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A Facile Preparation Method for α,α-Difluoro-alkanecarboxylic Acids and Esters. A Formal Difluoromethylene Insertion to Alkanecarboxylic Acids Using Radical Reaction[1]

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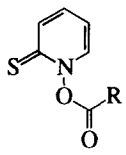
Abstract: Various alkyl radicals generated by the photoreaction of a series of Barton esters reacted with 1,1-dichloro-2,2-difluoroethene to give radical adducts as the major product accompanied with self-trapping products. Primary, secondary, tertiary, benzyl, and some unsaturated alkyl radicals as well as those with another functional group such as ether, carbonyl, and azide were applicable. Barton esters of diacids also afford 1:2 adducts with a small amount of 1:1 adducts and bis-self-trapping products except for the succinic case. These adducts were hydrolyzed with $AgNO_3/H_2O$-THF to α,α-difluoroalkanecarboxylic acids and methanolyzed with $AgNO_3$/MeOH to the corresponding methyl esters. 4-Azido-2,2-difluorobutylic acid and the methyl ester were converted to difluoro-GABA and difluoro-γ-lactams.

Difluoromethylene ketone derivatives are known as potential competitive inhibitors of protease,[2] and synthesis of difluoromethylene compounds is a currently important area of the organofluorine chemistry.[3] α,α-Difluoroalkanecarboxylic acids and their esters are versatile starting materials for the synthesis of the difluoromethylene ketones and difluoroalkanamides as difluoromethylene analogs of peptides. Reformatsky reaction of $BrZnCF_2COOEt$ with aldehydes is a common procedure to obtain alcohols $RCH(OH)CF_2COOEt$.[4] As an analogous reaction, Taguchi *et al.*[5] used difluoroketene silylacetal for the alternative of the less reactive Reformatsky reagent. While Ullmann-type reaction of ICF_2COOEt with organic halides[6] and radical addition of the iodide to olefins catalyzed by Ni(0) affords difluoroalkanecarboxylates,[7] all these methods have structural limitations of the products and starting materials.

Radical chemistry recently developed by Barton *et al.* using thiohydroxamate provided a new Arnt-Eistert-type methylene group elongation method of alkanecarboxylic acids adopting electron-deficient olefins as radical traps of the generated electron-rich alkyl radicals.[8] When one use geminally difluoro-substituted electron-deficient olefin in the radical reaction, the expected products would be a precursor for the difluorocarboxylic acids. As Muramatsu[9] reported, 1,1-dichloro-2,2-difluoroethene (**1**) accepts regiospecific addition of α-hydroxyalkyl radical on the fluorinated carbon. We report here a novel and general method of preparation of α,α-difluoroalkanecarboxylic acids and their methyl esters which are obtained by hydrolysis or methanolysis from the primary radical adducts of fluoroolefin **1** and alkyl radicals photochemically generated from *N*-alkanoyloxy-2-thiopyridones (Barton esters).



2, 3

2a: R = $C_6H_5C_2H_4$- **3a:** R = CH_2=$CHCH_2$- **4a:** Y = -$(CH_2)_2$-
b: R = *n*-C_6H_{13}- **b:** R = (*Z*)-$CH_3(CH_2)_7CH$=$CH(CH_2)_7$- **b:** Y = -$(CH_2)_3$-
c: R = *c*-C_6H_{11}- **c:** R = 2-Tetrahydrofuryl **c:** Y = -$(CH_2)_4$-
d: R = 1-Adamantyl **d:** R = $C_2H_5OC_2H_4$-
e: R = $(CH_3)_3C$- **e:** R = $C_6H_5(CO)C_2H_4$-
f: R = $C_6H_5CH_2$- **f:** R = $CH_3O(CO)C_2H_4$-
g: R = $CH_3(CO)OCH_2$-
h: R = $N_3C_2H_4$-

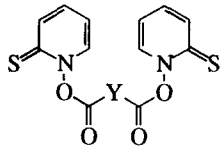


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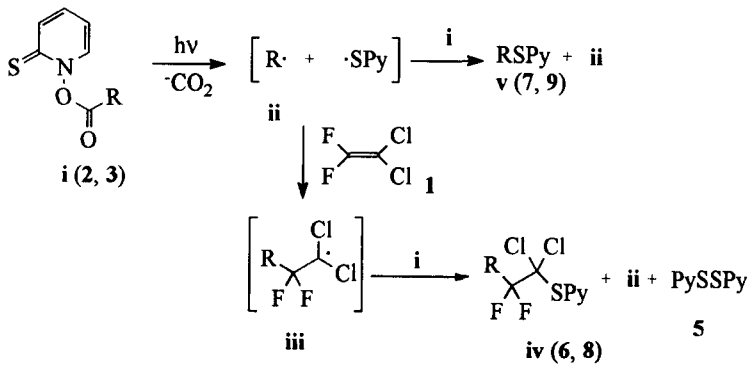
Chart I

RESULTS AND DISCUSSION

Photolysis of Barton esters in the presence of 1,1-Dichloro-2,2-difluoroethene (1). Barton esters of hydrocarbon carboxylic acids (**2a–f**), functionalized carboxylic acids (**3a–h**), and hydrocarbon diacids (**4a–c**) were prepared by standard methods; condensation of carboxylic acids and *N*-hydroxypyridine-2-thione with dicyclohexylcarbodiimide (DCC) or of acyl chlorides and the thione with Et_3N (Chart I). Barton esters **2–4** were irradiated in the presence of 10-molar amount of fluoroolefin **1** with a 500-W tungsten lamp at room temperature. As illustrated in Scheme I, alkyl radical **ii** formed in the radical chain reaction of a Barton ester **i** reacts with **1** to give the intermediate dichloroalkyl radical **iii** which subsequently attacks to the parent Barton ester **i** to yield the addition product **iv**. Competitive reaction of **ii** with **i** gives self-trapping product **v**. The less reactive nature and volatility (bp. 18 °C) of the fluoroolefin **1** decides the product ratios of **iv/v**, so that, in some cases, the yields of **iv** and **v** were comparable or **v** was the major product even in large excess use of **1** against **i** (10-molar amounts). Since the intermediate **iii** is no longer electron-rich radical, no further radical C–C bond formation occurred and actually any oligomer of **1** was not found in the reaction mixture. Another identified by-product of the reaction was thiopyridyl radical coupling product, disulfide **5**. The regiochemistry of the radical addition was confirmed by the ^1H and ^{19}F NMR spectra, in which coupling constants of a range of

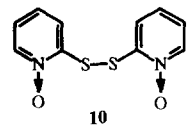


Scheme I

Table I. Photoreaction of Barton Esters 2a-f and 3a-h with 1,1-Dichloro-2,2-difluoroethene (1).

Entry	Barton ester	Solvent	Products (%)					
			RCF_2CCl_2SPy		RSPy		PySSPy (5)	
1	**2a**	CH_2Cl_2	**6a**	(45)	**7a**	(27)	(8)	
2	**2a**	CH_3CN	**6a**	(40)	**7a**	(36)	(-)	
3	**2a**	THF	**6a**	(29)	**7a**	(30)	(33)	
4	**2b**	CH_3CN	**6b**	(77)	**7b**	(11)	(11)	
5	**2c**	CH_3CN	**6c**	(76)	**7c**	(10)	(6)	
6	**2d**	CH_3CN	**6d**	(62)	**7d**	(7)	(14)	
7	**2e**	CH_3CN	**6e**	(52)	**7e**	(9)	(-)	
8	**2f**	CH_3CN	**6f**	(44)	**7f**	(28)	(13)	
9	**3a**	CH_2Cl_2	**8a**	(11)	**9a**	(2)	(11)[a]	
10	**3b**	CH_2Cl_2	**8b**	(52)	**9b**	(7)	(9)	
11	**3c**	CH_2Cl_2	**8c**	(43)		(-)	(-)	
12	**3d**	CH_2Cl_2	**8d**	(44)	**9d**	(21)	(5)	
13	**3e**	CH_2Cl_2	**8e**	(47)	**9e**	(33)	(9)	
14	**3f**	CH_2Cl_2	**8f**	(50)	**9f**	(34)	(4)	
15	**3g**	CH_2Cl_2	**8g**	(34)	**9g**	(27)	(-)	
16	**3h**	CH_2Cl_2	**8h**	(32)	**9h**	(51)	(-)	

[a] Dipyridyldisulfide-*N*,*N*'-dioxide (**10**) was also isolated in 39 % yield with a recovery of **3a** (23%).



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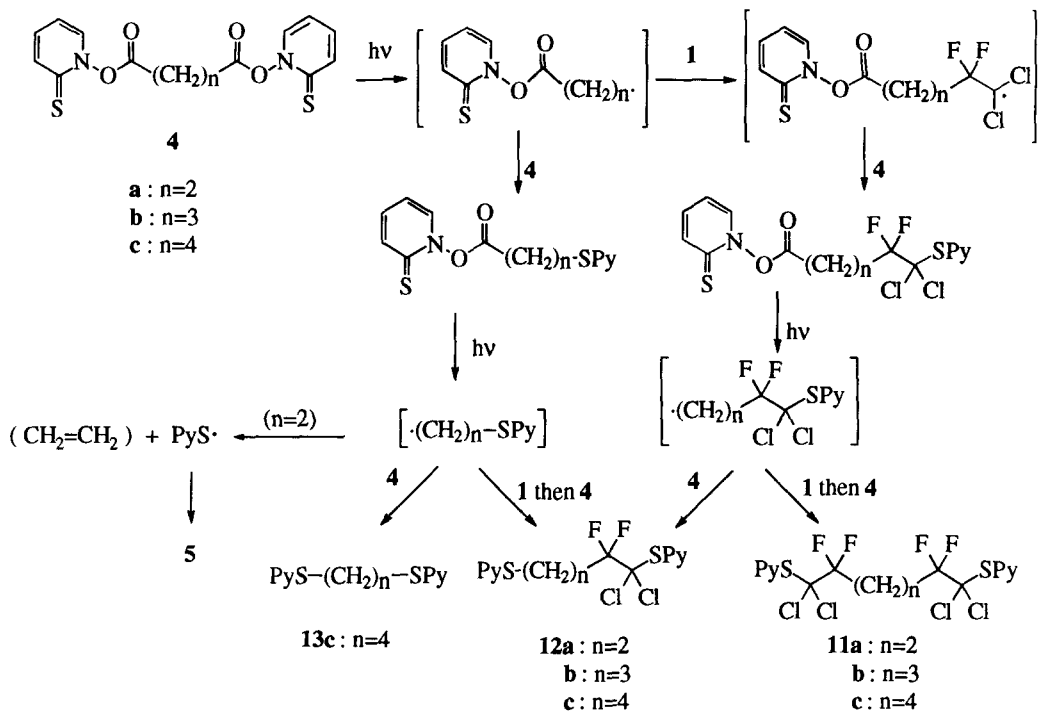
15–19 Hz were assigned to the vicinal coupling of ^1H and ^{19}F. In Table I, the yields of the products of the reaction of Barton esters of mono acids **2** and **3** are summarized. Among the non-functionalized alkyl group series, primary, secondary, tertiary and also benzyl radicals gave the adducts and they were isolated after chromatographic separation. Barton ester **3a** that should be the precursor of allyl radical was surprisingly less reactive and remained unreactive after normal irradiation period (5 h at 2.5 mmol scale; 23 % of **3a** was recovered). Low yields of allyl radical products **8a** and **9a** (totally 13 %) and substantial formation of dipyridyldisulfide-*N*,*N*'-dioxide (**10**; 39 %) suggests slow decarboxylation from allylcarboxy radical[10] or termination of radical chain process by the rapid recombination of the generated allyl radical.[11] Reactions of alkenyl radicals with a C-C double bond at 3- and 4-position has complexity because the radical cyclization occurs after addition to **1**.[12] However, if the double bond was far from the radical center as **3b**, no cyclization occurred and the desired product **8b** was obtained in 52 % yield. In the photoreaction of **3b**, a longer-alkyl-chain substrate, an inseparable mixture of several unidentified hydrocarbons was also obtained as by-products after chromatography. Alkyl radicals, which escaped from the chain reaction system shown in Scheme I seem to give a complex mixture of hydrocarbons by complex radical reactions. The yield of **5** corresponds to the extent of such uncontrolled radical reactions.

Radical C-C bond forming reactions are highly functionality-selective, *i.e.* usually carbon radicals react only with C-C double bonds and no protecting group is necessary. Thus, functionalized Barton esters **3c-f** were applied to this transformation. Ether function and carbonyl function (both ketone and ester) can be used directly. Hydroxy and amino compounds might be used in the radical reactions, although their appropriate

protections were necessary for preparation of Barton esters from the parent acids. For hydroxy group, corresponding ester was employed as in **3g** which was the acetylated form of glycolic acid to yield adduct **8g**. Barton *et al.* reported the radical reaction from *N*-acylamino acids.[13] Nevertheless, no radical adducts were obtained from photoreaction of **1** and any attempted *N*-benzyloxycarbonyl-α-aminoacid (DL-alanine and L-proline) with **1**. For primary amino group, azide group can be considered as a masked form of amino group, and azide **3h** gave **8h** in a modest yield. As previously mentioned, the product ratios **iv/v** are largely affected by the nucleophilic nature of the alkyl radicals, and generally addition reaction is a minor process for these α- or β-hetero-atom-substituted radicals compared to alkyl radicals. Oxygen or nitrogen atom withdraws the unpaired electron by inductive effect, and particularly the β-C-X bond delocalizes the odd electron to lower SOMO level of alkyl radicals and consequently lower the nucleophilic nature of the radical.

Some Barton esters of diacids (**4a**[14]-**c**) were photolyzed in the presence of 20-molar amount of **1** (Table II). Although the competitive self-trapping reaction made the system rather complex, chromatographically separable mixtures of 1:2 adducts (**11a-c**), 1:1 adducts (**12a-c**), bis-self-trapping product **13c**, and disulfide **5** were yielded as shown in Scheme II. The intramolecular radical trapping of initially formed alkyl radical,



Scheme II

Table II. Photoreaction of Barton Esters of Diacids (4a-c) in the Presence of 1.

Entry	Barton ester (4)	n	Products (Yield %) 11	12	13	PySSPy (5)
1	**4a**	2	**11a** (50)	**12a** (10)	(-)	(24)
2	**4b**	3	**11b** (62)	**12b** (20)	(-)	(-)
3	**4c**	4	**11c** (48)	**12c** (28)	**13c** (4)	(-)

which reduces the yield of the 1:2 adduct, appears unlikely to occur according to the observed nearly statistical product ratios. The reason for relatively higher yield of **5** in the case of photoreaction of **4a** can be explained by formation of unstable 2-thiopyridylethyl radical and extrusion of ethene in the second-step photoreaction.

Hydrolysis and Methanolysis of Primary Radical Adducts to α,α-Difluoroalkanecarboxylic acids and Methyl Esters. Oxidation state of the primary radical adducts is the same as carboxylic acid, and thus silver-ion-assisted hydrolysis smoothly gave the desired α,α-difluoroalkanecarboxylic acids in good yields as summarized in Table III. Radical adducts were treated with an excess amount of silver nitrate in 1:1 (v/v) mixture of H_2O-THF at reflux temperature. This silver-ion-assisted hydrolysis reaction is considerably promoted by the α-thiopyridyl group since hydrolysis of compounds which have $RCH(SPy)CH_2CCl_2CF_2R'$ moiety hardly occurs under the same conditions due to a strong inductive effect of difluoromethylene group.[12,15]

Table III. Hydrolysis of Radical Adducts to Difluoroalkanecarboxylic Acid.

$$RCF_2CCl_2SPy \xrightarrow[\text{reflux}]{AgNO_3,\ H_2O\text{-}THF} RCF_2COOH$$

14-16

Entry	Radical adduct	R	Difluoroalkanecarboxlic acid (Yield %)	
1	**6a**	$C_6H_5C_2H_4$-	**14a**	(86)
2	**6b**	*n*-C_6H_{13}-	**14b**	(89)
3	**6c**	*c*-C_6H_{11}-	**14c**	(84)
4	**6d**	1-Adamantyl	**14d**	(58)
5	**6e**	$(CH_3)_3C$-	**14e**	(91)
6	**6f**	$C_6H_5CH_2$-	**14f**	(53)
7	**8e**	$C_6H_5(CO)C_2H_4$-	**15e**	(60)
8	**8h**	$N_3C_2H_4$-	**15h**	(89)
9	**11b**	-$(CH_2)_3$-	**16b**	(74)
10	**11c**	-$(CH_2)_4$-	**16c**	(86)

Table IV. Methanolysis of Radical Adducts to Methyl Difluoroalkanecarboxylates.

$$RCF_2CCl_2SPy \xrightarrow[\text{reflux}]{AgNO_3,\ CH_3OH} RCF_2COOCH_3$$

17-19

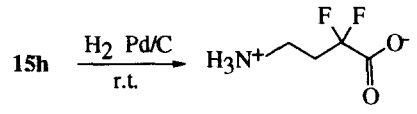
Entry	Radical adduct	R	Difluoroester	(Yield %)
1	**6a**	$C_6H_5C_2H_4$-	**17a**	(68)
2	**6b**	*n*-C_6H_{13}-	**17b**	(47)
3	**6c**	*c*-C_6H_{11}-	**17c**	(74)
4	**6d**	1-Adamantyl	**17d**	(77)
5	**8b**	(*Z*)-$CH_3(CH_2)_7CH{=}CH(CH_2)_7$-	**18b**	(88)
6	**8c**	2-Tetrahydrofuryl	**18c**	(63)
7	**8d**	$C_2H_5OC_2H_4$-	**18d**	(63)
8	**8e**	$C_6H_5(CO)C_2H_4$-	**18e**	(85)
9	**8f**	$CH_3O(CO)C_2H_4$-	**18f**	(86)
10	**8h**	$N_3C_2H_4$-	**18h**	(61)
11	**11a**	-$(CH_2)_2$-	**19a**	(88)
12	**11b**	-$(CH_2)_3$-	**19b**	(81)
13	**11c**	-$(CH_2)_4$-	**19c**	(75)

For convenience of handling or use as starting materials, a form of ester is sometimes superior to carboxylic acid form. Methyl α,α-difluoroalkanecarboxylates were obtained by reaction of the radical adducts with an excess amount of $AgNO_3$ in anhydrous MeOH at reflux temperature as summarized in Table IV. Formally, the products of this methanolysis should be orthoesters.[16] However, even if freshly distilled absolute MeOH was used, no orthoester was obtained from the filtrate of the reaction mixture (thiopyridyl group also precipitates as the silver salt). Probably, the formed orthoester was hydrolyzed or ester-exchanged with nitric acid which is a by-product of the reaction. Acid-catalyzed ester exchange also occurred in the methanolysis of adduct **8g** to afford deprotected β-hydroxy acid **20** in 40 % yield (Eq. 1).

$$\mathbf{8g} \xrightarrow{AgNO_3/MeOH} \underset{\mathbf{20}}{HOCH_2CF_2COOCH_3} \qquad (1)$$

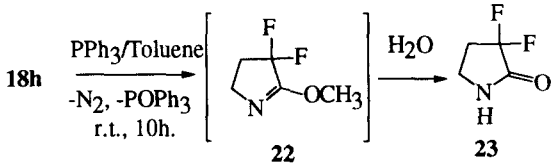
Reactions of 4-azido-2,2-difluorobutanoic acid 15h and methyl ester 18h. Derivatization of nitrogen-containing difluoromethylene compounds was exemplified by using azidoacid **15h** and ester **18h**. These derivatives are masked forms of γ-amino-α,α-difluorobutylic acid, a difluoro-derivative of neurotransmitter γ-aminobutylic acid (GABA). Difluoro-GABA **21**[17] was readily obtained by just only hydrogenolysis of **15h** in MeOH with 10%-Pd/C catalyst in 87 % yield (Eq. 2).

Cyclization of **21** to fluorinated γ-lactam was performed by our Staudinger/intramolecular-aza-Wittig approach[18] of azidoester **18h** with trialkylphosphine. The reaction of **18h** with PPh_3 in toluene at room temperature gave α,α-difluorobutanelactam **23** in 36 % yield. Usually, aza-Wittig products of azidoesters

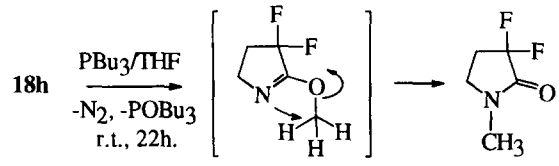


21 (2)

(imidates) can be isolated under these reaction conditions,[19] whereas intermediate **22** might have increased sensitivity against moisture due to the electron-withdrawing difluoromethylene group (Eq. 3). Product of the reaction of **18h** with more nucleophilic PBu_3 in THF was not either **22** or **23**. The ^1H NMR spectrum of the product has an additional signal at δ 2.98 as a singlet, and the proton-decoupled ^{13}C NMR spectrum has a singlet at δ 30.60 and all other four ^{13}C signals are triplets, and also the IR spectrum shows a carbonyl absorption (1728 cm^{-1}). These spectral data indicate existence of an *N*-CH_3 group in the product, and the assigned structure is *N*-methyl lactam **24** (59 % yield). This unexpected *N*-methylation product was probably derived from intramolecular transfer of methyl group from the methoxy group of the intermediate **22** during the longer reaction time due to the polarized C-O bond by the inductive effect of fluorine and the anhydrous THF solvent (Eq. 4).



22 23 (3)



22 24 (4)

In conclusion, we have developed a novel and general route to α,α-difluoroalkanecarboxylic acids and their esters through an addition process of alkyl radicals generated by photoreaction of various Barton esters in the presence of 1,1-dichloro-2,2-difluoroethene followed by hydrolytic or methanolytic treatment of the radical adducts. The insusceptible nature of the radical reaction against functional groups allows a wide variety of the structures of the difluorocarboxylic acids and esters. Versatility of the azide-group-containing acid and ester was demonstrated by conversion to difluoro-GABA and difluoro-γ-lactams.

EXPERIMENTAL SECTION

^1H and ^{13}C-NMR spectra of $CDCl_3$ or DMSO-d_6 solution were recorded at 200 MHz and 50 MHz, respectively, with TMS as an internal standard. ^{19}F NMR spectra of $CDCl_3$ or DMSO-d_6 solution were recorded at 87.67 MHz. Chemical shifts of the ^{19}F NMR spectra were reported in ppm (δ) relative to internal $CFCl_3$.

Barton esters **2-4** were prepared[20] by condensation of the corresponding carboxylic acids and *N*-hydroxy-2-pyridinethione with *N,N*-dicyclohexylcarbodiimide (DCC) (method A) or reaction of the corresponding alkanoyl chloride and *N*-hydroxy-2-pyridinethione with Et_3N (method B): A) a mixture of a carboxylic acid, equimolar amounts of *N*-hydroxypyridine-2-thione and DCC in CH_2Cl_2 was stirred at room temperature for 2-4 h, and the formed dicyclohexylurea was filtered off under the dark. Removal of the solvent under reduced pressure gave mostly pure Barton ester. B) To a stirred solution of *N*-hydroxypyridine-2-thione and an equimolar amount of Et_3N in dry THF, alkanoyl chloride was added dropwise under ice-cooling, and filtration of Et_3N·HCl and removal of the solvent gave mostly pure Barton ester. In this procedure, **3g**, **4a**,[14] and **4b** were prepared.

Usually Barton esters were used without further purification. When purification was necessary, solid Barton ester was recrystallized from CH_2Cl_2 - hexane under the dark conditions, and oily one was filtered through a short SiO_2 column eluting with CH_2Cl_2. Freshly prepared Barton esters were used as quickly as possible.

General procedure for the photoreaction of Barton esters and 1,1-dichloro-2,2-difluoroethene (1). An ice-cooled mixture of Barton ester and 10-fold amount of **1** in CH_3CN or CH_2Cl_2 in a reaction flask equipped with a reflux condenser, in which -30 °C coolant (EtOH - H_2O) was circulated, was irradiated by a 500-W tungsten lamp until the yellow color was disappeared. After recovery of the unreacted **1** by distillation at 30 °C, the solvent was removed under reduced pressure. The residue was chromatographed on an SiO_2 column eluting with hexane - EtOAc.

Photoreaction of 2a and 1 was performed as above using **2a** (1.036g, 4.00 mmol), **1** (5 mL, ca. 53 mmol), and CH_3CN (5 mL) with irradiation for 7h. **2-Phenyl-1-(2-pyridylthio)ethane (7a)**: 291 mg (36%). **1,1-Dichloro-2,2-difluoro-1-(2-pyridylthio)-4-phenylbutane (6a)**: 552 mg (40%); pale yellow oil; ^1H-NMR ($CDCl_3$) δ 2.63 - 2.84 (2 H, m), 2.86 - 3.01 (2 H, m), 7.19 - 7.34 (5 H, m), 7.40 (1 H, ddd, J = 8, 5, 2 Hz), 7.79 (1 H, td, J = 8, 2 Hz), 7.87 (1 H, ddd, J = 8, 2, 1 Hz), 7.50 (1H, ddd, J = 5, 2, 1 Hz); ^{13}C-NMR ($CDCl_3$) δ 27.92 (t, J = 4 Hz), 34.28 (t, J = 23 Hz), 94.36 (t, J = 32 Hz), 122.05 (t, J = 257 Hz), 124.99, 126.81, 128.79, 129.01, 132.19, 137.68, 140.34, 151.00, 152.03; ^{19}F-NMR ($CDCl_3$) δ -104.1 (t, J = 17 Hz); MS *m/z* (%) 347 (M^+, 1.6), 111 (100). Anal. Calcd for $C_{15}H_{13}Cl_2F_2NS$: C, 51.74; H, 3.76, N; 4.02. Found: C, 51.86; H, 3.88; N, 4.03.

Photoreaction of 2b and 1 was performed as above using **2b** (717 mg, 3.00 mmol), **1** (5 mL, ca. 53 mmol), and CH_3CN (5 mL) with irradiation for 5 h. **Di-2-pyridyldisulfide (5)**: 37 mg (11 %). **1-(2-Pyridylthio)hexane (7b)**: 65 mg (11 %). **1,1-Dichloro-2,2-difluoro-1-(2-pyridylthio)octane (6b)**: 760 mg (77 %); colorless oil, ^1H-NMR ($CDCl_3$) δ 0.91 (3H, t, J = 6 Hz), 1.35 (6H, m), 1.66 (2H, m), 2.30 - 2.57 (2H, m), 7.39 (1H, ddd, J = 8, 5, 1 Hz), 7.79 (1H, td, J = 8, 2 Hz), 7.88 (1H, dt, J = 8, 1 Hz), 8.71 (1H, ddd, J = 5, 2, 1 Hz); ^{13}C-NMR ($CDCl_3$) δ 14.08, 21.52 (t, J = 3 Hz), 22.55, 28.95, 31.62, 32.17 (t, J = 24 Hz), 94.71 (t,

J = 33 Hz), 122.50 (t, J = 256 Hz), 124.90, 132.10, 137.62, 150.99, 152.21; ^{19}F-NMR ($CDCl_3$) δ −104.1 (t, J = 19 Hz); MS *m/z* (%) 327 (M^+, 1.4), 110 (100). Anal. Calcd for $C_{13}H_{17}Cl_2F_2NS$: C, 47.57; H, 5.22; N, 4.27. Found: C, 47.92; H, 5.28; N 4.20.

Photoreaction of 2c and 1 was performed as above using **2c** (949 mg, 4.00 mmol), **1** (5 mL, ca. 53 mmol), and CH_3CN (5 mL) with irradiation for 6 h. **5**: 25 mg (6 %). **1-(2-pyridylthio)cyclohexane (7c)**: 80 mg (10 %). **1,1-Dichloro-2,2-difluoro-1-(2-pyridylthio)-2-cyclohexylethane (6c)**: 993 mg (76 %); colorless oil; ^{1}H-NMR ($CDCl_3$) δ 1.18 – 1.40 (4H, m), 1.64 – 1.87 (4H, m), 2.14 – 2.21 (2H, m), 2.44 – 2.72 (1H, m), 7.39 (1H, ddd, J = 8, 5, 1 Hz), 7.79 (1H, td, J = 8, 2 Hz), 7.89 (1H, dt, J = 8, 1 Hz), 8.71 (1H, ddd, J = 5, 2, 1 Hz); ^{13}C-NMR ($CDCl_3$) δ 25.71, 25.93, 27.18 (t, J = 6 Hz), 42.63 (t, J = 23 Hz), 95.07 (t, J = 35 Hz), 121.79 (t, J = 260 Hz), 124.82, 132.21, 137.59, 150.94, 152.27; ^{19}F-NMR ($CDCl_3$) δ −103.1 (t, J = 15 Hz); MS *m/z* (%) 325 (M^+, 1.4), 110 (100). Anal. Calcd for $C_{13}H_{15}Cl_2F_2NS$: C, 47.86; H, 4.63; N, 4.29. Found: C, 47.69; H, 4.67; N, 4.26.

Photoreaction of 2d and 1 was performed as above using **2d** (1.16 g, 4.00 mmol), **1** (5 mL, ca. 53 mmol), and CH_3CN (5 mL) with irradiation for 6 h. **5**: 60 mg (14 %). **1-(2-Pyridylthio)adamantane (7d)**: 70 mg (7 %). **2-Adamant-1-yl-1,1-dichloro-2,2-difluoro-1-(2-pyridylthio)ethane (6a)**: 941 mg (62 %); pale yellow solid; mp 86–91 °C; ^{1}H-NMR ($CDCl_3$) δ 1.71 (6H, t, J = 3 Hz), 2.08 (3H, br s), 2.16 (6H, s), 7.46 (1H, ddd, J = 8, 5, 1 Hz), 7.79 (1H, td, J = 8, 2 Hz), 7.91 (1H, dt, J = 8, 1 Hz), 8.72 (1H, ddd, J = 5, 2, 1 Hz); ^{13}C-NMR ($CDCl_3$) δ 28.24, 36.42, 36.42, 37.03 (t, J = 4 Hz), 44.10 (t, J = 22 Hz), 95.33 (t, J = 37 Hz), 121.54 (t, J = 263 Hz), 124.82, 132.41, 137.64, 150.78, 152.42; ^{19}F-NMR ($CDCl_3$) δ −104.2(s); MS *m/z* (%) 377 (M^+, 2.9). Anal. Calcd for $C_{17}H_{19}Cl_2F_2NS$: C, 53.97; H, 5.06; N, 3.70. Found: C, 53.64; H, 5.10; N, 3.96.

Photoreaction of 2e and 1 was performed as above using **2e** (212 mg, 1.00 mmol), **1** (1 mL, ca. 10 mmol), and CH_3CN (3 mL) with irradiation for 7 h. **2-Methyl-2-(2-pyridylthio)propane (7e)**: 15 mg (9 %). **1,1-Dichloro-2,2-difluoro-3,3-dimethyl-1-(2-pyridylthio)butane (6e)**: 157 mg (52 %); pale yellow oil; ^{1}H-NMR ($CDCl_3$) δ 1.39 (9H, t, J = 1 Hz), 7.40 (1H, ddd, J = 8, 5, 1 Hz), 7.89 (1H, td, J = 8, 2 Hz), 7.91 (1H, dt, J = 8, 1 Hz), 8.73 (1H, ddd, J = 5, 2, 1 Hz); ^{13}C-NMR ($CDCl_3$) δ 27.09 (t, J = 5 Hz), 41.88 (t, J = 23 Hz), 95.51 (t, J = 37 Hz), 112.95 (t, J = 263 Hz), 126.02, 133.75, 139.97, 149.28, 150.34; ^{19}F-NMR ($CDCl_3$) δ −100.6 (s); MS *m/z* (%) 299 (M^+, 12.1), 192 (100). Anal. Calcd for $C_{11}H_{13}Cl_2F_2NS$: C, 44.01; H, 4.36; N, 4.67. Found: C, 44.02; H, 4.37; N, 4.64.

Photoreaction of 2f and 1 was performed as above using **2f** (490 mg, 2.00 mmol), **1** (2 mL, ca. 21 mmol), and CH_3CN (5 mL) with irradiation for 7 h. **5**: 29 mg (13 %). **Phenyl(2-pyridylthio)methane (7f)**: 113 mg (28 %). **1,1-Dichloro-2,2-difluoro-1-(2-pyridylthio)-3-phenylpropane (6f)**: 293 mg (44 %); colorless solid; mp 60–62 °C; ^{1}H-NMR ($CDCl_3$) δ 3.78 (2H, dd, J = 19, 17 Hz), 7.34 (5H, m), 7.38 –7.42 (1H, m), 7.77 (1H, td, J = 8, 2 Hz), 7.88 (1H, dt, J = 8, 1 Hz), 8.72 (1H, ddd, J = 5, 2, 1 Hz); ^{13}C-NMR ($CDCl_3$) δ 38.39 (t, J = 23 Hz), 94.37 (t, J = 32 Hz), 120.97 (t, J = 257 Hz), 125.10, 128.06, 128.75, 131.34, 131.70, 132.27, 137.71, 151.02, 152.07; ^{19}F-NMR ($CDCl_3$) δ −102.2 (t, J = 19 Hz); MS *m/z* (%) 333 (M^+, 0.19), 91 (100). Anal. Calcd for $C_{14}H_{11}Cl_2F_2NS$: C, 50.31; H, 3.32; N, 4.19. Found: C, 50.58; H, 3.44; N, 4.10.

Photoreaction of 3a and 1 was performed as above using **3a** (486 mg, 2.50 mmol), **1** (2.5 mL, ca. 26 mmol), and CH_2Cl_2 (2.5 mL) with irradiation for 5 h. Recovery of **3a**: 112 mg (23%). **5**: 30 mg (11 %). **Di-2-pyridyldisulfide *N,N'*-dioxide (10)**: 124 mg (39 %). **1-(2-pyridylthio)-2-propene (9a)**: 7 mg (2 %). **1,1-Dichloro-2,2-difluoro-1-(2-pyridylthio)-4-pentene (8a)**: 75 mg (11 %); colorless oil; ^{1}H-NMR ($CDCl_3$) δ 3.24 (2H, dddt, J = 19, 17, 7, 1 Hz), 5.28 – 5.31 (1H, m), 5.35 (1H, m), 5.90 (1H, ddt, J = 17,

9, 7 Hz), 7.40 (1H, ddd, J = 8, 5, 2 Hz), 7.79 (1H, td, J = 8, 2 Hz), 7.87 (1H, ddd, *J* = 8, 2, 1 Hz), 8.71 (1H, ddd, *J* = 5, 2, 1 Hz); ^{13}C-NMR ($CDCl_3$) δ 37.01 (t, *J* = 24 Hz), 94.14 (t, *J* = 32 Hz), 121.29 (t, *J* = 257 Hz), 121.92, 125.03, 127.80 (t, *J* = 4 Hz), 132.22, 137.69, 151.03, 151.03, 152.04; ^{19}F-NMR ($CDCl_3$) δ −102.8 (t, *J* = 19 Hz); MS *m/z* (%) 283 (M^+, 2.9), 136 (100). Anal. Calcd for $C_{10}H_9Cl_2F_2NS$: C, 42.27; H, 3.19; N 4.93. Found: C, 42.29; H 3.21; N 4.89.

Photoreaction of 3b and 1 was performed as above using **3b** (783 mg, 2.00 mmol), **1** (2 mL, ca. 21 mmol), and CH_2Cl_2 (2 mL) with irradiation for 5 h. **5**: 20 mg (9 %). **(Z)-1-(2-Pyridylthio)-8-pentadecene (9b)**: 45 mg (7%). **(Z)-1,1-Dichloro-2,2-difluoro-1-(2-pyridylthio)-10-nonadecene (8b)**: 498 mg (52 %); ^{1}H-NMR ($CDCl_3$) δ 0.88 (3H, t, *J* = 6 Hz), 1.27 – 1.34 (20H, m), 1.64 (2H, m), 2.02 (4H, m), 2.30 – 2.56 (2H, m), 5.36 (2H, m), 7.39 (1H, ddd, *J* = 8, 5, 1 Hz), 7.78 (1H, td, *J* = 8, 2 Hz), 7.88 (1H, dt, *J* = 8, 2 Hz), 8.70 (1H, ddd, *J* = 5, 2, 1 Hz); ^{13}C-NMR ($CDCl_3$) δ 14.17, 21.58 (t, *J* = 3 Hz), 22.76, 27.25, 27.31, 29.18, 29.28, 29.35, 29.42, 29.51, 29.62, 29.77, 29.86, 32.01, 32.17(t, *J* = 24 Hz), 94.69 (t, *J* = 32 Hz), 122.48 (t, *J* = 256 Hz), 124.91, 130.10, 130.43, 132.11, 132.11, 137.64, 137.64, 150.96, 152.19; ^{19}F-NMR ($CDCl_3$) δ −104.1 (t, *J* = 17 Hz); MS *m/z* (%) 479 (M^+, 1.7), 110 (42). Anal. Calcd for $C_{24}H_{37}Cl_2F_2NS$: C, 59.99; H, 7.76; N, 2.91. Found: C, 59.86; H, 7.90; N, 2.96.

Photoreaction of 3c and 1 was performed as above using **3c** (371 mg, 1.65 mmol), **1** (2 mL, ca. 21 mmol), and CH_2Cl_2 (2 mL) with irradiation for 5 h. **2-[1,1-Difluoro-2,2-dichloro-2-(2-pyridylthio)-ethyl]tetrahydrofuran (8c)**: 224 mg (43 %); colorless oil; ^{1}H-NMR ($CDCl_3$) δ 1.87 – 2.39 (4H, m), 3.983 (2H, t, *J* = 6.8 Hz), 4.82 – 5.01 (1H, m), 7.38 (1H, ddd, *J* = 8, 5, 1 Hz), 7.78 (1H, td, *J* = 8, 2 Hz), 7.90 (1H, br d, *J* = 8 Hz), 8.10 (1H, br d, *J* = 4 Hz); ^{13}C-NMR ($CDCl_3$) δ 24.58, 26.35 (t, *J* = 3 Hz), 69.06, 92.62 (dd, *J* = 33, 22 Hz), 118.50 (dd, *J* = 265, 259 Hz), 123.79, 123.79, 131.10, 136.52, 119.90, 151.45; ^{19}F-NMR ($CDCl_3$) δ −104.1 (d, *J* = 248 Hz), −115.8 (dd, *J* = 248, 20 Hz); MS *m/z* (%) 313 (M^+, 0.9), 110 (100). Anal. Calcd for $C_{11}H_{11}Cl_2F_2NOS$: C, 42.05; H, 3.53; N, 4.46. Found: C, 42.12; H, 3.54; N, 4.38.

Photoreaction of 3d and 1 was performed as above using **3d** (304 mg, 1.50 mmol), **1** (1.5 mL, ca. 16 mmol), and CH_2Cl_2 (1.5 mL) with irradiation for 5 h. **5**: 9 mg (5 %). **2-Ethoxy-1-(2-pyridylthio)ethane (9d)**: 57 mg (21 %). **4-Ethoxy-1,1-dichloro-2,2-difluoro-1-(2-pyridylthio)butane (8d)**: 207 mg (44 %); colorless oil; ^{1}H-NMR ($CDCl_3$) δ 1.22 (3H, t, *J* = 7 Hz), 2.80 (2H, ddt, *J* = 19, 18, 7 Hz), 3.54 (2H, q, *J* = 7 Hz), 3.76 (2H, t, *J* = 7 Hz), 7.39 (1H, ddd, *J* = 8, 5, 2 Hz), 7.78 (1H, td, *J* = 8, 2 Hz), 7.86 (1H, ddd, *J* = 8, 2, 1 Hz), 8.70 (1H, ddd, *J* = 5, 2, 1 Hz); ^{13}C-NMR ($CDCl_3$) δ 15.15, 32.71 (t, *J* = 23 Hz), 63.86 (t, *J* = 4 Hz), 66.65, 94.19(t, *J* = 32 Hz), 121.81 (t, *J* = 257 Hz), 124.97, 132.21, 137.65, 150.98, 152.01; ^{19}F-NMR ($CDCl_3$) δ −102.9 (t, *J* = 17 Hz); MS *m/z* (%) 315 (M^+, 2.2), 110 (100). Anal. Calcd for $C_{11}H_{13}Cl_2F_2NOS$: C, 41.79; H, 4.14; N, 4.43. Found: C, 41.93; H, 4.18; N, 4.60.

Photoreaction of 3e and 1 was performed as above using **3e** (826 mg, 3.00 mmol), **1** (3 mL, ca. 31 mmol), and CH_2Cl_2 (5 mL) with irradiation for 5 h. **5**: 30 mg (9 %). **3-Phenyl-1-(2-pyridylthio)propan-3-one (9e)**: 243 mg (33 %). **1,1-Dichloro-2,2-difluoro-5-phenyl-1-(2-pyridylthio)pentan-5-one (8e)**: 528 mg (47 %) colorless solid; mp 65–68 °C; ^{1}H-NMR ($CDCl_3$) δ 2.86 – 3.12 (2H, m), 3.32 – 3.40 (2H, m), 7.40 (1H, ddd, *J* = 8, 5, 1 Hz), 7.45 – 7.62 (4H, m), 7.79 (1H, td, *J* = 8, 2 Hz), 7.88 (1H, ddd, *J* = 8, 1, 1 Hz), 7.99 – 8.04 (2H, m), 8.71 (1H, ddd, *J* = 5, 2, 1 Hz); ^{13}C-NMR ($CDCl_3$) δ 27.36 (t, *J* = 23 Hz), 31.13 (t, *J* = 3 Hz), 94.09 (t, *J* = 32 Hz), 122.53 (t, *J* = 256 Hz), 125.02, 127.65, 128.43, 129.09, 132.33, 133.81, 136.79, 137.68, 151.03, 151.99, 197.84; ^{19}F-NMR ($CDCl_3$) δ −103.4 (t, *J* = 17 Hz); IR (neat film) 1687 cm^{-1}; MS *m/z* (%) 375 (M^+, 1.5), 105(100). Anal. Calcd for $C_{16}H_{13}Cl_2F_2NOS$: C, 51.08; H, 3.48; N, 3.72. Found: C, 51.27;

H, 3.49; N, 3.66.

Photoreaction of 3f and 1 was performed as above using **3f** (915 mg, 3.80 mmol), **1** (4 mL, ca. 42 mmol), and CH_2Cl_2 (4 mL) with irradiation for 5 h. **Methyl 3-(2-pyridylthio)propanoate (9f)**: 253 mg (34 %). **Methyl 5,5-dichloro-4,4-difluoro-5-(2-pyridylthio)pentanoate (8f)**: 632 mg (50 %); pale yellow oil; ^{1}H-NMR ($CDCl_3$) δ 2.63 – 3.00 (4H, m), 3.73 (3H, s), 7.40 (1H, ddd, J = 7, 5, 5 Hz), 7.79 (1H, ddd, *J* = 8, 7, 2 Hz), 7.86 (1H, ddd, *J* = 8, 2, 1 Hz), 8.71 (1H, ddd, *J* = 5, 2, 1 Hz); ^{13}C-NMR ($CDCl_3$) δ 26.78 (t, *J* = 4 Hz), 27.97 (t, *J* = 23 Hz), 52.18, 93.87 (t, *J* = 32 Hz), 121.90 (t, *J* = 257 Hz), 125.05, 132.30, 137.68, 151.03, 151.89, 172.63; ^{19}F-NMR ($CDCl_3$) δ −104.2 (t, *J* = 17 Hz); IR (neat film) 1741 cm^{-1}; MS *m/z* (%) 329 (M^+, 1.3), 294 (100). Anal. Calcd for $C_{11}H_{11}Cl_2F_2NO_2S$: C, 40.01; H, 3.36; N, 4.24. Found: C, 40.27; H, 3.28; N, 4.08.

Photoreaction of 3g and 1 was performed as above using **3g** (213 mg, 0.94 mmol), **1** (1 mL, ca. 10 mmol), and CH_2Cl_2 (1 mL) with irradiation for 5 h. **(2-Pyridylthio)methyl acetate (9g)**: 46 mg (27 %). **3,3-Dichloro-2,2-difluoro-3-(2-pyridylthio)propyl acetate (8g)**: 110 mg (34 %); colorless oil; ^{1}H-NMR ($CDCl_3$) δ 2.18 (3H, s), 4.98 (2H, t, *J* = 14 Hz), 7.39 – 7.45 (1H, m), 7.75 (2H, m), 8.71 (1H, br s); ^{13}C-NMR ($CDCl_3$) δ 20.61, 61.24 (t, *J* = 24 Hz), 91.76 (t, *J* = 30 Hz), 118.46 (t, *J* = 260 Hz), 125.30, 132.49, 137.81, 151.14, 151.5, 170.23; ^{19}F-NMR ($CDCl_3$) δ −108.0 (t, *J* = 15 Hz); IR (neat film) 1759 cm^{-1}; MS *m/z* (%) 315 (M^+, 1.4), 110 (100). Anal. Calcd for $C_{10}H_9Cl_2F_2NO_2S$: C, 37.99; H, 2.87; N, 4.43. Found: C, 37.81; H, 2.84; N, 4.34.

Photoreaction of 3h and 1 was performed as above using **3h** (1.77 g, 7.90 mmol), **1** (10 mL, ca. 105 mmol), and CH_2Cl_2 (8 mL) with irradiation for 5 h. **1-Azido-2-(2-pyridylthio)ethane (9h)**: 725 mg (32 %). **4-Azido-1,1-dichloro-2,2-difluoro-1-(2-pyridylthio)butane (8h)**: 795 mg (32 %); pale yellow oil; ^{1}H-NMR ($CDCl_3$) δ 2.81 (2H, ddt, *J* = 18, 17, 7 Hz), 3.63 (2H, t, *J* = 7 Hz), 7.41 (1H, ddd, *J* = 7, 5, 2 Hz), 7.75 – 7.89 (1H, m), 8.71 (1H, ddd, *J* = 5, 2, 1 Hz); ^{13}C-NMR ($CDCl_3$) δ 32.12 (t, *J* = 23 Hz), 44.83 (t, *J* = 4 Hz), 93.70 (t, *J* = 32 Hz), 121.40 (t, *J* = 257 Hz), 125.24, 132.44, 137.79, 151.10, 151.73; ^{19}F-NMR ($CDCl_3$) δ −102.9 (t, *J* = 17 Hz); IR (neat film) 2104 cm^{-1}; MS (CI) *m/z* (%) 313 (M + H^+, 100). Anal. Calcd for $C_9H_8Cl_2F_2N_4S$: C, 34.52; H, 2.57; N, 17.89. Found: C, 34.69; H, 2.80; N, 17.61.

Photoreaction of 4a and 1 was performed as above using a mixture containing **4a** (1.13 g, 3.4 mmol), **1** (7 mL, ca. 70 mmol), and DMF (16 mL) with irradiation for 4 h. **5**: 180 mg (24 %). **1,1-Dichloro-2,2-difluoro-1,4-bis(2-pyridylthio)butane (12a)**: 120 mg (10 %); pale yellow oil; ^{1}H-NMR ($CDCl_3$) δ 2.81 – 3.07 (2H, m), 3.40 – 3.48 (2H, m), 7.00 (1H, ddd, *J* = 7, 5, 1 Hz), 7.19 (1H, td, *J* = 8, 1 Hz), 7.39 (1H, ddd, *J* = 7, 5, 1 Hz), 7.50 (1H, ddd, *J* = 8, 7, 2 Hz), 7.78 (1H, ddd, *J* = 8, 7, 2 Hz), 7.86 (1H, ddd, *J* = 8, 1, 1 Hz), 8.46 (1H, ddd, *J* = 5, 2, 1 Hz), 8.69 (1H, ddd, *J* = 5, 2, 1 Hz); ^{13}C-NMR ($CDCl_3$) δ 22.41(t, *J* = 4 Hz), 33.18 (t, *J* = 23 Hz), 94.04 (t, *J* = 32 Hz), 121.76 (t, *J* = 257 Hz), 119.94, 122.57, 124.99, 132.22, 136.40, 137.65, 150.07, 151.01, 151.99, 158.27; ^{19}F-NMR ($CDCl_3$) δ −103.6 (t, *J* =17 Hz); MS *m/z* (%) 380 (M^+, 9). Anal. Calcd for $C_{14}H_{12}Cl_2F_2N_2S_2$: C, 44.10; H, 3.17; N; 7.35. Found: C, 44.07, H; 2.85, N; 7.70. **1,1,6,6-Tetrachloro-2,2,5,5-tetrafluoro-1,6-bis(2-pyridylthio)hexane (11a)**: 860 mg (50 %); colorless solid; mp 139 – 141°C; ^{1}H-NMR ($CDCl_3$) δ 2.67 – 3.01 (4H, m), 7.41 (2 H, ddd, *J* = 7, 5, 2 Hz), 7.80 (2H, ddd, *J* = 8, 7, 2 Hz), 7.87 (2 H, ddd, *J* = 8, 2, 1 Hz), 8.72 (2H, ddd, *J* = 5, 2, 1 Hz); ^{13}C-NMR ($CDCl_3$) δ 25.59 (tt, *J* = 24, 4 Hz), 93.89 (t, *J* = 32 Hz), 121.87 (t, *J* = 257 Hz), 125.15, 132.37, 137.75, 151.12, 151.83; ^{19}F-NMR ($CDCl_3$) δ −103.9 (m); MS *m/z* (%) 512 (M^+, 27). Anal. Calcd for $C_{16}H_{12}Cl_4F_4N_2S_2$: C, 37.37; H, 2.35; N; 5.45. Found: C, 37.07, H; 2.07, N; 5.31.

Photoreaction of 4b and 1 was performed as above using **4b** (1.38 g, 3.93 mmol), **1** (8 mL, ca. 80

mmol), and CH_2Cl_2 (6 mL) with irradiation for 3.5 h. **1,1-Dichloro-2,2-difluoro-1,5-bis(2-pyridylthio)pentane (12b)**: 310 mg (20 %); pale yellow oil; ^{1}H-NMR ($CDCl_3$) δ 2.07 (2H, quintet, J = 7 Hz), 2.64 (2H, tt, J = 18, 7 Hz), 3.29 (2H, t, J = 7 Hz), 6.99 (1H, ddd, J = 7, 5, 1 Hz), 7.19 (1H, td, J = 8, 1 Hz), 7.39 (1H, ddd, J = 8, 5, 2 Hz), 7.49 (1H, ddd, J = 8, 7, 2 Hz), 7.78 (1H, ddd, J = 8, 8, 2 Hz), 7.86 (1H, ddd, J = 8, 2, 1 Hz), 8.44 (1H, ddd, J = 5, 2, 1 Hz), 8.70 (1H, ddd, J = 5, 2, 1 Hz); ^{13}C-NMR ($CDCl_3$) δ 22.03 (t, J = 3 Hz), 29.40, 31.36 (t, J = 24 Hz), 94.40 (t, J = 32 Hz), 119.81, 122.36 (t, J = 257 Hz), 122.77, 124.95, 132.16, 136.21, 137.63, 149.94, 151.00, 152.09, 158.87; ^{19}F-NMR ($CDCl_3$) δ −103.6 (t, J = 17 Hz); MS *m/z* (%) 394 (M^+, 3), 111 (100). Anal. Calcd for $C_{15}H_{14}Cl_2F_2N_2S_2$: C, 45.57; H, 3.57; N, 7.09. Found: C, 45.43; H, 3.48; N, 7.31. **1,1,7,7-Tetrachloro-2,2,6,6-tetrafluoro-1,7-bis(2-pyridylthio)heptane (11b)**: 1.29 g (62 %); colorless solid; mp 48.5 – 50.5 °C; ^{1}H-NMR ($CDCl_3$) δ 1.93 – 2.09 (2H, m), 2.61 (4H, tt, J = 18, 8 Hz), 7.40 (2H, ddd, J = 7, 5, 2 Hz), 7.79 (2H, ddd, J = 8, 7, 2 Hz), 7.87 (2H, ddd, J = 8, 2, 1 Hz), 8.71 (2H, ddd, J = 5, 2, 1 Hz); ^{13}C-NMR ($CDCl_3$) δ 14.53 (t, J = 4 Hz), 31.63 (t, J = 24 Hz), 94.20 (t, J = 32 Hz), 122.15 (t, J = 257 Hz), 125.72, 132.27, 137.71, 151.03, 151.94; ^{19}F-NMR ($CDCl_3$) δ −104.0 (t, J = 18 Hz); MS *m/z* (%) 526 (M^+, 10). Anal. Calcd for $C_{17}H_{14}Cl_4F_4N_2S_2$: C, 38.65; H, 2.67; N, 5.30. Found: C, 38.56; H, 2.58; N, 5.48.

Photoreaction of 4c and 1 was performed as above using **4c** (364 mg, 1.00 mmol), **1** (2 mL, ca. 21 mmol), and CH_3CN (16 mL) with irradiation for 4.5 h. **1,4-Bis(2-pyridylthio)butane (13c)**: 12 mg (4 %). **1,1-Dichloro-2,2-difluoro-1,6-bis(2-pyridylthio)hexane (12c)**: 116 mg (28 %); colorless oil; ^{1}H-NMR ($CDCl_3$) δ 1.80 – 1.86 (4H, m), 2.37 – 2.63 (2H, m), 3.23 (2H, t, J = 7 Hz), 6.98 (1H, ddd, J = 5, 5, 2 Hz), 7.18 (1H, td, J = 8, 1 Hz), 7.39 (1H, ddd, J = 8, 5, 2 Hz), 7.48 (1H, ddd, J = 10, 8, 2 Hz), 7.78 (1H, td, J = 8, 2 Hz), 7.87 (1H, dt, J = 8, 1 Hz), 8.43 (1H, ddd, J = 5, 2, 1 Hz), 8.70 (1H, ddd, J = 5, 2, 1 Hz); ^{13}C-NMR ($CDCl_3$) δ 20.92 (t, J = 3 Hz), 29.15, 29.52, 31.75 (t, J = 24 Hz), 94.51 (t, J = 32 Hz), 119.66, 122.32 (t, J = 266 Hz), 122.63, 124.93, 132.13, 136.26, 137.62, 149.83, 150.96, 152.05, 159.36; ^{19}F-NMR ($CDCl_3$) δ −104.0 (t, J = 19 Hz); MS *m/z* (%) 408 (M^+, 8.5), 111 (100). Anal. Calcd for $C_{16}H_{16}Cl_2F_2N_2S_2$: C, 46.95; H, 3.94; N, 6.84. Found: C, 47.02; H, 4.01; N, 6.70. **1,1,8,8-Tetrachloro-2,2,7,7-tetrafluoro-1,8-bis(2-pyridylthio)octane (11c)**: 259 mg (48%); colorless solid; mp 99–102 °C; ^{1}H-NMR ($CDCl_3$) δ 1.73 –1.81 (4H, m), 2.40 – 2.67 (4H, m) , 7.40 (2H, ddd, J = 8, 5, 2 Hz), 7.79 (2H, td, J = 8, 2 Hz), 7.88 (2H, ddd, J = 8, 2, 1 Hz), 8.71 (2H, ddd, J = 5, 2, 1 Hz); ^{13}C-NMR ($CDCl_3$) δ 21.40 (t, J = 4 Hz), 32.01 (t, J = 24 Hz), 94.45 (t, J = 32 Hz), 122.29 (t, J = 257 Hz), 125.03, 132.26, 137.68, 151.04, 152.07; ^{19}F-NMR ($CDCl_3$) δ −103.9 (t, J = 19 Hz); MS (CI) *m/z* (%) 541 (M + H^+, 78). Anal. Calcd for $C_{18}H_{16}Cl_4F_4N_2S_2$: C, 39.87; H, 2.97; N, 5.17. Found: C, 39.78; H, 2.99; N, 5.22.

General procedure of hydrolysis of radical adducts to α,α-difluoroalkanecarboxylic acids. A THF solution of the adduct and the same volume of aqueous solution of 4-molar amount of silver nitrate were mixed and refluxed under stirring. After disappearance of the starting material, the reaction mixture was filtered and the precipitates were washed with THF. Saturated aqueous $NaHCO_3$ solution was added into the filtrate until the solution became basic, and then the solution was once washed with Et_2O. The solution was carefully acidified with 50% H_2SO_4 and extracted with CH_2Cl_2 several (5 to 7) times. The combined extracts were dried with Na_2SO_4. Removal of the solvent gave almost pure difluorocarboxylic acid.

2,2-Difluoro-4-phenylbutanoic acid (14a) was obtained as above from **6a** (244 mg , 0.700 mmol), $AgNO_3$ (476 mg, 2.80 mmol), THF (5 mL), and H_2O (5 mL); reaction time, 21 h: 120 mg (86 %); colorless oil; ^{1}H-NMR ($CDCl_3$) δ 2.29 – 2.54 (2H, m), 2.81 – 2.89 (2H, m), 6.62 (1H, br s), 7.19 – 7.36 (5H, m); ^{13}C-NMR

($CDCl_3$) δ 27.73 (t, J = 5 Hz), 36.25 (t, J = 23 Hz), 115.96 (t, J = 250 Hz), 126.92, 128.71, 129.03, 139.77, 168.01 (t, J = 33 Hz); ^{19}F-NMR ($CDCl_3$) δ −107.4 (t, J = 16 Hz); IR (neat film) 1757 cm^{-1}; MS *m/z* (%) 200 (M^+, 5). Anal. Calcd for $C_{10}H_{10}F_2O_2$: C, 60.00; H, 5.04. Found: C, 59.67; H, 5.23.

2,2-Difluorooctanoic acid (14b) was obtained as above from **6b** (98 mg, 0.30 mmol), $AgNO_3$ (204 mg, 1.20 mmol), THF (4 mL), and H_2O (4 mL); reaction time, 11 h: 48 mg (89 %); colorless oil; ^{1}H-NMR ($CDCl_3$) δ 0.89 (3H, t, J = 6 Hz), 1.26 – 1.54 (8H, m), 1.93 – 2.21 (2H, m), 7.96 (1H, br s); ^{13}C-NMR ($CDCl_3$) δ 14.02, 21.40 (t, J = 4 Hz), 22.49, 28.81, 31.48, 34.44 (t, J = 23 Hz), 116.57 (t, J = 249 Hz), 168.96 (t, J = 34 Hz); ^{19}F-NMR ($CDCl_3$) δ −106.9 (t, J = 16 Hz); IR (neat film) 1757 cm^{-1}; MS (CI) *m/z* (%) 181 (M + H^+, 100). Anal. Calcd for $C_8H_{14}F_2O_2$: C, 53.32; H, 7.83. Found: C, 53.15; H, 7.96.

2-Cyclohexyl-2,2-difluoroacetic acid (14c) was obtained as above from **6c** (65 mg, 0.20 mmol), $AgNO_3$ (102 mg, 0.60 mmol), THF (1 mL), and H_2O (1 mL); reaction time, 10 h: 30 mg (84 %); colorless oil; ^{1}H-NMR ($CDCl_3$) δ 1.10 – 1.40 (5H, m), 1.70–1.90 (5H, m), 1.95 – 2.20 (1H, m), 7.36 (1H, br s); ^{13}C-NMR ($CDCl_3$) δ 24.77 (t, J = 4 Hz), 25.36, 25.85, 42.17 (t, J = 22 Hz), 117.57 (t, J = 251 Hz), 168.66 (t, J = 34 Hz); ^{19}F-NMR ($CDCl_3$) δ −114.3 (t, J = 15 Hz); IR (neat film) 1755 cm^{-1}; MS (CI) *m/z* (%) 179 (M + H^+, 43), 129 (100). Anal. Calcd for $C_8H_{12}F_2O_2$: C, 53.93; H, 6.79. Found: C, 53.78; H, 7.00.

2-Adamant-1-yl-2,2-difluoroacetic acid (14d) was obtained as above from **6d** (113 mg, 0.30 mmol), $AgNO_3$ (204 mg, 1.20 mmol), THF (3 mL), and H_2O (3 mL); reaction time, 15 h: 40 mg (58 %); colorless solid; mp 163 – 167 °C; ^{1}H-NMR ($CDCl_3$) δ 1.71 (6H, m), 1.78 (6H, m), 2.06 (3H, br s), 7.42 (1H, br s); ^{13}C-NMR ($CDCl_3$) δ 27.56, 34.72 (t, J = 3 Hz), 36.50, 38.85 (t, J = 22 Hz), 118.63 (t, J = 253 Hz), 168.54(t, J = 34 Hz); ^{19}F-NMR ($CDCl_3$) δ −120.5 (s); IR (KBr) 1743 cm^{-1}; MS *m/z* (%) 230 (M^+, 4.3), 135 (100). Anal. Calcd for $C_{12}H_{16}F_2O_2$: C, 62.60; H, 7.00. Found: C, 62.75; H, 7.14.

2,2-Difluoro-3,3-dimethylpropanoic acid (14e) was obtained as above from **6e** (110 mg, 0.37 mmol), $AgNO_3$ (251 mg, 1.48 mmol), THF (3 mL), and H_2O (3 mL); reaction time, 16 h: 30 mg (53 %); colorless oil; ^{1}H-NMR ($CDCl_3$) δ 1.13 (9H, s), 7.61 (1H, br s); ^{13}C-NMR ($CDCl_3$) δ 23.51 (t, J = 4 Hz), 37.30 (t, J = 22 Hz), 119.22 (t, J = 254 Hz), 168.72 (t, J = 33 Hz); ^{19}F-NMR ($CDCl_3$) δ −116.2 (s); IR (neat film) 1751 cm^{-1}; MS *m/z* (%) 152 (M^+, 2.1), 95 (100). Anal. Calcd for $C_6H_{10}F_2O_2$: C, 47.37; H, 6.63. Found: C, 47.31; H, 6.69.

2,2-Difluoro-3-phenylpropanoic acid (14f) was obtained as above from **6f** (100 mg, 0.30 mmol), $AgNO_3$ (204 mg, 1.20 mmol), THF (3 mL), and H_2O (3 mL); reaction time, 21 h: 51 mg (91 %); colorless solid; mp 76.5 – 78 °C; ^{1}H-NMR ($CDCl_3$) δ 3.38 (2H, t, J = 17 Hz), 6.19 (1H, br s), 7.31 (5H, m); ^{13}C-NMR ($CDCl_3$) δ 40.80 (t, J = 24 Hz), 115.53 (t, J = 251 Hz), 128.33, 128.99, 130.74, 130.84, 167.22 (t, J = 33 Hz); ^{19}F-NMR ($CDCl_3$) δ −105.8 (t, J = 17 Hz); IR (KBr) 1749 cm^{-1}; MS *m/z* (%) 186 (M^+, 6), 91 (100). Anal. Calcd for $C_9H_8F_2O_2$: C, 58.07; H, 4.33. Found: C, 58.01; H 4.39.

2,2-Difluoro-5-oxo-5-phenylpentanoic acid (15e) was obtained as above from **8e** (200 mg, 0.53 mmol), $AgNO_3$ (360 mg, 2.12 mmol), THF (3 mL), and H_2O (3 mL), reaction time, 10 h: colorless solid; mp 99 – 102 °C; 108 mg (89 %); ^{1}H-NMR ($CDCl_3$) δ 2.61 (2H, tt, J = 17, 8 Hz), 3.29 (2H, t, J = 8 Hz), 7.44 – 7.65 (3H, m), 7.96 – 8.00 (2H, m), 8.83 (1H, br s); ^{13}C-NMR ($CDCl_3$) δ 28.93 (t, J = 24 Hz), 30.86 (t, J = 4 Hz), 116.01 (t, J = 249 Hz), 128.52, 129.16, 134.04, 136.48, 167.58 (t, J = 33 Hz), 198.44; ^{19}F-NMR ($CDCl_3$) δ −106.6 (t, J = 16 Hz); IR (neat film) 1766, 1687 cm^{-1}; MS *m/z* (%) 288 (M^+, 15), 77 (100). Anal. Calcd for $C_{11}H_{10}F_2O_3$: C, 57.90; H, 4.42. Found: C, 57.59; H, 4.49.

4-Azido-2,2-difluorobutanoic acid (15h) was obtained as above from **8h** (820 mg, 2.60 mmol), $AgNO_3$ (2.04 g, 12.0 mmol), THF (15 mL), and H_2O (15 mL); reaction time, 8 h: 367 mg (86 %); colorless oil;

^{1}H-NMR ($CDCl_3$) δ 2.402 (2H, tt, J = 16.0, 7.0 Hz), 3.556 (2H, t, J = 7.0 Hz), 9.197 (1H, s); ^{13}C-NMR ($CDCl_3$) δ 33.98 (t, J = 24 Hz), 44.45 (t, J = 5 Hz), 114.96 (t, J = 247 Hz), 166.97 (t, J = 32 Hz); ^{19}F-NMR ($CDCl_3$) δ −107.0 (t, J = 15 Hz); IR (neat film) 2108, 1740 cm^{-1}; MS (CI) *m/z* (%) 166 (M + H$^+$, 40). Anal. Calcd for $C_4H_5F_2N_3O_2$: C, 29.10; H, 3.05; N, 25.45. Found: C, 29.02; H, 2.92; N, 25.66.

2,2,6,6-Tetrafluoroheptanedioic acid (16b) was obtained as above from **11b** (1.49 g, 2.80 mmol), $AgNO_3$ (3.81 g, 22.4 mmol), THF (10 mL), and H_2O (10 mL); reaction time, 9 h: 480 mg (74 %); colorless solid; mp 149 – 151 °C; ^{1}H-NMR (DMSO-d_6) δ 1.533 (2H, quintet, J = 8.4 Hz), 2.162 (4H, tt, J = 16.8, 8.4 Hz), 6 – 10 (2H, br s); ^{13}C-NMR (DMSO-d_6) δ 14.13 (quintet, J = 5 Hz), 32.74 (t, J = 23 Hz), 116.58 (t, J = 248 Hz), 165.42 (t, J = 32 Hz); ^{19}F-NMR (DMSO-d_6) δ −105.1 (m); IR (KBr) 1761 cm^{-1}; MS (CI) *m/z* (%) 233 (M + H$^+$, 100). Anal Calcd for $C_7H_8F_4O_4$: C, 36.22; H, 3.47. Found: C, 36.25; H, 3.40.

2,2,7,7-Tetrafluorooctanedioic acid (16c) was obtained as above from **11c** (270 mg, 0.50 mmol), $AgNO_3$ (849 mg, 5.00 mmol), THF (8 mL), and H_2O (8 mL); reaction time, 25 h: 74 mg (60 %): colorless solid; mp 144 – 147 °C; ^{1}H-NMR (DMSO-d_6) δ 1.39 – 1.48 (4H, m), 1.94 – 2.19 (4H, m); ^{13}C-NMR (DMSO-d_6) δ 20.74 (t, J = 5 Hz), 33.28 (t, J = 23 Hz), 116.82 (t, J = 248 Hz), 165.55 (t, J = 32 Hz); ^{19}F-NMR (DMSO-d_6) δ −104.7 (t, J = 16 Hz); IR (KBr) 1757 cm^{-1}; MS (CI) *m/z* (%) 247 (M + H$^+$,100). Anal. Calcd for $C_8H_{14}F_4O_4$: C, 39.03; H, 4.09. Found: C, 39.06; H, 4.04.

General method of the methanolysis of the radical adducts to obtain difluoroalkanecarboxylic acid methyl esters. Adduct was dissolved in anhydrous methanol. Into the stirred solution under N_2 atmosphere, 4- to 5-molar amount of $AgNO_3$ was added and the mixture was heated to reflux. After disappearance of the starting material, the reaction mixture was filtered. The resulted solid was washed with methanol. The solvent of combined filtrate and washings was evaporated under reduced pressure, and then CH_2Cl_2 was added into the residue. The CH_2Cl_2 solution was filtered through celite. The filtrate was once washed with saturated aqueous $NaHCO_3$ solution and dried with Na_2SO_4. Removal of the solvent under reduced pressure gave almost pure difluoro ester. If necessary, the product was purified by chromatography on a short SiO_2 column eluting with CH_2Cl_2.

Methyl 2,2-difluoro-4-phenylbutanoate (17a) was obtained as above from **6a** (103 mg, 0.30 mmol), $AgNO_3$ (204 mg, 1.20 mmol), and anhydrous CH_3OH (5 mL); reaction time, 10 h: 44 mg (68 %); colorless oil; ^{1}H-NMR ($CDCl_3$) δ 2.27 – 2.52 (2H, m), 2.77 – 2.86 (2H, m), 3.82 (3H, s), 7.17 – 7.35 (5H, m); ^{13}C-NMR ($CDCl_3$) δ 27.75 (t, J = 5 Hz), 36.35 (t, J = 23 Hz), 53.44, 116.14 (t, J = 233 Hz), 126.86, 128.69, 128.99, 139.80, 165.07 (t, J = 33 Hz); ^{19}F-NMR ($CDCl_3$) δ −105.58 (t, J = 15 Hz); IR (neat film) 1770 cm^{-1}; MS *m/z* (%) 214 (M$^+$, 50), 91 (100). Anal. Calcd for $C_{11}H_{12}F_2O_2$: C, 61.68; H, 5.65. Found: C, 61.43; H, 5.75.

Methyl 2,2-difluorooctanoate (17b) was obtained as above from **6b** (100 mg, 0.30 mmol), $AgNO_3$ (204 mg, 1.20 mmol), and anhydrous CH_3OH (6 mL); reaction time, 12 h: 27 mg (47 %); colorless oil; ^{1}H-NMR ($CDCl_3$) δ 0.89 (3H, t, J = 7 Hz), 1.25 – 1.50 (10H, m), 1.93 – 2.18 (2H, m), 3.88 (3H, s); ^{13}C-NMR ($CDCl_3$) δ 14.03, 21.45 (t, J = 4 Hz), 22.49, 28.81, 31.50, 34.65 (t, J = 23 Hz), 53.41, 116.83 (t, J = 249 Hz), 165.47 (t, J = 33 Hz); ^{19}F-NMR ($CDCl_3$) δ −106.2 (t, J = 16 Hz); IR (neat film) 1770 cm^{-1}; MS (CI) *m/z* (%) 195 (M + H$^+$, 100). Anal. Calcd for $C_9H_{16}F_2O_2$: C, 55.66; H, 8.30. Found: C, 55.65; H, 8.31.

Methyl 2-cyclohexyl-2,2-difluoroacetate (17c) was obtained as above from **6c** (326 mg, 1.00 mmol), $AgNO_3$ (479 mg, 4.00 mmol), and anhydrous CH_3OH (15 mL); reaction time, 9 h: 143 mg (74 %); colorless oil; ^{1}H-NMR ($CDCl_3$) δ 1.17 – 1.30 (5H, m), 1.66 – 1.85 (5H, m), 1.98 – 2.13 (1H, m), 3.87 (3H, s); ^{13}C-

NMR ($CDCl_3$) δ 24.80 (t, J = 4 Hz), 25.37, 25.85, 42.36 (t, J = 22 Hz), 53.24, 117.79 (t, J = 251 Hz), 165.46 (t, J = 33 Hz); ^{19}F-NMR ($CDCl_3$) δ −113.9 (t, J = 15 Hz); IR (neat film) 1768 cm^{-1}; MS *m/z* (%) 192 (M^+, 5), 110 (100). Anal. Calcd for $C_9H_{14}F_2O_2$: C, 56.24; H, 7.34. Found: C, 56.48; H, 7.15.

Methyl 2-adamant-1-yl-2,2-difluoroacetate (17d) was obtained as above from **6d** (113 mg, 0.30 mmol), $AgNO_3$ (204 mg, 1.20 mmol), and anhydrous CH_3OH (9 mL); reaction time, 12 h: 56 mg (77 %); colorless oil; ^{1}H-NMR ($CDCl_3$) δ 1.60 – 1.77 (12H, m), 2.04 (3H, br s), 3.87 (3H, s); ^{13}C-NMR ($CDCl_3$) δ 26.56, 33.80 (t, J = 4 Hz), 35.52, 37.93 (t, J = 22 Hz), 51.96, 117.88 (t, J = 253 Hz), 163.99 (t, J = 34 Hz); ^{19}F-NMR ($CDCl_3$) δ −119.9 (s); IR (neat film) 1765 cm^{-1}; MS *m/z* (%) 244 (M^+, 1), 134 (100). Anal. Calcd for $C_{13}H_{18}F_2O_2$: C, 63.92; H, 7.43. Found: C, 64.11; H, 7.52.

Methyl (Z)-2,2-difluoro-10-nonadecenoate (18b) was obtained as above from **8b** (487 mg, 1.00 mmol), $AgNO_3$ (679 mg, 4.00 mmol), and anhydrous CH_3OH (12 mL); reaction time, 10 h: 307 mg (88 %); colorless oil; ^{1}H-NMR ($CDCl_3$) δ 0.88 (3H, t, J = 6 Hz), 1.25–1.50 (22H, m), 1.92 – 2.17 (6H, m), 3.88 (3H, s), 5.38 (2H, m); ^{13}C-NMR ($CDCl_3$) δ 14.17, 21.48 (t, J = 4 Hz), 22.78, 28.96, 29.13, 29.18, 29.29, 29.43, 29.62, 29.76, 32.02, 32.64, 32.72, 34.64, 34.62 (t, J = 23 Hz), 53.40, 116.81(t, J = 249 Hz), 130.54, 130.95, 165.45 (t, J = 33 Hz); ^{19}F-NMR ($CDCl_3$) δ −106.2 (t, J = 16 Hz); IR (neat film) 1774 cm^{-1}; MS *m/z* (%) 346 (M^+, 2). Anal. Calcd for $C_{20}H_{36}F_2O_2$: C, 69.33; H, 10.47. Found: C, 69.30; H, 10.49.

Methyl 2,2-difluoro-2-(2-tetrahydrofuryl)acetate (18c) was obtained as above from **8c** (170 mg, 0.50 mmol), $AgNO_3$ (340 mg, 2.00 mmol), and anhydrous CH_3OH (5 mL); reaction time, 10 h: 57 mg (63 %); colorless oil; ^{1}H-NMR ($CDCl_3$) δ 1.89 – 2.19 (4H, m), 3.91 (3H, s), 3.80 – 4.00 (2H, m), 4.28 – 4.51 (1H, m); ^{13}C-NMR ($CDCl_3$) δ 25.13 (d, J = 4 Hz), 25.70, 53.56, 70.02, 77.6 (dd, J = 31, 40 Hz), 114.88 (dd, J = 258, 251 Hz), 164.48 (dd, J = 34, 30 Hz); ^{19}F-NMR ($CDCl_3$) δ −113.3 (d, J = 270 Hz), −124.4 (dd, J = 270, 19 Hz); IR (neat film) 1765 cm^{-1}; MS (CI) *m/z* (%) 181 (M + H^+, 100). Anal. Calcd for $C_7H_{10}F_2O_3$: C, 46.67; H, 5.60. Found: C, 46.65; H, 5.62.

Methyl 4-ethoxy-2,2-difluorobutanoate (18d) was obtained as above from **8d** (316 mg, 1.00 mmol), $AgNO_3$ (679 mg, 4.00 mmol), and anhydrous CH_3OH (10 mL); reaction time, 5 h: 115 mg (63 %): colorless oil; ^{1}H-NMR ($CDCl_3$) δ 1.15 (3H, t, J = 7 Hz), 2.39 (2H, tt, J = 15, 6 Hz), 3.43 (2H, q, J = 7 Hz), 3.58 (2H, t, J = 6 Hz), 3.86 (3H, s); ^{13}C-NMR ($CDCl_3$) δ 14.99, 35.50 (t, J = 24 Hz), 53.28, 63.68 (t, J = 6 Hz), 66.74, 115.71 (t, J = 249 Hz), 165.02 (t, J = 25 Hz); ^{19}F-NMR ($CDCl_3$) δ −106.4 (t, J = 15 Hz); IR (neat film) 1774 cm^{-1}; MS *m/z* (%) 182 (M^+, 2), 137(100). Anal. Calcd for $C_7H_{12}F_2O_3$: C, 46.15; H, 6.64. Found: C, 46.16; H, 6.62.

Methyl 2,2-difluoro-5-oxo-5-phenylpentanoate (18e) was obtained as above from **8e** (188 mg, 0.50 mmol), $AgNO_3$ (340 mg, 2.00 mmol), and anhydrous CH_3OH (10 mL); reaction time, 10 h: 103 mg (85 %); colorless solid; mp 45 – 48 °C; ^{1}H-NMR ($CDCl_3$) δ 2.57 (2H, tt, J = 17, 8 Hz), 3.25 (2H, m), 3.89 (3H, s), 7.44 – 7.64 (3H, m), 7.95 – 8.01 (3H, m); ^{13}C-NMR ($CDCl_3$) δ 29.04 (t, J = 24 Hz), 30.78 (t, J = 4 Hz), 53.61, 116.22 (t, J = 249 Hz), 128.40, 129.10, 133.89, 136.64, 164.93 (t, J = 33 Hz), 197.60; ^{19}F-NMR ($CDCl_3$) δ −106.6 (t, J = 17 Hz); IR (neat film) 1770, 1689 cm^{-1}; MS *m/z* (%) 242 (M^+, 5), 105 (100). Anal. Calcd for $C_{12}H_{12}F_2O_3$: C, 59.50; H, 4.99. Found: C, 59.66; H, 5.18.

Dimethyl 2,2-difluorobutanedioate (18f) was obtained as above from **8f** (330 mg, 1.00 mmol), $AgNO_3$ (679 mg, 4.00 mmol), and anhydrous CH_3OH (10 mL); reaction time, 10 h: 168 mg (86 %); colorless oil; ^{1}H-NMR ($CDCl_3$) δ 2.32–2.61 (4H, m), 3.71 (3H, s), 3.89 (3H, s); ^{13}C-NMR ($CDCl_3$) δ 26.42 (t, J = 5 Hz), 29.93 (t, J = 24 Hz), 52.18, 53.60, 115.64 (t, J = 250 Hz), 164.68 (t, J = 33 Hz), 172.44; ^{19}F-NMR ($CDCl_3$) δ −107.1

(t, J = 15 Hz); IR (neat film) 1768, 1745 cm^{-1}; MS *m/z* (%) 196 (M^+, 0.9), 137 (100). Anal. Calcd for $C_7H_{10}F_2O_4$: C, 42.86; H, 5.14. Found: C, 42.85; H, 5.14.

Methyl 4-azido-2,2-difluorobutanoate (18h) was obtained as above from **8h** (1.253 g, 4.00 mmol), $AgNO_3$ (2.718 g, 16.00 mmol), and anhydrous CH_3OH (50 mL); reaction time, 8 h: 440 mg (61 %); pale yellow oil; ^1H-NMR ($CDCl_3$) δ 2.38 (2H, tt, J = 16, 7 Hz), 3.54 (2H, t, J = 7 Hz), 3.91 (3H, s); ^{13}C-NMR ($CDCl_3$) δ 34.21 (t, J = 24 Hz), 44.49 (t, J = 5 Hz), 53.76, 115.01 (t, J = 250 Hz), 164.48 (t, J = 33 Hz); ^{19}F-NMR ($CDCl_3$) δ 106.3 (t, J = 16 Hz); IR (neat film) 2104, 1770 cm^{-1}; MS (CI) *m/z* (%) 180 (M + H^+, 100). Anal. Calcd for $C_5H_7N_3F_2O_2$: C, 33.53; H, 3.94; N, 23.46. Found: C, 33.55; H, 3.82; N, 23.56.

Dimethyl 2,2,5,5-Tetrafluorohexanedioate (19a) was obtained as above from **11a** (690 mg, 1.34 mmol), $AgNO_3$ (1.83 g, 10.8 mmol), and anhydrous CH_3OH (20 mL); reaction time, 9 h: 290 mg (88 %); pale yellow oil; ^1H-NMR ($CDCl_3$) δ 2.17 - 2.47 (4H, m), 3.91 (6H, s); ^{13}C-NMR ($CDCl_3$) δ 27.15 (tt, J = 24, 5 Hz), 53.79, 115.34 (t, J = 250 Hz), 164.42 (t, J = 33 Hz); ^{19}F-NMR ($CDCl_3$) δ -107.1 (m); IR (neat film) 1771 cm^{-1}; MS (CI) *m/z* (%) 247 (M + H^+, 100). Anal. Calcd for $C_8H_{10}F_4O_4$: C, 39.03; H, 4.09. Found: C, 38.92; H, 4.09.

Dimethyl 2,2,6,6-Tetrafluoroheptanedioate (19b) was obtained as above from **11b** (840 mg, 1.59 mmol), $AgNO_3$ (2.16 g, 12.7 mmol), and anhydrous CH_3OH (20 mL); reaction time, 9 h: 330 mg (81 %); pale yellow oil; ^1H-NMR ($CDCl_3$) δ 1.63 - 1.81 (2H, m), 2.16 (4H, tt, J = 16, 8 Hz), 3.89 (6H, s); ^{13}C-NMR ($CDCl_3$) δ 13.97 (quintet, J = 5 Hz), 33.78 (t, J = 23 Hz), 53.60, 116.10 (t, J = 250 Hz), 164.89 (t, J = 33 Hz); ^{19}F-NMR ($CDCl_3$) δ -106.6 (t, J = 16 Hz); IR (neat film) 1769 cm^{-1}; MS (CI) *m/z* (%) 261 (M + H^+, 100). Anal. Calcd for $C_9H_{12}F_4O_4$: C, 41.55; H, 4.65. Found: C, 41.39; H, 4.80.

Dimethyl 2,2,7,7-Tetrafluorooctanedioate (19c) was obtained as above from **11c** (1.26 g, 2.32 mmol), $AgNO_3$ (3.16 g, 18.6 mmol), and anhydrous CH_3OH (25 mL); reaction time, 9 h: 480 mg (75 %); pale yellow oil; ^1H-NMR ($CDCl_3$) δ 1.51 - 1.63 (4H, m), 2.09 (4H, tt, J = 17, 8 Hz), 3.89 (6H, s); ^{13}C-NMR ($CDCl_3$) δ 21.05 (t, J = 4 Hz), 34.06 (t, J = 23 Hz), 53.49, 116.33 (t, J = 250 Hz), 165.13 (t, J = 33 Hz); ^{19}F-NMR ($CDCl_3$) δ -106.4 (t, J = 17 Hz); IR (neat film) 1769 cm^{-1}; MS (CI) *m/z* (%) 275 (M + H^+, 100). Anal. Calcd for $C_{10}H_{14}F_4O_4$: C, 43.78; H, 5.15. Found: C, 43.79; H, 5.04.

Methyl 2,2-difluoro-3-hydroxypropanoate (20) was obtained as above from **8g** (230 mg, 0.73 mmol), $AgNO_3$ (493 mg, 2.9 mmol), and anhydrous CH_3OH (5 mL); reaction time, 10 h: 45 mg (40%); colorless oil; ^1H-NMR ($CDCl_3$) δ 3.93 (3H, s), 4.03 (2H, t, J = 12 Hz), 4.25 (1H, br s); ^{13}C-NMR ($CDCl_3$) δ 53.84, 62.89 (t, J = 29 Hz), 114.06, 164.35 (t, J = 32 Hz); ^{19}F-NMR ($CDCl_3$) δ -116.0 (t, J = 12 Hz); IR (neat film) 3445, 1766 cm^{-1}; MS (CI) *m/z* (%) 141 (M + H^+, 100). Anal. Calcd for $C_4H_6F_2O_3$: C, 33.81; H, 5.67. Found: C, 38.69; H, 5.50.

4-Amino-2,2-difluorobutanoic acid (21). Azido acid **15h** (46 mg, 0.28 mmol) was dissolved into anhydrous methanol (1 mL) and palladium on activated carbon (10 %; 9 mg, 4 mmol) was added into the mixture. The mixture was stirred under H_2 (1 atm) at room temperature for 5 h. After filtration, the catalyst was washed with methanol several times. The solvent was removed under reduced pressure to give **21** as colorless solid: 34 mg (87 %); mp 243 - 245°C; (lit.[14] 245 - 247 °C).

2,2-Difluoro-4-butanelactam (23). A mixture of **18h** (70 mg, 0.39 mmol) and PPh_3 (113 mg, 0.43 mmol) in toluene (8 mL) was stirred overnight at room temperature. After removal of the solvent under reduced

pressure, the residue was chromatographed on an SiO_2 column (hexane – EtOAc; 5 : 3) to give **23** as pale yellow solid: 17 mg (36 %); mp 69–72 °C; ^{1}H-NMR ($CDCl_3$) δ 2.572 (2H, tt, J = 15.2, 6.4 Hz), 3.500 (2H, tq, J = 6.4, 1.2 Hz), 7.73 (1H, br s); ^{13}C-NMR ($CDCl_3$) δ 30.69 (t, J = 23 Hz), 36.78 (t, J = 4 Hz), 117.77 (t, J = 249 Hz), 167.34 (t, J = 31 Hz); ^{19}F-NMR ($CDCl_3$) δ −108.4 (t, J = 15 Hz); IR (KBr) 3238, 1734 cm^{-1}; MS *m/z* (%) 121 (M^+, 100). Anal. Calcd for $C_4H_5F_2NO$: C, 39.68; H, 4.16; N, 11.57. Found: C, 40.04; H, 4.12; N, 11.23.

2,2-Difluoro-*N*-methyl-4-butanelactam (24). A mixture of **18h** (100 mg, 0.55 mmol) and PBu_3 (0.15 mL, ca 0.6 mmol) in anhydrous THF (5 mL) was stirred under N_2 atmosphere at room temperature for 22 h. After removal of the solvent under reduced pressure, the residue was chromatographed on an SiO_2 column (*n*-hexane – EtOAc ; 1 : 1) to give **38** as pale yellow oil: 44 mg (59 %); ^{1}H-NMR ($CDCl_3$) δ 2.528 (2H, tt, J = 15.0, 6.5 Hz), 2.976 (3H, s), 3.458 (2H, tt, J = 6.4, 1.8 Hz); ^{13}C-NMR ($CDCl_3$) δ 29.10 (t, J = 23 Hz), 30.60, 43.41 (t, J = 3 Hz), 118.26 (t, J = 248 Hz), 164.01 (t, J = 31 Hz); ^{19}F-NMR ($CDCl_3$) δ −107.2 (t, J = 16 Hz); IR (neat film) 1728 cm^{-1}; MS *m/z* (%) 135 (M^+, 100) 78 (32), 77 (48). Anal. Calcd for $C_5H_7F_2NO$: C, 44.45; H, 5.22; N, 10.37. Found: C, 44.30; H, 5.20; N, 10.34.

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