α-Bromo-α,α-difluoroallyl Derivatives as Synthetic Intermediate: Nucleophilic Substitution of α-Bromo-α,α-difluoroallyl Derivatives in the Presence of Palladium Catalysts

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The palladium catalyzed nucleophilic substitution of α-bromo-α,α-difluoroallyl derivatives turned out to be an efficient method for the preparation of several fluorinated organic molecules. Several soft carbon nucleophiles regioselectively reacted with 3-bromo-3,3-difluoropropene (BDFP) to give the 3-substituted 1,1-difluoroalkenes. Phenylzinc chloride and tributylphenyltin afforded 1-fluoro-1,3-diphenylpropene. The radical bromination of 3-substituted 1,1-difluoroalkenes provided 1-substituted BDFPs, and a 1-substituted BDFP reacted with carbon nucleophiles to give 1,3-disubstituted 3,3-difluoroalkenes. For the reaction of nitrogen nucleophiles with BDFP, an amine and the sodium salts of the carbamates reacted with BDFP at the γ-position. However, the sodium salts of the sulfoneamide predominantly attacked at the α-position.

Key words 3-bromo-3,3-difluoropropene; α-bromo-α,α-difluoroallyl derivative; difluoroallyl-palladium

The introduction of a *gem*-difluoromethylene moiety (CF_2) into organic molecules has provided us with attractive results in a wide range of application fields.[1] This moiety has been recognized as an isopolar-isosteric substitute for oxygen and used as one strategy for the modification of biologically active compounds.[2] Some building blocks have been developed to introduce CF_2 into organic compounds.[1] Among them, 3-bromo-3,3-difluoropropene (BDFP) and its derivatives (**1**) are some of the most important ones. The *gem*-difluoroallylic metal species, available by treatment of **1** with alkyllithium,[3] zinc-metal[4] or indium-metal,[5] react with carbonyl compounds to afford *gem*-difluorohomoallyl alcohols. Tellier *et al.* reported that the treatment of **1** with organometallic reagents in the presence of copper and lithium salts gives various 1,1-difluoroalkenes.[6] (Chart 1). This method is quite important because 1,1-difluoroalkenes are critical for certain mechanism-based enzyme inhibitors, and they can function as bioisosteres for aldehydes and ketones.[2]

In this paper, we report that α-bromo-α,α-difluoroallyl derivatives (**1**) are versatile fluorinated building blocks through palladium catalyzed nucleophilic substitutions (Chart 2).

The 1,1-difluoroalkenes were obtained from the reaction of BDFP (**1a**) with several soft nucleophiles in the presence of 4 mol% palladium acetate and 16 mol% triphenylphosphine. These results are summarized in Table 1. Interestingly, the 3-substituted 1,1-difluoroalkenes (**2**) (γ-substitution) were the only isolated products, and the 3-substituted 3,3-difluoroalkenes (**2′**) (α-substitution) were not obtained in all cases. This reaction might be an excellent method for synthesizing the 1,1-difluoroalkenes.

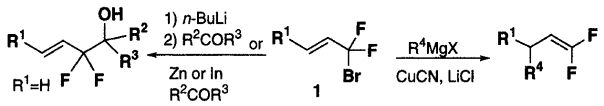


Chart 1

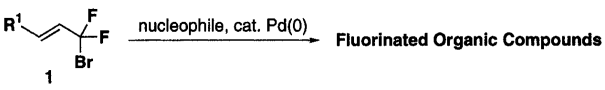
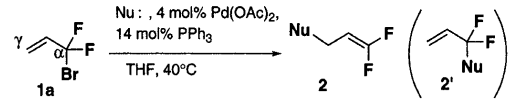


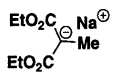
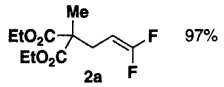
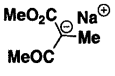
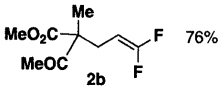
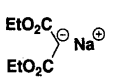
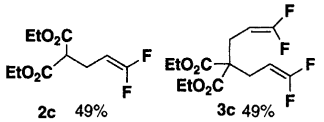
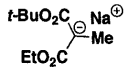
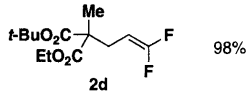
Chart 2

The reaction might proceed through the (difluoroallyl)palladium complex (**4**), which is formed by the oxidative addition of **1** to Pd(0) (generated from palladium acetate and triphenylphosphine), as a reaction intermediate (Chart 3). Shi *et al.* reported that the reaction of the 3,3-difluoroallyl acetates with nucleophiles in the presence of Pd(0) catalysts caused γ-substitution which produced the 1,1-difluoroalkenes and also postulated a similar mechanism.[7]

We then examined the reaction of **1a** with phenylzinc chloride or tributylphenyltin in the presence of the Pd(0) catalyst. In these cases, we did not obtain **2e** but 1-fluoro-1,3-diphenylpropene (**5**). These results are consistent with the reaction of the 3,3-difluoroallyl acetates with nucleophiles in

Table 1.



Entry	Nucleophile	Products
1		 97%
2		 76%
3		 2c 49% 3c 49%
4		 98%

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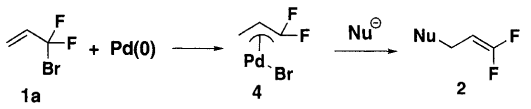


Chart 3

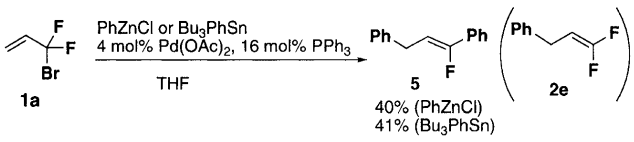


Chart 4

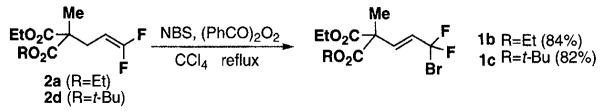


Chart 5

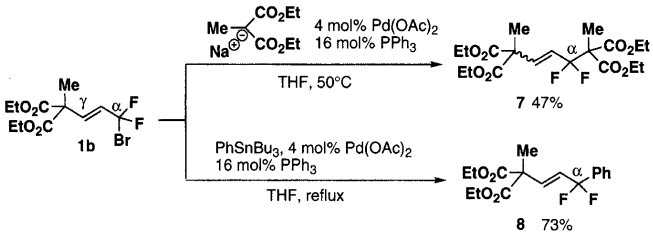


Chart 6

the presence of Pd(0) catalysts.[7] Phenylzinc chloride or tributylphenyltin reacted with allylpalladium at its fluorinated terminus to afford the 3,3-difluoro-3-phenylpropene (**6**) and a further *SN*2′ reaction of **6** with another equivalent of phenylzinc chloride or tributylphenyltin afforded **5** (Chart 4).

Next, we examined the radical bromination of **2** and found that 1-substituted BDFPs (**1b**, **c**) were selectively obtained (Chart 5).[8,9]

Interestingly, the palladium catalyzed nucleophilic substitution of **1b** afforded the 1,3-disubstituted 3,3-difluoroalkenes (**7**, **8**) (α-substitution) as the sole products in these cases (Chart 6).[10]

On the basis of these results, the steric effect plays an important role in the regioselectivity of this reaction. Although Shi *et al.* explained that the γ-selectivity of the nucleophilic substitution of **9** was only due to an electronic effect, the steric effect can not be ignored. There is the possibility that nucleophiles attack the less hindered carbon. For the reaction of tributylphenyltin, a further *SN*2′ reaction of **8** was prevented by the steric hindrance (Chart 7). Further investigation of the regioselectivity of the palladium-catalyzed nucleophilic substitution of **1** is currently in progress.

It is notable that the BDFP (**1a**) acts as the dication equivalent (**10**) in these successive reactions (Chart 8).

We then examined the reaction of **1** toward the several nitrogen nucleophiles in the presence of a palladium catalyst. As shown in Table 2, **1** regioselectively reacted with an

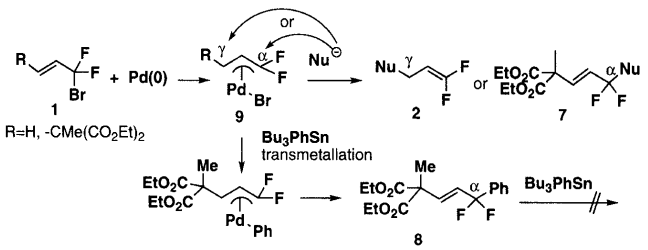


Chart 7

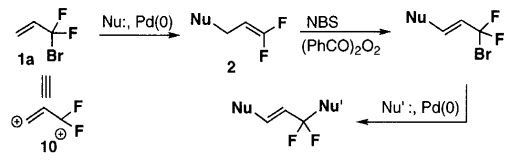
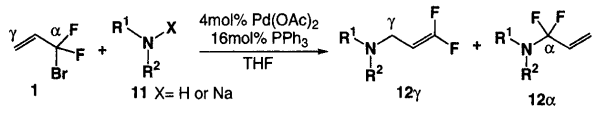
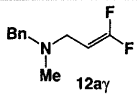
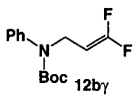
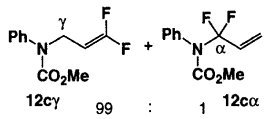
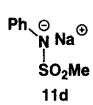
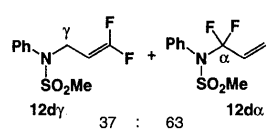
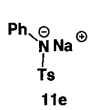
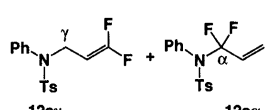


Chart 8

Table 2.



Entry	11	Products	Yield[a]
1			75%
2			71%
3			83%
4			86%
5			100%

a) Combined yield.

amine and the sodium salt of the carbamates (entries 1—3) at its γ-position. Interestingly, the α-position of **1** was predominantly attacked in the cases of the sodium salts of the sulfoneamide (entries 4 and 5). The reason for these interesting regioselectivities still remains unknown.

In conclusion, we found that the α-bromo-α,α-difluoroallyl derivatives (**1**) are very important building blocks for the preparation of several fluorinated organic compounds (Chart 9).

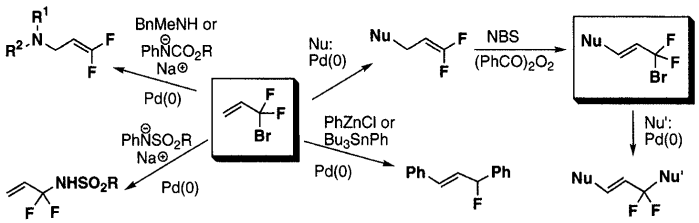


Chart 9

Experimental

The infrared spectra were measured using a Perkin–Elmer 1600 series Fourier transform (FT)-IR spectrophotometer. The ^{1}H- and ^{19}F-NMR spectra were obtained using a JEOL GX270, Varian Gemini 300 or Varian UNITY plus 500 instrument with tetramethylsilane (for ^{1}H) and chlorotrifluoromethane (for ^{19}F) as the internal standards. The mass spectra (MS) and high-resolution mass spectra (HR-MS) were measured on a JEOL JMS D-200 spectrometer. Column chromatography was performed on silica gel (Merck Kieselgel 60). Phenylzinc chloride was prepared according to the literature.[11]

General Procedure for the Palladium Catalyzed Nucleophilic Substitution of 1 To a solution of palladium acetate (9 mg, 0.04 mmol) and triphenylphosphine (42 mg, 0.16 mmol) in tetrahydrofuran (THF) (5 ml) was added **1** (1.00 mmol), and the mixture was stirred for 10 min at room temperature. A THF (1 ml) solution of a carbon nucleophile (2.00 mmol) was then added to the mixture and stirred for 2 h at 40 °C. Water (5 ml) was added to the mixture and the resulting mixture was extracted with dichloromethane (20 ml×3). The combined organic extract was dried over anhydrous magnesium sulfate, filtered, and the solvent was removed *in vacuo*. The residue was purified using chromatography on silica gel (*n*-hexane–ethyl acetate) to give **2**.

Diethyl 2-(3,3-Difluoroprop-2-enyl)isobutan-1,3-dioate (**2a**): A colorless oil. IR (neat) cm^{-1}: 1731. ^{1}H-NMR ($CDCl_3$) δ: 1.23 (6H, t, J=7.1 Hz), 1.38 (3H, s), 2.52 (2H, dt, J=8.3, 1.7 Hz), 4.07—4.23 (5H, m); ^{19}F-NMR ($CDCl_3$) δ: −85.77 (1F, d, J=40.7 Hz), −89.25 (1F, dd, J=40.7, 24.9 Hz). MS *m/z*: 250 (M^+). HR-MS Calcd for $C_{11}H_{16}F_2O_4$: 250.1016 (M^+). Found: 250.1002.

Methyl 2-Acetyl-5,5-difluoro-2-methylpent-4-enoate (**2b**): A colorless oil. IR (neat) cm^{-1}: 1748, 1717. ^{1}H-NMR ($CDCl_3$) δ: 1.28 (3H, s), 2.09 (3H, s), 2.32—2.56 (2H, m), 3.68 (3H, s), 4.04 (1H, dtd, J=24.0, 8.1, 2.5 Hz). ^{19}F-NMR ($CDCl_3$) δ: −85.54 (1F, d, J=39.8 Hz), −89.25 (1F, dd, J=39.8, 24.0 Hz). MS *m/z*: 206 (M^+). HR-MS Calcd for $C_9H_{12}F_2O_3$: 206.0754 (M^+). Found: 206.0755.

Diethyl 2-(3,3-Difluoroprop-2-enyl)propane-1,3-dioate (**2c**): A colorless oil. IR (neat) cm^{-1}: 1748. ^{1}H-NMR ($CDCl_3$) δ: 1.21 (6H, t, J=7.1 Hz), 2.50 (2H, td, J=7.4, 1.4 Hz), 4.10—4.25 (5H, m). ^{19}F-NMR ($CDCl_3$) δ: −86.30 (1F, dd, J=41.6, 6.5 Hz), −88.80 (1F, ddd, J=41.6, 25.0, 7.4 Hz). MS *m/z*: 236 (M^+). HR-MS Calcd for $C_{10}H_{14}F_2O_4$: 236.0824 (M^+). Found: 236.0837.

Diethyl 2,2-Di(3,3-difluoroprop-2-enyl)propane-1,3-dioate (**3c**): A colorless oil. IR (neat) cm^{-1}: 1747. ^{1}H-NMR ($CDCl_3$) δ: 1.23 (6H, t, J=7.1 Hz), 2.55 (4H, dt, J=8.4, 1.5 Hz), 4.00—4.22 (6H, m). ^{19}F-NMR ($CDCl_3$) δ: −85.00 (2F, d, J=39.8 Hz), −88.60 (1F, dd, J=39.8, 24.0 Hz). MS *m/z*: 312 (M^+). HR-MS Calcd for $C_{13}H_{16}F_4O_4$: 312.0985 (M^+). Found 312.0981.

tert-Butyl Ethyl 2-(3,3-Difluoroprop-2-enyl)isobutan-1,3-dioate (**2d**): A colorless oil. IR (neat) cm^{-1}: 1734; ^{1}H-NMR ($CDCl_3$) δ: 1.26 (3H, t, J=7.3 Hz), 1.36 (3H, s), 1.45 (9H, s), 2.50 (2H, d, J=8.4 Hz), 4.09—4.27 (3H, m); ^{19}F-NMR ($CDCl_3$) δ: −86.38—−86.70 (1F, m), −89.60—−90.00 (1F, m). MS *m/z*: 222 (M^++H−*tert*-Bu). HR-MS Calcd for $C_9H_{12}F_2O_4$: 222.0704 (M^++H−*tert*-Bu). Found: 222.0790.

(*Z*)-1-Fluoro-1,3-diphenylpropene (**5**): A colorless oil. IR (neat) cm^{-1}: 3030, 1482, 760, 738. ^{1}H-NMR ($CDCl_3$) δ: 3.56 (2H, dd, J=7.9, 1.7 Hz), 5.52 (1H, dt, J=36.1, 7.9 Hz), 7.20—7.44 (8H, m), 7.50—7.53 (2H, m); ^{19}F-NMR ($CDCl_3$) δ: −121.04 (1F d, J=39.1 Hz). MS *m/z*: 212 (M^+). HR-MS Calcd for $C_{15}H_{12}F$: 212.1001 (M^+). Found: 212.1006.

(3,3-Difluoroprop-2-enyl)methylbenzylamine (**12a**γ): A colorless oil. IR (neat) cm^{-1}: 1746. ^{1}H-NMR ($CDCl_3$) δ: 2.21 (3H, s), 3.06 (2H, dt, J=7.8, 1.7 Hz), 3.50 (2H, s), 4.40 (1H, dtd, J=24.8, 7.8, 2.5 Hz), 7.24—7.36 (5H, m). ^{19}F-NMR ($CDCl_3$) δ: −85.65 (1F, d, J=41.6 Hz), −88.54 (1F, dd, J=41.6, 24.8 Hz). MS *m/z*: 197 (M^+). HR-MS Calcd for $C_{11}H_{13}F_2N$: 197.1016 (M^+). Found: 197.1031.

N-Phenyl-*N*-(3,3-difluoroprop-2-enyl)methoxyformamide (**12b**γ): A colorless oil. IR (neat) cm^{-1}: 2978, 1746, 1700, 1392, 1367, 1251, 1166. ^{1}H-NMR ($CDCl_3$) δ: 1.36 (9H, s), 4.15 (2H, dt, J=7.3, 1.9 Hz), 4.31—4.46 (1H, m), 7.09—7.30 (5H, m). ^{19}F-NMR ($CDCl_3$) δ: −86.53 (1F, d, J=77.8 Hz), −87.98—−88.22 (1F, dd-like) . MS *m/z*: 269 (M^+). HR-MS Calcd for $C_{14}H_{17}F_2NO_2$: 269.1227 (M^+). Found: 269.1187.

A 99:1 mixture of *N*-Phenyl-*N*-(3,3-difluoroprop-2-enyl)methoxyformamide (**12c**γ) and *N*-Phenyl-*N*-(1,1-difluoroprop-2-enyl)methoxyformamide (**12c**α): A colorless oil. IR (neat) cm^{-1}: 2955, 1747, 1706, 1447, 1386, 1294, 697. ^{1}H-NMR ($CDCl_3$) δ: 3.70 (3H, s), 4.26 (2H, d, J=7.5 Hz), 4.39—4.54 (1H, dt-like), 7.15—7.64 (5H, m). ^{19}F-NMR ($CDCl_3$) δ: −74.87 (0.01F, d-like), −80.29 (0.01F, dd-like), −88.27 (0.99F, dd, J=37.9, 24.9 Hz), −86.35 (0.99F, d, J=37.9 Hz). MS *m/z*: 227 (M^+). HR-MS Calcd for $C_{11}H_{11}F_2NO_2$: 227.0758 (M^+). Found: 227.0740.

(3,3-Difluoroprop-2-enyl)(methylsulfonyl)phenylamine (**12d**γ): A colorless oil. IR (neat) cm^{-1}: 1748, 1734, 1653, 1559, 1154, 758, 668. ^{1}H-NMR ($CDCl_3$) δ: 2.90 (3H, s), 4.25—4.45 (3H, m), 7.29—7.40 (5H, m). ^{19}F-NMR ($CDCl_3$) δ: −84.65—−84.79 (1F, m), −87.34—−87.59 (1F, m). MS *m/z*: 247 (M^+). HR-MS Calcd for $C_{10}H_{11}F_2NO_2S$: 247.0479 (M^+). Found: 247.0511.

(1,1-Difluoroprop-2-enyl)(methylsulfonyl)phenylamine (**12d**α): A colorless oil. IR (neat) cm^{-1}: 3025, 1490, 1415, 1351, 1231, 1165, 1127, 978, 775, 756, 732, 694, 659. ^{1}H-NMR ($CDCl_3$) δ: 3.20 (3H, s), 5.45 (1H, d, J= 10.8 Hz), 5.74 (1H, dt, J=17.1, 2.0 Hz), 5.89—6.03 (1H, m), 7.33—7.46 (5H, m). ^{19}F-NMR ($CDCl_3$) δ: −72.86 (2F, d, J=9.3 Hz). MS *m/z*: 247 (M^+). HR-MS Calcd for $C_{10}H_{11}F_2NO_2S$: 247.0479 (M^+). Found: 247.0491.

A 21 : 79 mixture of (3,3-Difluoroprop-2-enyl)[(4-methylphenyl)sulfonyl]-phenylamine (**12e**γ) and (1,1-Difluoroprop-2-enyl)[(4-methylphenyl)sulfonyl]phenylamine (**12e**α): A colorless oil. IR (neat) cm^{-1}: 3064, 1747, 1700, 1684, 1653, 1597, 1559, 1489, 1453, 1368. ^{1}H-NMR ($CDCl_3$) δ: 2.43 (12/5H, s), 2.46 (3/5H, s), 4.17—4.34 (3/5H, m), 5.57—5.84 (8/5H, m), 6.39 (4/5H, dd, J=16.5, 1.6 Hz), 7.01—7.94 (9H, m). ^{19}F-NMR ($CDCl_3$) δ: −89.05—−89.01 (1.58F, d-like), −102.32—−105.42 (0.42F, m). MS *m/z*: 323 (M^+). HR-MS Calcd for $C_{16}H_{15}F_2NO_2S$: 323.0792 (M^+). Found: 323.0872.

General Procedure for the Radical Bromination of 2 A mixture of **2a** (1.00 g, 4.00 mmol), *N*-bromosuccinimide (NBS) (2.14 g, 12.0 mmol) and benzoyl peroxide (9.00 mg, 0.037 mmol) in carbon tetrachloride (20 ml) was refluxed under an inert atmosphere for 24 h. The reaction mixture was filtered and the resulting filtrate was concentrated *in vacuo*. The residue was purified by silica gel chromatography (*n*-hexane : ethyl acetate=100 : 1) and gave **1b** (1.11 g, 84%).

(*E*)-Diethyl 2-(3-Bromo-3,3-difluoroprop-1-enyl)isobutane-1,3-dioate (**1b**): A pale yellow oil. IR (neat) cm^{-1}: 2985, 1736, 964. ^{1}H-NMR ($CDCl_3$) δ: 1.27 (3H, t, J=7.1Hz), 1.58 (3H, s), 4.23 (4H, q, J=7.1 Hz), 5.98 (1H, dt, J=15.9, 9.7 Hz), 6.66 (1H, dt, J=15.9, 2.3 Hz). ^{19}F-NMR ($CDCl_3$) δ: −45.88 (2F, dd, J=9.7, 2.3 Hz). MS *m/z*: 331 (M^++H for ^{81}Br), 329 (M^++H for ^{79}Br). HR-MS Calcd for $C_{11}H_{15}{}^{79}BrF_2O_4$: 328.0322 ($M^+$). Found: 328.0165.

(*E*)-*tert*-Butyl Ethyl 2-(3-Bromo-3,3-difluoroprop-1-enyl)isobutane-1,3-dioate (**1c**): A pale yellow oil. IR (neat) cm^{-1}: 2985, 1736, 964. ^{1}H-NMR ($CDCl_3$) δ: 1.28 (3H, t, J=7.0 Hz), 1.46 (9H, s), 1.55 (3H, s), 4.23 (4H, q, J=7.0 Hz), 5.97 (1H, dt, J=16.1, 10.1 Hz), 6.62—6.73 (1H, m). ^{19}F-NMR ($CDCl_3$) δ: −46.33 (2F, dd, J=28.7, 10.1 Hz), MS *m/z*: 257 (M^+−CO_2*tert*-Bu for ^{81}Br), 255 (M^+−CO_2*tert*-Bu for ^{79}Br). HR-MS Calcd for $C_8H_{10}{}^{79}BrF_2O_2$: 254.9832 (M^+−CO_2*tert*-Bu). Found: 254.9859.

Diethyl 2,6-Di(ethoxycarbonyl)-5,5-difluoro-2,6-dimethylhept-3-ene-1,7-dioate (7) Using the procedure similar to the general procedure for the palladium catalyzed nucleophilic substitution of BDFP, **7** (100 mg, 47% as a mixture of *E* and *Z* isomers, *E* : *Z*=4.6 : 1) was obtained from **1b** (165 mg, 0.50 mmol) as a pale yellow oil. IR (neat) cm^{-1}: 2983, 1737, 1661, 1617, 1448, 928. ^{1}H-NMR ($CDCl_3$) δ: 1.19—1.27 (18H, m), 4.11—4.24 (8H, m), 5.82 (4.6/5.6H, dd, J=33.3, 11.5 Hz), 6.18 (1/5.6H, dd, J=22.3, 12.5 Hz) 7.02 (1/5.6H, d, J=12.5 Hz), 7.41 (4.6/5.6H, d, J=11.5 Hz). ^{19}F-NMR

($CDCl_3$) δ: −93.53 (2/5.6F, d, J=22.3 Hz), −101.16 (9.2/5.6F, d, J=33.3 Hz). *Anal.* Calcd for $C_{19}H_{28}F_2O_8$: C, 54.02; H, 6.68. Found: C, 54.24; H, 6.55.

Diethyl 2-(3,3-Difluoro-3-phenyl-1-enyl)isobutane-1,3-dioate (8) To a solution of **1b** (165 mg, 0.500 mmol), palladium acetate (3.4 mg, 0.010 mmol) and triphenylphosphine (7.9 mg, 0.030 mmol) in THF (12 ml) was added tributylphenyltin (220 mg, 0.60 mmol) in THF (4 ml) under an inert atmosphere, and the resulting mixture was heated under reflux for 24 h. The reaction mixture was poured onto a mixture of ether (30 ml) and 33% aqueous potassium fluoride (30 ml) and then the organic phase was separated. The aqueous layer was extracted with ether (30 ml×3). The combined organic phase was washed with brine, dried over anhydrous magnesium sulfate, filtered, and the solvent was removed *in vacuo*. The residue was purified using chromatography on silica gel (*n*-hexane : ethyl acetate=10 : 1) gave **8** (119 mg, 73%) as a yellow oil. IR (neat) cm^{-1}: 2984, 1735, 1674, 1452, 973. ^{1}H-NMR ($CDCl_3$) δ: 1.17 (6H, t, J=7.1 Hz), 1.51 (3H, s), 4.13 (4H, q, J=7.1 Hz), 5.84 (1H, dt, J=16.3, 9.4 Hz), 6.44 (1H, dt, J=16.3, 2.7 Hz), 7.34—7.44 (5H, m). ^{19}F-NMR ($CDCl_3$) δ: −91.68 (2F, dd, J=9.4, 2.7 Hz). MS *m/z*: 326 (M^+). HR-MS Calcd for $C_{17}H_{20}F_2O_4$: 326.1330 (M^+). Found: 326.1359.

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References and Notes

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8) A similar selectivity was observed during the radical bromination of 1,1-difluoro-2-phenylthio-1-propene; Jeong I. H., Kim M. S., Kim B. T., *Synth. Commun.*, **29**, 235—241 (1999).
9) Although the fluorine atom can stabilize an α-carboradical, its stabilizing effect is very low; Smart B. E., "Organofluorine Chemistry: Principles and Commercial Applications," ed. by Banks R. E., Smart B. E., Tatlow J. C., Plenum Press, New York, 1994, pp. 57—88. The steric effect might play an important role in the radical bromination of **2**.
10) We also synthesized methyl 2-aceto-5-bromo-5,5-difluoro-2-methylpent-3-enoate (**1d**) by the radical bromination of **2b**, and confirmed that **1d** exclusively reacted with nucleophiles at the α-position to afford the 1,3-disubstituted BDFP (**13**, **14**) in the presence of the palladium catalyst. However, we could not obtain a pure sample of them (**1d**, **13**, **14**) due to their instability (Chart 10).

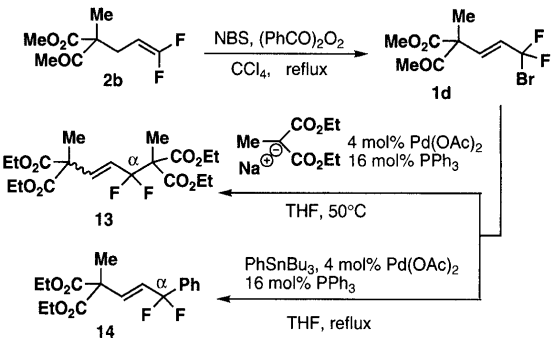

Chart 10

11) Minato A., *J. Org. Chem.*, **56**, 4052—4056 (1991).