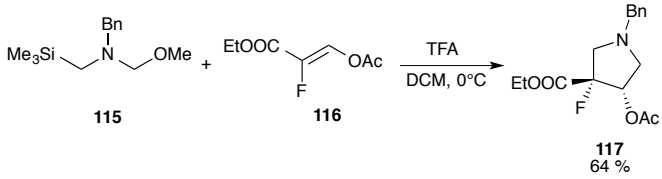
Scheme 124



Scheme 125



Scheme 126



Scheme 127

As mentioned above, Huang studied the reaction of difluorodiene **114** with various dienophiles. He showed that the reaction with acrylonitriles and acrylates led preferentially to [2+2]-cycloadducts, while quinones afforded Diels-Alder products and electron-poor alkynes produced mixtures of both (Scheme 125).[141] Finally, an intramolecular [2+2]-cycloaddition reaction between an alkyl fluoroenol ether and an internal aldehyde was also reported.[67]

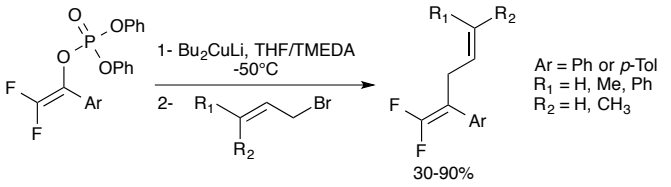
III.2.5 Miscellaneous pericyclic reactions

A 4π-electrocyclisation reaction of a difluorinated pentadienyl cation derived from a difluorinated *bis*-allylic alcohol was reported by Tius.[150] This postulated intermediate was obtained by addition of the lithiated difluoroenol ether derived from **21e** to α,β-unsaturated ketones and aldehydes and collapsed upon slightly acidic work-up through a Nazarov-like process. The resulting difluorocyclopentenones were obtained in moderate to high yields (Scheme 126). An example of 1,3-dipolar cycloaddition involving a fluorinated enol ether was also reported.[151] Monofluorinated enol ether **116** reacted with the ylide precursor **115** to afford fluorinated pyrrolidine **117** in fair yield (Scheme 127).

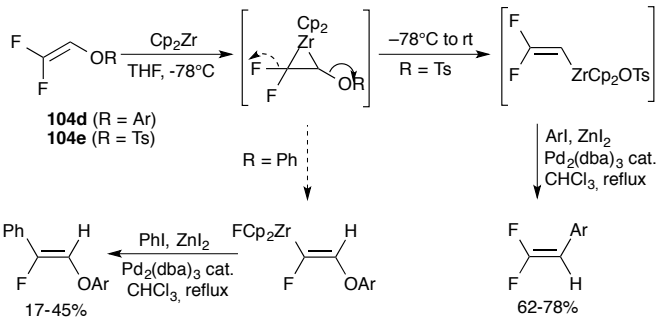
III.3 Conversion to fluoroolefins

Are gathered in this section all the reactions that convert a fluorinated enol ether into a standard fluoroolefin by replacing the C–O bond by a C–C or C–H bond.[63] The first reaction of this type was reported by Ishihara who demonstrated that difluoroenol phosphates could be allylated through the generation of a difluorovinylcopper species.[152] The difluoroolefins were obtained in moderate yields (Scheme 128). The scope of the reaction was however limited to fully aryl-substituted enolphosphates. The introduction of an alkyl group on the double bond or the use of a $P(O)(OEt)_2$ group resulted in fluorine substitution or in the deprotection of the enolphosphate. In contrast, the replacement of the aryl group by a diethylphosphonyl moiety led to a reduction reaction that provided the corresponding enephosphonate.[153]

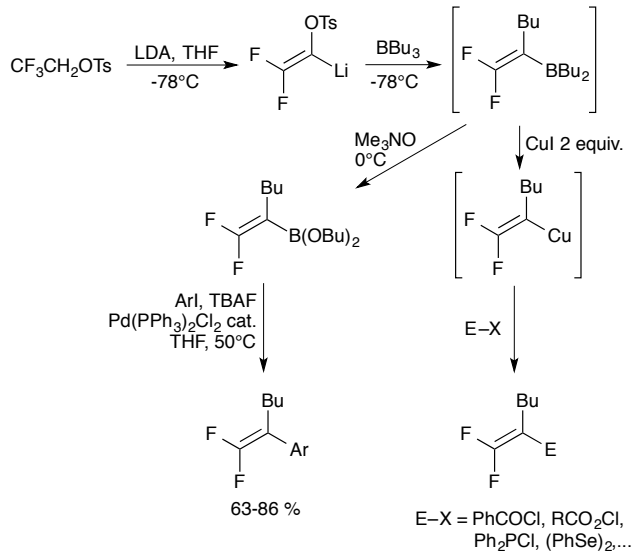
Ichikawa demonstrated that zirconocene was similarly able to convert difluoroenoltosylate **104e** to a difluorovinylzirconium species.[154] The latter was able to undergo cross-coupling reactions with aryl iodides, catalyzed by Pd(0) and promoted by zinc salts to ensure a Zr to Zn transmetallation (Scheme 129). Remarkably, starting from aryl difluoroenol ether **104d** in place of tosylate **104e** resulted in a different reaction pathway. A fluoride elimination indeed occured from the intermediate zirconacyclopropane to generate an α-fluorovinylzirconium species, and then a new monofluorinated enol ether after the coupling reaction. The same group had previously demonstrated that a difluorovinylboron species could also be obtained from metallated difluoroenol tosylate through a Matteson-type carbenoidic rearrangement.[155] After oxidation of the resulting vinylborane to the corresponding boronic ester, a Suzuki coupling afforded the corresponding difluoroolefins in good yields (Scheme 130). A more recent report demonstrated that this difluorovinylboron species could also be converted to the corresponding vinylcopper reagent and trapped with various electrophiles or coupled with alkyl halides (Scheme 130).[156]



Scheme 128

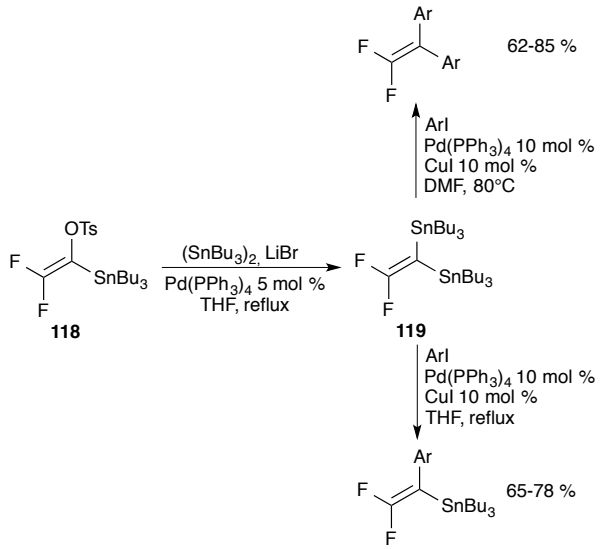


Scheme 129

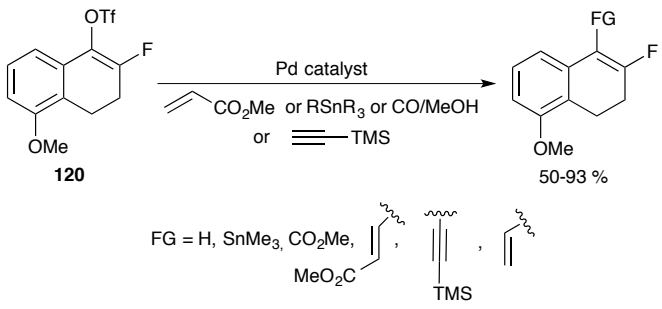


Scheme 130

More recently, *gem*-distannane **119** was prepared from stannylated difluoroenoltosylate **118**.[157] This intermediate could undergo either a direct, double cross-coupling reaction with an excess of aryl iodide, or a single cross-coupling reaction with one equivalent of reagent (Scheme 131).

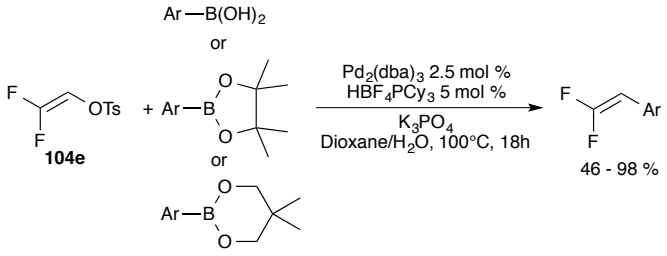


Scheme 131

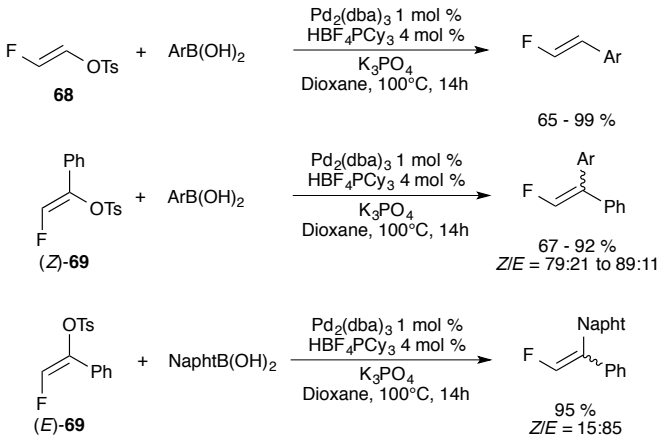


Scheme 132

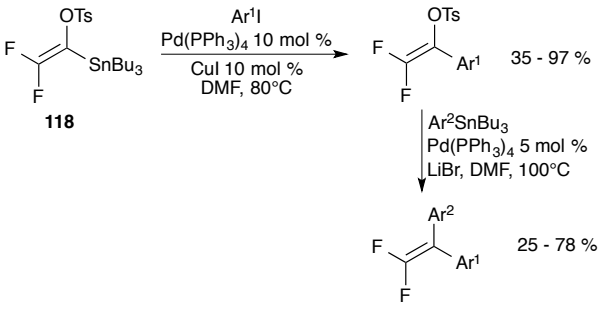
Conversion of the fluorinated enol ether to a vinylmetal or vinylmetalloid is not the only approach to cross-coupling reactions. The enol ether can also play the role of the electrophile in classical palladium-catalyzed reactions. Hossain reported Stille, Heck, Sonogashira and methoxycarbonylation reactions from fluoroenol triflate **120** (Scheme 132).[158] Much later, Skrydstrup reported a Suzuki coupling from difluoroenol tosylate **104e** which yielded efficiently the corresponding difluoroolefins (Scheme 133).[159] Shortly after, the monofluorinated version of this reaction was reported by Xiao and Hong.[77] While monofluorinated enol ether **68** was coupled to various arylboronic acids with perfect retention of the *E* configuration, trisubstituted substrates (*Z*)-**69** and (*E*)-**69** suffered from a slight loss of their stereochemical integrity through the reaction process (Scheme 134). Finally, Jeong demonstrated that stannylated difluoroenol tosylate **118** could undergo two successive Stille coupling reactions without conversion to the distannyl species (Scheme 135).[160]



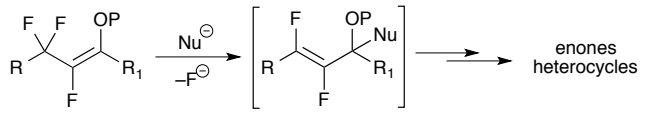
Scheme 133



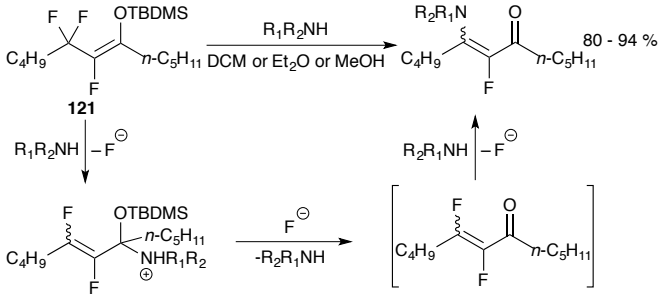
Scheme 134



Scheme 135



Scheme 136



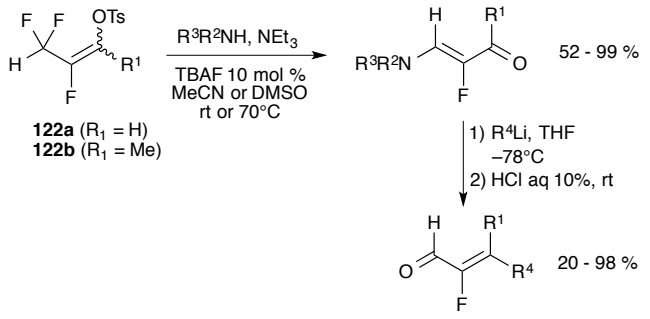
Scheme 137

III.4 Conversion to fluorinated enones and heterocycles

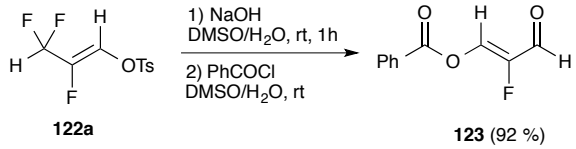
The presence of fluorine atoms and/or fluoroalkyl groups on the double bond of enol ethers ensures a certain degree of electrophilicity to species that are otherwise only nucleophilic. The consequence is that addition of nucleophiles to fluorinated enol ethers is possible, as illustrated by the numerous examples of addition of amines to enol ether featuring a perfluoroalkyl chain (Scheme 136). The latter reaction was exploited for enone and heterocycle synthesis though addition/elimination processes (Scheme 137).

Portella first reported the addition of secondary amines to **121** which resulted in the formation of the corresponding enaminones in good yields.[161] The reaction proceeded through a first addition of the amine at C–1 with elimination of fluoride via a S_N2' process, release of the ketone function by desilylation and finally a new addition of the amine at C–3.

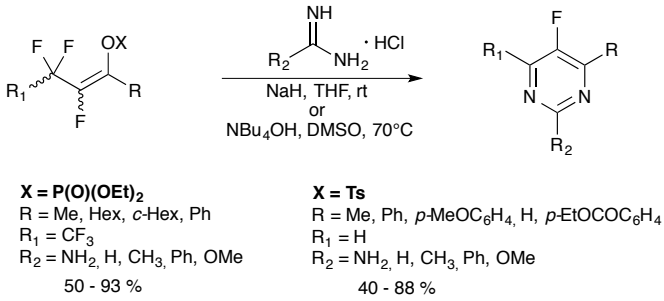
Following a similar process, Funabiki reported the conversion of fluoroenol tosylates **122** to enaminones and then α-fluoroenals (Scheme 138).[162] Conversion of a similar substrate to a fluorinated allylic alcohol by addition of a Grignard reagent was also reported by the same group.[163] The reaction of **122a** with sodium hydroxyde and trapping with benzoyl chloride afforded β-acyloxy-α-fluoroacrylaldehydes **123** (Scheme 139).[164] Addition of amidines to perfluoroenol phosphates or to fluoroenol tosylates resulted in the formation of pyrimidines in good yields (Scheme 140).[165]



Scheme 138



Scheme 139

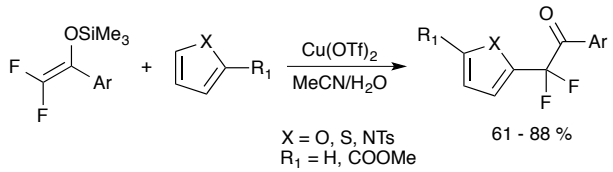


Scheme 140

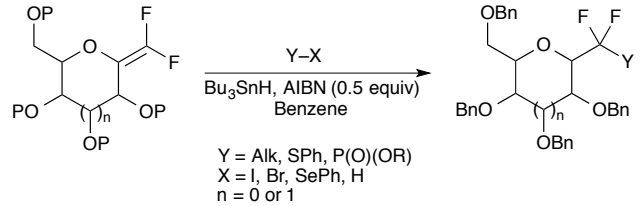
III.5 Miscellaneous applications

Other nucleophilic additions were reported, such as the conversion of a difluoroenoxysilane to an oxazolidine by addition of phenylglycinol reported by Portella.[166] Uneyama reported the oxidative addition of heteroaromatic compounds to difluoroenoxysilanes.[167] The reaction proceeded through oxidation of the latter to the corresponding radical cation, nucleophilic addition of the heteroaromatic and a final oxidation to deliver the corresponding arylated ketones in good yields (Scheme 141).

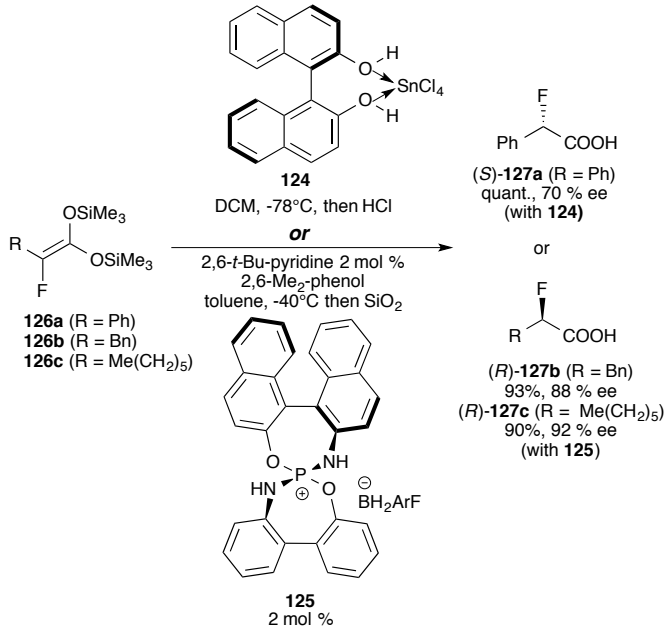
Radical additions to fluorinated enol ethers were also investigated and a remarkable example is the addition of a wide range of carbon or heteroatom-centered radicals to difluoromethylene *exo*-glycals (Scheme 142).[70,168]



Scheme 141



Scheme 142



Scheme 143

The hydrolysis of enol ethers provides of course the corresponding α-fluorocarbonyl compound.[21,169] This trivial transformation could however be performed in an asymmetric fashion through enantioselective protonation reactions of fluoroketene silyl acetals **126**, as pioneered by Yamamoto (Scheme 143, catalyst **124**).[170] Much later, Ooi improved the enantioselectivity of this reaction when **126** bears an alkyl substituent (Scheme 143, catalyst **125**).[171]

Lastly, a wide range of FEE were used as monomers in polymerization reactions based either on a [2+2]-cycloaddition reaction or on the nucleophilic addition of an alkoxide.[172]

Conclusions

As illustrated in the present review, fluorinated enol ethers are highly valuable building blocks for the preparation of complex fluorinated molecules. They exhibit a very versatile reactivity allowing a wide range of chemical transformations and giving access to a great molecular diversity through their synthetic elaboration. Due to the numerous methods summarized at the begining of the manuscript, almost any fluorinated enol ethers can be easily prepared from widely available fluorinated reagents, with the sole limitation of their intrisic stability. If both aspects are very well documented, these reagents still deserve to be investigated, especially in the field of asymmetric synthesis. Indeed, as one can notice from the present review, only few catalytic asymmetric reactions involving fluorinated enol ethers are reported. For that matter, the contrast with their non-fluorinated counterparts is striking and should encourage efforts in this direction.

Acknowledgements

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