Aromatic Substitution with Photochemically Generated Difluoromethyl Radicals Bearing Electron-Withdrawing Group

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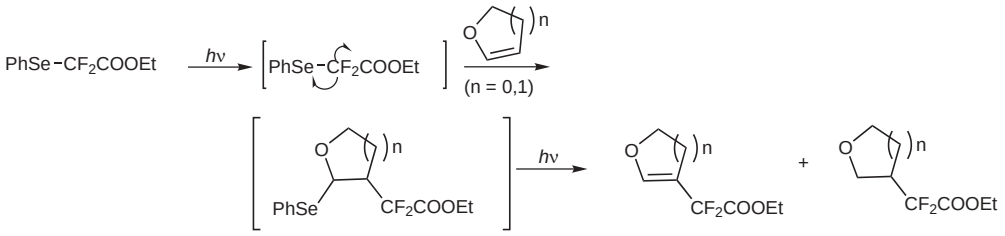
Abstract: Novel and facile aromatic and heteroaromatic substitutions with difluoromethyl radicals bearing electron-withdrawing group generated by the photo-initiated Se-CF_2 bond cleavage of ethyl α,α-difluoro-α-(phenylseleno)acetate and diethyl α,α-difluoromethyl-α-(phenylseleno)phosphonate were successfully carried out to provide the corresponding α-aryl-α,α-difluoroacetates and α-aryl-α,α-difluoromethylphosphonates in good to moderate yields.

Key words: radical aromatic substitution, photoreaction, α-aryl-α,α-difluoroacetate, α-aryl-α,α-difluoromethylphosphonate, selenide

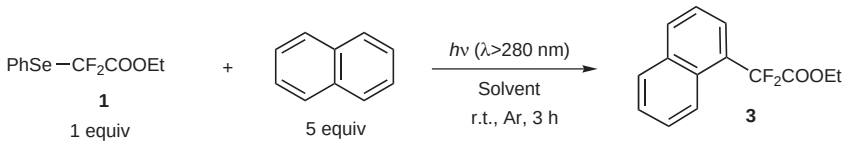
Difluoromethylene compounds have attracted a great deal of interest due to their unique biological activities.[1] For example, CF_2/O transposition in methylenephosphonate has proven to be one of the most valuable approaches to the preparation of hydrolytically stable functional groups as phosphonate mimetics.[2] Moreover, a number of aryldifluoromethylene compounds have potential biological activities.[3] In general, aryldifluorometylene compounds have been prepared using DAST,[4] NFBS,[5] cross coupling reactions,[3,6] and electrochemical oxidation.[7] However, their preparation, particularly synthesis of heteroaryldifluoromethylene compounds is still limited.

On the other hand, homolytic aromatic substitution with electrophilic carbon radicals is known to be one of the useful C-C bond formation at an aromatic ring. Baciocchi et al.[8] and Byers et al.[9] have demonstrated radical aromatic substitution of heteroaromatics with methyl radicals having various electron-withdrawing group(s) generated from the corresponding bromides and iodides using $Et_3B/O_2/Fe^{3+}$ and photoirradiation, respectively.



Scheme1

Table 1 Photoreaction of **1** with Naphthalene in Various Solvents



Run	Solvent	Yield (%)[a]
1	CH_2Cl_2	53 (49)
2	MeCN	35
3	*n*-Hexane	35
4	*i*-PrOH	15

[a] Determined by ^{19}F NMR spectroscopy. In parenthesis, isolated yield.

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In our previous work, we showed that photolysis of ethyl α,α-difluoro-α-(phenylseleno)acetate (**1**) in the presence of various olefins afforded saturated and unsaturated regioselective difluoromethylene adducts as shown in Scheme 1.[10]

These facts prompted us to carry out photochemical aromatic and heteroaromatic substitution reactions with CF_2EWG [EWG = COOEt, P(O)$(OEt)_2$] generated from **1** and diethyl α,α-difluoromethyl-α-(phenylseleno)phosphonate (**2**).[11]

At first, the photolysis of **1** in the presence of naphthalene as a model aromatic compound was carried out in various solvents for 3 hours.[12] The results are summarized in Table 1.

In all cases, the expected aromatic substitution took place and the difluoromethylene group was introduced regioselectively to the α-position of naphthalene. The best result (57%) was obtained in dichloromethane (run 1). On the other hand, the use of acetonitrile and hexane gave the desired product **3**[13] in lower yields (runs 2 and 3). In contrast, when *i*-PrOH was employed as a hydrogen atom donor, the yield of **3** decreased drastically (run 4).

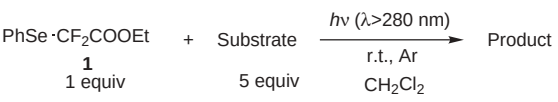
Since dichloromethane was found to be the most suitable solvent, the photochemical reaction was extended to various benzene derivatives, using dichloromethane as a solvent.

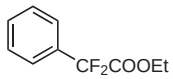
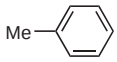
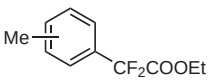
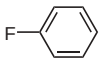
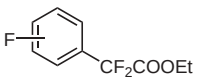
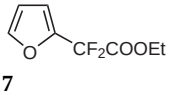
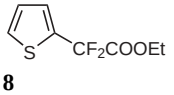
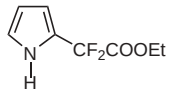
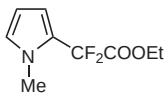
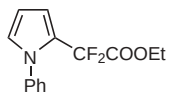
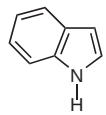
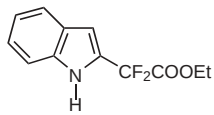
As shown in Table 2,[14] the substitution reaction proceeded to give difluorometylene-substituted products in good to moderate yields and their structures were established by analyses of ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, MS, and HRMS spectra. Photoreactions of **1** with toluene provided a mixture of *o*-, *m*-, and *p*- substituted products in good total yield (run 2). However, the regioisomers could not be specified. Moreover, the reaction was applicable to various heteroaromatic compounds: the substitution with the difluoromethylene group at the α-position of heteroaromatic compounds proceeded regioselectively to provide the corresponding products **7**–**12** in moderate to reasonable yields (runs 4–9). Notably, even in the photochemical reactions of **1** with 1-phenylpyrrole and indole, the substitution at the α-position of the pyrrole ring took place exclusively and the substitution on the benzene ring did not take place at all (runs 8 and 9).

Finally, we tried similarly the photochemical reactions of diethyl α,α-difluoromethyl-α-(phenylseleno)phosphonate (**2**) with aromatic and heteroaromatic compounds in order to prepare potential inhibitors of protein tyrosine phosphatases (PTPs) and sugar analogues. The results are summarized in Table 3.[15]

Regardless of aromatics, the difluoromethylene unit was introduced to their α-positions exclusively (runs 2–4). The photoreaction of **2** with benzene gave the desired substitution product **13** in the highest yield (59%). Even heteroaromatics like furan and *N*-methylpyrrole underwent similar regioselective substitution reactions to provide the desired products **15** and **16** in reasonable yields. In all cases except for run 3, diethyl α,α-difluoromethylphosphonate (**17**) was formed as a by-product and a considerable amount of diphenyl diselenide was also detected in all cases (Table 1–3). These facts clearly indicate that homolytic cleavage of a Se-CF_2 bond took place by the photolysis of **1** and **2**. Although the detailed reaction mechanism for the photochemical aromatic substitution has not been clarified yet, the reaction seems to involve phenylselenyl transfer at the early stage followed by the elimination of a phenylselenyl group from the adducts **A**

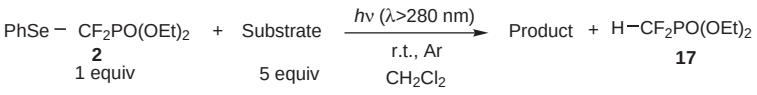
Table 2 Photoreaction of **1** with Various Aromatic and Heteroaromatic Compounds

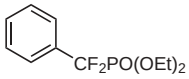
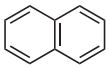
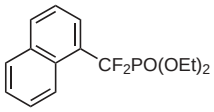
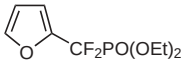
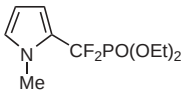


Run	Substrate	Time (h)	Product	Yield (%)[a]
1[b]		9	 **4**	60 (53)
2[b]		3	 **5**	70 (60)[c]
3[b]		8	 **6**	66 (44) (o:*m*:*p* = 2:3:1)
4[b]		6	 **7**	29 (26)
5[b]		8	 **8**	44 (34)
6		4	 **9**	44 (40)
7		4	 **10**	68 (65)
8		6	 **11**	49 (46)
9		9	 **12**	16 (13)

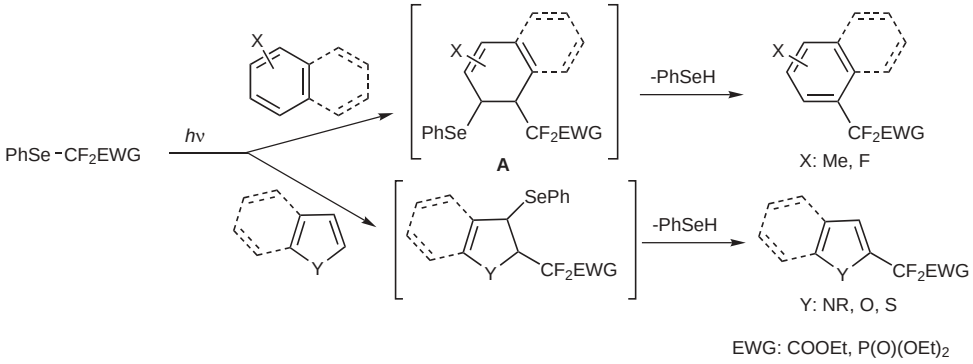
[a] Determined by ^{19}F NMR spectroscopy. In parentheses, isolated yields.
[b] Neat condition.
[c] Diastereomeric mixture.

Table 3 Photoreaction of **2** with Various Aromatic and Heteroaromatic Compounds



Run	Substrate	Time (h)	Product	Yield[a] Product (%)	**17** (%)
1[b]		9	 **13**	59 (53)	8
2		3	 **14**	25 (20)	36
3[b]		6	 **15**	37 (26)	–
4		8	 **16**	26 (20)	23

[a] Determined by ^{19}F NMR spectroscopy. In parentheses, isolated yields.
[b] Neat condition.



Scheme 2

once formed to provide aromatized products substituted with difluoromethylene groups as shown in Scheme 2.[16]

In conclusion, we have developed the novel and facile aryl-CF_2 bond formation reaction using photo-initiated Se-CF_2 bond cleavage of ethyl α,α-difluoro-α-(phenylseleno)acetate and diethyl α,α-difluoromethyl-α-(phenylseleno)phosphonate in the presence of various aromatic and heteroaromatic compounds. This method seems to be highly useful for the preparation of various aryl-CF_2 compounds in one-step.

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(12) **Typical Procedure for Photoreaction:** A solution of **1** or **2** (0.17 mmol) and an aromatic compound (0.85 mmol) in CH_2Cl_2 (40 mL) or without solvent was bubbled with Ar at r.t. for 0.5 h and then photolyzed for 3 h with 100 W high-pressure mercury-vapor lamp. The reaction was conducted using 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 eluent) to provide pure products.
(13) Ethyl α,α-difluoro-α-[1-(naphthyl)]acetate (**3**):^{1}H NMR: δ = 8.19 (d, 1 H, *J* = 7.3 Hz), 7.99–7.84 (m, 3 H), 7.59–7.49 (m, 3 H), 4.28 (q, 2 H, *J* = 7.0 Hz), 1.23 (t, 3 H, *J* = 7.0 Hz). ^{13}C NMR: δ = 164.25 (t, *J* = 34.6 Hz), 133.75, 131.83, 129.25 (t, *J* = 2.8 Hz), 128.74, 128.36, 127.21, 126.20, 124.79 (t, *J* = 11.5 Hz), 124.47, 124.14 (t, *J* = 3.3 Hz), 114.27 (t, *J* = 251.6 Hz), 63.27, 13.93. ^{19}F NMR: δ = –23.49 (s, 2 F). MS: *m/z* = 250 (M^+), 177. HRMS calcd for $C_{14}H_{12}F_2O_2$: *m/z* = 250.0805. Found: 250.0804.
(14) (a) Ethyl α,α-difluoro-α-(phenyl)acetate (**4**): See ref.[6]. (b) A mixture of ethyl α,α-difluoro-α-(*o*-, *m*-, and *p*-tolyl)acetates (**5**): ^{1}H NMR: δ = 7.58–7.21 (m, 4 H), 4.32 (q, 0.9 H, *J* = 7.1 Hz), 4.30 (q, 0.7 H, *J* = 7.1 Hz), 4.29 (q, 0.4 H, *J* = 7.1 Hz), 2.42 (s, 1 H), 2.41 (s, 0.7 H), 2.40 (s, 1.3 H), 1.31 (t, 1.3 H, *J* = 7.1 Hz), 1.30 (t, 1.7 H, *J* = 7.1 Hz). ^{19}F NMR: δ = –24.8 (s, 2 F), –26.9 (s, 2 F), –27.2 (s, 2 F). MS: *m/z* = 214 (M^+), 141. (c) Ethyl α,α-difluoro-α-(*o*-fluorophenyl)acetate (**6**): ^{1}H NMR: δ = 7.68–7.62 (m, 1 H), 7.54–7.46 (m, 1 H), 7.29–7.23 (m, 1 H), 7.17–7.10 (m, 1 H), 4.36 (q, 2 H, *J* = 7.0 Hz), 1.32 (t, 3 H, *J* = 7.0 Hz). ^{13}C NMR: δ = 163.09 (t, *J* = 34.0 Hz), 132.93 (d, *J* = 8.4 Hz), 127.00 (dt, *J* = 7.3, 2.2 Hz), 124.17 (d, *J* = 3.4 Hz), 120.84 (dt, *J* = 25.7, 12.3 Hz), 116.34, 116.03, 115.52 (t, *J* = 251.0 Hz), 63.36, 13.90. ^{19}F NMR: δ = –25.45 (d, 2 F, *J* = 5.6 Hz), –37.78–37.93 (m, 1 F). MS: *m/z* = 218 (M^+), 145, 95. HRMS calcd for $C_{10}H_9F_3O_2$: *m/z* = 218.0555. Found: 218.0563. (d) Ethyl α,α-difluoro-α-(*m*-fluorophenyl)acetate (**6**): ^{1}H NMR: δ = 7.48–7.11 (m, 4 H), 4.31 (q, 2 H, *J* = 7.0 Hz), 1.31 (t, 3 H, *J* = 7.0 Hz). ^{13}C NMR: δ = 163.55 (t, *J* = 35.2 Hz), 130.41 (d, *J* = 8.4 Hz), 121.15 (dt, *J* = 6.1, 2.8 Hz), 118.22 (t, *J* = 3.7 Hz), 117.91 (t, *J* = 3.7 Hz), 115.92 (t, *J* = 22.4 Hz), 112.96 (dt, *J* = 24.1, 6.7 Hz), 112.15 (t, *J* = 252.7 Hz), 63.4, 14.2. ^{19}F NMR: δ = –27.25 (s, 2 F), –34.63–35.54 (m, 1 F). MS: *m/z* = 218 (M^+), 145, 95. HRMS calcd for $C_{10}H_9F_3O_2$: *m/z* = 218.0555. Found: 218.0538. (e) Ethyl α,α-difluoro-α-(*p*-fluorophenyl)acetate (**6**): ^{1}H NMR: δ = 7.63–7.58 (m, 2 H), 7.17–7.11 (m, 2 H), 4.30 (q, 2 H, *J* = 7.3 Hz), 1.31 (t, 3 H, *J* = 7.1 Hz). ^{19}F NMR: δ = –26.47 (s, 2 F), –32.41–32.49 (m, 1 F). MS: *m/z* = 218 (M^+), 145, 95. HRMS calcd for $C_{10}H_9F_3O_2$: *m/z* = 218.0555. Found: 218.0560. (f) Ethyl α,α-difluoro-α-[2-(furyl)]acetate(**7**): ^{1}H NMR: δ = 7.52 (dd, 1 H, *J* = 1.65, 0.8 Hz), 6.76 (dd, 1 H, *J* = 3.3, 0.8 Hz), 6.46 (dd, 1 H, *J* = 3.3, 1.7 Hz), 4.38 (q, 2 H, *J* = 7.0 Hz), 1.36 (t, 3 H, *J* = 7.0 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, 2 F). MS: *m/z* = 190 (M^+), 117. HRMS calcd for $C_8H_8F_2O_3$: *m/z* = 190.0442. Found: 190.0424. (g) Ethyl α,α-difluoro-α-[2-(thienyl)]acetate (**8**): See ref. 3b. (h) Ethyl α,α-difluoro-α-[2-(pyrrolyl)]acetate (**9**): ^{1}H NMR: δ = 9.03–8.55 (br. 1 H), 6.90 (dd, 1 H, *J* = 2.6, 1.8 Hz), 6.55 (dd, 1 H, *J* = 3.3, 1.8 Hz), 6.24 (dd, 1 H, *J* = 3.3, 2.6 Hz), 4.36 (q, 2 H, *J* = 7.3 Hz), 1.37 (t, 3 H, *J* = 7.3 Hz). ^{19}F NMR: δ = –21.32 (s, 2 F). MS: *m/z* = 189 (M^+), 116. HRMS calcd for $C_8H_9F_2NO_2$: *m/z* = 189.0601. Found: 189.0591. (i) Ethyl α,α-difluoro-α-[2-(1-methyl-pyrrolyl)]acetate (**10**):^{1}H NMR: δ = 6.70 (dd, 1 H, *J* = 2.8, 2.0 Hz), 6.40 (dd, 1 H, *J* = 3.8, 2.0 Hz), 6.10 (dd, 1 H, *J* = 3.8, 2.8 Hz), 4.38 (q, 2 H, *J* = 7.0 Hz), 3.76 (s, 3 H), 1.37 (t, 3 H, *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, 2 F). MS: *m/z* = 203 (M^+), 130. HRMS calcd for $C_9H_{11}F_2NO_2$: *m/z* = 203.0758. Found: 203.0764. (j) Ethyl α,α-difluoro-α-[2-(1phenyl-pyrrolyl)]acetate (**11**):^{1}H NMR: δ = 7.40–7.30 (m, 5 H), 6.90 (dd, 1 H, *J* = 2.6, 2.0 Hz), 6.60 (dd, 1 H, *J* = 3.6, 2.0 Hz), 6.30 (dd, 1 H, *J* = 3.6, 2.6 Hz), 4.13 (q, 2 H, *J* = 7.3 Hz), 1.21 (t, 3 H, *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, 2 F). MS: *m/z* = 265 (M^+), 192, 77. HRMS calcd for $C_{14}H_{13}F_2NO_2$: *m/z* = 265.0914. Found: 265.0922. (k) Ethyl α,α-difluoro-α-[2-(indolyl)]acetate (**12**): ^{1}H NMR: δ = 8.68–8.46 (br, 1 H), 7.66 (d, 1 H, *J* = 7.7 Hz), 7.43 (dd, 1 H, *J* = 8.1, 0.7 Hz), 7.30 (dt, 1 H, *J* = 7.7, 0.7 Hz), 7.16 (dt, 1 H, *J* = 8.1, 0.6 Hz), 6.89–6.86 (m, 1 H), 4.38 (q, 2 H, *J* = 7.0 Hz), 1.30 (t, 3 H, *J* = 7.0 Hz). ^{13}C NMR: δ = 163.22 (t, *J* = 34.7 Hz), 136.36, 127.81 (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, 2 F). MS: *m/z* = 239 (M^+), 166. HRMS calcd for $C_{12}H_{11}F_2NO_2$: *m/z* = 239.0758. Found: 239.0756.
(15) (a) Diethyl α,α-difluoromethyl-α-(phenyl)phosphonate(**13**): See ref.[3a] (b) Diethyl α,α-difluoromethyl-α-[1-(naphthyl)]phosphonate (**14**): See ref.[3a] (c) Diethyl α,α-difluoromethyl-α-[2-(furyl)]phosphonate (**15**):^{1}H NMR: δ = 7.55 (dd, 1 H, *J* = 1.3, 1.0 Hz), 6.82 (dd, 1 H, *J* = 3.6, 1.0 Hz), 6.48 (dd, 1 H, *J* = 3.6, 1.3 Hz), 4.35–4.27 (m, 4 H), 1.36 (t, 6 H, *J* = 6.9 Hz). ^{19}F NMR: δ = –110.97 (d, 2 F, *J* = 31.2 Hz). MS: *m/z* = 254 (M^+), 117. HRMS calcd for $C_{10}H_{16}F_2NO_3P$: *m/z* = 254.0520. Found: 254.0539. (d) Diethyl α,α-difluoromethyl-α-[2-(1-methyl-pyrrolyl)]phosphonate (**16**): ^{1}H NMR: δ = 6.69 (dd, 1 H, *J* = 2.6, 1.8 Hz), 6.56 (dd, 1 H, *J* = 3.4, 1.8 Hz), 6.10 (dd, 1 H, *J* = 3.4, 2.6 Hz), 4.33–4.09 (m, 4 H), 3.80 (s, 3 H), 1.34 (t, 6 H, *J* = 7.0 Hz). ^{19}F NMR: δ = –24.48 (d, 2 F, *J* = 116.7 Hz). MS: *m/z* = 267 (M^+), 130. HRMS calcd for $C_{10}H_{16}F_2NO_3P$: *m/z* = 267.0836. Found: 267.0823.
(16) In support of this, Byers et al. detected a phenylselenyl transfer product as an intermediate in the photolysis of phenyl-selenomalonates in the presence of indoles.[9] The inter-mediate adduct was too unstable to be isolated and the elimination of PhSeH provided the substituted indole derivatives.