

**RADICAL REACTION USING AN ORGANOCOPPER REAGENT
DERIVED FROM ETHYL BROMODIFLUOROACETATE**

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Received April 12, 2002

Accepted June 10, 2002

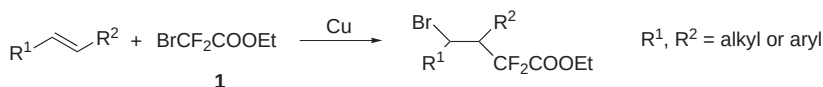
Dedicated to the memory of Professor Miloš Hudlický.

In our previous work, reaction of ethyl bromodifluoroacetate (**1**) in the presence of Cu powder with olefins activated by an electron-withdrawing group gave the Michael-type adducts through an anionic intermediate. The same reaction with non-activated olefins was found to give addition products by a radical mechanism. The radical intermediate from α -methylstyrene was stabilized by a benzene ring and gave novel dimerization products. This reaction with 1-decene provided a convenient route to 2,2-difluorododecanoic acid.

Keywords: Radical additions; Radicals; Alkenes; Fluorine; Fluorinated compounds; Ethyl bromodifluoroacetate; Copper powder.

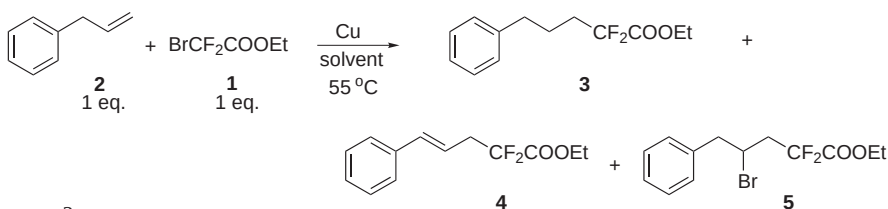
Nowadays, organofluorine compounds have been attracting much attention in biomedical fields, since they have various biological activities¹. Among them, difluoromethylene (CF₂) compounds are very important, and their syntheses have been reported by many workers². The Reformatsky reaction of halodifluoroacetate is one of the most useful methodologies to insert a CF₂ moiety³. However, this method introduces one hydroxyl group adjacent to the CF₂ group, which is very difficult to remove⁴. To solve the difficulty, we have developed a cross-coupling reaction⁵ of ethyl bromodifluoroacetate (**1**) with alkenyl or aryl iodides in the presence of copper powder. A similar reaction of ester **1** with several Michael acceptors gave 1,4-addition products⁶. This Michael-type reaction smoothly proceeded with common Michael acceptors, but formation of considerable amounts of by-products through radical mechanism was observed in the reaction of 4-phenyl-3-buten-2-one, the phenyl ring of which would stabilize the radical intermediate⁶. This suggested that some radical reaction might proceed

if a suitable electron-withdrawing group was absent on the double bond. Namely, this reaction would produce ethyl 4-bromo-2,2-difluoroalkanoates from non-activated alkenes as shown in Scheme 1.



SCHEME 1

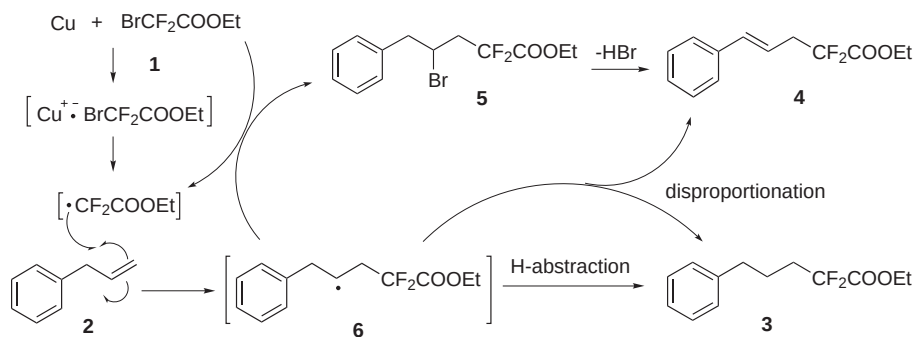
First, we examined the reaction of allylbenzene (**2**) with ester **1** under the same condition as the previous ones^{5,6}. Here, we obtained ethyl 4-bromo-2,2-difluoro-5-phenylpentanoate (**5**) along with ethyl 2,2-difluoro-5-phenylpentanoate (**3**) and ethyl (*E*)-2,2-difluoro-5-phenyl-4-pentenoate (**4**), as expected (Scheme 2).



SCHEME 2

Next, we examined various reaction conditions to improve the yield of ester **5** (see Table I).

The reaction proceeded in polar aprotic solvents, but did not in poorly coordinating solvents such as benzene or THF (entries 1–5). This suggested that some copper complex, possibly an anion-radical complex, played an important role. In addition, we found that the reaction proceeded even with a catalytic amount of copper, although a prolonged reaction time was necessary (entries 6–8), and that the higher concentration was better for formation of bromo ester **5** in a shorter reaction time (entries 6 and 9). This is obvious comparing entries 1, 10 and 11. All yields were estimated from the peak areas in GLC traces, and the structures were determined by the examination of spectral data of the samples purified by repeated column chromatography. The tentative mechanism is shown in Scheme 3. The radical formed from ester **1** and copper attacks alkene **2**, giving another radical intermediate **6**. This radical reacts with ester **1** to afford bromo ester **5** and the first radical, confirming thus that copper acts as a catalyst. Compound **3** might be formed from radical **6** by hydrogen abstraction from a solvent or disproportionation, while unsaturated ester **4** from bromo ester **5** by dehydrobromination or disproportionation.



SCHEME 3

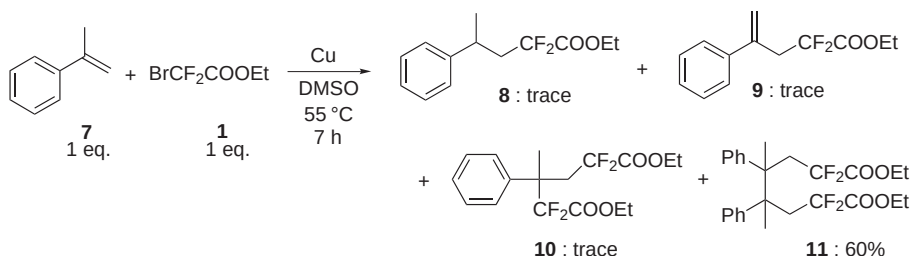
To extend the scope of this reaction, we examined the reaction of ester **1** with various olefins. The reaction of α -methylstyrene (**7**) did not give the expected compound, ethyl 4-bromo-2,2-difluoro-4-phenylpentanoate, but diethyl 2,2,7,7-tetrafluoro-4,5-dimethyl-4,5-diphenyloctanedioate (**11**) along with a trace of ethyl 2,2-difluoro-4-phenylpentanoate (**8**), ethyl

TABLE I
Examination of solvent and concentration effects

Entry	Solvent	Cu, eq.	Concentration of 1 mol l ⁻¹	Time ^{a,b}	Yield ^{b,c} , %			
					3	4	5	2
1	DMSO	2.2	0.2	8 h	13	13	41	25
2	HMPA	2.2	0.2	3 days	4	4	tr	88
3	DMF	2.2	0.2	2 days	tr	24	8	55
4	THF	2.2	0.2	4 days	0	0	0	99
5	Benzene	2.2	0.2	4 days	0	0	0	99
6	DMSO	0.3	0.2	5 days	13	12	45	14
7	HMPA	0.3	0.2	2 weeks	tr	tr	tr	99
8	DMF	0.3	0.2	2 weeks	49	1	35	15
9	DMSO	0.3	1.0	4 days	8	12	70	6
10	DMSO	2.2	1.0	5 h	6	11	64	1
11	DMSO	2.2	0.04	24 h	23	13	7	48

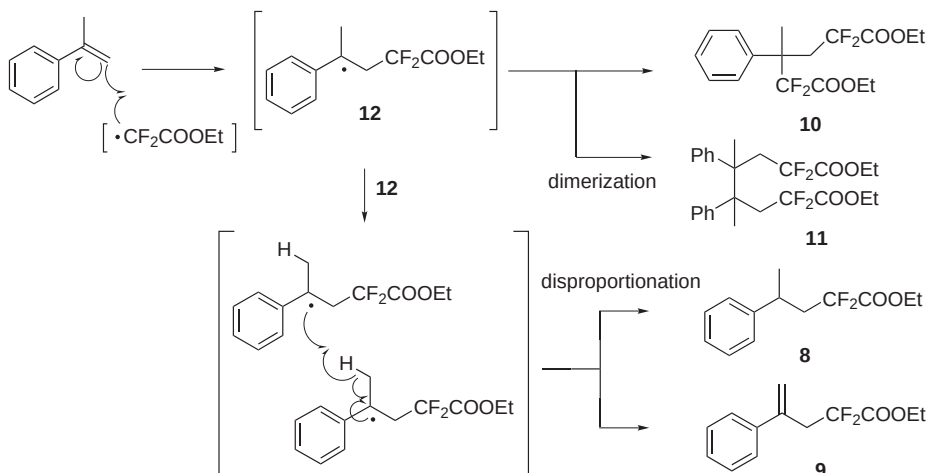
^a Until the peak of **1** was no more detected by GLC. ^b tr = trace. ^c Calculated from peak area of GLC.

2,2-difluoro-4-phenyl-4-pentenoate (**9**) and diethyl 2,2,5,5-tetrafluoro-3-methyl-3-phenylhexanedioate (**10**) (Scheme 4).



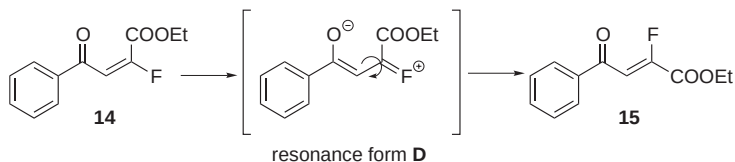
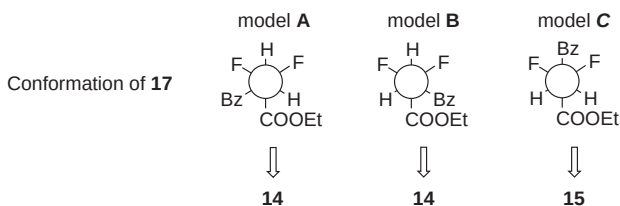
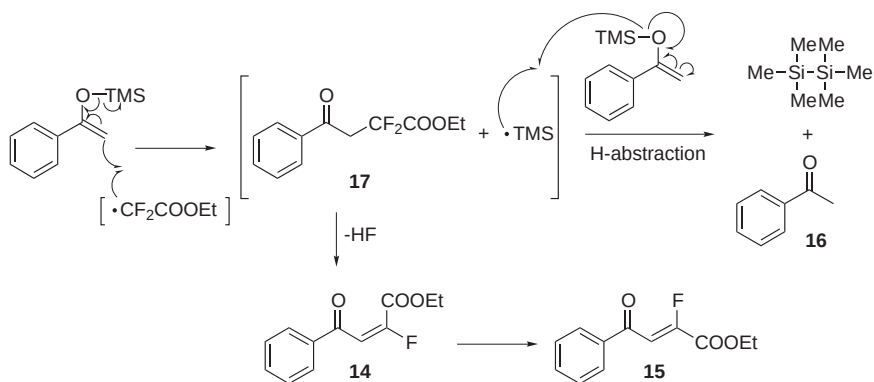
SCHEME 4

Suggested mechanism for the formation of these products is shown in Scheme 5. Initially formed benzylic radical **12** reacts with ester **1** to give diester **10**, but it is very stable and has a life time long enough to dimerize to diester **11**. Some radical **12** may react with each other through disproportionation to give esters **8** and **9**.



SCHEME 5

Next, we examined the reaction of a silyl enol ether, 1-phenyl-1-[(trimethylsilyl)oxy]ethene (**13**). Here, we obtained ethyl (*E*)-2-fluoro-4-oxo-4-phenyl-2-butenolate (**14**) and ethyl (*Z*)-2-fluoro-4-oxo-4-phenyl-2-butenolate (**15**). GLC analysis suggested that first ethyl 2,2-difluoro-4-oxo-4-phenylbutanoate (**17**) was formed, followed by elimination of HF leading to ester **14**. At first, ester **14** was observed as a major peak on GLC. It decreased gradually, while that of isomeric ester **15** increased. Based on the conformation analysis of the intermediate **17**, the antiperiplanar elimina-

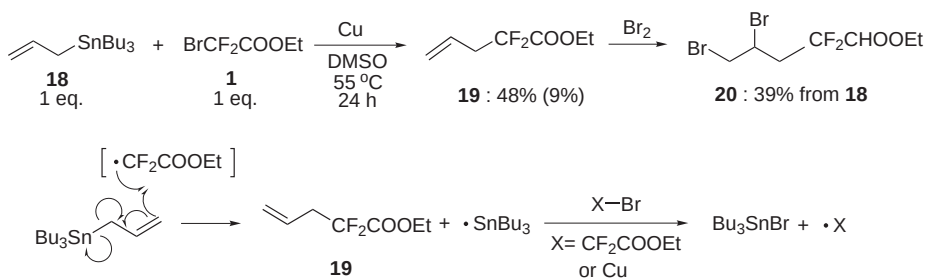


Collect. Czech. Chem. Commun. (Vol. 67) (2002)

sion between the benzoyl and the ethoxycarbonyl groups. This isomerization might occur due to low isomerization barrier at the double bond as indicated by a resonance form **D**. The total yield of esters **14** and **15** was low, probably due to the formation of acetophenone (**16**) as a by-product. This might be formed by the attack of the temporally formed TMS radical (TMS $\cdot$) on silyl ether **13**. Both ketone **16** and hexamethyldisilane were detected by GC-MS. The above results are shown in Scheme 6 with the proposed mechanism.

Since the TMS radical attacked silyl ether **13** rather than ester **1**, we examined the reaction of allyltributyltin (**18**), reaction of which with halofluoro compounds has been reported by many workers⁷.

As expected, stannane **18** smoothly reacted with ester **1** and gave ethyl 2,2-difluoro-4-pentenoate (**19**) as a single product (Scheme 7). ^1H NMR showed that ester **19** was obtained in moderate yield (48%), but the isolation yield was low (9%) owing to its high volatility. So, we examined bromination of ester **19** *in situ*. The dibromide **20** was isolated in a better yield (39% from ester **18**). The reaction mechanism is shown in the bottom of Scheme 7.

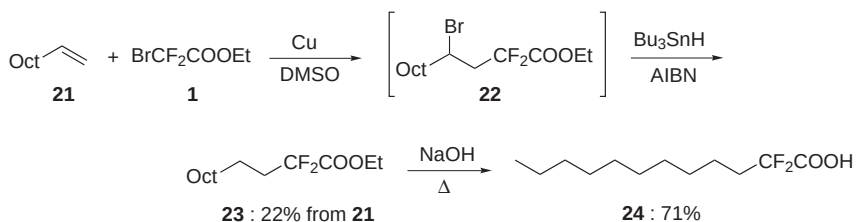


SCHEME 7

Fluorine compounds show a significant difference in their character from that of original compounds, owing to chemical and/or physical properties of fluorine. Recently, O'Hagan and coworkers reported to synthesis and properties of difluorostearic acids⁸. They concluded that difluoromethylene group changed the nature of stearic acid significantly. We thought that our radical reaction could be applied to syntheses of 2,2-difluoro fatty acids. Now, we describe the synthesis of 2,2-difluorododecanoic acid (**24**).

The reaction of ester **1** with 1-decene (**21**) in the presence of Cu powder gave ethyl 4-bromo-2,2-difluorododecanoate (**22**), although a few organofluorine compounds were detected as by-product by ^{19}F NMR. The crude es-

ter **22** was treated with Bu_3SnH , followed by hydrolysis to give the target acid **24** (Scheme 8).



SCHEME 8

In conclusion, ester **1** reacted with various olefins to give several adducts. This suggested that the intermediate of these reactions might be radical species, although the intermediate of the cross-coupling reaction and the Michael-type reaction might be anionic.

Thus, we found that the reaction of ethyl bromodifluoroacetate (**1**) in the presence of Cu powder could give various products depending on the substrates in these reactions. We believe that these reactions using commercially available ester **1** provide useful methodologies for introduction of the difluoromethylene containing functional groups.

EXPERIMENTAL

^1H NMR spectra were recorded on JEOL-FX90Q and JNM-GX400 spectrometers. Tetramethylsilane was used as an internal standard. ^{19}F NMR spectra were recorded on Hitachi FT-NMR R-1500, JEOL-FX90Q and GE-Omega 600 spectrometers. Benzotrifluoride was used as an internal standard. Chemical shifts (δ) are given in ppm, coupling constants (J) in Hz. Mass spectra were obtained on JEOL JMS-DX-300 and JEOL JMS-700T spectrometers. Gas-liquid chromatography (GLC) was carried out on a Hitachi 263-50 gas chromatograph (column, 5% SE-30 3 mm $\times$ 2 m, carrier, N_2 at 30 ml/min). Peak areas were calculated on a Shimadzu C-R5A Chromatopac. Melting points were measured on an Ishii Shoten melting point apparatus. All commercially available reagents were used without further purification. The activated Cu powder was prepared according to the reference⁹.

Reaction of Ethyl Bromodifluoroacetate with Allylbenzene (**2**)

In an atmosphere of Ar, ethyl bromodifluoroacetate (**1**; 0.25 ml, 2.0 mmol) and allylbenzene (**2**; 0.26 ml, 2.0 mmol) were added to a suspension of activated Cu powder (280 mg, 4.4 mmol) in DMSO (2 ml), and the mixture was stirred at 55 $^\circ\text{C}$ for 5 h. After this time, **1** was not detected by GLC. The mixture was poured onto a mixture of ice and saturated NH_4Cl solution, and extracted with Et_2O . The Et_2O layer was washed with saturated NH_4Cl solution and saturated NaCl solution, and dried over MgSO_4 . After evaporation of the solvent, the residue was purified by column chromatography (SiO_2 , AcOEt –hexane 1 : 4)

to give a mixture of ethyl 2,2-difluoro-5-phenylpentanoate (**3**), ethyl (*E*)-2,2-difluoro-5-phenyl-4-pentenoate (**4**) and ethyl 4-bromo-2,2-difluoro-5-phenylpentanoate (**5**). Yields of these products were estimated to be 17, 4 and 40%, respectively, based on analysis of this mixture by ^1H NMR spectroscopy using dioxane as internal standard. This mixture was further separated by repeated column chromatography to give pure samples for analysis.

Compound **3**: A colorless oil. MS, m/z : 242 (M^+). HRMS: calculated for $\text{C}_{13}\text{H}_{16}\text{F}_2\text{O}_2$: 242.112 (M^+); found: 242.113. ^1H NMR (CDCl_3): 7.14–7.32 (m, 5 H); 4.30 (q, 2 H, $J = 7.3$); 2.68 (t, 2 H, $J = 7.8$); 2.08 (m, 2 H); 1.82 (m, 2 H); 1.33 (t, 3 H, $J = 7.3$). ^{19}F NMR (CDCl_3): –40.3 (t, 2 F, $^3J_{\text{HF}} = 16.1$). Compound **4**: A colorless oil. MS, m/z : 240 (M^+). HRMS: calculated for $\text{C}_{13}\text{H}_{14}\text{F}_2\text{O}_2$: 240.096 (M^+); found: 240.096. ^1H NMR (CDCl_3): 7.22–7.38 (m, 5 H); 6.56 (d, 1 H, $J = 15.6$); 6.09 (dt, 1 H, $J = 15.6, 7.3$); 4.32 (q, 2 H, $J = 7.3$); 2.99 (td, 2 H, $^3J_{\text{HF}} = 16.1, J = 7.8$); 1.32 (t, 3 H, $J = 7.3$). ^{19}F NMR (CDCl_3): –39.7 (t, 2 F, $^3J_{\text{HF}} = 16.1$). Compound **5**: A colorless oil. MS, m/z : 275 ($\text{M}^+ - \text{OEt}$), 241 ($\text{M}^+ - \text{Br}$). HRMS: calculated for $\text{C}_{11}\text{H}_{10}\text{BrF}_2\text{O}$: 274.988 ($\text{M}^+ - \text{OEt}$), $\text{C}_{13}\text{H}_{15}\text{F}_2\text{O}_2$: 241.104 ($\text{M}^+ - \text{Br}$); found: 274.986 ($\text{M}^+ - \text{OEt}$), 241.104 ($\text{M}^+ - \text{Br}$). ^1H NMR (CDCl_3): 7.18–7.37 (m, 5 H); 4.35 (m, 1 H); 4.33 (q, 2 H, $J = 7.3$); 3.22 (m, 2 H); 2.61–2.88 (m, 2 H); 1.36 (t, 3 H, $J = 7.3$). ^{19}F NMR (CDCl_3): –35.3 (dt, 1 F, $^2J_{\text{FF}} = 263.7, ^3J_{\text{HF}} = 14.7$); –42.1 (dt, 1 F, $^2J_{\text{FF}} = 263.7, ^3J_{\text{HF}} = 16.1$).

Reaction of Ethyl Bromodifluoroacetate with α -Methylstyrene (**7**)

In an atmosphere of Ar, ethyl bromodifluoroacetate (**1**; 0.25 ml, 2.0 mmol) and α -methylstyrene (**7**; 0.26 ml, 2.0 mmol) were added to a suspension of activated Cu powder (280 mg, 4.4 mmol) in DMSO (2 ml), and the mixture was stirred at 55 °C for 7 h. After this time, **1** was not detected by GLC. The mixture was poured onto a mixture of ice and saturated NH_4Cl solution, and extracted with Et_2O . The Et_2O layer was washed with saturated NH_4Cl solution and saturated NaCl solution, and dried over MgSO_4 . After evaporation of the solvent, the residue was purified by column chromatography (SiO_2 , Et_2O –hexane 1 : 4) to give ethyl 2,2-difluoro-4-phenylpentanoate (**8**, trace), ethyl 2,2-difluoro-4-phenyl-4-pentenoate (**9**, trace) and diethyl 2,2,5,5-tetrafluoro-3-methyl-3-phenylhexanedioate (**10**, trace). The solvent was changed to AcOEt –hexane 2 : 3 to give diethyl 2,2,7,7-tetrafluoro-4,5-dimethyl-4,5-diphenyloctanedioate (**11**; 293 mg, 60%) as a mixture of meso form and racemate (1 : 1). Each diastereomer of **11** could be purified by recrystallization from hexane or EtOH .

Compound **8**: A colorless oil. MS, m/z : 242 (M^+). HRMS: calculated for $\text{C}_{13}\text{H}_{16}\text{F}_2\text{O}_2$: 242.112 (M^+); found: 242.112. ^1H NMR (CDCl_3): 7.30 (m, 2 H); 7.20 (m, 3 H); 4.04 (dq, 1 H, $J = 19.3, 7.0$); 4.01 (dq, 1 H, $J = 19.3, 7.0$); 3.07 (m, 1 H); 2.49 (m, 1 H); 2.32 (m, 1 H); 1.34 (d, 3 H, $J = 7.0$); 1.24 (t, 3 H, $J = 7.0$). ^{19}F NMR (CDCl_3): –35.3 (dt, 1 F, $^2J_{\text{FF}} = 259.3, ^3J_{\text{HF}} = 16.1$); –41.6 (dt, 1 F, $^2J_{\text{FF}} = 259.3, ^3J_{\text{HF}} = 16.1$). Compound **9**: A colorless oil. MS, m/z : 240 (M^+). HRMS: calculated for $\text{C}_{13}\text{H}_{14}\text{F}_2\text{O}_2$: 240.096 (M^+); found: 240.095. ^1H NMR (CDCl_3): 7.27–7.39 (m, 5 H); 5.51 (t, 1 H, $J = 1.0$); 5.32 (s, 1 H); 4.05 (q, 2 H, $J = 7.3$); 3.30 (dt, 2 H, $^3J_{\text{HF}} = 15.7, J = 1.0$); 1.21 (t, 3 H, $J = 7.3$). ^{19}F NMR (CDCl_3): –38.0 (t, 2 F, $^3J_{\text{HF}} = 15.7$). Compound **10**: A colorless oil. MS, m/z : 364 (M^+). HRMS: calculated for $\text{C}_{17}\text{H}_{20}\text{F}_4\text{O}_4$: 364.130 (M^+); found: 364.129. ^1H NMR (CDCl_3): 7.26–7.43 (m, 5 H); 4.01 (q, 1 H, $J = 7.4$); 4.00 (q, 1 H, $J = 7.4$); 3.76 (dq, 1 H, $J = 34.2, 7.2$); 3.74 (dq, 1 H, $J = 34.2, 7.2$); 3.19 (dt, 1 H, $^3J_{\text{HF}} = 22.1, J = 15.6$); 2.77 (td, 1 H, $J = 15.6, ^3J_{\text{HF}} = 12.0$); 1.77 (bs, 3 H); 1.17 (t, 3 H, $J = 7.4$); 1.00 (t, 3 H, $J = 7.2$); ^{19}F NMR (CDCl_3): –29.3 (dt, 1 F, $^2J_{\text{FF}} = 259.3, ^3J_{\text{HF}} = 12.0$); –36.3 (dt, 1 F, $^2J_{\text{FF}} = 259.3, ^3J_{\text{HF}} = 22.1$); –43.4 (d, 1 F, $^2J_{\text{FF}} = 244.6$); –48.0 (d, 1 F, $^2J_{\text{FF}} = 244.6$). One diastereomer

of **11** (recrystallized from hexane): Colorless crystals; m.p. 118–120 °C. MS, m/z : 482 (M^+). HRMS: calculated for $C_{26}H_{30}F_4O_4$: 482.208 (M^+); found: 482.208. 1H NMR ($CDCl_3$): 7.22 (m, 6 H); 6.98 (m, 4 H); 3.68 (dq, 2 H, $J = 31.6, 7.3$); 3.65 (dq, 2 H, $J = 31.6, 7.3$); 3.04 (m, 2 H); 2.35 (m, 2 H); 1.49 (bs, 6 H); 1.11 (t, 6 H, $J = 7.3$). ^{19}F NMR ($CDCl_3$): –28.0 (dt, 2 F, $^2J_{FF} = 256.4$, $^3J_{HF} = 16.1$); –33.8 (ddd, 2 F, $^2J_{FF} = 256.4$, $^3J_{HF} = 20.0, 15.4$). The other diastereomer of **11** (recrystallized from EtOH): Colorless crystals; m.p. 83–85 °C. MS, m/z : 482 (M^+). HRMS: calculated for $C_{26}H_{30}F_4O_4$: 482.207 (M^+); found: 482.208. 1H NMR ($CDCl_3$): 7.26–6.90 (m, 10 H); 3.69 (dq, 2 H, $J = 43.2, 7.3$); 3.66 (dq, 2 H, $J = 43.2, 7.3$); 2.52 (m, 4 H); 1.49 (bs, 6 H); 1.10 (t, 6 H, $J = 7.3$). ^{19}F NMR ($CDCl_3$): –35.8 (dt, 2 F, $^2J_{FF} = 260.0$, $^3J_{HF} = 16.5$); –39.4 (dt, 2 F, $^2J_{FF} = 260.0$, $^3J_{HF} = 15.0$).

Reaction of Ethyl Bromodifluoroacetate with 1-Phenyl-1-[(trimethylsilyl)oxy]ethene (**13**)

In an atmosphere of Ar, ethyl bromodifluoroacetate (**1**; 0.25 ml, 2.0 mmol) and 1-phenyl-1-[(trimethylsilyl)oxy]ethene (**13**; 0.4 ml, 2.0 mmol) were added to a suspension of activated Cu powder (280 mg, 4.4 mmol) in DMSO (2 ml), and the mixture was stirred at 55 °C for 10 h. After this time, **1** was not detected by GLC. The mixture was poured onto a mixture of ice and saturated NH_4Cl solution, and extracted with Et_2O . The Et_2O layer was washed with saturated NH_4Cl solution and saturated NaCl solution, and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by column chromatography (SiO_2 , AcOEt–hexane 1 : 4) to give ethyl (*E*)-2-fluoro-4-oxo-4-phenyl-2-butenolate (**14**; 18 mg, 4%) and ethyl (*Z*)-2-fluoro-4-oxo-4-phenyl-2-butenolate (**15**; 64 mg, 14%). The yield of acetophenone (**16**) was estimated by GLC. Structures of **16** and hexamethyldisilane were determined by GC-MS.

Compound **14**: A colorless oil. MS, m/z : 222 (M^+). HRMS: calculated for $C_{12}H_{11}FO_3$: 222.069 (M^+); found: 222.070. 1H NMR ($CDCl_3$): 7.96 (m, 2 H); 7.63 (tt, 1 H, $J = 7.2, 1.5$); 7.51 (m, 2 H); 6.65 (d, 1 H, $^3J_{HF} = 16.4$); 4.12 (q, 2 H, $J = 7.0$); 1.40 (t, 3 H, $J = 7.0$). ^{19}F NMR ($CDCl_3$): –48.5 (d, 1 F, $^3J_{HF} = 16.4$). Compound **15**: A yellow oil. MS, m/z : 222 (M^+). HRMS: calculated for $C_{12}H_{11}FO_3$: 222.069 (M^+); found: 222.069. 1H NMR ($CDCl_3$): 7.96 (m, 2 H); 7.62 (tt, 1 H, $J = 7.2, 1.5$); 7.50 (m, 2 H); 7.13 (d, 1 H, $^3J_{HF} = 30.7$); 4.40 (q, 2 H, $J = 7.0$); 1.06 (t, 3 H, $J = 7.0$). ^{19}F NMR ($CDCl_3$): –44.8 (d, 1 F, $^3J_{HF} = 30.7$).

Reaction of Ethyl Bromodifluoroacetate with Allyltributyltin (**18**)

In an atmosphere of Ar, ethyl bromodifluoroacetate (**1**; 0.25 ml, 2.0 mmol) and allyltributyltin (**18**; 0.62 ml, 2.0 mmol) were added to a suspension of activated Cu powder (280 mg, 4.4 mmol) in DMSO (2 ml) with THF (1 ml), and the mixture was stirred at 55 °C for 24 h. After this time, **1** was not detected by GLC. The mixture was poured onto a mixture of ice and saturated NH_4Cl solution, and extracted with Et_2O . The Et_2O layer was washed with saturated NH_4Cl solution and saturated NaCl solution, and dried over $MgSO_4$. The extract was allowed to react with bromine solution (Br_2-CHCl_3 1 : 1) until **19** was not detected by GLC. After evaporation of the solvent, the residue was purified by gradient column chromatography (SiO_2 , hexane, then AcOEt–hexane 1 : 19) to give ethyl 4,5-dibromo-2,2-difluoropentanoate (**20**; 249 mg, 39%).

Compound **19**: A colorless oil. 1H NMR ($CDCl_3$): 5.75 (m, 1 H); 5.30 (m, 2 H); 5.26 (m, 2 H); 4.32 (q, 2 H, $J = 7.0$); 2.89 (tdt, 2 H, $^3J_{HF} = 16.1, 7.3, 1.0$); 1.35 (t, 3 H, $J = 7.0$). ^{19}F NMR ($CDCl_3$): –40.0 (t, 2 F, $^3J_{HF} = 16.1$). Compound **20**: A colorless oil. MS, m/z : 243 ($M^+ - Br$),

245 ($M^+ + 2 - Br$). HRMS: calculated for $C_{12}H_{11}FO_3$: 242.983 ($M^+ - Br$), 244.981 ($M^+ + 2 - Br$); found: 242.983, 244.981. 1H NMR ($CDCl_3$): 4.37 (q, 2 H, $J = 7.1$); 4.34 (m, 1 H); 3.89 (dd, 1 H, $J = 10.7, 4.3$); 3.67 (dd, 1 H, $J = 10.7, 8.9$); 3.08 (m, 1 H); 2.73 (m, 1 H); 1.39 (t, 3 H, $J = 7.1$). ^{19}F NMR ($CDCl_3$): -36.5 (dt, 1 F, $^2J_{FF} = 265.1$, $^3J_{HF} = 14.6$); -42.0 (dt, 1 F, $^2J_{FF} = 265.1$, $^3J_{HF} = 16.1$).

Synthesis of 2,2-Difluorododecanoic Acid

Ethyl 2,2-difluorododecanoate (23). In an atmosphere of Ar, ethyl bromodifluoroacetate (**1**; 0.5 ml, 4.0 mmol) and 1-decene (**21**; 0.73 ml, 4.0 mmol) were added to a suspension of activated Cu powder (530 mg, 8.8 mmol) in DMSO (4 ml), and the mixture was stirred at 55 °C for 5 h. After this time, **1** (0.25 ml, 2.0 mmol) was added to the reaction mixture at the same temperature and stirred for another 9 h. The mixture was poured onto a mixture of ice and saturated NH_4Cl solution, and extracted with Et_2O . The Et_2O layer was washed with saturated NH_4Cl solution and saturated NaCl solution, and dried over $MgSO_4$. After evaporation of the solvent, the residue was passed through a column (SiO_2 , AcOEt–hexane 1 : 9) to give a colorless oil, the main fraction of which was estimated to be ethyl 4-bromo-2,2-difluorododecanoate (**22**) by 1H and ^{19}F NMR. The crude **22** was heated with Bu_3SnH (1.08 ml, 4.0 mmol) in the presence of AIBN (0.18 mmol, 30 mg) in boiling benzene (20 ml) for 3 h. The cooled reaction mixture was poured onto 10% KF and stirred for 1 h. The mixture was extracted with Et_2O , washed with saturated NaCl solution, and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by gradient column chromatography (SiO_2 , hexane, then AcOEt–hexane 1 : 9) to give ethyl 2,2-difluorododecanoate (**23**; 232 mg, 22%).

Compound **23**: A colorless oil. MS, m/z : 264 (M^+). HRMS: calculated for $C_{14}H_{26}F_2O_2$: 264.190 (M^+); found: 264.191. 1H NMR ($CDCl_3$): 4.33 (q, 2 H, $J = 7.2$); 2.04 (m, 2 H); 1.46 (m, 2 H); 1.35 (t, 3 H, $J = 7.2$); 1.21–1.38 (m, 14 H); 0.88 (t, 3 H, $J = 7.1$). ^{19}F NMR ($CDCl_3$): -40.3 (t, 2 F, $^3J_{HF} = 16.1$).

2,2-Difluorododecanoic acid (24). A mixture of ethyl 2,2-difluorododecanoate (**23**; 232 mg, 0.88 mmol), MeOH (5.3 ml) and aqueous NaOH (0.6 mol/l, 5.3 ml) was refluxed for 2 h. After the reaction mixture was evaporated, the residue was acidified with 10% HCl and extracted with Et_2O . The Et_2O layer was dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by column chromatography (octadecyl silicate (ODS), MeOH) to give 2,2-difluorododecanoic acid (**24**; 148 mg, 71%).

Compound **24**: A colorless oil. MS, m/z : 236 (M^+). HRMS: calculated for $C_{12}H_{22}F_2O_2$: 236.159 (M^+); found: 236.159. 1H NMR ($CDCl_3$): 7.78 (bs, 1 H); 2.09 (m, 2 H); 1.50 (m, 2 H); 1.21–1.42 (m, 14 H); 0.88 (t, 3 H, $J = 7.1$). ^{19}F NMR ($CDCl_3$): -40.9 (t, 2 F, $^3J_{HF} = 16.1$).

This work was partly supported by Grant-in-Aid for Scientific Research (C) from the Japan Society for the Promotion of Science.

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