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Photochemical generation of difluoromethyl radicals having various functional groups and their highly regioselective addition to olefins and aromatic substitution

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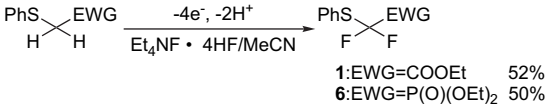
Dedicated to the late Professor Yoshihiko Ito of Kyoto University

Abstract—Difluoromethyl radicals bearing ester, phosphonate, nitrile, cyclic carbonate, and carbamate groups were generated by the photoinitiated S–CF_2 bond cleavage of electrosynthesized α,α-difluorosulfides, and their addition to olefins and aromatic substitution were successfully carried out to provide the regioselective adducts and substitution products in moderate yields. The yields of substitution products increased by the addition of diphenyl diselenide and 2,4,6-trimethylpyridine.

1. Introduction

As building blocks for constructing biologically active compounds, organofluorine molecules hold huge promise for the pharmaceutical and agrochemical industry due to the high electronegativity and the small van der Waals radius of a fluorine atom.[1] In particular, a variety of difluoromethylene compounds have attracted much attention in medicinal science.[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. For the synthesis of various difluoromethylene compounds, molecular conversion is commonly used as the CF_2-synthon approach. For example, the Reformatsky reactions of halodifluoroacetates have been reported.[4] The conversions of trifluoromethylated compounds such as α,α,α-trifluoroketons[5] and β,β,β-trifluoroethanol[6] to *gem*-difluorinated compounds have also been reported. Moreover, metal[7] and radical initiator catalyzed,[8] and electrocatalytic[9] radical addition of difluorohalo esters, ketones and phosphonates across alkenes has been studied intensively.

On the other hand, chemical fluorination is also a common tool for the construction of difluoromethylene group.[1] Diethylamino sulfurtrifluoride (DAST),[10] 2,2-difluoro-1,3-dimethylimidazolidine (DFI),[11] and (1-chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]-octane bis(tetrafluoroborate) (Selectfluor)[12] serve as the reagents of direct difluorination. In particular, electrochemical partial fluorination of organic compounds has been shown to be a powerful method for selective fluorination.[13] Previously, we successfully carried out anodic difluorination of various sulfides to provide the corresponding *gem*-difluorinated products in moderate yields (Scheme 1).[14]



Scheme 1.

In the anodic fluorination, phenylsulfanyl groups have been used as electroauxiliaries. α,α-Difluorosulfides are expected to be good precursors to difluoromethyl radicals by the homolytic cleavage of the S–CF_2 bond. In fact, Lequex, Piettre and co-workers reported homolytic cleavage of the S–CF_2 bond of sulfanyldifluoromethylphosphonate using AIBN/*n*-Bu_3SnH in the presence of various olefins to provide saturated adducts.[15] However, the reaction requires a toxic reagent like *n*-Bu_3SnH. On the other hand, photochemical reaction is a typical green sustainable process. Therefore in this paper, we investigated photoinitiated S–CF_2 bond cleavage of various α,α-difluorinated sulfides in order to generate the corresponding difluoromethyl radicals, which can be trapped with various unsaturated compounds. This concept has prompted us to develop a synthetic method for various difluoromethylene compounds.

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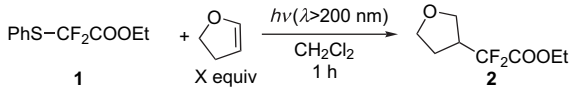
Table 1. Photoreaction of **1** in the presence of 2,3-dihydrofuran



Run	X	Yield of **2**[a] (%)
1	5	34
2	10	56
3	30	65
4	50	73
5	100	78

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

2. Results and discussions

2.1. The photoreaction of ethyl α,α-difluoro-α-(phenylthio)acetate (1) with various olefins

At first, we examined the potential of **1** as the precursor of difluoromethyl radical by the homolytic dissociation of the S–CF_2 bond using ultra-violet light. The photolysis of **1** in CH_2Cl_2 using a 6-W low-pressure mercury-vapor lamp through quartz filter in the presence of electron rich olefin, 2,3-dihydrofuran as a model olefin, was carried out until **1** was completely consumed. The results are summarized in Table 1.

In all cases, the homolysis of the S–CF_2 bond took place to provide a radical adduct **2** in good to moderate yields. Moreover, the difluoromethyl group was introduced to the 3-position of 2,3-dihydrofuran exclusively. The yield increased with amount of 2,3-dihydrofuran used (runs 1–5). However, in the cases of runs 3–5, the reaction became complicated owing to considerable formation of unidentified by-products like oligomer or polymer, which deposited on the wall of the reaction vessel. Therefore, the use of 10 equiv amounts of 2,3-dihydrofuran seems to be the most suitable reaction condition (run 2). Previously, we obtained the mixture of the difluoromethylene-substituted products (unsaturated products) and the radical adducts (saturated products) via the phenylselenyl group transfer reactions by the photochemical cleavage of the Se–CF_2 bond in the presence of various olefins as shown in Scheme 2.[16]

Interestingly, in contrast to the selenide (Scheme 2), the radical adduct (saturated product) such as compound **2** was formed exclusively in the case of sulfide **1**.

In order to disclose differences of the reactivity between sulfide and selenide, we investigated the time-course of the photochemical reaction of **1** with 2,3-dihydrofuran, 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

Figure 1. The yield of **2** (■) and the recovery of **1** (◆) in the time-course of photoreaction of 1 with 2,3-dihydrofuran.

radical adduct **2** increased linearly. The phenylsulfanyl group transfer adduct was not observed. Instead, the formation of diphenyl disulfide was confirmed by GC–MS. Therefore, this reaction seems to be normal radical reaction (Scheme 3).

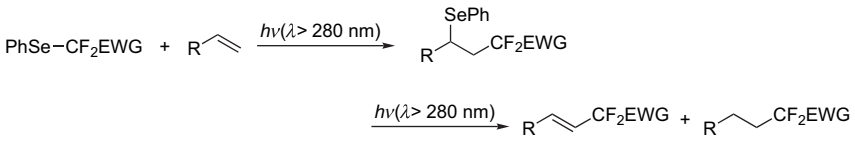
When the homolytic cleavage of the S–CF_2 bond takes place by photolysis of **1** in the presence of 2,3-dihydrofuran, the radical addition proceeds to provide the radical intermediate **A**, and then the intermediate **A** seems to abstract a hydrogen atom from unreacted 2,3-dihydrofuran or the solvent.

Therefore, we examined the photoreaction of **1** with 2,3-dihydrofuran in CD_2Cl_2 as shown in Scheme 4.

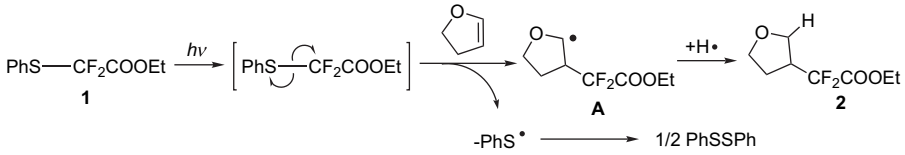
In this reaction, deuterated product **2′** was not formed at all and **2** was obtained exclusively. This clearly suggested that the radical intermediate **A** (Scheme 3) does not abstract a hydrogen atom from CH_2Cl_2 solvent. Therefore, the hydrogen radical source for the formation of **2** would be unreacted 2,3-dihydrofuran.

Next, we carried out the photochemical reaction of **1** with various olefins. The results are shown in Table 2.

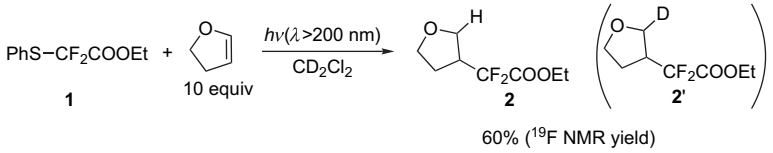
Regardless of the molecular structures of olefins employed, the homolytic cleavage of the S–CF_2 bond of **1** took place, and the expected radical adducts **3–5** were formed in moderate yields. Notably, the addition of difluoromethyl radical to the terminal position of acyclic vinyl ether and olefin took place exclusively (runs 1 and 3).



Scheme 2.

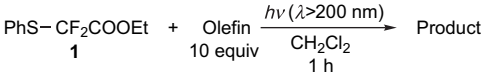


Scheme 3.



Scheme 4.

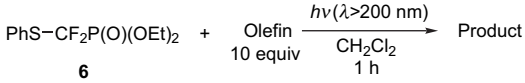
Table 2. Photoreaction of **1** with various olefins



Run	Olefin	Product	Yield[a] (%)
1	*t*-BuO	*t*-BuO, CF$_2$COOEt, **3**	44
2		CF$_2$COOEt, **4**	32
3	*n*-C$_5$H$_{11}$	*n*-C$_5$H$_{11}$, CF$_2$COOEt, **5**	37

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

Table 3. Photoreaction of **6** with various olefins



Run	Olefin	Product	Yield[a] (%)
1		CF$_2$P(O)(OEt)$_2$, **7**	56
2	*t*-BuO	*t*-BuO, CF$_2$P(O)(OEt)$_2$, **8**	49
3		CF$_2$P(O)(OEt)$_2$, **9**	31
4	*n*-C$_5$H$_{11}$	*n*-C$_5$H$_{11}$, CF$_2$P(O)(OEt)$_2$, **10**	44

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

2.2. The photoreaction of diethyl α,α-difluoromethyl-α-(phenylthio)phosphonate (6) with various olefins

Next, we extended the photochemical reaction to sulfides **6** having a phosphonate group. The results are summarized in Table 3.

Regardless of olefins, the photoreaction proceeded to give difluoromethylene adducts **7**–**10** in moderate yields. Interestingly, the difluoromethyl radical derived from **6** was introduced to the 3-position of 2,3-dihydrofuran (run 1) and the terminal position of *tert*-butyl vinyl ether and 1-heptene exclusively (runs 2 and 4).

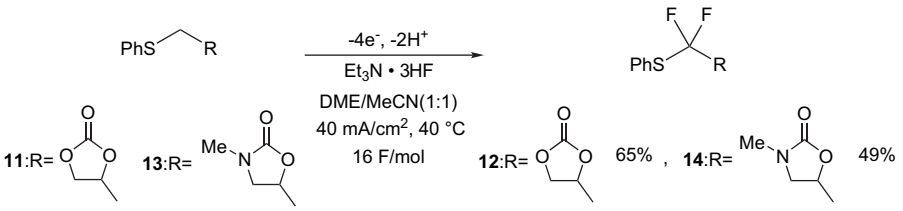
Thus, we successfully carried out the photoinitiated homolytic cleavage of the S–CF$_2$ bond leading to the generation of difluoromethyl radicals bearing electron-withdrawing groups such as ester and phosphonate, and we achieved their regioselective addition to various cyclic and acyclic olefins.

2.3. The photoreaction of 4-[difluoro(phenylthio)-methyl]-1,3-dioxolane (12) and 5-[difluoro(phenylthio)-methyl]-3-methyloxazolidinone (14) with various olefins

Next, we examined the photoreaction similarly using α,α-difluorosulfides **12** and **14** having cyclic carbonate and cyclic carbamate groups. Since **12** and **14** have multiple functional groups, we expected that difluorinated compounds derived from **12** and **14** can be converted to other useful organofluorine compounds.

Previously, we successfully carried out anodic fluorination of 4-[(phenylthio)methyl]-1,3-dioxolan-2-one (**11**)[17] to provide the corresponding *gem*-difluorinated product **12** in moderate yield (Scheme 5). Therefore, in order to obtain α,α-difluorinated sulfide bearing an oxazolidinone ring **14**, we first attempted α,α-difluorination of 4-[(phenylthio)-methyl]-*N*-methyloxazolidinone (**13**). The anodic difluorination of **13** was carried out under constant current at platinum electrodes in DME/MeCN (1:1) containing Et$_3$N·3HF at 40 °C using an undivided cell to provide the corresponding *gem*-difluorinated product **14** in ca. 50% yield (Scheme 5).

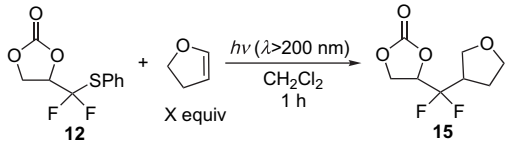
At first, we investigated the homolytic dissociation of the S–CF$_2$ bond of **12** using ultra-violet light in the presence of olefins. The photolysis of **12** was carried out in the presence of 2,3-dihydrofuran as a model olefin in CH$_2$Cl$_2$ using



Scheme 5.

a 6-W low-pressure mercury-vapor lamp through a quartz filter until **12** was completely consumed. The results are summarized in Table 4.

Table 4. Photoreaction of **12** in the presence of 2,3-dihydrofuran



Run	X	Yield of **15**[a] (%)
1	5	38
2	10	49
3	20	67(58)[b]

[a] Determined by ^{19}F NMR analyses. Isolated yield is shown in parenthesis.
[b] Diastereomeric mixture.

In all cases, the expected radical addition took place and the difluoromethylene group was introduced exclusively to the 3-position of 2,3-dihydrofuran. The yield increased with the amount of 2,3-dihydrofuran used, and the best result was obtained by using 20 equiv amounts of 2,3-dihydrofuran to **12** (run 3). Thus, we also achieved photoinitiated cleavage of S–CF_2 bond bearing cyclic carbonate followed by regioselective radical addition to 2,3-dihydrofuran.

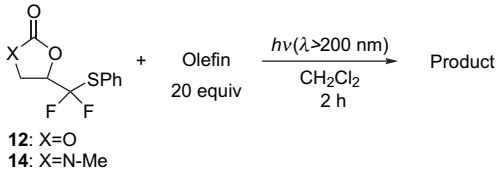
Next, we extended this photoreaction to various olefins. The results are shown in Table 5.

As expected, the radical adducts **16**–**18** were formed in moderate yields. Notably, the difluoromethylene group was also introduced to the terminal position of acyclic olefins exclusively (runs 1 and 3). In the case of **14**, the additions onto acyclic olefins using the photo-irradiation also took place smoothly and showed a complete regioselectivity (runs 5 and 7). Similarly to the photoreaction of **12**, the reaction of **14** in the presence of 2,3-dihydrofuran provided the regioselective adduct **19** exclusively in 66% yield (run 4). From these results, it is noted that sulfides bearing electron-withdrawing groups such as ester, phosphonate, cyclic carbonate, and cyclic carbamate behaved similarly as radical precursors under photo-irradiation.

2.4. The photochemical substitution of aromatic compounds with 12 and 14

Finally, we investigated aromatic substitution with photogenerated CF_2 radical having cyclic carbamate and carbonate. The photochemical substitution of aromatic compounds

Table 5. Photoreaction of **12** and **14** with various olefins



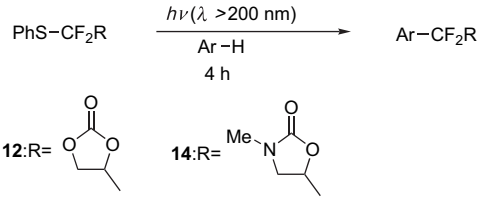
Run	X	Olefin	Product	Yield[a] (%)
1	O	*t*-BuO	*t*-BuO, F F **16**	45(40)
2			F F **17**	43(38)
3		n-C_5H_{11}	n-C_5H_{11}, F F **18**	48(40)
4	*N*–Me		Me, F F **19**	66(61)[b]
5		*t*-BuO	Me, *t*-BuO, F F **20**	58(52)
6			Me, F F **21**	66(57)
7		n-C_5H_{11}	Me, n-C_5H_{11}, F F **22**	50(45)

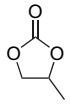
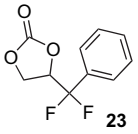
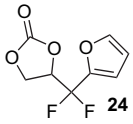
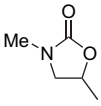
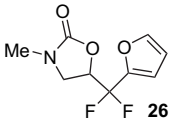
[a] Determined by ^{19}F NMR analyses. Isolated yield is shown in parenthesis.
[b] Diastereomeric mixture: ca. 1:1.

such as benzene and furan with **12** and **14** was carried out without any solvents. The results are summarized in Table 6.

Interestingly, in all cases, the aromatic substitution took place and the corresponding cross-coupling products

Table 6. Photoreaction of **12** and **14** with aromatic compounds



Run	R	Ar–H	Product	Yield[a] (%)
1			 **23**	22(20)
2			 **24**	24(20)
3			 **25**	22(19)
4			 **26**	19(16)

[a] Determined by ^{19}F NMR analyses. Isolated yields are shown in parentheses.

23–26 were obtained. Notably, in the case of furan, the substitution with the difluoromethyl radicals derived from **12** and **14** at the α-position of furan proceeded exclusively to provide the corresponding products **24** and **26** (runs 2 and 4). However, the yields of all products were low.

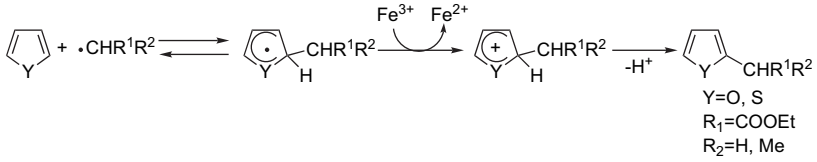
By the way, Baciocchi et al. reported heteroaromatic substitution with electrophilic carbon radicals generated by alkyl halides and triethylborane.[18] In the case of furan and thiophene, the yields of the substitution products were also low. They assume that the radical addition step is reversible, which results in low yields. Therefore, an oxidizing reagent like Fe^{3+} was added to shift the equilibrium to the right side to increase the yields as shown in Scheme 6.

On the other hand, we found recently that the aromatic substitution of α,α-difluoroselenides **27** having ester and phosphonate groups under photo-irradiation provided the corresponding substitution products in good to moderate yields.[19] This reaction seemed to involve phenylselenyl transfer followed by the elimination of a phenylselenol from the group transfer adduct **B** once formed to provide aromatized products (Scheme 7). Additionally, we found that the yields increased by the addition of diphenyl diselenide and 2,4,6-trimethylpyridine.[20] In this reaction, the radical intermediate **C** was converted into **B** by the addition of diphenyl diselenide, while the addition of 2,4,6-trimethylpyridine suppressed the behavior of phenylselenol as a good hydrogen atom donor to radical (Scheme 7).

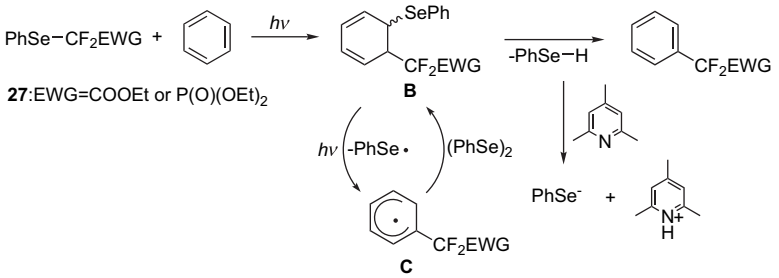
In the case of our aromatic substitution using **12** and **14**, the cleavage of the aryl–CF_2 bond of radical σ-complex **D** probably occurred similarly to Baciocchi's case as shown in Scheme 8. So, we tried to improve the yields of photochemical aromatic substitution using **12** and **14** by the addition of diphenyl diselenide to form phenylselenyl group transfer adduct **E** (Scheme 8).

We carried out the photoinduced substitution of aromatic compounds such as benzene and furan with **12** and **14** in the presence of diphenyl diselenide and 2,4,6-trimethylpyridine. The results are shown in Table 7.

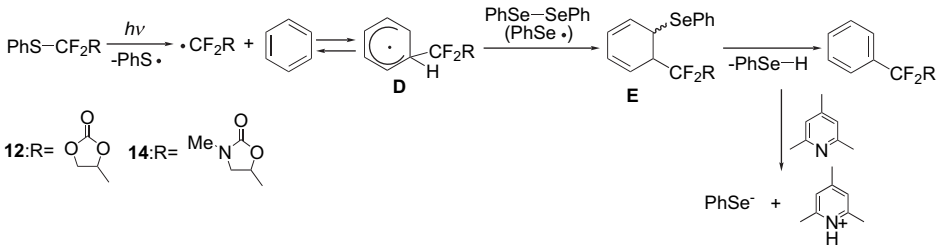
As expected, the yields increased twice for both benzene and furan in all cases although much longer photo-irradiation was required to complete the reaction. In the case of furan, the substitution with **12** and **14** at the α-position of furan also proceeded exclusively to provide the corresponding products **24** and **26** (runs 2 and 4).



Scheme 6.



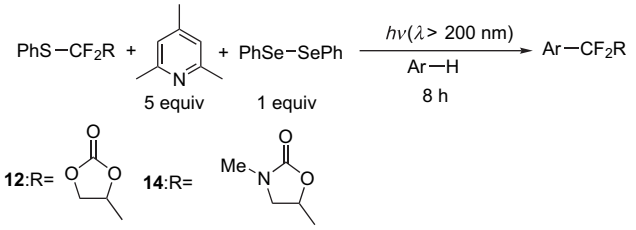
Scheme 7.

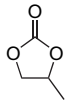
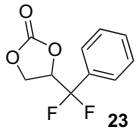
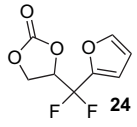
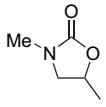
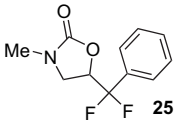
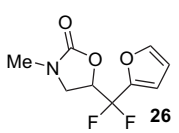


Scheme 8.

It is notable that the substitution of the difluoromethylene group took place at the α-position of furan exclusively while in the case of 2,3-dihydrofuran the addition of the difluoromethylene group occurred at its β-position exclusively. Such regioselectivities were similar to those of CF_2-containing selenides.[16,19,20]

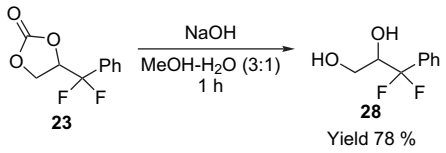
Table 7. Photoreaction of **12** and **14** with aromatic compounds in the presence of 2,4,6-trimethylpyridine and diphenyl diselenide



Run	R	Ar–H	Product	Yield[a] (%)
1			 **23**	46(44)
2			 **24**	44(41)
3			 **25**	40(37)
4			 **26**	43(39)

[a] Determined by ^{19}F NMR analyses. Isolated yields are shown in parentheses.

Finally, the utility of the products was demonstrated. Since a cyclic carbonate is a protecting group of 1,2-diols, the deprotection of the carbonate group of **23** as a model substrate was attempted as shown in Scheme 9. Alkaline hydrolysis of **23** was readily accomplished to provide the corresponding difluorinated diol **28** in good yield.



Scheme 9.

3. Conclusion

We have successfully carried out the photoinitiated S–CF_2 bond cleavage in the presence of various unsaturated compounds such as olefins and aromatics to provide regioselective addition and substitution products, respectively. Moreover, in the case of aromatic substitution, the yields were increased in the presence of diphenyl diselenide and 2,4,6-trimethylpyridine. Thus, we demonstrated that the photochemical generation of difluoromethyl radicals bearing various substituent groups from the corresponding electrosynthesized α,α-difluorosulfides followed by their additions onto alkenes and aromatic substitutions provides new approach for the construction of potentially bioactive compounds.

4. Experimental

4.1. General procedure

^1H, ^{13}C, and ^{19}F NMR spectra were recorded at 270, 68, and 254 MHz, respectively, on a JEOL-NM-EX 270 in $CDCl_3$ as a solvent with tetramethylsilane (0.00 ppm) as internal standard. ^{31}P NMR spectra were recorded at 122 MHz on a JEOL ECP-300 in $CDCl_3$ as a solvent. The chemical shifts for ^{19}F and ^{31}P are given in δ parts per million downfield from internal monofluorobenzene and phosphoric acid, respectively. The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet and m, multiplet. Mass spectra were obtained by EI method with a SHIMADZU Model GCMS-QP5050A. High-resolution mass spectra (HRMS) were taken on a JEOL MStation JMS-700 mass spectrometer in the electron impact mode at 70 eV. FAB mass spectra (HRFAB-MS) were also recorded on a JEOL MStation JMS-700 mass spectrometer using 3-nitrobenzyl alcohol as a matrix. Preparative photoreactions were carried out using a low-pressure mercury-vapor lamp UVL6DH-12 (SEN LIGHTS CORP. products).

4.2. General procedure for photoreaction

A solution of **1** or **6** (0.043 mmol) and olefin (0.43 mmol) in CH_2Cl_2 (10 mL) was bubbled with Ar at room temperature

for 0.5 h and then photolyzed for 1 h with 6-W low-pressure mercury-vapor lamp. The reaction was conducted using a quartz vessel inside the light source. After the photolysis, the resulting solution was evaporated under vacuum and the residue was purified by preparative thin-layer chromatography (MERCK Silica gel 60 GF_{254}, 20% or 50% EtOAc in hexane) or by HPLC (Develosil ODS-5, MeCN as eluant) to provide pure products.

4.3. Synthesis of 5-(phenylthio)methyl-3-methyloxazolidinone (13)

To a solution of 5-chloromethyl-2-oxazolidine (0.68 g, 5 mmol) and benzenethiol(0.66 g, 6 mmol) in DMF (30 mL) was added potassium carbonate (1.38 g, 10 mmol) at room temperature and the solution was stirred for 12 h. After the reaction, water was added to the solution. The resulting solution was extracted repeatedly with ethyl acetate and the extracts were dried over $MgSO_4$. The extracted solvent was concentrated in vacuo and the residue was dissolved in DMF (30 mL), and then sodium hydride (0.24 g, 10 mmol) was added to the DMF solution at −20 °C. After the solution was stirred for 30 min, methyl iodide (1.41 g, 10 mmol) was added and stirred at room temperature for 1 h. After the reaction, water was added. The resulting solution was extracted repeatedly with ethyl acetate and the extracts were dried over $MgSO_4$. The extracted solvent was removed by evaporation, and the remaining material was subjected to column chromatography on silica gel (hexane:EtOAc=4:1) to give 0.85 g (76% yield) of pure 5-(phenylthio)methyl-3-methyloxazolidinone (**13**).

4.4. Electrochemical difluorination of 5-(phenylthio)-methyl-3-methyloxazolidinone (13)

Constant current electrolysis (40 mA/cm^2) of **13** was carried out at platinum electrodes (2×2 cm^2) at 40 °C in DME/MeCN (5 mL/5 mL) containing 0.3 M $Et_3N{\cdot}3HF$ using an undivided cell. After electrolysis, the supporting electrolyte was removed by silica gel short column chromatography. The product **14** was isolated in 49% yield by silica gel column chromatography (EtOAc:hexane=1:3).

4.5. Ethyl α,α-difluoro-α-(phenylthio)acetate (1)

See Ref. 14.

4.6. 3-(Ethoxycarbonyldifluoromethyl)tetrahydrofuran (2)

See Ref. 16.

4.7. Ethyl 5-*tert*-butoxy-2,2-difluorobutanoate (3)

See Ref. 16.

4.8. Ethyl 2,2-difluoro-2-cyclohexylacetate (4)

See Ref. 16.

4.9. Ethyl 2,2-difluorononanate (5)

See Ref. 7(b).

4.10. Diethyl α,α-difluoromethyl-α-(phenylthio) phosphonate (6)

See Ref. 14.

4.11. 3-(Diethoxyphosphonyldifluoromethyl)tetrahydrofuran (7)

See Ref. 20.

4.12. Diethyl 3-*tert*-butoxy-1,1-difluoropropylphosphonate (8)

Oil; ^1H NMR δ 4.27 (m, 4H), 3.64 (t, 2H, J=7.4 Hz), 2.33 (m, 2H), 1.38 (t, 6H, J=7.1 Hz), 1.20 (s, 9H). ^{19}F NMR δ −35.7 (dt, 2F, J=107.1, 20.0 Hz). ^{13}C NMR δ 120.0 (td, J=258.8, 216.3 Hz), 73.4, 64.4 (d, J=6.7 Hz), 54.5 (td, J=6.1, 6.1 Hz), 35.4 (td, J=19.6, 14.5 Hz), 27.5, 16.5 (d, J=5.6 Hz). HRFAB-MS m/z calcd for $C_{11}H_{24}F_2O_4P$ (M^++H): 289.1380. Found: 289.1382.

4.13. Diethyl 1-cyclohexyl-1,1-difluoromethylphosphonate (9)

See Ref. 8(b).

4.14. Diethyl 1,1-difluorooctylphosphonate (10)

See Ref. 7(c).

4.15. 4-(Phenylthio)methyl-1,3-dioxlan-2-one (11)

See Ref. 17(b).

4.16. 4,4-Difluoro-4-(phenylthio)methyl-1,3-dioxlan-2-one (12)

See Ref. 17(a).

4.17. 5-(Phenylthio)methyl-3-methyloxazolidinone (13)

Oil; ^1H NMR δ 7.42–7.22 (m, 5H), 4.60–4.50 (m, 1H), 3.64 (t, 1H, J=8.8 Hz), 3.41–3.33 (m, 2H), 3.00 (dd, 1H, J=13.8, 8.9 Hz), 2.87 (s, 3H). ^{13}C NMR δ 157.40, 133.76, 130.22, 129.06, 127.02, 71.05, 51.09, 37.69, 30.93. MS (m/z) 223 (M^+). HRMS m/z calcd for $C_{11}H_{13}NO_2S$: 223.0667. Found: 223.0669.

4.18. 5-[Difluoro(phenylthio)methyl]-3-methyloxazolidinone (14)

Oil; ^1H NMR δ 7.63–7.60 (m, 2H), 7.49–7.35 (m, 3H), 4.71–4.57 (m, 1H), 3.74–3.61 (m, 2H), 2.88 (s, 3H). ^{13}C NMR δ 156.09, 138.46 (dd, J=8.9, 0.6 Hz), 136.34, 130.23, 129.11, 126.41 (dd, J=282.3, 280.6 Hz), 71.86 (dd, J=31.9, 27.9 Hz), 46.48 (t, J=2.8 Hz), 30.67. ^{19}F NMR δ −11.22 (dd, 1F, J=218.2, 9.2 Hz), −12.91 (dd, 1F, J=218.2, 9.2 Hz). MS (m/z) 259 (M^+), 159, 77. HRMS m/z calcd for $C_{11}H_{11}F_2NO_2S$: 259.0479. Found: 259.0485.

4.19. 4-[Difluoro-(3-tetrahydrofuryl)methyl]-1,3-dioxolan-2-one (15) (diastereomeric mixture)

Oil; ^{1}H NMR δ 4.86–4.54 (m, 3H), 4.02–3.74 (m, 4H), 3.09–2.83 (m, 1H), 2.20–1.89 (m, 2H). ^{19}F NMR δ −41.91 to −44.34 (m, 2F). MS (*m*/*z*) 207 (M^+−H), 189 (M^+−F), 87 (M^+−F_2C–C_4H_7O). HRFAB-MS *m*/*z* calcd for $C_8H_{10}F_2O_4Na$ (M^++Na): 231.0439. Found: 231.0441.

4.20. 4-[(3-*tert*-Butoxy-1,1-difluoro)propyl]-1,3-dioxolan-2-one (16)

Oil; ^{1}H NMR δ 5.10–4.97 (m, 1H), 4.59–4.48 (m, 2H), 3.55 (t, 2H, *J*=5.8 Hz), 2.44–2.09 (m, 2H), 1.19 (s, 9H). ^{13}C NMR δ 153.82, 120.56 (dd, *J*=247.0, 243.1 Hz), 74.89 (dd, *J*=34.7, 26.3 Hz), 73.63, 64.26 (dd, *J*=5.0, 2.8 Hz), 54.76 (t, *J*=6.7 Hz), 34.54 (dd, *J*=23.5, 22.9 Hz), 27.41. ^{19}F NMR δ −33.90 to −35.17 (m, 1F), −36.78 to −37.93 (m, 1F). FAB-MS (*m*/*z*) 239 (M^++H). HRFAB-MS *m*/*z* calcd for $C_{10}H_{17}F_2O_4$: 239.1095. Found: 239.1091.

4.21. 4-[(Cyclohexyl)difluoromethyl]-1,3-dioxolan-2-one (17)

Oil; ^{1}H NMR δ 4.92–4.78 (m, 1H), 4.69–4.50 (m, 2H), 2.01–1.74 (m, 6H), 1.31–1.24 (m, 5H). ^{13}C NMR δ 153.61, 121.25 (dd, *J*=249.8, 243.7 Hz), 72.36 (dd, *J*=41.4, 28.5 Hz), 64.02 (dd, *J*=5.6, 3.9 Hz), 40.80 (t, *J*=21.8 Hz), 25.76 (dd, *J*=5.6, 2.8 Hz), 25.69, 25.46 (d, *J*=1.1 Hz), 25.29, 24.04 (dd, *J*=4.5, 3.9 Hz). ^{19}F NMR δ −54.11 (ddd, 1F, *J*=303.3, 53.6, 3.7 Hz), −59.75 (ddd, 1F, *J*=303.3, 55.5, 16.6 Hz). FAB-MS (*m*/*z*) 221 (M^++H). HRFAB-MS *m*/*z* calcd for $C_{10}H_{15}F_2O_3$: 221.0989. Found: 221.0986.

4.22. 4-(1,1-Difluorooctyl)-1,3-dioxolan-2-one (18)

Oil; ^{1}H NMR δ 4.80–4.51 (m, 3H), 2.18–1.81 (m, 2H), 1.60–1.48 (m, 2H), 1.39–1.23 (m, 8H), 0.89 (t, 3H, *J*=7.1 Hz). ^{13}C NMR δ 153.49, 120.72 (dd, *J*=249.3, 241.5 Hz), 74.16 (dd, *J*=40.8, 27.9 Hz), 63.96 (dd, *J*=5.0, 3.4 Hz), 33.11 (dd, *J*=23.5, 22.4 Hz), 31.65, 29.18, 28.98, 22.65, 21.25 (dd, *J*=5.6, 2.8 Hz), 14.41. ^{19}F NMR δ −35.57 to −36.76 (m, 1F), −40.22 to −41.43 (m, 1F). MS (*m*/*z*) 236 (M^+), 149. HRMS *m*/*z* calcd for $C_{11}H_{18}F_2O_3$: 236.1224. Found: 236.1232.

4.23. 5-[Difluoro(3-tetrahydrofuryl)methyl]-3-methyloxazolidinone (19) (1:1 diastereomeric mixture)

Oil; ^{1}H NMR δ 4.67–4.44 (m, 1H), 4.01–3.63 (m, 6H), 3.18–2.92 (m, 4H), 2.22–1.87 (m, 2H). ^{19}F NMR δ −43.16 (ddd, 1F, *J*=262.6, 18.5, 12.9 Hz), −44.43 (ddd, 1F, *J*=262.4, 20.2, 3.7 Hz). MS (*m*/*z*) 222 (M^++H). HRFAB-MS *m*/*z* calcd for $C_9H_{14}F_2NO_3$: 222.0942. Found: 222.0945.

4.24. 5-[(3-*tert*-Butoxy-1,1-difluoro)propyl]-3-methyloxazolidinone (20)

Oil; ^{1}H NMR δ 4.81–4.67 (m, 1H), 3.64–3.54 (m, 4H), 2.90 (s, 3H), 2.44–2.06 (m, 2H), 1.19 (s, 9H). ^{13}C NMR δ 156.82, 121.00 (dd, *J*=246.5, 244.3 Hz), 73.36, 71.69 (dd, *J*=34.1, 30.2 Hz), 54.91 (dd, *J*=6.7, 6.1 Hz), 46.10 (dd, *J*=4.5, 3.4 Hz), 34.37 (dd, *J*=23.5, 22.9 Hz), 30.95, 27.45. ^{19}F NMR δ −35.48- −37.81 (m, 2F). FAB-MS (*m*/*z*) 252 (M^++H). HRFAB-MS *m*/*z* calcd for $C_{11}H_{20}F_2NO_3$: 252.1411. Found: 252.1407.

4.25. 5-[(Cyclohexyl)difluoromethyl]-3-methyloxazolidinone (21)

Oil; ^{1}H NMR δ 4.73–4.59 (m, 1H), 3.74–3.58 (m, 2H), 2.91 (s, 3H), 2.14–1.62 (m, 6H), 1.33–1.13 (m, 5H). ^{13}C NMR δ 156.69, 121.84 (dd, *J*=250.1, 244.3 Hz), 69.41 (dd, *J*=39.17, 29.1 Hz), 45.79 (dd, *J*=5.3, 3.4 Hz), 40.66 (t, *J*=21.8 Hz), 30.94, 29.77, 25.95 (dd, *J*=6.1, 2.8 Hz), 25.84, 25.43, 24.06 (dd, *J*=5.0, 3.9 Hz). ^{19}F NMR δ −45.35 (ddd, 1F, *J*=258.9, 20.3, 3.7 Hz), −46.72 (ddd, 1F, *J*=258.9, 18.5, 9.2 Hz). MS (*m*/*z*) 233 (M^+), 100. HRMS *m*/*z* calcd for $C_{11}H_{17}F_2NO_2$: 233.1227. Found: 233.1222.

4.26. 5-(1,1-Difluorooctyl)-3-methyloxazolidinone (22)

Oil; ^{1}H NMR δ 4.60–4.446 (m, 1H), 3.71–3.60 (m, 2H), 2.91 (s, 3H), 2.17–1.84 (m, 2H), 1.58–1.46 (m, 2H), 1.37–1.25 (m, 8H), 0.89 (t, 3H, *J*=6.8 Hz). ^{13}C NMR δ 156.65, 121.36 (dd, *J*=248.2, 239.8 Hz), 71.22 (dd, *J*=40.2, 27.9 Hz), 45.81 (dd, *J*=4.5, 3.4 Hz), 33.07 (dd, *J*=23.5, 22.9 Hz), 31.67, 30.94, 29.25, 29.03, 22.65, 21.36 (dd, *J*=5.6, 2.8 Hz), 14.14. ^{19}F NMR δ −35.55 to −36.72 (m, 1F), −40.22 to −41.43 (m, 1F). MS (*m*/*z*) 249 (M^+), 149, 100. HRMS *m*/*z* calcd for $C_{12}H_{21}F_2NO_2$: 249.1540. Found: 249.1539.

4.27. 4-[Difluoro(phenyl)methyl]-1,3-dioxlan-2-one (23)

Oil; ^{1}H NMR δ 7.56–7.45 (m, 5H), 5.04–4.92 (m, 1H), 4.68–4.43 (m, 2H). ^{13}C NMR δ 153.32, 131.36 (dd, *J*=25.2, 24.6 Hz), 131.21 (dd, *J*=2.2, 1.7 Hz), 128.83, 125.59 (t, *J*=6.1 Hz), 118.15 (dd, *J*=249.3, 244.3 Hz), 75.88 (dd, *J*=39.7, 32.4 Hz), 64.21 (t, *J*=3.3 Hz). ^{19}F NMR δ −30.95 (dd, 1F, *J*=262.6, 5.5 Hz), −37.90 (dd, 1F, *J*=262.6, 12.9 Hz). MS (*m*/*z*) 214 (M^+), 127. HRMS *m*/*z* calcd for $C_{10}H_8F_2O_3$: 214.0442. Found: 214.0443.

4.28. 4-[Difluoro(2-furyl)methyl]-1,3-dioxolan-2-one (24)

Oil; ^{1}H NMR δ 7.55–7.54 (m, 1H), 6.83–6.81 (m, 1H), 6.51–6.50 (m, 1H), 5.23–5.11 (m, 1H), 4.72–4.56 (m, 2H). ^{13}C NMR δ 153.24, 144.97 (dd, *J*=2.2, 1.7 Hz), 143.58 (dd, *J*=37.4, 33.0 Hz), 113.82 (dd, *J*=243.7, 240.3 Hz), 112.33 (dd, *J*=3.4, 2.8 Hz), 111.00 (t, *J*=1.1 Hz), 74.21 (dd, *J*=37.4, 29.6 Hz), 63.94 (t, *J*=3.4 Hz). ^{19}F NMR δ −28.80 (dd, 1F, *J*=280.0, 5.5 Hz), −38.17 (dd, 1F, *J*=280.0, 11.1 Hz). MS (*m*/*z*) 204 (M^+), 117. HRMS *m*/*z* calcd for $C_8H_6F_2O_4$: 204.0234. Found: 204.0237.

4.29. 5-[Difluoro(phenyl)methyl]-3-methyloxazolidinone (25)

Oil; ^{1}H NMR δ 7.55–7.42 (m, 5H), 4.85–4.73 (m, 1H), 3.67 (d, 2H, *J*=7.4 Hz), 2.82 (s, 3H). ^{13}C NMR δ 156.45, 132.20 (dd, *J*=25.7, 25.2 Hz), 130.72 (t, *J*=1.7 Hz), 128.51, 125.69 (t, *J*=6.1 Hz), 118.65 (dd, *J*=248.7, 244.3 Hz), 72.93 (dd, *J*=39.13, 32.42 Hz), 46.32 (t, *J*=3.35 Hz), 30.83. ^{19}F

NMR δ −30.25 (dd, 1F, J=258.9, 5.5 Hz), −38.53 (dd, 1F, J=258.9, 14.8 Hz). MS (m/z) 227 (M^+). HRMS m/z calcd for $C_{11}H_{11}F_2NO_2$: 227.0758. Found: 227.0748.

4.30. 5-[Difluoro(2-furyl)methyl]-3-methyloxazolidinone (26)

Oil; ^{1}H NMR δ 7.52–7.49 (m, 1H), 6.79–6.76 (m, 1H), 6.48–6.45 (m, 1H), 5.04–4.91 (m, 1H), 3.73 (d, 2H, J=7.6 Hz), 2.89 (s, 3H). ^{13}C NMR δ 156.36, 144.31 (dd, J=2.2, 1.7 Hz), 144.45 (dd, J=35.8, 33.0 Hz), 114.38 (dd, J=243.7, 240.3 Hz), 111.78 (dd, J=3.9, 2.8 Hz), 110.78 (t, J=1.1 Hz), 71.22 (dd, J=36.3, 29.6 Hz), 45.97 (t, J=3.4 Hz), 30.87. ^{19}F NMR δ −28.77 (dd, 1F, J=277.4, 5.5 Hz), −39.12 (dd, 1F, J=277.4, 12.9 Hz). MS (m/z) 217 (M^+), 117, 100. HRMS m/z calcd for $C_9H_9F_2NO_3$: 217.0550. Found: 217.0551.

4.31. 3,3-Difluoro-3-phenylpropan-1,2-diol (28)

Oil; ^{1}H NMR δ 7.55–7.45 (m, 5H), 4.14–4.02 (m, 1H), 3.78–3.64 (m, 2H), 3.22–1.93 (br, 2H). ^{13}C NMR δ 133.98 (t, J=25.7 Hz), 130.23 (t, J=1.7 Hz), 128.40, 125.50 (t, J=6.7 Hz), 120.72 (t, J=247.0 Hz), 74.23 (dd, J=30.2, 29.1 Hz), 61.14 (t, J=3.4 Hz). ^{19}F NMR δ −29.62 (dd, 1F, J=253.4, 9.2 Hz), −32.57 (dd, 1F, J=253.4, 12.9 Hz). MS (m/z) 188 (M^+), 127, 77. HRMS m/z calcd for $C_9H_{10}F_2O_2$: 188.0649; found: 188.0652.

Acknowledgements

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