Phenylselenofluorination of Alkenes and Alkynes Promoted by Difluoroiodotoluene and Diphenyldiselenide

Barbara Panunzi, Andrea Picardi, Marco Tingoli*

Facoltà di Agraria, Università di Napoli 'Federico II', Via Università, 100-I-80055 Portici (Napoli), Italy
Fax +39(081)2539186; E-mail: tingoli@unina.it

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Abstract: The oxidation of diphenyldiselenide with 4-iodotoluene difluoride (DFIT) in dichloromethane produces in situ an efficient phenylselenofluorinating agent of alkenes and internal alkynes.

Key words: alkenes, alkynes, hypervalent iodine(III) difluoride, diphenyldiselenide, oxidation

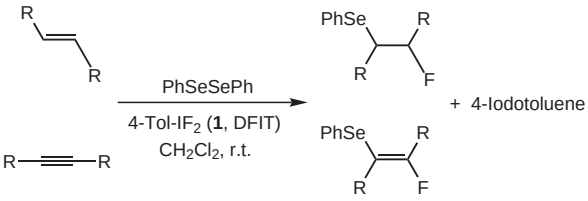
Our recent studies established that iodine(III) reagents are able to generate in situ both electrophilic phenylselenium and iodonium species starting from PhSeSePh and I_2, respectively.[1] When these reactive intermediates were produced in the presence of terminal alkenes and an oxygen-containing nucleophile, the corresponding addition products, with a Markovnikov orientation, were isolated.

More recently, we have also shown that the activated phenylselenium moiety, produced in methanol with phenyliodine(III) *bis*(trifluoroacetate) (BTI), gave α,α-dimethoxycarbonyl compounds starting from activated and enolisable alkyl aryl ketones.[2]

The common feature of all the reactions cited below is the incorporation of an oxygen-containing nucleophile via an inter- or an intramolecular pathway. Now it should be of interest to evaluate the possibility of using our easily accessible and mild source of electrophilic phenylselenium and iodonium species to develop new addition reactions, employing different types of nucleophiles.

In particular, the controlled introduction of one fluorine atom into organic molecules continues to be a challenge for organic chemists. Thus, we have tried to use BTI and PhSeSePh in the presence of an external source of fluorine anions, like the commercial available $Et_3N{\cdot}3HF$, in CH_2Cl_2 and choosing cyclohexene as starting material. An equimolecular amount of both hydroxy and fluorinated phenylselenylated cyclohexane are identified by GC-MS as final products. Two competitive reactions clearly occurred and the phenylselenonium intermediate thus formed is consumed both by the iodine(III) ligand CF_3COO, that easily hydrolyzes to OH, and by the F-anion initially added. On the basis of this experience, we moved our attention to a fluorinating agent based on the hypervalent iodoarene difluoride structure. This type of compounds should in principle be able to generate the activated phenylselenium species in situ and transfer the fluorine ligand, avoiding the competition of other nucleophiles. More recently, the Motherwell group have shown that the very old hypervalent iodine(III) reagent difluoroiodotoluene (DFIT) can be prepared on a multigram scale and used in a variety of useful transformations including selective fluorination of dithioketals,[3] arylthioglycosides,[4] xanthate esters[5] and α-phenylsulfanyl esters[6] and amides.[7] Thus, following this protocol, we have prepared the hypervalent iodine(III) difluoride [DFIT (**1**), Equation 1] and used in a new experiment starting from cyclohexene and PhSeSePh in CH_2Cl_2 at ambient temperature. In this case by GC-MS analysis the addition product of PhSeF species was identified as final compound, together with 4-iodotoluene coming from DFIT reduction.

As summarized in Equation 1, we decided to apply this simple and new phenylselenofluorination protocol to both olefins and disubstituted alkynes.



Equation 1

It is important to note that the addition of PhSeF elements to unsaturated compounds has some precedents in the literature.[8] The more recent contribution to this subject showed that the formal addition of PhSeF across the carbon-carbon double or triple bonds can be performed by using *N*-phenylselenophthalimide and pyridine–HF or $Et_3N{\cdot}3HF$ complexes.[9] Similar results have been obtained via electrolytic fluorination of diphenyldiselenide again in the presence of $Et_3N{\cdot}3HF$.[10]

Our method seems to be promising and efficient compared to those described in the literature. In fact DFIT quickly oxidizes diphenyldiselenide at room temperature and the subsequent addition of the starting unsaturated compound coincides with the complete decoloration of the red-brown solution and all the reactions carried out were completed in less than two hours.

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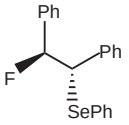
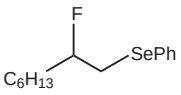
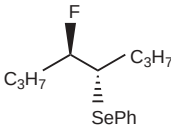
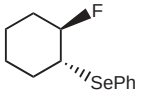
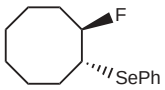
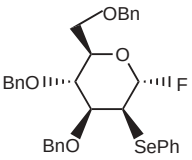
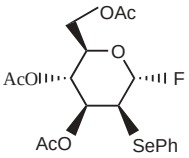
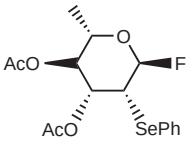
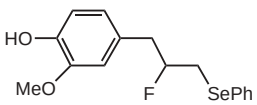
As depicted in Table 1, various kinds of alkenes were subjected to the phenylselenofluorination reaction and high stereo- and regioselectivity can be realized. In particular, very good results are obtained on starting from different kinds of protected glycals (entry 6, 7 and 8, Table 1). These compounds are indeed good precursors for the preparation of 2-phenylseleno-1-fluoro glycosyl donors like **6a**, recently proposed as a useful intermediate in the total synthesis of Everninomicin 13,384-1.[11]

The *anti*-addition of PhSeF elements to protected glycals is confirmed by observing the low value of the $^3J_{HH}$ coupling constant (below of 2 Hz) between H_1 and H_2 on ^{1}H NMR of products **6a**, **7a** and **8a**. These data suggest an α-configuration for the anomeric fluorides and a *manno*-stereochemistry for the PhSe linked to C-2 in both compounds **6a** and **7a**.[12]

The success of our reaction is confirmed by the result obtained on starting from a phenol derivative (entry 9, Table 1). Although yield of addition product was not so high, unprotected eugenol was easily transformed into addition product **9a**, without touching the remote phenol group. This last compound is an interesting precursor of monofluoro analog of eugenol methyl ether, an extremely potent and specific attractant for the oriental fruit fly, a major pest of a wide variety of plant species.[13]

Table 1 Phenylselenofluorination of Alkenes Promoted by Difluoroiodotoluene (DFIT) and PhSeSePh in CH_2Cl_2 at 25 °C[15]

Entry	Alkene	Reaction products		Yield (%)[a]
1	*cis*-Stilbene		**1a**	58
2	1-Octene		**2a**	65
3	(*E*)-4-Octene		**3a**	60
4	Cyclohexene		**4a**	78
5	Cyclooctene		**5a**	72
6	Tri-*O*-benzyl-D-glucal		**6a**[16]	67
7	3,4,6-Tri-*O*-acetyl-D-glucal		**7a**	81
8	3,4-Di-*O*-acetyl 6-deoxy-L-glucal		**8a**	70
9	Eugenol		**9a**[16]	62

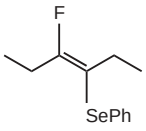
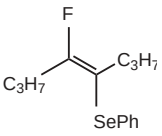
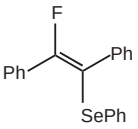
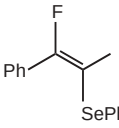
[a] Yields based on ^{19}F NMR using trifluoromethylbenzene as internal standard.

We finally have extended the methodology described above to some simple alkynyl derivatives. Concerning these substrates we were not completely surprised to observe that also the couple DFIT/PhSeSePh acts as simple PhSe-donor for terminal alkynes. Thus as we have observed early by using BTI/PhSeSePh, phenyl acetylene underwent only hydrogen substitution by PhSe group and no addition of PhSeF elements to the triple bond were detected. This result clearly indicates that the reactivity of terminal alkynes with PhSeSePh and I(III) species is independent of the structure of hypervalent iodine used.[14]

On the other hand, internal alkynes gave the expected *trans*-addition of PhSeF elements and, as depicted in Table 2, all the substrates employed were transformed at room temperature, in less than two hours, into the corresponding substituted alkenes showing *E*-configuration on double bonds.

The use of these last interesting stereo defined substrates as precursors of tetra-substituted olefins synthesis by using organometallic-mediated coupling reactions is under investigation in our laboratory.

Table 2 Phenylselenofluorination of Alkenes Promoted by Difluoroiodotoluene (DFIT) and PhSeSePh in CH_2Cl_2 at 25 °C[15]

Entry	Alkyne	Reaction products		Yield (%)[a]
1	3-Hexyne		**1b**[16]	74
2	4-Octyne		**2b**	78
3	Diphenylacetylene		**3b**	82
4	1-Phenyl-1-propyne		**4b**	92

[a] Isolated yields after flash chromatography.

Acknowledgment

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(12) (a) Unfortunately spectroscopic properties of compound **6a** were not reported in ref.[11]. Nevertheless, some analogs of our compounds **6a** and **7a** (Table 1) were recently described by: Cumpstey, I.; Fairbanks, A. J.; Redgrave, A. J. *Org. Lett.* **2001**, *3*, 2371. (b) The first one is the 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranosyl fluoride that shows in its ^1H NMR spectrum a $J_{1,2}$ between H-1 and H-2 of 6.1 Hz, while the second one named 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl fluoride shows a $J_{1,2}$ of 1.9 Hz beween H-1 nd H-2. This last value of $J_{1,2}$ is consistent with our data.
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(14) Tingoli, M.; Tiecco, M.; Testaferri, L.; Temperini, A. *Tetrahedron* **1995**, *51*, 4691.
(15) **A Typical Procedure for the Phenylselenofluorination Reaction Promoted by DFIT and PhSeSePh in CH_2Cl_2.** Diphenyldiselenide (0.16 mmol) was dissolved in CH_2Cl_2 (3 mL) in a 20 mL polyethylene erlenmeyer flask and DFIT (0.40 mmol) was added under stirring in Ar atmosphere. The initially yellow solution turns to a red-brown color in a few minutes. After 15 min a CH_2Cl_2 solution (3 mL) of the starting material (0.30 mmol) was added slowly. The color of the solution disappeared in a few minutes and all the reactions described on alkenes were completed in less than 90 min. All compounds described in Table 1, separated from organic layers previously washed with aq $NaHCO_3$, brine and dried over anhyd Na_2SO_4, do not tolerate acidic conditions and cannot be purified by a traditional column chromatography on silica gel. On the other hand, fast flash chromatography (mixture of light petroleum/*tert*-butyl methyl ether) can be successfully used to remove 4-iodotoluene and to obtain acceptable quantity of all compounds showing high level of purity useful for spectroscopic identification. As matter of fact, authors of ref.[6] have isolated compound **6a** and used it as glycosyl donor without any further purification. Spectral data of compounds **4a** and **5a** are identical with those reported in the literature.[9] The reaction conditions resumed above have been applied to alkynes. All the reactions reported in Table 2 are completed in less than 120 min and the crude materials isolated are successfully purified by flash chromatography (light petroleum/*tert*-butyl methyl ether) to obtain pure compounds. Products **2b**, **3b**, **4b** have spectral data identical with those reported in the literature.[9]
The chemical shift δ on ^{19}F NMR spectra are expressed in ppm using fluoro trichloromethane as internal reference. The presence of six natural isotopes of selenium leads to highly

characteristic groups of peaks for selenium-containing fragments. The values reported below refer to the prominent peak.

(16) Physical data of selected compounds:
Compound **6a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.6–7.5 (m, 2 H), 7.4–7.2 (m, 18 H), 5.8 (dd, *J* = 2.4 Hz, $J_{H,F}$ = 51.0 Hz, 1 H), 5.0–4.9 (ABq, J_{AB} = 10.5 Hz, 2 H), 4.8–4.5 (ABq, J_{AB} = 10.7 Hz, 2 H), 4.6–4.5 (ABq, J_{AB} = 12 Hz, 2 H), 4.1–3.9 (m, 2 H), 3.9–3.7 (m, 2 H), 3.7–3.6 (m, 1 H), 3.3 (ddd, *J* = 2.4 Hz, *J* = 11.2 Hz, $J_{H,F}$ = 32.7 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.0, 137.0, 134.0, 130.0, 129.0, 128.0, 108.5 (d, $J_{C,F}$ = 218.7 Hz), 81.0, 79.5, 76.5, 75.0, 73.0, 69.0. ^{19}F NMR (376 MHz, $CDCl_3/C_6H_5CF_3$): δ = –139.9 (dd, *J* = 51 Hz, *J* = 33 Hz, 1 F). GC-MS (EI): *m/z* (%) = 572 (1) [M^+ – HF], 224 (1), 207(1), 161 (2), 157 (1), 105 (2), 91 (100), 77 (9).
Compound **9a**: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.6–7.5 (m, 2 H), 7.4–7.3 (m, 3 H), 6.9 (d, *J* = 7.8 Hz, 1 H), 6.7, 6.6 (m, 3 H), 5.5 (br s, OH), 4.8 (dm, $J_{H,F}$ = 47.8 Hz, 1 H), 3.8 (s, 3 H), 3.2, 2.9 (m, 4 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 146.3, 144.0, 133.0, 129.1, 128.1, 127.0, 122.0, 114.0, 112.0, 93.2 (d, $J_{C,F}$ = 175.3 Hz), 55.8, 40.1 (d, *J* = 21.5 Hz), 30.9 (d, *J* = 23 Hz). ^{19}F NMR (376 MHz, $CDCl_3/C_6H_5CF_3$): δ = –171.8 to –172.2 (m, 1 F). GC-MS (EI): *m/z* (%) = 340 (8) [M^+], 310 (2), 182 (9), 162 (25), 157 (30), 137 (77), 119 (15), 103 (19), 91 (31), 77 (80).
Compound **1b**: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.6–7.5 (m, 2 H), 7.4–7.3 (m, 3 H), 2.7 (dq, *J* = 7.5 Hz, $J_{H,F}$ = 23.0 Hz, 2 H), 2.4 (dq, *J* = 7.5 Hz, $J_{H,F}$ = 2.7 Hz, 2 H), 1.1 (t, *J* = 7.5 Hz, 3 H), 1.0 (t, *J* = 7.5 Hz, 3 H). ^{13}C NMR (50 MHz $CDCl_3$): δ = 164.0 (d, $J_{C,F}$ = 267.5 Hz), 133.0, 129.2, 127.2, 110.0 (d, $J_{C,F}$ = 21.5 Hz), 25.0 (d, $J_{C,F}$ = 28.9 Hz), 24.0 (d, $J_{C,F}$ = 7.0 Hz), 13.8, 11.8. ^{19}F NMR (376 MHz, $CDCl_3/C_6H_5CF_3$): δ = –95.8 (dd, *J* = 23 Hz, 1 F). GC-MS (EI): *m/z* (%) = 258 (45) [M^+], 229 (4), 183 (5), 157 (40), 137 (41), 117 (27), 55 (43), 77 (81), 73 (74), 59 (91), 51 (100).