Synthesis of (α,α-Difluoroallyl)phosphonates from Alkenyl Halides or Acetylenes

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Introduction

Phosphonic acids often exhibit important biological properties by virtue of their similarity to phosphate,[1] while substitution of a fluorine atom in a biological molecule often leads to pronounced enhancement in the activity.[2] Recently, (difluoromethylene)phosphonates as hydrolytically stable analogues of naturally occurring phosphate esters have attracted attention because they mimic parental biophosphate more accurately than analogous nonfluorinated phosphonates in their isosteric and isopolar properties.[3] Although the concept of (difluoromethylene)phosphonate as analogues of phosphate esters has been much argued,[4] this replacement has provided several natural product analogues with significant activites.[5]

Previous approaches to prepare these compounds have included a variety of bond-forming reactions. A carbon−carbon bond formation using ionic displacement of electrophiles such as halides or primary triflates with metalated dialkyl (difluoromethyl)phosphonates has been applied as a convergent methods for introduction of the (difluoromethylene)phosphonate moiety.[6−9] The radical-mediated addition of (iodo- or (bromodifluoromethyl)-phosphonates across alkenes has also been reported.[10,11] Alternatively, electrophilic fluorinations of phosphonate-stabilized carbanions[12] and nucleophilic fluorination of benzilic α-oxophosphonates to the corresponding benzilic α,α-difluorophosphonate with (diethylamido)sulfur trifluoride (DAST)[13] have been developed. Although these methods exhibit great utility for construction of a variety of (difluoromethylene)phosphonates,[14] there is a conspicuous lack of methods for the preparation of the compounds in which (difluoromethylene)phosphonate moiety is directly attached to an olefinic carbon atom such as (α,α-difluoroallyl)phosphonates.[15,16] These compounds would be highly useful as conformationally restricted analogues of phosphate monoesters,[15a] but also as versatile synthetic intermediates toward a new type of (difluoromethylene)phosphonates through conversion of the double bond to other functional groups.[15b]

As a part of our program designed to explore the utility of (difluoromethylene)phosphonates for the synthesis of new (difluoromethylene)phosphonates of biological interest, we have examined the stereoselective synthesis of (α,α-difluoroallyl)phosphonates through copper(I)-catalyzed coupling or the addition reaction of [(diethoxyphosphinyl)difluoromethyl]zinc bromide (**2**)[7] with alkenyl halides and terminal acetylenes in dimethylformamide (DMF).

Table 1. Coupling Reaction of *β*-Halogenostyrenes with Copper Reagent 3 in THF or DMF

entry	substrate (*E*:*Z*)	solvent	time (h)	%yield of **4a**[a]	*E*:*Z*[b]
1	(*E*)-*β*-bromostyrene (86:14)[c]	THF	60	55	86:14
2	(*E*)-*β*-bromostyrene (86:14)[c]	DMF	60	67	86:14
3	(*E*)-*β*-iodostyrene (98:2)[d]	DMF	15	85	98:2
4	(*Z*)-*β*-bromostyrene (26:74)[e]	DMF	60	50	32:68

[a] Yield based on alkenyl halide. [b] Determined by NMR (^{1}H and/or ^{31}P) analysis. [c] Purchased from Wako Pure Chemical Industry Ltd. [d] Prepared from phenylacetylene according to the method of Zweifel: Zweifel, G.; Whitney, C. C. *J. Am. Chem. Soc.* **1967**, 89, 2753. [e] Prepared as described in the literature: Matsumoto, M.; Kuroda, K. *Tetrahedron Lett.* **1980**, *21*, 4021.

Results and Discussion

Copper(I)-Catalyzed Coupling Reaction of [(Diethoxyphosphinyl)difluoromethyl]zinc Bromides 2 with Alkenyl Halides. Among various possible methods for synthesis of (α,α-difluoroallyl)phosphonates, direct carbon−carbon bond formation using a coupling reaction of alkenyl halides with metalated dialkyl difluoromethylphosphonates[17] such as [(diethoxyphosphinyl)difluoromethyl]zinc bromide (**2**)[7] and [(diethoxyphosphinyl)-difluoromethyl]copper complex **3** would be desirable.[18] However such direct carbon−carbon formation has not been extensively studied previously.[19] Consequently, we have examined the possibility of coupling reaction of (*E*)- and (*Z*)-*β*-halogenostyrenes with zinc reagent **2** and

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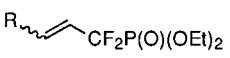
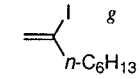
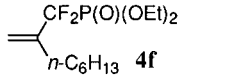
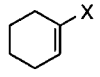
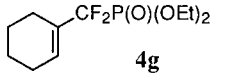
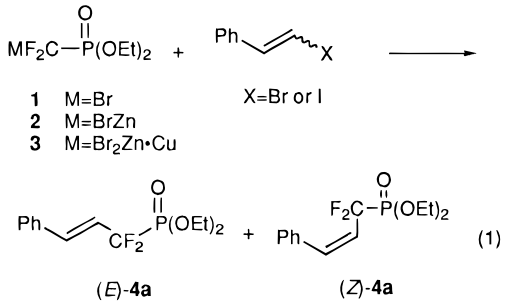
Table 2. Coupling Reaction of 3 with Alkenyl Halides in DMF

Entry[a]	Subst.(Stereopurity %)[b]	Product	Yield(%)[c]	Ratio E:Z[b]
				
1[d]	R=4-MeOC$_6$H$_4$, X=Br (*E*: 98%)[e]	(*E*)-**4b**	49	98:2
2	R=*n*-Bu, X=I (*E*: 99%)[f]	(*E*)-**4c**	81	99:1
3	R=THPOCH$_2$ X=I (*E*: 99%)[e]	(*E*)-**4d**	76	99:1
4	R=THPOCH$_2$ X=I (*Z*: 99%)[f]	(*Z*)-**4d**	86	1:99
5	R=THPO(CH$_2$)$_4$ X=I (*E*: 97%)[e]	(*E*)-**4e**	90	97:3
6		 **4f**	62	——
		 **4g**		——
7	X=I[h]		76	——
8	X=OTf[i]		0	——

[a] All reactions were carried out in DMF at 25 °C for 15 h unless stated otherwise. [b] Determined by NMR (^{1}H and/or ^{31}P) analysis. [c] Yield based on alkenyl halide. [d] The reaction time: 48 h. [e] Prepared from the corresponding acetylene *via* hydrozirconation: Ando, T.; Vu, M. H.; Yoshida, S.; Takahashi, N. *Agric. Biol. Chem.* **1982**, *46*, 717. [f] Prepared by tetrahydropyranylation of the corresponding iodoalcohol: Moss, R. A.; Wilk, B.; Krogh-Jespersen, K.; Westbrook, J. D. *J. Am. Chem. Soc.* **1989**, *111*, 6729. [g] Kamiya, N.; Chikami, Y.; Ishii, Y. *Synlett*, **1990**,675. [h] Pross, A.; Sternhell, S. *Aust. J. Chem.* **1970**, *23*, 989. [i] McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1983**, *24*, 979.

copper reagent **3**, prepared from diethyl (bromodifluoromethyl)phosphonate **1**, zinc, and CuBr according to method of Burton[7,18] (eq 1 and Table 1). Although the



1 M=Br
2 M=BrZn
3 M=Br$_2$Zn•Cu

X=Br or I

(*E*)-**4a** (*Z*)-**4a** (1)

reagent **2** by itself did not react with (*E*)-β-bromostyrene, the coupling reaction was found to proceed successfully with retention of the starting olefinic geometry after the transmetalation to **3** with a stoichiometric amount of CuBr. Treatment of **2** with CuBr, followed by the reaction with (*E*)-β-bromostyrene (*E*:*Z* = 86:14) at room temperature for 60 h in THF, gave (α,α-difluoroallyl)-phosphonates (*E*)-**4a** and (*Z*)-**4a** in a ratio of 86:14 in 55% yield (entry 1). The yield increased to 67% with the same product ratio of *E*- and *Z*-isomers when the reaction was carried out in DMF instead of THF (entry 2). The coupling reaction of (*E*)-β-iodostyrene (*E*:*Z* = 98:2) with the copper reagent **3** in DMF was found to proceed more rapidly (15 h), and (*E*)-**4a** of configurationally high purity (98%) was obtained in high yield (entry 3). (*Z*)-β-Bromostyrene (*E*:*Z* = 26:74) reacted with the copper reagent **3** in DMF to give (*E*)-**4a** and (*Z*)-**4a** in a ratio of 32:68 in 50% yield. Although the Z-enriched (α,α-difluoroallyl)-phosphonate was produced in this reaction, the *E*/*Z* ratio

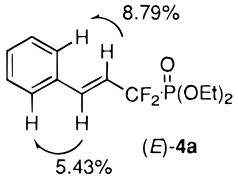


Figure 1.

was found to vary slightly owing to loss of starting geometry during the coupling reaction[20] (entry 4).

The stereochemistry of (*E*)-**4a** was determined on the basis of the occurrence of a larger vicinal alkenyl coupling constant (J = 16.2 Hz). On the other hand, the alternative isomer showed a vicinal coupling of J = 12.9 Hz which is consistent with that of a *Z*-isomer. The stereochemistry of (*E*)-**4a** was further confirmed by relatively strong NOEs between protons on the phenyl ring and C(2)-H as shown in Figure 1.

To explore the scope and applicability of the method, the reaction was further examined with a variety of alkenyl halides. The results of this exploratory study are summarized in Table 2. Introduction of a methoxy group onto the 4-position of β-bromostyrene was found to lower the yield, as compared with the reaction on β-bromostyrene (entry 1 *vs* entry 2 of Table 1). Both (*E*)- and (*Z*)-alkenyl halides possessing aliphatic substituents at the β position were found to proceed with complete retention of the starting geometry (entries 2−5), and both (*E*)-**4d** and (*Z*)-**4d** could be prepared stereospecifically (entries 3 and 4). Nonterminal alkenyl iodides also reacted with

(20) The loss of starting olefinic geometry might arise from nonstereospecific radical addition of **3** to phenylacetylene, a contamination product during the preparation of (*Z*)-β-bromostyrene.

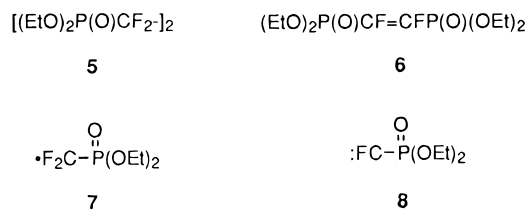
Table 3. ^{31}P NMR Data of Phosphonate Reagents in DMF and Monoglyme

$MCF_2P(O)(OEt)_2$	δ in DMF[a]	δ in monoglyme[a,b]
M = Br (**1**)	−1.0 (t, $^2J_{F-P}$ = 93.2 Hz)	−1.1 (t, $^2J_{F-P}$ = 93 Hz)
M = BrZn (**2**)	14.1 (t, $^2J_{F-P}$ = 92.5 Hz)	14.1 (t, $^2J_{F-P}$ = 89 Hz)
M = Br_2Zn·Cu (**3**)	12.8 (t, $^2J_{F-P}$ = 97.6 Hz)	13.0 (t, $^2J_{F-P}$ = 99 Hz)

[a] Relative values to 85% H_3PO_4. [b] Values reported by Burton (ref 18).

3 to give the corresponding adducts **4f** and **4g** in good yields (entries 6 and 7). However, the vinyl triflate derived from cyclohexanone proved to be a very poor reactant with **3** (entry 8).

Mechanistic Discussion. The formation of **2**, the subsequent transmetalation with CuBr, and the thermal stability of the prepared organometallic species in DMF were monitored by means of ^{31}P- and ^{19}F-NMR spectroscopy in order to gain insights into the mechanism for the coupling reaction of CuBr-catalyzed organozinc **2** with alkeny halides (Table 3). The signals due to diethyl (bromodifluoromethyl)phosphonate (**1**) (δ −1.0, t, $^2J_{P-F}$ = 93.2 Hz) disappeared within 3 h at room temperature after addition of zinc in DMF. New signals appeared at δ 14.1 (t, $^2J_{P-F}$ = 92.5 Hz), which are consistent with a reported δ value of organozinc **2** prepared in monoglyme.[18] The transmetalation with CuBr required 30 min to give a organocopper species, the signals of which appeared at δ 12.8 (t, $^2J_{P-F}$ = 97.6 Hz), closely related to those of [diethoxyphosphinyl)difluoromethyl]copper complex **3** in monoglyme as reported by Burton.[18] Thus, it was comfirmed that organocopper reagent **3** can be prepared even in DMF. The copper reagent **3** in DMF decomposed slowly to give many products at room temperature, and two signals corresponding to the dimeric decomposition products **5**[11] and **6**[18] were detected in the ^{19}F NMR spectrum.[21] The phosphonates **5** and **6** could



arise *via* [(diethoxyphosphinyl)difluoromethyl] radical **7** and fluoro(diethoxyphosphinyl)carbene **8**, respectively.[11,18] Burton has reported that organocopper reagent **3** in monoglyme decomposed slowly to yield the dimeric product **6** in 50% yield but not to yield **5**.[18] Thus, it is noteworthy that the decomposition process of **3** in DMF remarkably differs from that in monoglyme.

To gain further insights into the mechanism, the coupling reaction of **2** with β-bromostyrene (*E*:*Z* = 86:14) in the presence of a catalytic amount (10 mol % relative to **2**) of CuBr in DMF was carried out to give **4a** (*E*:*Z* = 86:14) in 41% yield. The reaction was found to involve a catalytic cycle with CuBr.

Based on the above results, the following mechanism is proposed (Figure 2). Smooth transmetalation of zinc reagent **2** to **3**, followed by oxidative addition to alkenyl halides, gave presumable intermediate **9** which reductively eliminates CuBr to give the coupling product with retention of stereochemistry.

(21) Characteristic signals were observed at δ −87.4, −82.8, and −65.1 in the ^{19}F NMR spectrum; these signals are consistent with those of (*E*)-**6**, **5**, and (*Z*)-**6**, respectively, as reported by Burton and Hu.[11,18]

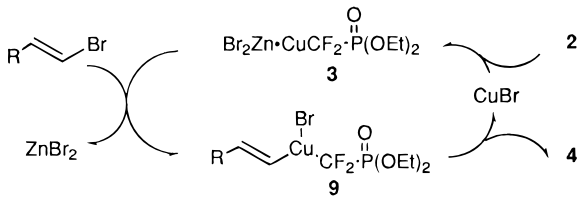
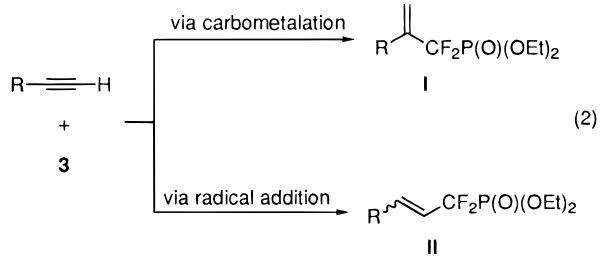


Figure 2.

Copper(I)-Catalyzed Addition Reaction of [(Diethoxyphosphinyl)difluoromethyl]zinc Bromides 2 to Terminal Acetylenes. The carbometalation reaction of copper reagent **3** with hexafluoro-2-butyne was briefly reported by Burton.[17] As described above, we have observed that the copper reagent **3** in DMF decomposed at room temperature to form the dimeric product **5** of [(diethoxyphosphinyl)difluoromethyl] radical **7** by means of ^{19}F NMR spectroscopy. On the basis of these findings and the report of Burton,[17] if the addition reaction of **3** to terminal acetylenes proceeds *via* carbometalation or radical addition, synthesis of (α,α-difluoroally)phosphonates of either types **I** or **II**, respectively, would be feasible as shown in eq 2.



In keeping with this strategy for the synthesis of (α,α-difluoroallyl)phosphonates, CuBr-catalyzed addition of **2** to terminal acetylenes was examined in DMF or THF under the given conditions in Table 4. It was found that all reactions gave (α,α-difluoroallyl)phosphonates of type **II**, and no regioisomers of type **I** as shown in eq 2 were detected. The reaction of phenylacetylene with **2** gave (*E*)-**4a** and (*Z*)-**4a** in 62% yield in a ratio of 83:17 (entry 2). The stereoselectivity slightly increased to 86:14 upon conducting the reaction at 0 °C (entry 1). The reaction on (4-methoxyphenyl)acetylene under similar conditions gave the corresponding (*E*)-(α,α-difluoroallyl)phosphonate (*E*)-**4b** in a high stereoselectivity (*E*/*Z* = 95:5), but in low yield (entry 5). 1-Hexyne also reacted with **2** under the same conditions to give **4c** without stereroselctivity in modest yield (entry 6). Moreover, it was found that a stoichiometric amount of CuBr was necessary to achieve the addition reaction effectively (entry 4). We also observed that DMF was superior to THF for these reactions (entries 2 *vs* 3).

The regiochemical results of the reaction of **2** with terminal acetylenes in the presence of CuBr may be attributed to an addition of [(diethoxyphosphinyl)difluoromethyl]radical **7** at the terminal alkyne positions.[22]

(22) Evidence consistent with the proposed mechanism is that the reaction of diallyl ether with **2** in DMF in the presence of CuBr proceeded in a 5-*exo*-*trig* mode to give radical-cyclization products **i** [δ 0.96 (d, *J* = 7.1 Hz); HRMS *m*/*z* 286.1143 (calcd for $C_{11}H_{21}O_4FP$: 286.1145)] in low yield.[23]

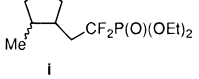


Table 4. Copper(I) Bromide-Catalyzed Addition of 2 to Terminal Acetylenes

entry[a]	acetylenes	temp (°C)	time (h)	CuBr (equiv)[b]	solvent	product	yield (%)[c]	ratio (*E*/*Z*)[d]
1	$C_6H_5-\equiv-H$	0	48	1.0	DMF	**4a**	55	86:14
2	$C_6H_5-\equiv-H$	25	15	1.0	DMF	**4a**	62	83:17
3	$C_6H_5-\equiv-H$	25	15	1.0	THF	**4a**	18	83:17
4	$C_6H_5-\equiv-H$	25	15	0.1	DMF	**4a**	<5	ND[f]
5	4-$MeOC_6H_4-\equiv-H$	25	15	1.0	DMF	**4b**	23	95:5
6	*n*-$Bu-\equiv-H$	25	24	1.0	DMF	**4c**	54	50:50

[a] Two equivalents of **2** was utilized. [b] Equivalent to **2**. [c] Yield based on acetylene. [d] Determined by NMR (^1H and ^{31}P) analysis of crude products. [f] Not determined.

Conclusion

In conclusion we have developed an efficient method for the stereoselective synthesis of (α,α-difluoroallyl)-phosphonates through the coupling reaction of [(diethoxyphosphinyl)difluoromethyl]zinc bromide **2** with alkenyl halides in the presence of cuprous bromide in DMF. In addition, we have found that this reagent system is applicable to radical addition of the (difluoromethylene)phosphonate moiety to terminal acetylenes. Further works on applications to the synthesis of polyfunctionalized (difluoromethylene)phosphonates of biological interest are now in progress.

Experimental Section

General. All reactions were carried out under nitrogen atmosphere. DMF was dried over molecular sieves (4 Å). THF was distilled from sodium benzophenone ketyl. Diethyl (bromodifluoromethyl)phosphonate (**1**) was prepared according to ref 24. ^1H NMR spectra were recorded at 300 or 400 MHz in $CDCl_3$ using TMS or residual $CHCl_3$ (7.26 ppm) as an internal references. ^{13}C NMR(100 or 75 MHz) and ^{31}P NMR (160 MHz) were taken in $CDCl_3$ using $CDCl_3$ (77.0 ppm) as an internal standard and 85% H_3PO_4 as an external standard, respectively, with broad-band ^1H decoupling. ^{19}F NMR spectra (376 MHz) was measured in $CDCl_3$ using benzotrifluoride (BTF) as an internal standard.

General Experimental Procedure for CuBr-Catalyzed Reaction of 2 with Alkenyl Halides or Acetylenes. To a stirred suspension of Zn dust (1.3 g, 20 mmol) in dry DMF (10 mL) was slowly added a solution of **1** (5.34 g, 20 mmol) in DMF (10 mL). During the addition, an exothermic reaction occurred. The addition was controlled so that the internal temperature was maintained at 50−60 °C. After addition was completed, the solution was stirred at room temperature for an additional 3 h, and then CuBr (3.02 g, 20 mmol) was added in one portion. The mixture was stirred at the same temperature for 30 min to give organocopper reagent **3** in DMF. Alkenyl halide or acetylene (10 mmol) was added dropwise at room temperature (exothermic reaction occurred). After the mixture was stirred at room temperature for the time indicated in Tables 1 and 2, HCl 2% was added to quench the reaction. Biphasic mixture was passed through Celite and extracted with Et_2O. The extract was washed with saturated $NaHCO_3$ and brine and dried over $MgSO_4$. Evaporation of the solvent, followed by chromatographic purification on silica gel (hexane:EtOAc = 5:1 to 3:1) gave (α,α-difluoroallyl)phosphonate **4**.

Diethyl (*E*)-(3-phenyl-1,1-difluoroprop-2-enyl)phosphonate (*E*)-4a: an oil; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.53−7.29 (5H, m), 7.07 (1H, ddt, J_{H-H} = 16.2, J_{H-P} = 3.0, J_{H-F} = 2.8 Hz), 6.30 (1H, ddt, J_{H-H} = 16.2, J_{H-F} = 12.9, J_{H-P} = 2.9 Hz), 4.38−4.19 (4H, m), 1.38 (6H, t, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 136.9 (dt, J_{C-F} = 10.5, J_{C-P} = 5.9 Hz), 134.2, 129.4, 128.7, 127.3, 118.6 (dt, J_{C-F} = 21.1, J_{C-P} = 12.9 Hz), 117.4 (dt, J_{C-F} = 257.9, J_{C-P} = 221.0 Hz), 64.7 (d, J_{C-P} = 6.7 Hz), 16.3 (d, J_{C-P} = 5.3 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz,) δ -45.6 (dd, J_{P-F} = 114.3, J_{H-F} = 12.9 Hz); ^{31}P NMR ($CDCl_3$, 160 MHz) δ 6.19 (t, J_{P-F} = 114.3 Hz); IR (neat) 1270, 1039 cm^{-1}; MS(EI) *m*/*z* 290 (M^+). Anal. Calcd for $C_{13}H_{17}O_3PF_2$: C, 53.78, H, 5.91. Found: C, 53.39, H, 5.86.

Diethyl (*Z*)-(3-phenyl-1,1-difluoro-2-propenyl)phosphonate (*Z*)-4a: obtained as an oil of a mixture of (*Z*)- and (*E*)-isomers in ratio of 68:32; These isomers could not be separated by column chromatography on silica gel. Spectroscopic data corresponding to (*Z*)-**4a** contaminated with the *E*-isomer: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.52−7.28 (5H, m), 7.07 (0.32H, ddt, J_{H-H} = 16.2, J_{H-P} = 3.0, J_{H-F} = 2.8 Hz), 6.95 (0.68H, dt, J_{H-H} = 12.9, J_{H-F} = 3.5 Hz), 6.30 (0.32H, ddt, J_{H-H} = 16.2, J_{H-F} = 12.9, J_{H-P} = 2.9 Hz), 5.76 (0.68H, ddt, J_{H-H} = 12.9, J_{H-P} = 2.1, J_{H-F} = 17.4 Hz), 4.37−4.17 (4H, m), 1.38 (1.92H, t, J = 7.1 Hz), 1.34 (4.08H, t, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.9 (dt J_{C-P} = 7.2, J_{C-F} = 6.5 Hz)*, 134.6*, 129.1*, 128.2*, 127.8*, 119.9 (dt, J_{C-P} = 13.8, J_{C-F} = 21.3 Hz)*, 117.3 (dt, J_{C-P} = 219.2, J_{C-F} = 259.8 Hz)*, 64.6 (d, J_{C-P} = 6.4 Hz)*, 16.2 (d, J_{C-P} = 5.5 Hz)* (*: signals corresponding to (*Z*)-**4a**); ^{19}F NMR ($CDCl_3$, 376 MHz) δ -45.6 (0.64F, dd, J_{P-F} = 114.3, J_{H-F} = 12.9 Hz), −41.09 (2.04F, dd, J_{H-F} = 17.4 Hz, J_{P-F} = 112.1 Hz), ^{31}P NMR ($CDCl_3$, 160 MHz) δ 6.42 (0.68P, t, J_{P-F} = 111.8 Hz), 6.19 (0.32P, t, J_{P-F} = 114.3 Hz); IR (neat) 1271, 1038 cm^{-1}; MS(EI) *m*/*z* 290 (M^+). High-resolution MS calcd for $C_{13}H_{17}O_3PF_2$: 290.0883. Found: 290.0883. Anal. Calcd for $C_{13}H_{17}O_3PF_2$: C, 53.78; H, 5.91. Found: C, 53.95; H, 6.14.

Diethyl (*E*)-[3-(4′-methoxyphenyl)-1,1-difluoro-2-propenyl]phosphonate (*E*)-4b: an oil; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.37 (2H, d, J = 8.7 Hz), 6.99 (1H, ddt, J = 16.1, J = 2.9, 2.9 Hz), 6.86 (2H, d, J = 8.7 Hz), 6.13 (1H, ddt, J_{H-H} = 13.0, J_{H-P} = 2.9, J_{H-F} = 16.1 Hz), 4.30−4.20 (4H, m), 3.78 (3H, s), 1.34 (6H, t, J = 7.1 Hz); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 160.6, 136.4 (dt J_{C-P} = 6.1, 10.6 Hz), 128.8, 126.9, 117.6 (dt, J = 221.7, 259.5 Hz), 116.1 (dt, J = 21.3, 12.8 Hz), 114.1, 64.5 (d, J_{C-P} = 6.3 Hz), 55.2, 16.3 (d, J_{C-P} = 4.9 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz) δ −44.93 (dd, J_{H-F} = 13.0 Hz, J_{P-F} = 116.4 Hz), ^{31}P NMR ($CDCl_3$, 160 MHz) 6.33 (t, J_{P-F} = 116.4 Hz); IR (neat) 1269, 1035 cm^{-1}; MS(EI) *m*/*z* 320 (M^+). High-resolution MS calcd for $C_{14}H_{19}O_4PF_2$: 320.0962. Found: 320.0989.

Diethyl (*E*)-(1,1-difluoro-2-hexenyl)phosphonate (*E*)-4c: an oil; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.37−6.21 (1H, m), 5.75−5.57 (1H, m), 4.33−4.18 (4H, m), 2.22−2.10 (2H, m), 1.49-1.27-(4H, m), 1.36 (6H, t, J = 7.1 Hz), 0.90 (3H, t, J = 7.2 Hz): ^{13}C NMR ($CDCl_3$, 75 MHz) δ 140.2 (dt, J = 5.9, 9.9 Hz), 120.6 (dt, J = 13.1, 21.1 Hz), 116.9 (dt, J = 219.2, 256.9 Hz), 64.4 (d, J = 6.7 Hz), 31.7, 30.2, 22.0, 16.3 (d, J = 5.4 Hz), 13.7; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −45.3 (dd, J_{H-F} = 12.4, J_{P-F} = 115.3 Hz); ^{31}P NMR ($CDCl_3$, 160 MHz) δ 6.52 (t, J_{P-F} = 115.3 Hz); IR (neat) 1273, 1040 cm^{-1}; MS(EI) *m*/*z* 270 (M^+). Anal. Calcd for $C_{11}H_{21}O_3PF_2$: C, 48.87; H, 7.84. Found: C, 48.60; H, 7.76.

(*E*)-4-(Diethylphosphono)-4,4-difluoro-2-buten-1-ol THP ether (*E*)-4d: an oil; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.40−6.26 (1H, m), 6.04−5.86 (1H, m), 4.26 (1H, t, J = 3.2 Hz), 4.40−4.28 (1H, m), 4.28−4.16 (4H, m), 4.13−3.98 (1H, m), 3.86−3.74 (1H, m), 3.54−3.42 (1H, m), 1.90−1.45 (6H, m), 1.43−1.30 (6H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) 135.9 (dt, J_{C-P} = 5.8 Hz, J_{C-F} = 9.9 Hz), 121.0 (dt, J_{C-P} = 13.3 Hz, J_{C-F} = 21.5 Hz), 116.9 (dt, J_{C-P} = 219.1, J_{C-F} = 256.8 Hz), 98.0, 65.3, 64.6 (d, J_{C-P} = 6.7 Hz), 61.9, 30.3, 25.3, 19.1, 16.3 (d, J_{C-P} = 5.4 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz) δ −45.9 (d, J_{P-F} = 113.4 Hz); ^{31}P NMR ($CDCl_3$, 160 MHz) δ 6.20 (t, J_{P-F} = 113.4 Hz); IR (neat) 1270, 1034 cm^{-1}; MS(EI) *m*/*z* 329 (M^+ + 1). Anal. Calcd for $C_{13}H_{23}O_5PF_2$: C,-47.54; H, 7.06. Found: C, 47.15; H, 6.99.

(*Z*)-4-(Diethylphosphono)-4,4-difluoro-2-buten-1-ol THP ether (*Z*)-4d: an oil; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.20−6.08 (1H, m), 5.71−5.52 (1H, m), 4.64−4.60 (1H, m), 4.59−4.46 (1H, m), 4.43-4.20 (5H, m), 3.90−3.80 (1H, m), 3.56−3.46 (1H, m),

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1.90−1.48 (6H, t, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) 139.3 (dt, J_{C-P} = 6.3, J_{C-F} = 6.4 Hz), 120.2 (dt, J_{C-P} = 13.3, J_{C-F} = 22.8 Hz), 117.6 (dt, J_{C-P} = 219.1, J_{C-F} = 259.7 Hz), 98.5, 64.6 (d, J_{C-P} = 6.2 Hz), 63.8, 62.2, 30.5, 25.3, 19.3, 16.3 (d, J_{C-P} = 4.6 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz) δ −43.3 (dd, J_{H-F} = 16.6, J_{P-F} = 112.8 Hz); ^{31}P NMR ($CDCl_3$, 160 MHz) δ 6.20 (t, J_{P-F} = 112.8 Hz); IR (neat) 1273, 1034 cm^{-1}; MS(EI) m/z 329 (M^+ + 1), 244 (MH^+ − THP); high-resolution MS calcd for $C_8H_{15}O_4PF_2$ (MH^+ − THP): 244.0696. Found: 244.0676. Anal. Calcd for $C_{13}H_{23}O_5PF_2$: C,47.54; H, 7.06. Found: C, 48.01; H, 7.15.

(*E*)-5-(Diethylphosphono)-7,7-difluoro-5-hepten-1-ol THP ether (*E*)-4e: an oil; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 6.37−6.21 (1H, m), 5.77−5.59 (1H, m), 4.60−4.54 (1H, m), 4.34−4.19 (4H, m), 3.90−3.80 (1H, m), 3.79−3.69 (1H, m), 3.55−3.45 (1H, m), 3.44−3.33 (1H, m), 2.28−2.14 (2H, m), 1.88−1.45 (10 H, m), 1.36 (6H, t, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 139.8 (dt, J_{C-P} = 13.2, J_{C-F} = 10.0 Hz), 121.0 (dt, J_{C-P} = 13.2, J_{C-F} = 21.2 Hz), 116.9 (dt, J_{C-P} = 219.0, J_{C-F} = 256.8 Hz), 98.8, 67.0, 64.4 (d, J_{C-P} = 6.4 Hz), 62.2, 31.8, 30.7, 29.1, 25.4, 25.0, 19.6, 16.3; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −45.4 (dd, J_{P-F} = 115.9, J_{H-F} = 12.4 Hz); ^{31}P NMR ($CDCl_3$, 160 MHz), 6.44 (t, J_{P-F} = 115.9 Hz); IR (neat) 1671, 1269, 1034 cm^{-1}; MS m/z 228, 138. Anal. Calcd for $C_{16}H_{29}O_5PF_2$: C, 51.89; H, 7.89. Found: C, 51.86; H, 7.81.

Diethyl (1,1-difluoro-2-hexyl-2-propenyl)phosphonate (4f) an oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.61−5.56 (1H, m), 5.34−5.30 (1H, m), 4.35−4.18 (4H, m), 2.28−2.18 (2H, m), 1.56−1.23 (8H, m), 1.36 (6H, t, J = 7.1 Hz), 0.88 (3H, t, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) 141.8 (dt, J_{C-P} = 12.4, J_{C-F} = 18.8 Hz), 118.5 (dt, J_{C-P} = 215.1, J_{C-F} = 262.4 Hz), 117.4 (dt, J_{C-P} = 4.8, J_{C-F} = 9.4 Hz), 64.5 (d, J_{C-P} = 6.5 Hz), 31.6, 29.7, 28.8, 27.7, 22.5, 16.3 (d, J_{P-C} = 4.5 Hz), 14.0; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −46.9 (d, J_{P-F} = 114.5 Hz); ^{31}P NMR ($CDCl_3$, 160 MHz)) δ 6.24 (t, J_{P-F} = 114.5 Hz); IR (neat) 1273, 1024 cm^{-1}; MS m/z 299 (M^+ + 1). Anal. Calcd for $C_{13}H_{25}O_3PF_2$: C,52.32; H, 8.45. Found: C, 51.83; H, 8.24.

Diethyl (cyclohexen-1-yldifluoromethyl)phosphonate (4g) an oil; ^{1}H NMR ($CDCl_3$, 300 MHz) 6.28−6.20 (1H, m), 4.32−4.18 (4H, m), 2.26−2.09 (4H, m), 1.72−1.55 (4H, m), 1.36 (6H, t, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) 130.7 (dt, J_{C-P} = 5.8 Hz, J_{C-F} = 9.3 Hz), 130.6, 118.4 (dt, J_{C-P} = 217.2 Hz, J_{C-F} = 216.0 Hz), 64.3 (d, J_{C-P} = 6.5 Hz) 24.8, 22.8, 21.8, 21.4, 16.3 (d, J_{C-P} = 5.2 Hz); ^{19}F NMR ($CDCl_3$, 376 MHz) δ −47.7 (d, J_{P-F} = 118.5 Hz); ^{31}P NMR ($CDCl_3$, 160 MHz) δ 6.60 (t, J_{P-F} = 118.5 Hz); IR (neat) 1665, 1270, 1045 cm^{-1}; MS m/z 269 (M^+ + 1). Anal. Calcd for $C_{11}H_{19}O_3PF_2$: C, 49.23; H, 7.14. Found: C, 48.85; H, 7.04.

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Supporting Information Available: Photocopies of ^{1}H and ^{13}C NMR spectra for (*E*)-**4a-d**, (*Z*)-**4a,c,d**, and **4f,g** (19 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masterhead page for ordering information.

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