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Review

Fluoro-functionalization mediated by the reactive chalcogen reagents

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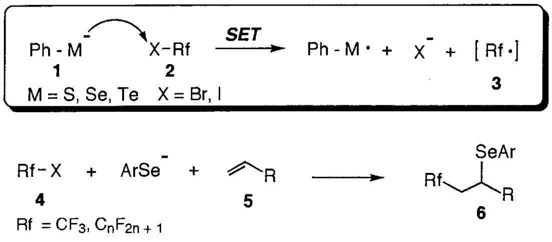
Abstract

Two types of fluoro-functionalizations mediated by reactive chalcogen reagents have been summarized. The first is a generation of benzeneselenenyl fluoride and its electrophilic reactions with alkenes, electron-deficient alkenes, isonitriles and α-diazocarbonyl compounds. The second is a single electron transfer (SET) reaction of benzene chalcogenolates to perfluoroalkyl halides such as trifluoromethyl bromide, dibromodifluoromethane, bromodifluoroacetates etc., where perfluorinated alkyl radicals generated in the SET reaction undergo addition to alkenes and alkynes to give perfluoroalkyl-chalcogenated molecules. © 2000 Elsevier Science S.A. All rights reserved.

Keywords: Fluoro-functionalization; Fluoro-selenenylation; Benzeneselenenyl fluoride; Single electron transfer; α,α-D-fluoro-γ-lactam; Difluoromethylene compound

1. Introduction

Introduction of fluorine functionality into organic molecules is one of the current important subjects for many scientists, since organofluorine molecules have been given much attention because of their unique properties for medicinal and material sciences [1]. On this basis, a number of fluorination reactions by conventional, organometal-mediated, electrochemical, photochemical methods etc. have been developed [2]. However, very few reactions mediated by chalcogen reagents have been reported. An introduction of both fluorine and chalcogen moieties into a molecule is promising for the possible preparation of fluorinated molecules by the versatile modification of the reactive chalcogen moiety. The carbon–chalcogen bonds are generally weak and can be cleaved easily and are thus reactive. Chalcogen molecules are thermally, photochemically and electrochemically susceptible so that they can accept or donate electrons from or to reaction partners, respectively, and thus they are readily reduced or oxidized [3]. All of these unique properties make the chalcogen functionality useful for the modification of organic substrates. On this basis, it is reasonable to choose chalcogen reagents as potential tools for fluoro-functionalization of organic substrates. Here a short account on chalcogeno-fluorination, in particular, seleno-fluorination leading to fluoro-functionalization of organic substrates, is presented.



Scheme 1.

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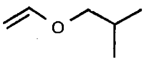
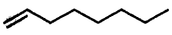
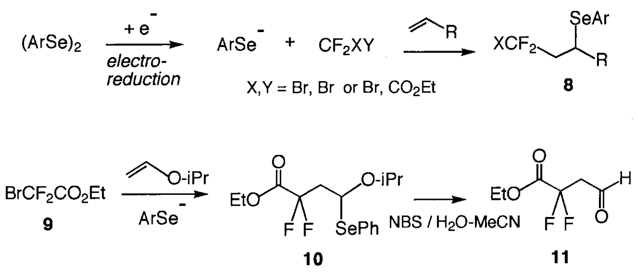
Table 1
Yield of **8** in bromodifluoromethyl-selenenylation and the related reaction of alkenes

Alkene	CF_2XY		
	CF_2Br_2	$BrCF_2CO_2Et$	C_4F_9I
	45	80	73
	57	58	71
	68	45	77



Scheme 2.

Table 2
SET reaction between benzenechalcogenolate and perfluoroalkyl halides

M	Rf–X	Solvent	Temperature
S	Rf–I	Ether	Reflux
Se	Rf–I (CF_3–Br)	DME	Room temperature
Te	Rf–I (CF_3–Br)	Ether–DME	−100 to −80°C

2. Results and discussion

2.1. A single electron transfer (SET) from chalcogenolate anions to perfluoroalkyl halides

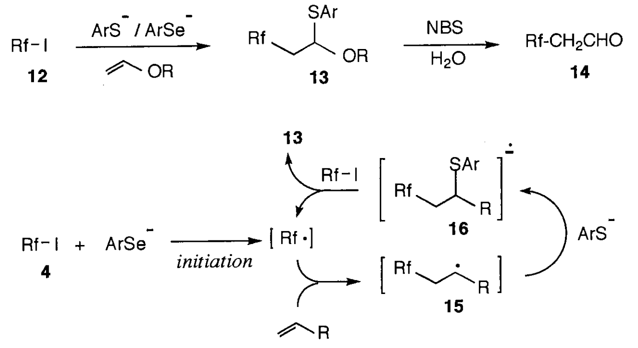
Chalcogenolate anions are readily oxidized and their oxidizability is in the order of $RTe^- > RSe^- > RS^-$. These facts suggest they are very strong nucleophiles and are likely to react with alkyl halides and to donate one electron to electron acceptors. Wakselman demonstrated the reaction of the benzenethiolate anion with perfluoroalkyl iodides leading to the formation of perfluoroalkyl phenyl sulfides is not a simple S_N2 reaction, but a radical chain reaction in which perfluoroalkyl radicals **3** generated by SET reaction between benzenethiolate anion **1** and perfluoroalkyl iodide **2** react with a benzenethiolate anion [4]. The mechanism reasonably suggests that the perfluoroalkyl radical and benzeneselenenyl moiety can be incorporated into a carbon–carbon multiple bond via a possible radical chain reaction (Scheme 1); the perfluoroalkyl radical generated by the SET reaction between Rf–I and $PhSe^-$ adds to a carbon–carbon double bond and the subsequently generated perfluoroalkylated radical then reacts with the benzeneselenolate anion to produce a perfluoroalkyl-benzeneselenolated anion radical. Finally, the anion radical transfers one electron to perfluoroalkyl iodide to produce the perfluoroalkyl-benzeneselenolated adduct **6** and propagate the radical chain reaction. Some anions and radical anions have already been demonstrated to mediate perfluoroalkyl-iodination of alkenes [5].

This working hypothesis has been found to be effective to prepare perfluoroalkyl-benzeneselenolated compounds **6** as shown in Scheme 1 [6,7]. Sodium benzeneselenolate generated by reduction of diphenyl diselenide with $NaBH_4$ in dry ethanol was allowed to react with perfluoroalkyl iodide at room temperature for 2 h. Electron-rich terminal alkenes such as 1-alkenes, vinyl ether and vinyl thioether reacted smoothly, affording the desired adducts in 59–86% yields for $Rf = C_4F_9$, C_6F_{13} and C_8F_{17}. Trifluoromethyl-iodination of vinyl isobutyl ether with CF_3Br provided **6** in a poor yield (38%). Internal alkenes such as cyclohexene reacted unsatisfactorily, affording the desired product in only 15% yield. The major product in this reaction of cyclohexene was perfluoroalkyl phenyl selenide (60%). The data suggest the perfluoroalkyl radical addition is highly susceptible to steric hindrance.

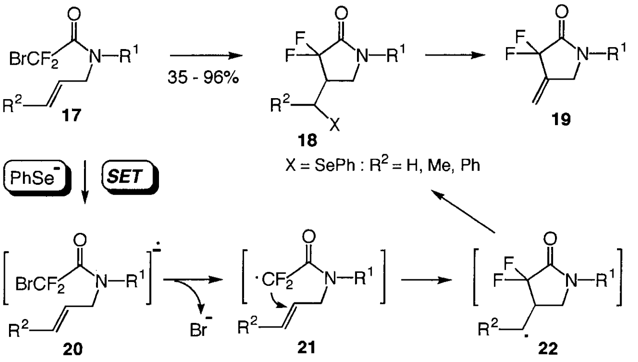
An electrochemical reduction is also useful for in situ generation of an arene selenolate anion from diaryl diselenide [8]. This method was used for the substituted difluoromethyl-selenenylation of alkenes (Table 1). Thus, reaction of ethyl bromodifluoroacetate with vinyl isopropyl ether and subsequent oxidative deselenation in aqueous medium provided **11**, a useful functionalized difluoromethylene ester (Scheme 2) [9].

The reaction rate of the generation of perfluoroalkyl radical by the SET reaction is highly dependent on the electron-transfer ability of the chalcogen atom. As shown in Table 2, the thiolate anion reacts so slowly that refluxing in ether for several hours is needed for the effective generation of perfluoroalkyl radical. Meanwhile, selenolate reacts reasonably fast and the desired reaction is complete within 2 h at room temperature. Most interestingly the corresponding tellurolate transfers one electron to perfluoroalkyl halides extremely fast. In fact it reacts with trifluoromethyl bromide at −100°C and it efficiently promotes trifluoromethyl-telluration of 1-octene (57%), allyl cyanide (44%), and ethylene (44%) [10].

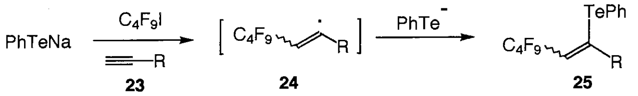
The low reactivity of thiolates as compared with selenolates is one of the disadvantages of perfluoroalkyl-sulfenylafion, which could be covered by the cooperative use of a catalytic amount of the more reactive selenolate. The idea is shown in Scheme 3. The reaction is initiated by a SET reaction from the selenolate anion to form the perfluoroalkylated radical **15**, which then reacts with a large excess amount of thiolate anion, generating the anion radical **16**. The usual SET reaction from **16** to **4** produces the sulfur product **13** and propagates the chain reaction. The yield of **13** (Rf = C_4F_9, C_6F_{13} and C_8F_{17}, R = *i*-Bu) in the presence of 10 mol% of the selenolate is in the range of 80–93%. In particular, *p*-nitrobenzenethiolate does not react with the vinyl ether, but it gives 45% of **13** in the presence of a selenolate anion as catalyst [11]. The *S*,*O*-acetals **13** can be transformed to perfluoroalkylated aldehydes **14** by NBS oxidation in aqueous medium (Scheme 3).



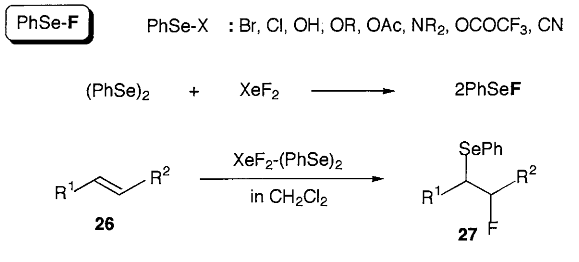
Scheme 3.



Scheme 4.



Scheme 5.



Scheme 6.

The SET reaction mediated by the selenolate anion is applicable for the first synthesis of α,α-difluoro-γ-lactam (**18**) and α,α-difluoro-β-methylene-γ-lactam (**19**) via intramolecular cyclization as shown in Scheme 4. Noteworthy is the fact that the yield of **18** is markedly affected by the geometry of the *N*-allyl group. *N*-allyl amide (**17**, R^1 = H, R^2 = H) provided no desired lactam **18**, instead it gave α-benzeneselenenyl amide (**17**, a replacement of Br with a PhSe group) in 45% yield. Meanwhile, *N*,*N*-diallyl amide (**17**) (R^1 = allyl, R^2 = H) gave **18** in 96% yield. Similarly, *N*,*N*-cinnamyl amide (**17**) (R^1 = cinnamyl, R^2 = Ph) produced the target lactam **18** in 72% yield. The *syn*-conformation of the carbon–carbon double bond to the initially formed difluorinated carbon radical is essential for the effective cyclization [12,13].

Introduction of perfluoroalkyl and aryltelluro groups into alkynes was also achieved by the tellurolate mediated reaction (Scheme 5). It is interesting that the efficiency of the chalcogenation of alkynes is the order of Te > Se > S. Thus, the telluro-compounds **25** for 1-hexyne were obtained in 81% for Rf = C_4F_9, 57% for Rf = C_8F_{17} and 50% for Rf = CF_3, respectively [14].

2.2. Electrophilic fluoro-selenenylation with benzeneselenenyl fluoride

Fluorinating reagents are divided into two categories, that is, electrophilic fluorinating reagents such as Selectrofluor (F–TEDA–BF_4), *N*-fluoropyridinium, *N*-fluorosulfonamide, xenon difluoride, etc. and nucleophilic fluorinating reagents such as cesium fluoride, potassium fluoride, tetraalkylammonium fluoride, hydrogen fluoride, iodo fluoride and so on. Benzeneselenenyl fluoride would be a promising reagent for fluoro-selenenylating, but it has not yet been characterized although a great number of works on benzeneselenenyl chloride and bromide have been carried out [15].

Electrophilic reactivity of benzeneselenenyl reagents (PhSeX) is undoubtedly dependent on the electronegativity of X or the electron-withdrawing ability of substituent X. Therefore, benzeneselenenyl cyanide, triflate and trifluoroacetate (X = CN, OTf and CF_3CO_2) are strong electrophilic selenenylating reagents. On this basis, benzeneselenenyl fluoride must be one of the strongest selenenylating reagents because of the strong electronegativity of the fluorine atom. Recently, Nicolaou and co-workers have demonstrated fluoro-selenenylation of alkenes by the use of *N*-phenylselenophthalimide, AgF–PhSeBr ultrasound system, AgF–PliSeCl–MeCN systems [16]. However, these results do not necessarily demonstrate the clearcut evidence of benzeneselenenyl fluoride as a reactive intermediate. Here a new method for generating a benzeneselenenyl fluoride and its reaction with several substrates is described (Scheme 6).

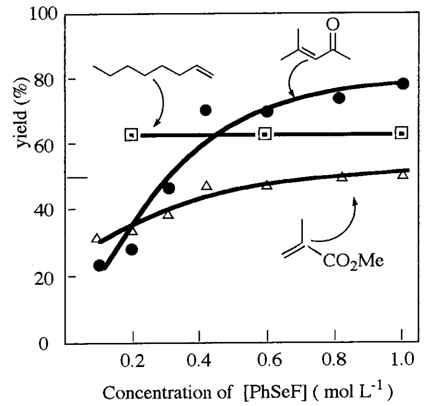
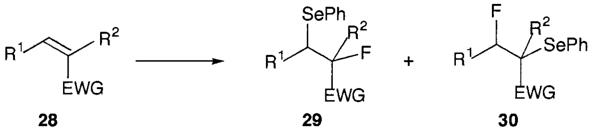
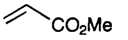
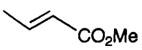
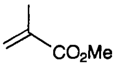
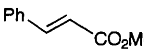
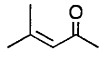


Fig. 1. Effect of the concentration of [PhSeF].

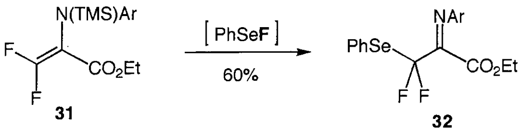


Scheme 7.

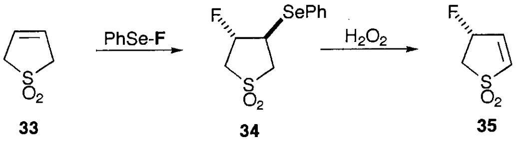
Table 3
Reaction of benzeneselenenyl fluoride with electron-deficient alkenes [a]

 58% (30:70)	 44% (0 : 100)	 57% (70 : 30)
 75% (0 : 100)	 79% (0 : 100)	

[a] Ratio of isomer (**29**:**30**).



Scheme 8.



Scheme 9.

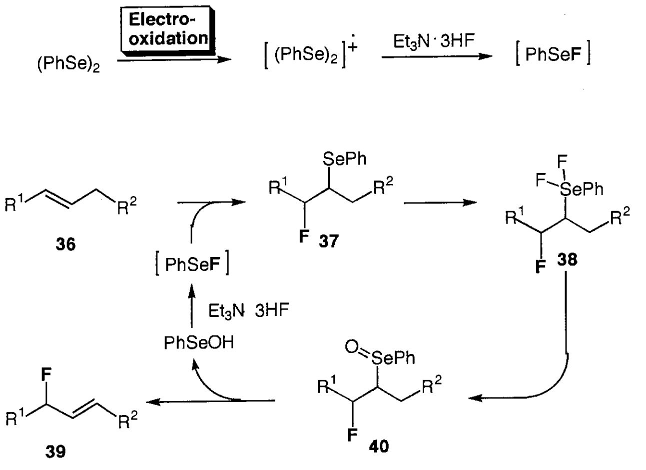
Benzeneselenenyl fluoride is generated by the reaction of diphenyl diselenide (1 mole eq) with xenon difluoride (1 mole eq) at −20°C in methylene chloride. Gas evolution was observed and the solution turned dark brown. ^{1}H-NMR of the solution in $CDCl_3$ shows a new set of phenyl protons at δ 7.96–8.03 ppm (m, 2H) and δ 7.62–7.75 ppm (m, 3H), which are downfield by about 0.4 ppm from those of $(PhSe)_2$ and are considerably broadened within 15 min, revealing instability of the active reagent [17]. The action of an excess amount of xenon difluoride to diphenyl diselenide provides PhSeF, and $PhSeF_5$ which do not fluoro-selenate alkenes, but simply fluorinate them [18]. The addition of alkenes makes the color of the dark brown solution fade within several minutes, suggesting fluoro-selenenylation to alkenes is extremely fast. The yields of adducts are in the range of 43–82%, but those of methyl acrylate and methyl methacrylate are very poor, 9 and 34%, respectively [17]. Prolonged reaction time was not effective for improvement of the yield because of the instability of the active reagent. To overcome this difficulty several reaction conditions were examined in detail and it was found that the higher concentration of the reagent makes the lifetime of the reagent markedly longer as shown in Fig. 1 (Scheme 7).

At the higher concentration, the yield of **30** for methyl acrylate improved from 9 to 58%. The results for other electron deficient alkenes are listed in Table 3 [19]. The longer lifetime may arise from the stabilization of PhSeF by a possible intermolecular association like a dimer or trimer of the reagent under the higher concentration conditions. Calculation of heats of formation of [PhSeF] as a monomer and its dimer by PM3 of MacSpartan Plus revealed that the dimer is more stable by 18 kcal mol^{-1} than the monomer. The high electrophilicity of [PhSeF] can be usable for the effective selenenylation of the strongly electron-deficient difluoroacrylate **31** of which difluoromethylene carbon is mostly attacked by nucleophiles (Scheme 8) [20].

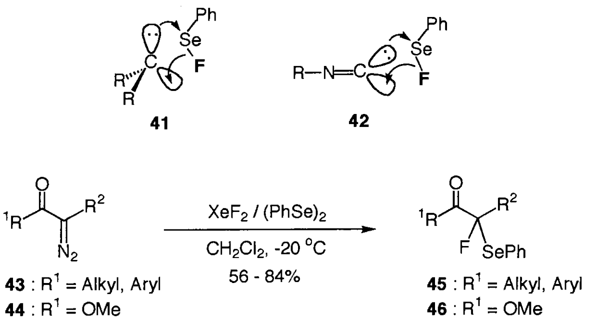
The conventional oxidation of fluoro-selenenyl compounds produced the corresponding allylic fluoride as shown in the transformations of **33** to **35**, via **34** (Scheme 9).

Therefore, it is highly interesting to design a series of reactions, namely generation of [PhSeF], fluoro-selenenylation of alkenes and oxidative removal of selenomoiety, and recycling the selenenyl reagent usable for one-pot preparation of allylic fluoride from alkenes. This hypothetical reaction design was found to be effective for the series of electrochemical oxidative transformation as shown in Scheme 10. Diphenyl diselenide is known to be electrochemically oxidized to selenenyl reagent (PhSeX: X = OH, OW, OAc, NCMe) in aqueous media, methanol, acetic acid and acetonitrile, respectively [21]. On this basis, benzeneselenenyl fluoride would be the most probable initial product produced by electrooxidation of diphenyl diselenide in the $Et_3N{\cdot}3HF–CH_2Cl_2$ system. The selenenylating reagent reacts with alkenes to form an adduct **37**, which is subsequently oxidized in situ to selenoxide **40**. *Syn*-elimination from selenoxide **40** would produce the desired allylic fluoride **39** and regenerate active selenenic acid, which is converted to selenenyl fluoride in situ in the presence of a large excess amount of amine complex of HF and is used for further fluoro-selenenylation (Scheme 10). The yields of **39** are in the range of 35–70% for internal aliphatic alkenes in the presence of 10 mol% of diphenyl diselenide [22].

It is reasonable to expect that benzeneselenenyl fluoride should transfer both fluoro and selenenyl moieties in a manner of 1,1-addition to the α-carbon atom of carbene-like reactive species such as isonitriles and α-diazocarbonyl compounds [23]. The selenium atom of the reagents would attack electrophilically the filled orbital of **41** and the fluorine atom would attack nucleophilically a vacant orbital as shown in Scheme 11. The reaction of [PhSeF] with isonitriles went smoothly, but the products were too unstable to be isolated.



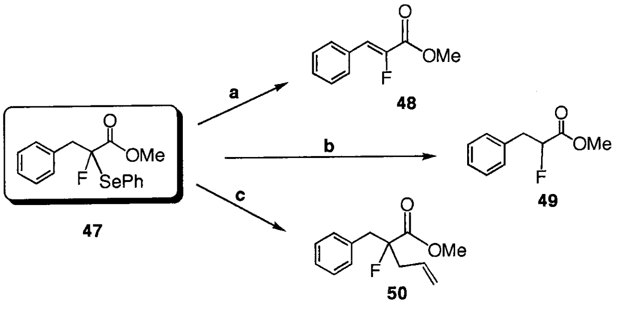
Scheme 10.



43 : R^1 = Alkyl, Aryl
44 : R^1 = OMe

45 : R^1 = Alkyl, Aryl
46 : R^1 = OMe

Scheme 11.



a) H_2O_2 (90%) b) Bu_3SnH / AIBN (81%) c) $AllylSnBu_3$ / AIBN (84%)

Scheme 12.

The reaction of [PhSeF] with α-diazocarbonyl compounds also went very smoothly and the reaction was completed within 15 min at −20°C. Soon after addition of the diazocarbonyl compounds to the [PhSeF] solution, nitrogen gas evolution was observed and the dark orange color of the solution faded immediately. α-Fluoro-α-selenenyl ketones and esters are stable enough to be isolated by column chromatography. The yields of the ketones and esters are 68–94% and 56–74%, respectively [24]. The selenenyl moiety of **47** is usable for carbon–carbon formation and other functionalization. Some oxidative and radical reactions are shown in Scheme 12.

Acknowledgements

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