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Fluorinated Enol Ethers: Synthesis and Reactivity

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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. 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. 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. 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. 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 covalently 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](image-url)
Scheme 1

\[
\begin{align*}
\text{1) LiHMDS, HMPA} & \quad \text{THF, } -78^\circ \text{C} \quad \text{2) TMSCl} \quad \text{THF, } -78^\circ \text{C} \\
\end{align*}
\]

yield not reported

Scheme 2

\[
\begin{align*}
\text{1) LiHMDS, HMPA} & \quad \text{THF, } -78^\circ \text{C} \quad \text{2) TMSCl 2.2 equiv.} \quad \text{THF, } -78^\circ \text{C} \\
\end{align*}
\]

Scheme 3

\[
\begin{align*}
\text{1) LiHMDS} & \quad \text{THF, } -78^\circ \text{C} \quad \text{2) R}_3\text{Si-Cl} \quad \text{THF, } -78^\circ \text{C} \\
\end{align*}
\]

Scheme 4

\[
\begin{align*}
\text{1) LDA, TMSCI 2.2 equiv.} & \quad \text{THF, } -78^\circ \text{C} \quad \text{2) TMSCl, LDA} \quad \text{THF, } -78^\circ \text{C} \\
\end{align*}
\]

Scheme 5

\[
\begin{align*}
\text{1) LiHMDS} & \quad \text{THF, } -78^\circ \text{C} \quad \text{2) TMSCI 2.2 equiv.} \quad \text{THF, } -78^\circ \text{C} \\
\end{align*}
\]

Scheme 6

\[
\begin{align*}
\text{1) LiHMDS} & \quad \text{THF, } -78^\circ \text{C} \quad \text{2) TMSCI 2.2 equiv.} \quad \text{THF, } -78^\circ \text{C} \\
\end{align*}
\]

LIHMDS in the presence of HMPA was used by Welch to deprotonate α-fluoroketone 1 and fluoroacetate 2. The resulting lithium enolate was trapped with TMSCI 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 TMSCI (Scheme 2). A similar approach provided tetrasubstituted silyl fluoroenol ethers that were isolated in good yields and with a high E selectivity (Scheme 3). 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. 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). 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). 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. 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. 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). 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 chlorodifluoroacetate has more recently been reported by Chen. 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). 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-sulfonyl or α-sulfonylcarbonyl compounds have also been used as precursors through triethylgermanate- or magnesium-mediated reduction processes.

The magnesium-mediated reduction of trifluoromethylketones is the second method of choice to produce difluoroenol ethers through a reduction/trapping process. 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. 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.
II.3 Elimination reactions

II.3.1 Base-mediated eliminations.

First investigated by Nakai and Ishikawa, the base-mediated elimination reaction of trifluoroethoxy ethers is a widespread method for the preparation of difluoroenol ethers and follows the general trend illustrated in scheme 17. This reaction was afterwards extensively applied to various trifluoroethanol (TFE) derivatives, substituted or not, featuring a wide range of substituents, from standard alkyl or aryl groups to carboxylate or tosylate functions. However, it should be mentioned that reactions with unsubstituted TFE ethers \( \text{(R=H)} \) required the use of an excess of base. Indeed, the vinylic proton is more acidic than the methylene protons and this results in the \textit{in situ} formation of difluoroalkylidenes. 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 difluoroethyl and tosyl enolate onto aldehydes and ketones.\textsuperscript{27b,27c,28}

Percy has afterwards extensively developed the reaction of lithium MEM difluoroenol ethers and difluoroenol carbamates with carbonyl compounds.\textsuperscript{29,30} Other electrophiles such as alkyl triflates,\textsuperscript{31} chlorotrialkylsilanes,\textsuperscript{28,29a,32} tributyltin chloride,\textsuperscript{34} trialkylborates,\textsuperscript{35} or iodine\textsuperscript{36} 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.\textsuperscript{29,30}

The elimination/metalation sequence from 21a followed by trapping with TMSCI or Bu<sub>3</sub>SnCl 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 iodosylmethylboronate was a particular case in which the intermediate \textit{ate}-complex directly led to allylboration 24 through a Matteson 1,2-rearrangement.\textsuperscript{36} 24 subsequently reacted with benzaldehyde to afford compound 25 in good overall yield from 21d (scheme 21).

\[ \text{Scheme 14} \]

\[ \text{Scheme 15} \]

\[ \text{Scheme 16} \]

An iterative process can also allow the formation of monofluorinated enoxysilanes as illustrated by the work of Prakash.\textsuperscript{22} Hydrolysis of the previous difluoroenoxysilane led to the corresponding difluoromethylketone that could undergo a second Mg-mediated reduction in the presence of TMSCI 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 fluoroenoxysilanes.\textsuperscript{22} This method has also been applied to the preparation of difluorinated Danishefsky's diene 18 from enone 17 (Scheme 15).\textsuperscript{23} This magnesium mediated-reduction applied to trifluoroacetates or trifluoroacetamides as substrates provided only C-silylation products.\textsuperscript{24} However, the electrophilic 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).\textsuperscript{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.\textsuperscript{26}

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The silylation of lithiated fluoroenol ethers is also possible and Welch has reported an interesting preparation of α-silylated difluoroenoxysilanes directly from trifluoroethanol. 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. 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).

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. 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 EtO. Other polyfluorinated enol tosylates have been prepared by Funabiki by n-Buli-mediated elimination of the corresponding tosylates. The preparation of difluoroacetone acetals or hemiaminals using a fluoride elimination reaction has been reported in only two cases.

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. 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 sulfynyl 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. 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 exoglycal has been reported, this time by elimination of a trifluoroacetate. Precursor 36, obtained by fluoroxyrydroxylation of the corresponding unsaturated compound, is directly converted to 37 in the presence of trifluoroacetic anhydride (TFAA) and DMAP (Scheme 27).
The addition/elimination sequence resulting from the reaction between fluoroolefins and alkoxides is a long known access to fluorinated enol ethers. The reaction often leads to α-silylated enol ethers 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 enol ethers 38 in good yields, while the same reaction with tetrafluoroethylene is much less efficient. A similar reaction using fluoroolefins such as 39 provides compounds 40 in fair yields.

**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 silylmethyl 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. 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. 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).
A complementary approach based on the addition of Ruppert-Prakash reagent to acrylimethylsilanes was reported by Portella shortly after Xu’s first report. The intermediate alkoxy can indeed undergo a Brook/elimination sequence (Scheme 29) to afford trimethyloxyl difluoroenol ethers 13d-e (Scheme 32). The addition of CF$_3$TMS to acrylimethylsilanes required the use of an uncommon fluoride source, tetrabutylammonium difluorotriphenylstannate (DFTPS), since 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. 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.

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. 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.

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 alkoxy 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. Difluoroenolophosphates 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.
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. 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. 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 carbocation B was then reprotonated with tert-butanol and a fluoride elimination reaction occurred (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 carbocation 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.

**II.3.5 Carbenoidic rearrangement (α-elimination).**

The Fritsch-Buttenberg-Wiechell rearrangement of sp² carbonoids is a well-known reaction for the synthesis of alkynes from bromoalkenes (Scheme 39). The rearrangement of sp³ carbonoids 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 carbonoid to the carbene (Scheme 39). The first efficient rearrangement of this type leading to a fluoroenol ether was reported by Utimoto. The reaction of halogenated alcohol 47 with LDA led directly to fluoroenoxyphosphane 48 upon warming of the reaction mixture, presumably via a lithium carbenoid intermediate (Scheme 40).

**Scheme 37**

**Scheme 38**

**Scheme 39**

**Scheme 40**

**Scheme 41**

**Scheme 42**

**Scheme 43**
A similar methodology was later extended to a range of fluorinated substrates by Taguchi. 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 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 protected with a "supersilyl" group was prepared from 2,2-dichloro-2-fluoroethyl ether 51 (Scheme 43).

The strong Z-selectivity observed in these rearrangements has been rationalized for non fluorinated substrates. In the case of lithium carbenoids, 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). 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).

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. Regarding difluoromethylation reactions, all existing methods derive from the pioneering work of Burton based on the use of dibromodifluromethane in the presence of triphenylphosphine or tris(dimethylamino)phosphine (HMPT), presumably to generate in situ a phosphorus ylide. The first application of this difluoromethylation method to an ester was reported by Fried. Difluoroenol ether 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). 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).

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A Julia-Kociensky difluoromethylation reaction was recently devised by Gueyrard. Difluoromethyl-2-pyridyl sulfone was prepared in three steps and 29% overall yield and was added to glyconolactones in the presence of LiHMDS and BF₂Et₂O. 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. 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 chlorofluoromethylation of carbonyl compounds was also studied by Burton. The reaction of iso-propyl trifluoroacetate with phosphonium salt afforded chlorofluoroenol ether in 67% yield and with a surprising 10:1 selectivity in favor of the Z isomer (Scheme 53). Burton also developed an ethoxycarboxyfluoromethylene phosphonium ylide that can react with activated esters (such as ethyl formate or perfluorinated esters) to afford the corresponding 3-ethoxy-2-fluoroacylates in fair yields and substantial E selectivity.

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 was for example reported by Snieckus. 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 Et₂O (Scheme 55).
The addition of soft nucleophiles was also reported. Cuprate reagents were, for example, added to 1-alkoxy-2,2-difuoroacrylates. The addition of triphenylphosphate to difluoroenol carbamate 61 was also described by Percy, affording compound 70 in 87% yield and as a single E isomer (Scheme 60). The addition of sodium phenoxide to aryl perfluoroenol ethers was recently published.

II.5.2 Cross-coupling reactions of functionalized fluoroenol ethers

As seen in section II.3.1, lithiated difluoroenol ethers, generated from trifluoroethyll ethers using an excess of base, can be trapped with various electrophiles such as trialkyl 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. Ethoxycarbonylation reactions or Stille cross-couplings with aryl or vinyl iodide were for example reported with substrates 23 and 71 (Scheme 61). 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).

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).

Scheme 60

Scheme 60 shows the cross-coupling reaction of compound 61 with tin reagents, leading to the formation of compound 70.

Scheme 61

Scheme 61 depicts the palladium-catalyzed coupling reaction of compound 71 with tin reagents, resulting in compound 72.

Scheme 62

Scheme 62 illustrates the coupling reaction of compound 33 with aryl iodide, affording compound 73.

Scheme 63

Scheme 63 presents the coupling reaction of compound 21a with tin reagents, leading to the formation of compound 74.
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). 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. 23

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 TiCl4, affording the corresponding aldols in moderate to good yields (Scheme 66). It should be mentioned that the corresponding dimethylphenylsilyl and tert-butyldiphenylsilyl 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 TiCl4-mediated aldol reaction. 50 In a following report, they demonstrated that stoichiometric amounts of TiCl4 and BF3·Et2O could efficiently be replaced by a catalytic amount of Yb(OTf)3 (Scheme 67). 83

The Bf3·Et2O-promoted addition of a difluoroenoxysilane (generated according to Uneyama’s methodology) to an artemisin-related aldehyde was also used in a synthesis of fluorooartemisinin reported by Bégue and Bonnet-Delpon. 84 Methyl difluoroenol ethers were used in one instance in the Lewis acid-promoted addition to aldehydes. 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). 85 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 64

Scheme 65

Scheme 66

Scheme 67

Scheme 68
Beside ketone-derived difluoroenoxysilanes, other difluorinated enol ethers were used as nucleophiles. β-Hydroxy-α,α-difluoroacilsilanes were as well prepared through a TiCl4-mediated addition of the corresponding enoxysilane to aldehydes (Scheme 69). Many examples of aldol reaction starting from difluoroketene silyl acetals were also reported, starting with the work of Kobayashi. The nucleophiles were prepared in situ from the corresponding iodofluoroketene 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). 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](image)

**Scheme 69**

Difluoroketene hemiaminal 80 derived from a trifluoroacetamide was also added, under TOSIMe3 catalysis to a small range of aromatic and aliphatic aldehydes (Scheme 72). 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. In contrast with non-fluorinated enoxysilanes that were able to react at low temperature, the BF3·Et2O-mediated reaction occurred only at room temperature. The yields were good but the diastereoselectivity 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 TMSI 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 carbenebend rearrangement, was added to wide range of aromatic and aliphatic aldehydes. The aldol reaction was catalyzed by C6F5CHTF2 and provided the corresponding β-hydroxy-α-fluoroaldehydes in good yields and with high anti selectivities (Scheme 74).

![Scheme 72](image)

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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-cis-fluoroketones were also prepared with the same efficiency (Scheme 75).

Other examples of monofluorinated aldols featuring a fluorinated quaternary stereogenic centre were also reported. Guo reported the TiCl₄-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).

An example of acyclic control to generate a fluorinated quaternary stereogenic centre was formerly reported by Iseki through the catalytic asymmetric Mukayama aldol reaction of bromofluoroketene silyl ethyl acetal 17.¹⁰ 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 occurred 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).¹⁹ 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 aldol 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 enol phosphates by generating in situ the corresponding copper or aluminium enolate (Scheme 80).³⁴

**Mannich reactions.** The addition of ketone-derived enoxysilane to iminium ions was first reported by Whitten.⁴⁴ The AlCl₃-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 difluoroacetol ether. The triflic anhydride-mediated addition to aliphatic aminals afforded Mannich products in good yields (Scheme 81).⁵⁵
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. 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. Chiral phosphoric acid 99 was better suited to this purpose as demonstrated by Akiyama one year later. The addition of ketone-derived difluoroenoxysilanes to a wide range of aromatic N-Boc aldimes afforded the corresponding β-amino-α,α-difluoro ketones in good yields and high ee’s (Scheme 82). The reaction was however totally inefficient with aliphatic aldimes. This drawback was partially addressed by Li using hydrazones as starting materials and a chiral zinc complex as the catalyst. Aliphatic hydrazones were indeed suitable partners, although a decrease in yields and ee’s was observed (Scheme 83).

Michael and S$_n$2’ reactions. The Michael addition of fluorinated enoxysilanes was first investigated by Taguchi using difluoroketene silyl acetal 15a and 15b and various acceptors. 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.

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

Miscellaneous addition reactions. Acylsilanes were also used as electrophiles for the Lewis acid-mediated addition of fluorinated enol ethers. 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 hemiaminal 80. The addition to acetics was more widely investigated. Portella first reported the SnCl$_4$-promoted addition of difluoroenoxysilane 13d to various glycosyl donors. 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 glycols (Scheme 86 and 87). Artemisinin-derived acetics were also successfully used for such glycosylation-type reactions.
A similar procedure was used by Leclerc for the addition of difluoroketene ethyl trimethylsilyl acetal to tri-O-acetylgulcal (Scheme 88). The addition of 2,2-difluoro-1-trimethylsilyloxyacrylate 82 to aldehyde-derived methyl acetals was also reported by Shi and Uneyama (Scheme 89). Nucleophilic substitution reactions were also investigated, mostly using “activated” electrophiles. Portella reported the addition of difluoroensilanes 13d-f to a benzylc 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). Fluorinated carbasugars were prepared by Sollogoub et al using a sugar-to-carbocycle rearrangement, based on an intramolecular Nicholas reaction (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 trivalent 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).

Fluorination reactions of fluorinated enol ethers demonstrated their utility in the radiosynthesis of [18F]-labelled compounds (Scheme 93). Addition of electrophilic sources of chalcogens were also reported, affording the corresponding α-thio or α-seleno difluorinated carbonyl compounds (Scheme 94).
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. 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-difluoro ketones 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-difluoro ketones in high yield and enantioselectivities (Scheme 97).117 A similar catalytic system allowed the intramolecular allylation reaction of allyl fluoroacetates 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 101

Shi and co-workers developed an efficient [3,3]-rearrangement of 2,2-difluoro-1-allyloxyacrylates, that were first prepared from trifluoromethyldiazooacetate 89 then from ethyl trifluoropyruvate 90. The addition of the corresponding allylic alcohols to either reagent indeed afforded a trifluoroalactyl 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 occurred at a lower temperature than what is required for their non-fluorinated counterparts. A greater stability of the sp³-hybridized CF₂ group compared to the sp²-hybridized CF₂ group was invoked to support this experimental feature. An enantioselective Claisen rearrangement catalyzed by a chiral boron Lewis acid was reported by Taguchi. 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-trimethylysil or 2,2-difluoro-1-tri(n-butyl)stannylvinyl allyl ethers, affording the corresponding acylsilanes and acylstannanes (Scheme 102). The latter were afterwards converted to ketones using standard chemistry.

Scheme 102

Scheme 103

Scheme 104

Difluoroketene allytrimethylsilyl acetics were also used in such rearrangements as illustrated by Chen in his synthesis of a difluoropropylene (Scheme 103). The sequence was improved with conditions more compatible with large-scale production. Trifluoroacetalddehyde 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).

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. Much later, Tellier reported the Claisen rearrangement of transient allyl 1,2-difuorovinyl ethers, affording the corresponding homoallylic fluorides in fair yields and good diastereoselectivities (Scheme 105). A similar strategy was used by Sandfor for fluorotrifluoromethylvinyl allyl ethers. 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).
Difluoroallyl vinyl ethers. The addition of lithiated difluoroenoic 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).126 Percy extensively studied and performed all types of [3,3]-rearrangements to afford [1,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).

Another difference was that deprotected esters were directly isolated from α-alkoxysters 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-difluoroallyl 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 occurring only from the non-fluorinated terminus (Scheme 112).129b

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).129b N-Boc and N-Cbz aminoacetates underwent the [3,3]-rearrangement using the Kazmaier modification of the reaction conditions (Scheme 111).130

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The Johnson-Claisen rearrangement of other highly fluorinated allylic alcohols was also reported by Funabiki (Scheme 113).

Finally, in a study of the oxy-Cope rearrangement of difluorinated dienes, Percy reported one example in which the difluoroallyl moiety is substituted by an oxygen atom. This substrate 100 undergoes a clean rearrangement to produce cyclic ketone 101 in 84% yield (Scheme 114).

### 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. Percy demonstrated that the introduction of an oxygen atom could restore the ability of difluoroolefins 104 to undergo a [4+2]-cycloaddition. 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 \( \beta,\beta' \)-difluoro-\( \alpha,\alpha' \)-unsaturated ketones or esters with various cyclic dienes (Scheme 118).

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Possner also reported the Diels-Alder reaction of 104c with 3-methoxycarbonyl-2-pyrene under high pressure conditions (Scheme 119). Monofluorinated derivatives were also used as dienophiles as illustrated by the reaction of 110 with various dienes under thermal conditions. 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. In contrast, the reaction with heterodienophiles was fairly efficient, as first illustrated by the work of Taguchi with aldehydes. Later on, Uneyama reported a similar [4+2]-cycloaddition between difluorinated 111 diene and aldehydes or imines (Scheme 121). The reaction of some monofluorinated dienes with standard dienophiles was also reported, as well as a study by Ghosez on the [4+2]-cycloaddition of monofluorinated azadienes with aldehydes.

III.2.4 [2+2]-Cycloaddition reactions

The [2+2]-cycloaddition reaction of fluoroolefins was investigated by Viehe. 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 perfluoroalene. 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 fluoine substitution” (Scheme 123). The cyclodimerization of difluoroenol ethers was also studied, first by Uneyama and later on by Smith (Scheme 124).
difluoroolefins were obtained by addition of the lithiated difluoroenol ether derived from the corresponding enolate. \(^{126}\) Remarkably, starting from aryl difluoroether \(104d\) in place of tosylate \(104e\) resulted in a different reaction pathway. A fluoride elimination indeed occurred from the intermediate zirconacyclopropane to generate an \(\alpha\)-fluoroolefin species, and then a new monofluorinated enol ether after the coupling reaction. The same group had previously demonstrated that a difluoroarylboron species could also be obtained from metallated difluoroether tosylate through a Matteson-type carbene rearrangement. \(^{155}\) After oxidation of the resulting vinylborane to the corresponding boronic ester, a Suzuki coupling afforded the corresponding fluoroolefins in good yields (Scheme 130). A more recent report demonstrated that this difluoroarylboron species could also be converted to the corresponding vinylcopper reagent and trapped with various electrophiles or coupled with alkyl halides (Scheme 130). \(^{156}\)

### 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 difluoroether derived from \(21e\) to \(\alpha,\beta\)-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. \(^{153}\) Mono- and difluorinated 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 enene phosphonate. \(^{153}\) 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). A fluoroene elimination indeed occurred from the intermediate zirconacyclopropane to generate an \(\alpha\)-fluoroolefin species, and then a new monofluorinated enol ether after the coupling reaction. The same group had previously demonstrated that a difluoroarylboron species could also be obtained from metallated difluoroether tosylate through a Matteson-type carbene rearrangement. After oxidation of the resulting vinylborane to the corresponding boronic ester, a Suzuki coupling afforded the corresponding fluoroolefins in good yields (Scheme 130). A more recent report demonstrated that this difluoroarylboron species could also be converted to the corresponding vinylcopper reagent and trapped with various electrophiles or coupled with alkyl halides (Scheme 130). \(^{156}\)
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, Stryker 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 stereocchemically 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).\(^{160}\)

More recently, gem-distannane 119 was prepared from stannylated difluoroenol tosylate 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).

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**Scheme 130**

**Scheme 131**

**Scheme 132**

**Scheme 133**

**Scheme 134**

**Scheme 135**
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 fluoroalkyl 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 through addition/elimination processes (Scheme 137).

Portella first reported the addition of secondary amines to 121, which resulted in the formation of the corresponding enamones in good yields. 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 enamones and then α-fluoroenones (Scheme 138). Conversion of a similar substrate to a fluorinated allylic alcohol by addition of a Grignard reagent was also reported by the same group. The reaction of 122a with sodium hydroxide and trapping with benzoyl chloride afforded β-acyloxy-α-fluoroacrylaldehydes 123 (Scheme 139). Addition of amides to perfluoroenol phosphates or to fluoroenol tosylates resulted in the formation of pyrimidines in good yields (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. Umeyama reported the oxidative addition of heteroaromatic compounds to difluoroenoxysilanes. 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).
The hydrolysis of enol ethers provides of course the corresponding α-fluorocarbonyl compound.\textsuperscript{21,166} This trivial transformation could however be performed in an asymmetric fashion through enantioselective protonation reactions of fluoroacetone silyl acetal \textbf{126}, as pioneered by Yamamoto (Scheme 143, catalyst \textbf{124}).\textsuperscript{110} Much later, Ooi improved the enantioselectivity of this reaction when \textbf{126} bears an alkyl substituent (Scheme 143, catalyst \textbf{125}).\textsuperscript{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 alkoxy.\textsuperscript{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 beginning of the manuscript, almost any fluorinated enol ethers can be easily prepared from widely available fluorinated reagents, with the sole limitation of their intrinsic 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.

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Notes and references

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