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Photochemical substitution of olefins and aromatic compounds with difluoromethyl radicals bearing ester and phosphonate groups

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Abstract—Efficient and selective substitution of cyclic and acyclic vinyl ethers with photo-generated difluoromethyl radicals bearing ester and phosphonate groups, in the presence of 2,4,6-trimethylpyridine and diphenyl diselenide was successfully carried out to provide the corresponding regioselective unsaturated difluoromethylene adducts selectively. The reaction involves phenylselenyl transfer at an early stage followed by elimination of phenylselenol from the adducts once formed to provide the unsaturated difluoromethylene adducts selectively. This novel photochemical method was successfully extended to aromatic and heteroaromatic substitutions to provide the corresponding α-aryl-α,α-difluoroacetates and α-aryl-α,α-difluoromethylphosphonates in good to moderate yields.

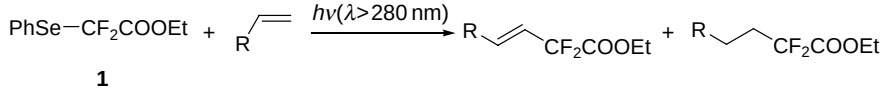
1. Introduction

It is well known that introduction of a fluorine atom into an organic molecule causes dramatic changes in its biological activities, mainly due to the high electoronegativity of fluorine, the strong carbon–fluorine bond, increased solubility in lipids, and mimic effect.[1] Therefore, fluorinated compounds are of great importance in the pharmaceutical and agrochemical industries. In particular, difluoromethylene compounds have attracted a great deal of interest due to their unique biological activities.[2] For example, CF_2/O transposition in methylenephosphonate has proven to be one of the most valuable approaches to the preparation of hydrolytically stable functional groups as phosphonate mimetics.[3] Therefore, their synthesis has become a major interest in organic chemistry. In general, difluorometylene compounds have been prepared using DAST,[4] NFBS,[5] cross-coupling reactions,[6] electrochemical oxidations[7] and radical additions.[8] However, their preparation is still limited.

Previously, we reported photochemical reaction of ethyl α,α-difluoro-α-(phenylseleno)acetate (**1**) with various olefins as shown in Scheme 1.[9]

Interestingly, we obtained not only radical adducts (saturated products) but also difluoromethylene-substituted products (unsaturated products). The formation of difluoromethylene-substituted products prompted us to carry out aromatic and heteroaromatic substitutions with difluoromethyl radicals photo-generated from **1** and diethyl α,α-difluoromethyl-α-(phenylseleno)phosphonate (**5**) as shown in Scheme 2.[10]

However, the selectivity of the substitution of olefins in Scheme 1 was low,[9] and the yields of aromatic and



Scheme 1.

Keywords: Photoreaction; Difluoromethyl radicals; C–CF_2 bond formation; Group transfer; Selenide.
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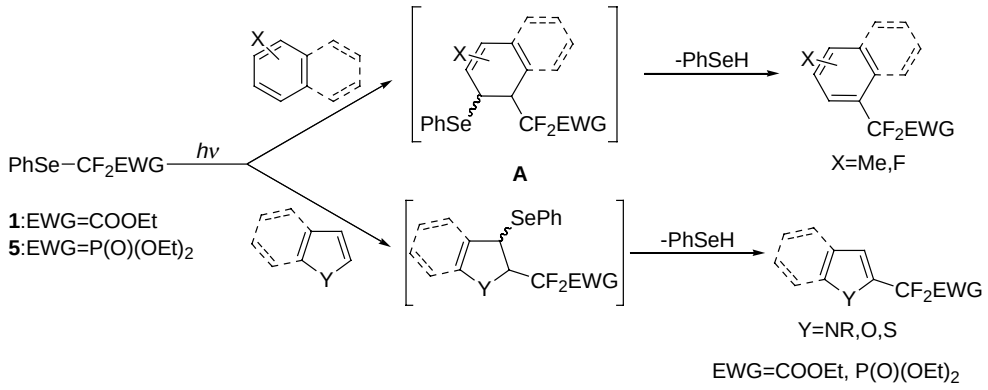


Scheme 2.

heteroaromatic substitutions with difluoromethyl radicals were moderate to low.[10]

In order to improve the selectivity and yields, we investigated photochemical substitutions under various conditions. In this paper, we report the substitution of various vinyl ethers and aromatic compounds with difluoromethylene groups photo-generated from **1** and **5**.

2. Results and discussion

2.1. Photoreaction of ethyl α,α-difluoro-α-(phenylseleno)-acetate (1) with 2,3-dihydrofuran

We attempted the photoreaction of **1** with a large excess amount of 2,3-dihydrofuran as the electron-rich olefin in CH_2Cl_2 (Scheme 3). The reaction was conducted using a 100-W high-pressure mercury-vapor lamp with a Pyrex vessel inside the light source.

As shown in Scheme 3, the group transfer reaction took place to provide a phenylselenyl group transfer adduct **2**, a difluoromethyl-substituted product **3** and a radical adduct **4** in good total yields (25, 28, 28%, respectively). Moreover, the difluoromethyl unit was regioselectively introduced to the 3-position of 2,3-dihydrofuran in all products. Byers et al. obtained always phenylselenyl group transfer products by the photolysis of dialkyl α-(phenylseleno)malonates[11,12] and tetraethyl phenylselenomethylenediphosphonate[13] in the presence of olefins, and they did not obtain selenium-free adducts like **3** and **4** at all. Although the adducts **2** is a single stereoisomer, we could not establish its stereochemistry.

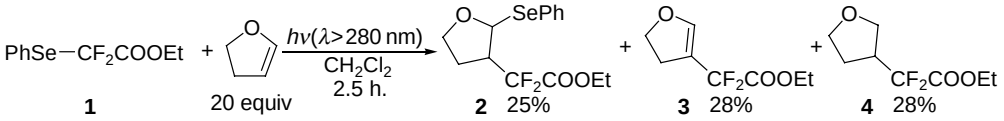
In order to disclose the mechanism for the formation of **3** and **4**, we investigated the photolysis of the phenylselenyl group transfer adduct **2**. We found that compounds **3** and **4** were formed from the adduct **2** (Scheme 4).

This result clearly indicates that the phenylselenyl group transfer adduct **2** is a precursor to compounds **3** and **4**.

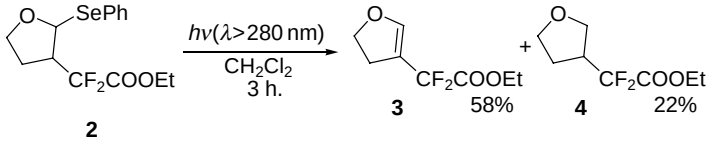
2.2. Time-conversion of the photoreaction of ethyl α,α-difluoro-α-(phenylseleno)acetate (1) with 2,3-dihydrofuran

In order to obtain more information on the reaction mechanism, the yields of **2**–**4** and the recovery of **1** in the time course of the photochemical reaction of **1** in the presence of 2,3-dihydrofuran were investigated and the results are illustrated in Figure 1.

As shown in Figure 1, the starting material **1** was consumed linearly with the photo-irradiation time while the yield of the phenylselenyl group transfer adducts **2** also increased linearly to ca. 50% with the reaction time, and then the yield of **2** gradually decreased. Additionally, difluoromethylene-substituted product **3** also increased gradually with the time and no maximum yield was observed even after long



Scheme 3.



Scheme 4.

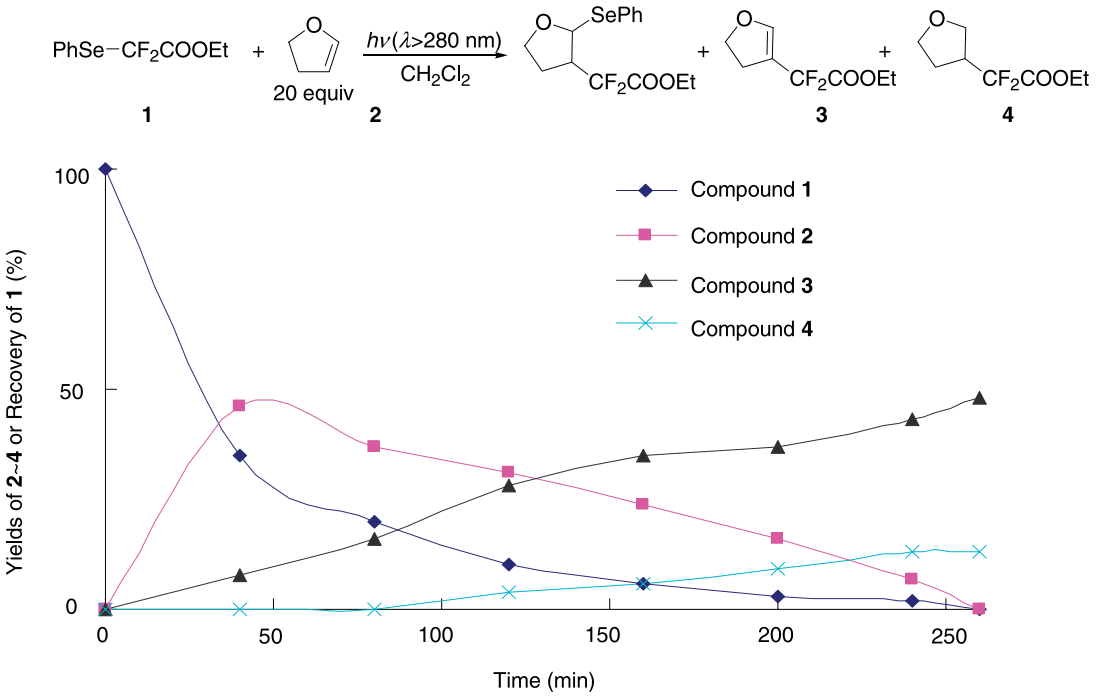


Figure 1. The yields of **2**–**4** and the recovery of **1** in the time-course of the photoreaction of **1** in the presence of 2,3-dihydrofuran.

photo-irradiation. In sharp contrast, the formation of the radical adduct product **4** started after 80 min and gradually increased. When the starting compound **1** and the adduct **2** completely vanished after prolonged photo-irradiation time, the yields of the substituted product **3** and the radical adduct **4** reached maxima. Moreover, a considerable amount of diphenyl diselenide was detected. From the above result, we assumed the substituted product **3** is formed probably by the elimination of phenylselenol from the adduct **2** and the resulting phenylselenol would be involved in the formation of **4** since phenylselenol is a good hydrogen atom donor.

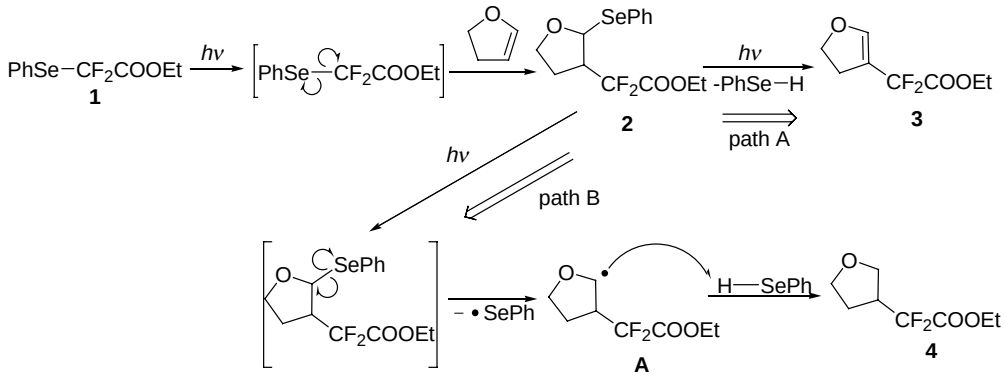
In consideration to the above results and the UV absorption bands of **1** at 265, 217 nm, we propose a plausible reaction mechanism as shown in Scheme 5.

When the homolytic cleavage of the Se–CF_2 bond takes place by photolysis of **1** in the presence of 2,3-dihydrofuran, the phenylselenyl group transfer reaction proceeds quickly to provide **2**, and then further photolysis of **2** once formed results in the formation of the difluoromethyl-substituted product **3** eliminating phenylselenol (path A). Since the formation of **4** required induction time, **4** would be formed by the photochemically homolytic cleavage of the Se–C bond followed by abstraction of a hydrogen atom from phenylselenol (path B).

2.3. Effect of a base

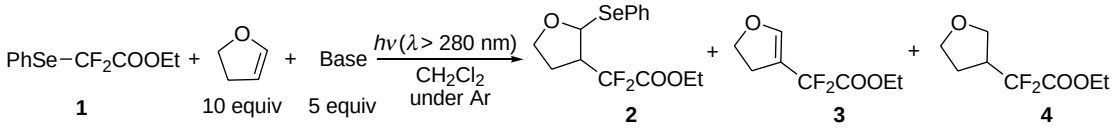
From the above hypothesis, it is expected that when the formation of phenylselenol as a good hydrogen atom donor is inhibited by using a base for deprotonation of phenylselenol, the formation of **4** would be suppressed. Consequently, the selectivity for the formation of **3** would be increased.

In order to confirm our assumption, photochemical reaction of **1** with 2,3-dihydrofuran was investigated in the presence of various bases. The results are summarized in Table 1.



Scheme 5.

Table 1. Photoreaction of **1** in the presence of 2,3-dihydrofuran with various bases



Run	Base	Time (h)	Yield (%)[a]			Ratio **3/4**
			2	**3**	**4**	
1	None	3	—	51	40	1.3
2	DBU	5	—	7	—	—
3	Pyridine	5	—	41	22	1.9
4	DMAP	5	65	20	—	—
5	DMAP	10	31	21	2	10.5
6	Imidazole	10	—	61	18	3.4
7	2,6-Lutidine	10	—	58	32	1.8
8	2,4,6-Trimethylpyridine	10	—	66	15	4.4

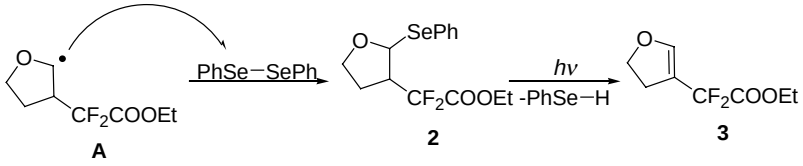
[a] Determined by ^{19}F NMR.

As shown in Table 1, when 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was used, **3** was formed solely although the yield was extremely low (run 2). When 4-(*N*,*N*-dimethylamino)-pyridine (DMAP) was used, the reaction proceeded smoothly to provide **2** and **3** in good total yield and saturated adduct **4** was not formed at all (run 4). However, in this case, group transfer adduct **2** was mainly formed. Therefore, the reaction time was doubled (10 h). However, the yield of **3** did not increase although the yield of the group transfer adduct **2** decreased (run 5). In sharp contrast, when pyridine and 2,6-lutidine were used, the product selectivity (the ratio of **3** to **4**) was not so different from the case in the absence of a base (run 1, vs runs 3 and 7). The photochemical reaction in the presence of imidazole and 2,4,6-trimethylpyridine provided **3** and **4** in good yields and high product selectivities (runs 6 and 7). Since the addition of 2,4,6-trimethylpyridine resulted in higher selectivity compared with imidazole, 2,4,6-trimethylpyridine was found to be the most suitable base for the selective photochemical reaction.

2.4. Effect of diphenyl diselenide

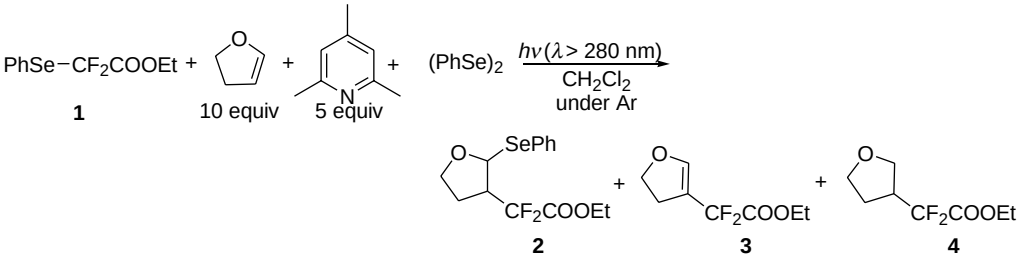
We found 2,4,6-trimethylpyridine as the most suitable base to suppress the formation of **4**, but **4** was still formed. From path B in Scheme 5, we assumed that radical intermediate **A** would also abstract the hydrogen atom from dichloromethane as a solvent. It is expected that the addition of diphenyl diselenide to the reaction system would suppress the hydrogen abstraction of **A** to provide **4** as shown in Scheme 6. In this case, **3** would be formed mainly via **2** derived from **A** and diphenyl diselenide.

In order to suppress the formation of **4**, we investigated the photochemical reaction in the presence of both diphenyl



Scheme 6.

Table 2. Photoreaction of **1** in the presence of diphenyl diselenide and 2,4,6-trimethylpyridine



Run	$(PhSe)_2$ (equiv)	Time (h)	Yield (%)[a]		
			2	**3**	**4**
1	0.1	12	—	68	12
2	0.5	12	—	78	16
3	1	16	—	80 (78)	—

[a] Determined by ^{19}F NMR. Figure in parenthesis shows isolated yield.

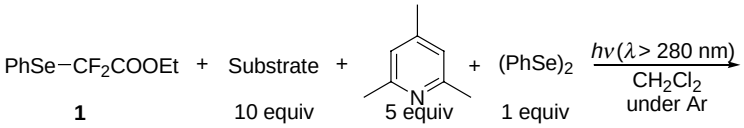
diselenide and 2,4,6-trimethylpyridine. The results are summarized in Table 2.

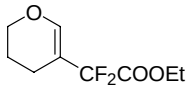
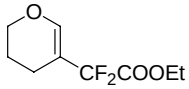
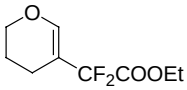
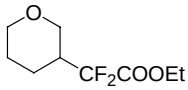
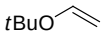
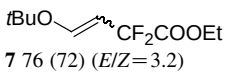
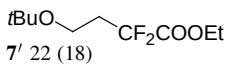
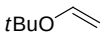
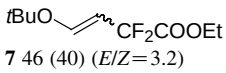
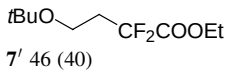
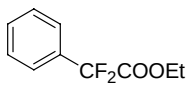
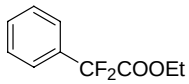
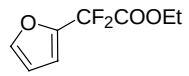
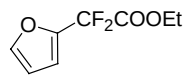
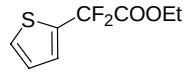
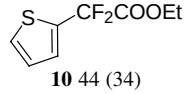
As shown in Table 2, the yield of **3** was increased in all cases. Especially, the photochemical reaction of **1** in the presence of 1 equiv of diphenyl diselenide provided product **3** solely in good yield (run 3) although the reaction time was longer. Therefore, 1 equiv of diphenyl diselenide was found to be the most suitable additive for the selective formation of **3**.

2.5. Photochemical reaction of ethyl α,α-difluoro-α-(phenylseleno)acetate (1) and diethyl α,α-difluoromethyl-α-(phenylseleno)phosphonate (5) with various unsaturated compounds

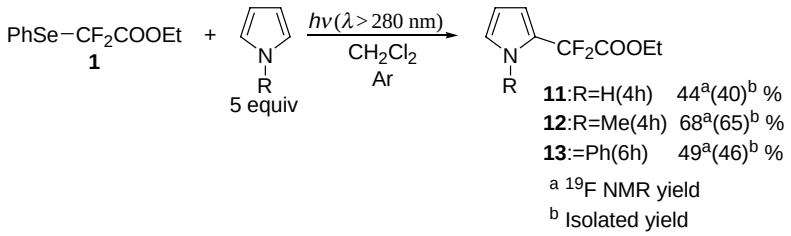
Next, we carried out the photo-induced substitution of **1** with various unsaturated substrates in the presence of 2,4,6-trimethylpyridine and diphenyl diselenide. The results are shown in Table 3.

Table 3. Photoreaction of **1** in the presence of 2,4,6-trimethylpyridine and diphenyl diselenide



Run	Substrate	Time (h)	Recovery of **1** (%)[a]	Yield (%)[a]
1		16	25	 **6** 46 (41)
2		30	25	 **6** 43
3[b]		3	—	 **6** 44 (40)  **6′** 34 (31)
4		18	—	 **7** 76 (72) (*E*/*Z*=3.2)  **7′** 22 (18)
5[b]		3	—	 **7** 46 (40) (*E*/*Z*=3.2)  **7′** 46 (40)
6[c]		25	—	 **8** 79 (70)
7[b,c]		9	—	 **8** 60 (53)
8[c]		25	—	 **9** 72 (67)
9[b,c]		6	—	 **9** 29 (26)
10[c]		25	—	 **10** 62 (53)
11[b,c]		8	—	 **10** 44 (34)

[a] Determined by ^{19}F NMR. Figures in parentheses show islated yields.
[b] Without 2,4,6-trimethylpyridine and diphenyl diselenide.
[c] Neat conditions.



Scheme 7.

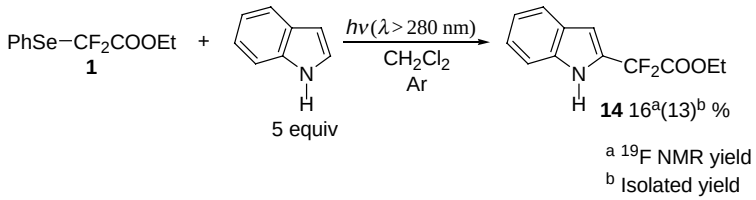
Regardless of substrates, the selectivity of products and yields were improved when 2,4,6-trimethylpyridine and diphenyl diselenide were used. In contrast to run 3, the photochemical reaction with 3,4-dihydro-2*H*-pyran in the presence of 2,4,6-trimethylpyridine and diphenyl diselenide gave a difluoromethyl-substituted product **6** solely in moderate yield and radical adduct **6′** was not formed at all (run 1). In this case, a considerable amount of starting material **1** still remained. In order to obtain better yield, the reaction time was extended to almost double, but the yield of **6** was not increased and the conversion of **1** did not change (run 2). A similar photochemical reaction with *tert*-butyl vinyl ether proceeded to afford difluoromethyl-substituted product **7** in much higher yield (run 4) compared with the reaction in the absence of diphenyl diselenide and a base (run 5). In this case, the product selectivity (**7**/**7′**) was also improved. Photochemical reaction with benzene in the presence of 2,4,6-trimethylpyridine and diphenyl diselenide also gave a much higher yield of the substituted product **8** (run 6) compared with the reaction without these additives (run 7). Moreover, the reaction was applicable to heteroaromatic compounds: the substitution with the difluoromethylene group at the α-position of heteroaromatic compounds proceeded selectivity to provide the corresponding substitution products **9**–**10** in much better yields (runs 8 and 10) compared with the reactions in the absence of the additives (runs 9 and 11). Notably, the yield of **9** was markedly increased.

Next, photochemical substitution with nitrogen-containing heterocycles was investigated. As shown in Schemes 7 and 8, the reactions proceeded to provide the corresponding substitution products in moderate to reasonable yields. Notably, in the case of 1-phenylpyrrole and indole, the substitution at the α-position of the pyrrole ring took place exclusively and the substitution at the benzene ring did not take place at all. In these cases, the yields were not increased in the presence of 2,4,6-trimethylpyridine and diphenyl diselenide, which is in sharp contrast to the cases of furan and thiophene. Even when the reaction time was extended longer in the case of indole, the conversion of **1** did not change and a considerable amount of **1** was recovered. This seems to be due to the formation of dark colored by-products adsorbed on the wall of the Pyrex vessel, which interfered with UV light absorption of **1** to result in the low conversion of **1**.

Finally, we tried similarly the photo-induced substitution of α,αdifluoromethylphosphonate **5** with various unsaturated substrates in the presence of 2,4,6-trimethylpyridine and diphenyl diselenide. The results are summarized in Table 4.

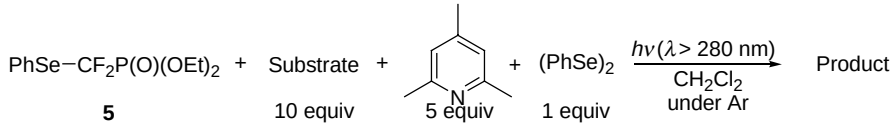
Regardless of substrates, the conversion of **5** became much lower (runs 1 and 3) or lower (run 5 and 7) in the presence of the additives. However, the yields of substitution products based on the consumed **5** increased without exception. Interestingly, substitution product **15** was formed exclusively in the reaction with 1,2-dihydrofuran. Notably, the absolute yield of **17** markedly increased to 55% in the presence of the additives (run 5). These results suggest that the photochemical substitution proceeds selectively in the presence of the additives although the reaction became much slower. However, in the case of 1-methylpyrrole, the yield did not increase even in the presence of additives. In the reactions, diethyl difluoromethylphosphonate, HCF_2-$P(O)(OEt)_2$ was formed as a by-product except for runs 5 and 6 and a considerable amount of diphenyl diselenide was also detected. These facts also clearly indicate that homolytic cleavage of the Se–CF_2 bond took place by photolysis of **5**.

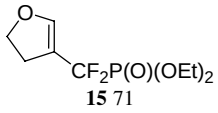
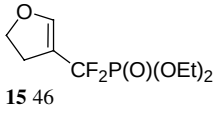
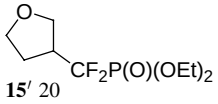
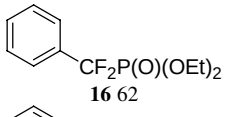
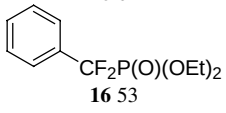
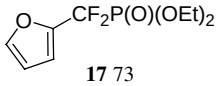
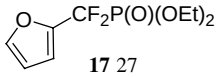
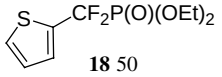
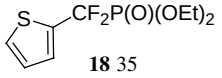
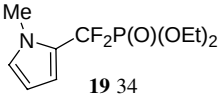
By the way, the substitution of the difluoromethylene group at the α-position of furan proceeded exclusively while the substitution of the difluoromethylene group at the β-position of 2,3-dihydrofuran exclusively. Since the difluoromethyl radicals generated from **1** and **5** are electron deficient, they usually react as electrophiles. Therefore, the regioselectivity of these radical reactions seems to be controlled by SOMO–HOMO interaction between radicals and substrates. The HOMOs of 2,3-dihydrofuran and furan calculated by CAChe MOPAC AM1 are shown in Figure 2.



Scheme 8.

Table 4. Photoreaction of 5 in the presence of 2,4,6-trimethylpyridine and diphenyl diselenide



Run	Substrate	Time (h)	Conversion (%)[a]	Yield (%)[b]
1		18	35	 **15** 71
2[c]		3	69	 **15** 46  **15′** 20
3[d]		60	60	 **16** 62
4[c,d]		9	100	 **16** 53
5[d]		30	75	 **17** 73
6[c,d]		6	96	 **17** 27
7[d]		57	60	 **18** 50
8[c,d]		8	72	 **18** 35
9[c,d]		8	68	 **19** 34

[a] Determined by ^{19}F NMR.
[b] Isolated yield based on consumed starting material **5**.
[c] Without 2,4,6-trimethylpyridine and diphenyl diselenide.
[d] Neat conditions.

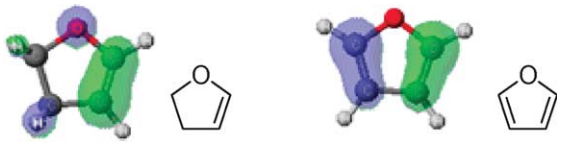


Figure 2. The HOMOs of 2,3-dihydrofuran and furan calculated by CAChe MOPAC AM1.

The β-position of 2,3-dihydrofuran has the largest coefficient of HOMO while the α-position of furan has the largest one. Therefore, the different regioselectivity of the radical reactions with furan and 2,3-dihydrofuran can be reasonably explained.

3. Conclusion

We have developed novel and efficient substitution using photo-generated difluoromethyl radicals with cyclic, acyclic vinyl ethers together with aromatic and heteroaromatic compounds. In the presence of 2,4,6-trimethylpyridine and diphenyl diselenide, the yields and product selectivity were increased in many cases. This method may be highly useful for the preparation of various CF_2-containing building blocks towards biological activities.

4. Experimental

4.1. General procedure for photoreaction

A solution of ethyl α,α-difluoro-α-phenyselenolacetate (**1**)[9] or diethyl α,α-difluoromethyl-α-phenyselenolphosphonate (**5**)[8b] (0.17 mmol) and an olefin (1.70 mmol) in CH_2Cl_2 (40 ml) in the presence of 2,4,6-trimethylpyridine (0.85 mmol) and diphenyl diselenide (0.17 mmol) was bubbled with Ar at room temperature for 0.5 h and then photolyzed with 100-W high-pressure mercury-vapor lamp.

The reaction was conducted using a Pyrex vessel inside the light source. After the photoreaction, the resulting solution was evaporated under vacuum and the residue was purified by silica gel column chromatography (linear gradient of 0–20% EtOAc in hexane) or by HPLC (Develosil ODS-5, MeCN as an eluent) to provide pure products.

4.1.1. 3-(Ethoxycarbonyldifluoromethyl)-2-(phenylselenyl)tetrahydrofuran (2). ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.62–7.27 (m, 5H), 5.99 (d, 1H, J=3.5 Hz), 4.06–4.01 (m, 2H), 4.32 (q, 2H, J=7.0 Hz), 3.16–2.98 (m, 1H), 2.19–1.98 (m, 2H), 1.33 (t, 3H, J=7.0 Hz); ^{13}C NMR δ 162.96 (t, J=32.4 Hz), 137.21 (t, J=253.8 Hz), 133.98, 128.89, 127.67, 114.76 (t, J=253.20 Hz), 81.89 (t, J=3.9 Hz), 66.81, 63.20, 51.21 (dd, J=23.48, 22.92 Hz), 25.15 (dd, J=3.35, 2.80 Hz), 13.90. ^{19}F NMR (254 MHz, $CDCl_3$) δ −34.10 (dd, 1F, J=257.0, 14.7 Hz), −35.32 (dd, 1F, J=257.0, 14.7 Hz); MS (m/z) 350 (M^+), 305, 277, 77; HRMS m/z Calcd for $C_{14}H_{16}F_2O_3Se$: 350.0233. Found: 350.0203.

4.1.2. 3-(Ethoxycarbonyldifluoromethyl)-2,3-dihydrofuran (3). See Ref. 9.

4.1.3. 3-(Ethoxycarbonyldifluoromethyl)tetrahydrofuran (4). See Ref. 9.

4.1.4. 2*H*-3,4-Dihydro-5-(ethoxycarbonyldifluoromethyl)pyran (6). See Ref. 9.

4.1.5. 2*H*-3,4,5,6-Tetrahydro-3-(ethoxycarbonyldifluoromethyl)pyran (6′). See Ref. 9.

4.1.6. *trans*-Ethyl 5-*t*-butoxy-2,2-difluoro-3-butenoate (7). See Ref. 9.

4.1.7. *cis*-Ethyl 5-*t*-butoxy-2,2-difluoro-3-butenoate (7). See Ref. 9.

4.1.8. Ethyl 5-*t*-butoxy-2,2-difluorobutanoate (7′). See Ref. 9.

4.1.9. Ethyl α,α-difluoro-α-phenylacetate (8). See Ref. 6d.

4.1.10. Ethyl α,α-difluoro-α-[2-(furyl)]acetate (9). ^{1}H NMR δ 7.52 (dd, 1H, J=1.65, 0.82 Hz), 6.76 (dd, 1H, J=3.30, 0.82 Hz), 6.46 (dd, 1H, J=3.30, 1.65 Hz), 4.38 (q, 2H, J=7.02 Hz), 1.36 (t, 3H, J=7.02 Hz); ^{13}C NMR δ 162.25 (t, J=33.5 Hz), 144.73 (t, J=2.2 Hz), 131.86, 111.56 (t, J=3.4 Hz), 110.68 (t, J=1.1 Hz), 108.59 (t, J=248.2 Hz), 63.55, 14.00. ^{19}F NMR δ −25.95 (s, 2F); MS (m/z) 190 (M^+), 117; HRMS Calcd for $C_8H_8F_2O_3$: m/z 190.0442. Found: 190.0424.

4.1.11. Ethyl α,α-difluoro-α-[2-(thienyl)]acetate (10). See Ref. 6b.

4.1.12. Ethyl α,α-difluoro-α-[2-(pyrrolyl)]acetate (11). ^{1}H NMR δ 9.03–8.55 (br, 1H), 6.90 (dd, 1H, J=2.6, 1.8 Hz), 6.55 (dd, 1H, J=3.3, 1.8 Hz), 6.24 (dd, 1H, J=3.3, 2.6 Hz), 4.36 (q, 2H, J=7.3 Hz), 1.37 (t, 3H, J=7.3 Hz). ^{19}F NMR δ −21.32 (s, 2F); MS (m/z) 189 (M^+), 116; HRMS Calcd for $C_8H_9F_2NO_2$: m/z 189.0601. Found: 189.0591.

4.1.13. Ethyl α,α-difluoro-α-[2-(1-methylpyrrolyl)]-acetate (12). ^{1}H NMR δ 6.7 (dd, 1H, J=2.8, 2.0 Hz), 6.4 (dd, 1H, J=3.8, 2.0 Hz), 6.1 (dd, 1H, J=3.8, 2.8 Hz), 4.38 (q, 2H, J=7.0 Hz), 3.76 (s, 3H), 1.37 (t, 3H, J=7.0 Hz); ^{13}C NMR δ 163.28 (t, J=34.1 Hz), 129.06, 126.98 (t, J=2.2 Hz), 112.22 (t, J=5.6 Hz), 111.16 (t, J=245.9 Hz), 107.29, 63.22, 35.48 (t, J=3.4 Hz), 14.03. ^{19}F NMR δ −19.62 (s, 2F); MS (m/z) 203 (M^+), 130; HRMS Calcd for $C_9H_{11}F_2NO_2$: m/z 203.0758. Found: 203.0764.

4.1.14. Ethyl α,α-difluoro-α-[2-(1phenylpyrrolyl)]-acetate (13). ^{1}H NMR δ 7.4–7.3 (m, 5H), 6.9 (dd, 1H, J=2.6, 2.0 Hz), 6.6 (dd, 1H, J=3.6, 2.0 Hz), 6.3 (dd, 1H, J=3.6, 2.6 Hz), 4.13 (q, 2H, J=7.3 Hz), 1.21 (t, 3H, J=7.3 Hz); ^{13}C NMR δ 162.95 (t, J=34.1 Hz), 139.23, 132.42, 128.73, 128.27, 127.16 (t, J=2.2 Hz), 126.86 (t, J=1.6 Hz), 112.90 (t, J=5.0 Hz), 110.62 (t, J=245.4 Hz), 108.36, 63.09, 13.87. ^{19}F NMR δ −15.65 (s, 2F); MS (m/z) 265 (M^+), 192, 77; HRMS Calcd for $C_{14}H_{13}F_2NO_2$: m/z 265.0914. Found: 265.0922.

4.1.15. Ethyl α,α-difluoro-α-[2-(indolyl)]acetate (14). ^{1}H NMR δ 8.68–8.46 (br, 1H), 7.66 (d, 1H, J=7.7 Hz), 7.43 (dd, 1H, J=8.1, 0.7 Hz), 7.30 (dt, 1H, J=7.7, 0.7 Hz), 7.16 (dt, 1H, J=8.1, 0.6 Hz), 6.89–6.86 (m, 1H), 4.38 (q, 2H, J=7.0 Hz), 1.3 (t, 3H, J=7.0 Hz); ^{13}C NMR δ 163.22 (t, J=34.7 Hz), 136.36, 127.814 (t, J=30.7 Hz), 126.18, 124.20, 121.69, 120.72, 111.56, 110.09 (t, J=248.7 Hz), 104.17 (t, J=5.0 Hz), 63.68, 13.99. ^{19}F NMR δ −24.12 (s, 2F); MS (m/z) 239 (M^+), 166; HRMS Calcd for $C_{12}H_{11}F_2NO_2$: m/z 239.0758. Found: 239.0756.

4.1.16. 3-(Diethoxyphosphonyldifluoromethyl)-2,3-dihydrofuran (15). ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.88–6.78(m, 1H), 4.51 (t, 2H, J=9.7 Hz), 4.34–4.23 (m, 4H), 2.87 (ddt, 2H, J=2.0, 2.0, 9.7 Hz), 1.39 (t, 6H, J=7.1 Hz). ^{31}P NMR δ 6.32 (ttt, 1P, J=117.3, 7.4, 7.4 Hz). ^{19}F NMR (254 MHz, $CDCl_3$) δ −27.68 (d, 2F, J=116.7 Hz); MS ((m/z) 256 (M^+), 119; HRMS m/z Calcd for $C_9H_{15}F_2O_4P$: 256.0676. Found: 256.0685.

4.1.17. 3-(Diethoxyphosphonyldifluorometyl)tetrahydrofuran (15′). ^{1}H NMR (270 MHz, $CDCl_3$) δ 4.34–4.23 (m, 4H), 4.00–3.74 (m, 4H), 3.09–2.82 (m, 1H), 2.21–2.01 (m, 2H), 1.39 (t, 6H, J=7.1 Hz). ^{31}P NMR δ 7.03 (tttd, 1P, J=108.4, 7.4, 7.4, 3.0 Hz). ^{19}F NMR (254 MHz, $CDCl_3$) δ −38.53 (ddd, 1F, J=301.5, 109.1, 16.6 Hz), −39.90 (ddd, 1F, J=301.5, 109.1, 16.6 Hz); MS (m/z) 258 (M^+); HRMS m/z Calcd for $C_9H_{17}F_2O_4P$: 258.0833. Found: 258.0848.

4.1.18. Diethyl α,α-difluoromethyl-α-phenylphosphonate (16). See Ref. 6a.

4.1.19. Diethyl α,α-difluoromethyl-α-[2-(furyl)]phosphonate (17). ^{1}H NMR δ 7.55 (dd, 1H, J=1.3, 1.0 Hz), 6.82 (dd, 1H, J=3.6, 1.0 Hz), 6.48 (dd, 1H, J=3.6, 1.3 Hz), 4.35–4.27 (m, 4H), 1.36 (t, 6H, J=6.9 Hz); ^{31}P NMR δ 4.93 (ttt, 1P, J=109.9, 7.4, 7.4 Hz). ^{19}F NMR δ −30.81 (d, 2F, J=109.0 Hz); MS (m/z) 254 (M^+); HRMS Calcd for $C_9H_{13}F_2O_4P$: m/z 254.0520. Found: 254.0539.

See Ref. 14.

4.1.20. Diethyl α,α-difluoromethyl-α-[2-(1-methylpyrrolyl)]phosphonate (19). ^{1}H NMR δ 6.69 (dd, 1H, $J=2.6$, 1.8 Hz), 6.56 (dd, 1H, $J=3.4$, 1.8 Hz), 6.10 (dd, 1H, $J=3.4$, 2.6 Hz), 4.33–4.09 (m, 4H), 3.80 (s, 3H), 1.34 (t, 6H, $J=$ 7.0 Hz); ^{31}P NMR δ 6.36 (ttt, 1P, $J=117.3$, 7.4, 7.4 Hz). ^{19}F NMR δ −24.48 (d, 2F, $J=116.67$ Hz); MS (*m*/*z*) 267 (M^+), 130; HRMS Calcd for $C_{10}H_{16}F_2NO_3P$: *m*/*z* 267.0836. Found: 267.0823.

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